New Pharmaceutical, Nutraceutical & Industrial Products

The Potential for Australian Agriculture

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Foreword

This report was commissioned as a scoping study about the role of Australian agriculture in supplying inputs for the new pharmaceutical, nutraceutical and industrial products that have emerged with the revolution in biotechnology, information technology and growing consumer awareness that diet is an important factor in health and quality of life. There is growing concern about developing further dependency on carbon rich raw materials from declining non-renewable fossil resources and this underpins the renewed interest in biomaterials and sustainable agricultural production systems. There is also growing concern about biodiversity of living species as human populations grow and biotechnology assumes an ever-increasing position in satisfying the demands of commercial markets. Finally, there is in western societies in particular, growing interest in health and the role of nutrition in generating longer and better quality lives.

This scoping study provides insights into the potential for Australian agriculture to supply materials for these new markets. There is increasing demand for natural products but they have conditions attached including greater interest by users in nutrient levels and product efficacy. Industrial product markets will always be sensitive to the price of raw materials.

The study points to increasingly segmented and polarised markets for functional foods, organic foods, nutraceuticals, pharmaceuticals and cosmeceuticals made from natural products. These segmented markets are likely to be more demanding of not only producers, in terms of nutrient content and product efficacy, but also research organisations in terms of the type of projects that will generate higher returns. These new markets present new challenges for research project design and screening techniques.

A major challenge for Australian agriculture and research organisations is how the benefits of a more segmented market and breakthroughs in the biological sciences can the captured at the farm gate. The concentrated nature of processing and sometimes even an absence of processing will present new challenges. But there is also a range of new opportunities.

This project was funded from RIRDC Core Funds which are provided by the Federal Government.

This report, a new addition to RIRDC's diverse range of more than 600 research publications, forms part of our Resilient Agricultural Systems Sub-Program, which is part of RIRDC's Future Agricultural Systems Program.

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- downloads at www.rirdc.gov.au/reports/Index.htm
- purchases at www.rirdc.gov.au/eshop

Peter Core
Managing Director
Rural Industries Research and Development Corporation

Disclaimer

All care has been taken in the conduct of this scoping study and in preparation of the report. The evaluation has, however, been undertaken largely on the basis of information from existing research on the use of agricultural plants and animals in the development of new pharmaceutical, nutraceutical and industrial products. New technologies, new information and new philosophies of thought about the role of food, the environment and science in human welfare mean that there is a large body of research that falls short of having substantial scientific evidence to support it. That doesn't mean that it is not valid, simply that it remains unproven. Nutrition research is recognized in medical journals as laborious and undeveloped.

We report on much of this research and have endeavoured to present different views and opposing research results within the constraints of limited resources available for the study. Small numbers of clinical trials, with variable and inconclusive results, create the potential for error. Our resources did not enable auditing or on-site verification of claims though we have visited, through our own staff and research associate Middlesex University, a number of research institutions in Australia and Europe to enhance our understanding of the new technologies. Accordingly we do not express any opinion about, or responsibility for, the accuracy of the information collected.

Where we report on research results we do urge caution in the interpretation of the results as they may be preliminary or in conflict with other results. This applies in particular to the health claims of dietary supplements, functional foods and natural products. Predictions based upon the results of some of this research should be treated with particular caution.

David Michael
Project Manager

Acknowledgments

This study was conducted with significant cooperation of personnel from a number of research organisations in Australia. These included the agricultural commodity based R&D corporations, CRCs, State Government Departments, Commonwealth Government Departments, private companies, industry associations, specialised research institutions and various program managers within RIRDC. In addition, we held Steering Committee meetings to generate feedback from our evaluation and draft reports. Tony Byrne, the Project Manager, and Roslyn Prinsley, the Program Manager, provided us with numerous valuable contacts and linkages and constructive critical comment on drafts that helped us to draw together the state of current knowledge on the subject. Dennis Richards also provided useful comments on the Draft and earlier reports. Sandra Thomas from the Bureau of Rural Sciences prepared a constructive critical note on an early draft of the Report.

Out work associates, Middlesex University in London, through their nominated representative Dr John Wilkinson [Head of the Phytochemistry Research Group], and Dr Erich Lassak, of Phtytochemical Services made a significant contribution to this study. With the benefit of their substantial experience and expertise this became a study with content, relevance, insight and vision.

While we have made use of numerous contacts in the industries concerned the views finally presented here are the responsibility of the author and they may not always fully reflect those of the numerous people who helped make our task a little easier.

David Michael
Research Consultant Manager

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Abbreviations

ACCC Australian Competition and Consumer Commission
ANZFA Australia New Zealand Food Authority,responsible for developing varying and reviewing standards for food available in Australia and New Zealand and for a range of other functions including coordinating national food surveillance and recall systems, conducting research, assessing policies about imported food and developing codes of practice with industry.
AFGC Australian Food and Grocery Council
AHA Alpha hydroxy acids
ANZFSC Australian New Zealand Food Standards Committee, receives and considers recommendations from ANZFA which, if approved, are incorporated into NZ and Australian State and Territory food laws.
ARTG Australian Register of Therapeutic Goods, a register of all products for which therapeutic claims is made.
BHT Butylated hydroxy toluene.
BRS Bureau of Rural Sciences
CBD Convention on Biological Diversity, a legally binding UN framework to which Australia is a signatory for the conservation and sustainable use of agricultural biological diversity in particular and the transition towards sustainable agriculture in general. The objectives of the CBD are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilisation of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding.
CHCF Complementary Healthcare Consultative Forum, high level consultative forum under the Chairmanship of the Australian Commonwealth Parliamentary Secretary for Health & Aged Care.
CMEC Complementary Medicines Evaluation Committee, an expert group that evaluates complementary medicines and advises the TGA on regulatory decisions.
CNS Central Nervous System (brain and spinal cord)
CRC Cooperative Research Centre, an Australian Government program to support collaborative research and education in the fields of natural science and engineering with a strong focus on commercial and other applications. About $1.5 billion has been allocated to CRCs over the last 15 years. Industry, government agencies and research and educational institutions have invested a further $4 billion over the same time.
FDA Federal Drug Administration, US equivalent of the Australian TGA.
GABA Gamma-aminobutyric acid
GMP Good Manufacturing Practice, a standard to which Australian manufacturers of therapeutic goods must comply to ensure that medicines and medical devices meet definable standards of quality assurance and are manufactured in conditions that are clean and free of contaminants.
ICRAF International Centre for Research into Agroforestry
MSCI Morgan Stanley Capital International
NCCTG National Coordinating Committee on Therapeutic Goods
NCI National Cancer Institute (USA)
OGTR Office of the Gene Technology Regulator, Australia. Operates from within the Health and Aged Care portfolio to regulate the application of gene technology. Main task is to help realise benefits of gene technology for the Australian community, industry and the environment, whilst ensuring human safety and environment protection, through regulation that is timely, science based, consistent with Australia's international obligations and takes account of ethical and socioeconomic concerns.
PMS Pre-menstrual syndrome
TGA Therapeutic Goods Administration, a division of the Australian Federal Department of Health and Aged Care with responsibility for administration of the *Therapeutic Goods Act*.
TGACC Therapeutic Goods Advertising Code Council, an industry advertising code council.
TGAC Therapeutic Goods Advertising Code

Executive Summary

It is at once, frightening, intimidating and exhilarating[1]

Sharp shifts in demand and supply of new pharmaceutical, nutraceutical and industrial products using bio-based materials may have as much impact on the structure of Australian agriculture as did many of the major events and discoveries of the last century – including deregulation of markets, plant breeding and new information and communication technologies. **Few agricultural industries will escape the impact of the 21st century revolution in biological and chemical sciences, process engineering and growing consumer demand for improved quality of life**. The implications for producers and research organisations will be significant as markets and influential manufacturers will demand more differentiated products with more consistent content for more sharply segmented markets. New farm management challenges will be presented in the form of a continuing demand for improved product quality with increased nutrient content, which new technology and expert farm management may be able to deliver at lower cost and prices.

The position of commodity based marketing organisations will be challenged further by **more vertically integrated supply chains, backed by well resourced food, pharmaceutical, chemical and power companies**. Strategic alliances, partnerships, joint ventures and vertically integrated structures will be a standard feature of these supply chains.

The demand for new pharmaceutical, nutraceutical and industrial products is being driven by **fundamental shifts in demand for improved health and quality of life and renewed concern about the long-term availability of petroleum based products** that replaced bio-based materials in the last century. We expect there will be **increasingly differentiated products for polarised market segments**, driven by the demand of various consumer groups, each motivated by different priorities such as health benefits, cost, ecological benefits, ethical issues, food safety and sustainability of supply.

Against this background, demand for natural products as raw material for new pharmaceutical, nutraceutical and industrial products seems assured, but there will be increased interest in the composition and active ingredients of materials for specific end uses. New technologies that offer specific and reliable traits for specific end uses, lower costs and higher quality will, not surprisingly, lead the way and offer a competitive advantage for those enterprises ready enough to adopt them when they become available. Traditional, organic and GMO production systems all have opportunities for these markets and one of the challenges will be to enable these systems to co-exist with each other.

Key Positive Observations

The 10 key positive observations that shaped the conclusions of this study are:

1. 25% of the active components of prescribed pharmaceuticals have their origin in flowering plants (page 30) and this is expected to increase to 30% (p66) over the next decade. This is a $US30 billion global market, growing at 6%/year (p34).

2. Herbal supplements, minerals and vitamins, already a global market of $US45 billion (page 37), are expected to continue to experience growth of 10% or more in many segments. To this market add cosmeceuticals, growing at 8% (p65) and with sound prospects for sustained development.

[1] Professor Peter Rathjen, Head of Molecular Biosciences, University of Adelaide, describing the speed of developments in human stem cell therapy. [ABC, 'Four Corners', 3 July '00]. We believe the statement applies equally to biotechnology and the speed with which it is changing consumer perceptions and production processes.

3. The functional food market could grow to account for 50% of food retail turnover in developed economies (p2).

4. Scientific and market research suggests that biotech-based products can challenge the dominance of oil in the polymer and chemical markets, capturing within 10 years some 50% of the fast growing multi-billion dollar polymer market and 15% of the markets for basic chemicals (p18 and p87).

5. Australia has capacity and is internationally competitive in growing most animals and crops that have the primary content sought by functional food markets (p72-75. It also has potential to supply many of the herbs with significant markets and growth prospects (garlic, ginkgo, ginseng, Echinacea, golden seal, St. John's Wort and Saw palmetto) (p76 and 77).

6. Medicinal and industrial products from perennial plants have potential to improve cash flow and generate external benefits from tree plantings in areas where rising water tables and salinity is a problem (p90-104).

7. Regulatory policies have potential to increase the use of renewable resources (eg the greenhouse gas abatement program) and biodegradable products made from natural materials (p98).

8. Upward volatility in the price of oil, which increases the viability of bio-based fuels such as ethanol and other energy products, made from natural materials (p99-100).

9. Corporate strategies of some large chemical and pharmaceutical companies to expand significantly their use of renewable energies and natural materials (p86). This is increasing the R&D resources available for research into natural products and improving the prospects for significant breakthroughs in cost reducing processing technologies.

10. Capital markets are starting to find favour with companies that have firm policies and strategies on environmental management and use of renewable resources (p23).

Major Constraints in Australia

We also identify 10 major constraints in Australia to exploitation of the new markets for pharmaceutical, nutraceutical and industrial products:

1. High risk and uncertain planning environment.(p105).

2. A number of the products discussed need the approval of regulatory processes before they can be marketed (p23, 106). This can add to costs of development and commercialisation.

3. Land, water and climatic environment (p83).

4. Lack of domestic processing capacity in chemicals (p74) and vitamins (p76), limitations that may be more important for these products than traditional food and fibre.

5. Economies of scale (p20-21 and p106-107), leading to market concentration and adverse pricing behaviour, making it challenging to capture high returns at the farm gate.

6. Lack of development capital, a reflection of Australia's status as a net capital importer (page 85-86), but the presence of large multinational food, pharmaceuticals and chemical companies is a major asset in terms of solving the capital shortage problem.

7. Low labour productivity in some enterprises (p112).

8. Negotiating skills in a framework featuring more partnerships, joint ventures, strategic alliances and vertically integrated firms.

9. Information for consumers to make more effective decisions about product quality and content and impact (p106-107)

10. Leadership to advance Australia's position in the supply of natural products for new pharmaceutical, nutraceutical and industrial products (page 110) and in compliance with the Convention on Biological Diversity (p24-26).

Comparative Advantage

The Australian agricultural resource available for responding to the opportunities for new pharmaceutical, nutraceutical and industrial products is substantial in terms of native plants, land resources, production infrastructure and production management skills. It comprises one of the world's largest holdings of diverse native plants, about which much is both known and unknown.

At the manufacturing level, large well-resourced and often foreign owned pharmaceutical and food manufacturing companies are critical to success. They have resources plus access to markets and technology. Effective solutions to the processing gap are likely to involve increased use of partnerships and alliances with these firms.

The best immediate and mid-term prospects rest with exploiting the capacity of the farm production sector to meet the demands of these more segmented markets. This means having policies, strategies and programs that enhance farm access to these segmented markets, to the best available biotechnology, to quality management skills, to negotiating skills and to supply chain management skills. Prospects for biotechnology as an industry by itself in Australia are unclear because of the prevalence of a large number of small-sized firms (page 82), spread across too many specialised areas for it to establish an effective position in any global market. We believe this industry would have better prospects if it focussed more on the agricultural end of biotechnology where there is a large local market emerging and which may give it the base for international expansion.

The human resource skill in Australian agricultural production is significant and reflected in its capacity to produce and export, with no government assistance in a high labour cost country. This is a major asset in terms of exploiting the potential of the emerging markets for new pharmaceutical, nutraceutical and industrial products. In horticulture alone there are about 81,000 growers, 1100 research scientists and 375 research centres. In Tasmania, in particular, there is significant expertise in dealing with the crops and supply chain institutional structures that are likely to figure prominently in these new industries.

It is important to recognise, however, that climatic constraints, limited rainfall in particular, do present serious barriers to the development of commercially viable enterprises in many areas of Australia irrespective of the product potential of medicinal plants. In these circumstances, the enterprise needs to be examined for joint products and external benefits.

While this study points to the plant industries as the areas with most potential there are also significant opportunities in animal production. Kangaroo meat, beef (through anti-carcogenic fatty acid), shark cartilage, emu oil, cane toads, dairy whey, yoghurt, colostrum and various organs from a range of animals offer significant potential. Moreover, the animal industries are a key business-to-business market for vitamin enhanced feed grains.

Food, Pharmaceuticals and Nutraceuticals

The largest and lowest risk of the markets that Australia is immediately positioned to supply is for functional foods, defined as those that may provide a health benefit over and above the traditional nutrients it may have contained. For instance, the inclusion of Echinacea in biscuits, or breakfast cereals with added bran, or low fat yoghurt or wild Italian broccoli with high levels of anti-oxidants might be seen as examples.

Up to 50% of food manufacturing is estimated to be potentially within the scope of the functional food classification. It is clearly therefore the largest potential market for which Australia is already positioned to supply. Nevertheless, medicinal and pharmaceutical products including nutraceutical supplements are the strongest growing export markets even though many of the inputs for it are sourced from imports. Growth in both exports and domestic consumption is expected to continue with natural based medicinal products accounting for an increasing market share. Products for the cardiovascular market which stands at $US30 billion/year will find most favour, with potential to be supplied by plants such as *Digitalis* spp., *Strophanthus fratus*, *Cinchona* spp. and *Rauwolfia serpentina*. *Ginkgo biloba*, ginseng, garlic and echinacea are likely to continue to experience strong growth in demand in Europe and the USA.

Industrial Products

Industrial product potential is high for grains, sugar, potatoes, whole crops, wastes and woody materials in making ethanol and methanol and bioplastics, though commercial viability is often dependent on significant increases in oil prices, improved processing efficiency and/or generation of external benefits (eg. environmental). At present oil prices ($US33/barrel) there is still a cost advantage in favour of petrol over ethanol, but as the price approaches $US40/barrel ethanol starts to becomes competitive, particularly in large-scale plants. After a century of domination by fossil materials in energy conversion there is now renewed interest in biomass for energy, fuels and chemicals. Thirty John Deere tractors have just come off the production line with seat arm rests made from soybean bioplastics. Mercedes Benz is experimenting with a plan to use a significant proportion of bio-based materials.

By 2010-2015 raw material costs of biopolymers produced from plants are predicted to be competitive with those made from oil. A new lignocellulosic economy, albeit small and undeveloped, is emerging to complement the petrochemical economy. The potential size of this market, even with a small share, is significant in terms of supplying just a small part of the materials used in automobiles, building and construction material. Advances in genetic engineering and fermentation technologies hold the promise of reducing material costs in making industrial products that currently rely heavily on the use of non-sustainable petro-chemical resources. That is, genetically engineered crops offer the prospect of a better environmental performance in industrial processes.

Environmental Impacts

If government intervention forms the basis of mass plantings of perennial plants in the wheatbelt it is likely to be unsustainable and at best subject to high risk of continued support. Instead, we suggest, a better option would be to have more diversified land enterprise systems with a mix of annual and perennial crops. Increased plantings of perennial plants are viewed as one potential solution to the salinity problem and at the same time one that could generate biomass for a range of energy intensive products. It is important that these plants also yield other products. A recent British Columbian study shows the yield of non-timber products from forests could represent over one third of forest revenue.

Other research shows the external benefits of measures that reduce water tables and dry-land salinity can be internalised, suggesting the problem can be corrected in a more sustainable way with improved farm management. In this setting there would be scope for a mix of biomass crops for ethanol, plants for medicinal and therapeutic products [as outlined in this report] and continuation of the basic annual cropping systems which form the basis of Australian agricultural prosperity. Moreover, it is relevant to note that cash crop residues such as wheat straw remain one of the lowest cost raw materials for ethanol production in certain locations, even after allowing for replacement costs of fertiliser.

Unstable Planning Scenarios

Notwithstanding our concerns about the risks of investment in large scale plantings of deep rooted perennials there is a need for improved knowledge about scenarios that may unfold with significant implications for the expected pay-off from research projects. Future scenarios that need to be examined include the impact of various oil prices on the viability of investments in plantations for bio-based materials. Over the last 12 months oil prices have increased 100%. Energy analysts are now factoring in relatively high probabilities (10%) of another 100% increase in the next 18 months (Goldman Sachs 2000). At the same time, new cellulose conversion technology may generate a significant reduction in costs of producing ethanol. If large areas of land are allocated to bio-based materials for energy products this, in turn, will have implications for the supply and prices of products currently produced by that land.

For consumer products such as nutraceuticals, genetic engineering may increase the nutritional values of certain plants and, regulations permitting, this has significant potential to meet the demands of a high growth market. The discovery and development of "Golden Rice" with high levels of Vitamin A is a current example. Major pharmaceutical companies are examining the scope for incorporating anti-oxidant specific-trait genes in a range of food crops. Identification of scenarios and incorporation in research project allocation procedures is likely to improve risk management and pay-offs to research projects.

Institutional Arrangements

To take advantage of the opportunities for new pharmaceutical, nutraceutical and industrial products, institutional capacity is essential, along the whole supply chain from supplier, through producer and processor to retailers. Supply chain integration is a feature of the pharmaceutical industry that is likely to extend into biotechnology and functional food manufacturing. To participate as a supplier for an organisation that adheres to good manufacturing practices will require skills and resources. If processors cannot secure reliable supplies of high quality material they are likely to integrate backwards to supply those materials internally. Improved farm management planning and skills are required to take advantage of the new opportunities which are likely to feature more price volatility, joint products, external costs and benefits, supply chain partnerships/alliances and more demands to keep abreast of new plant technologies and production techniques.

High levels of market concentration, a consequence of economies of scale, is a prominent feature of pharmaceutical, nutraceutical and many of the new industrial product industries. Compliance with Australian competition policy would ensure that producers receive fair treatment with processors.

It is emphasised that this is a scoping study. Many of the products discussed require considerable research before they could be considered ready for commercial production. In fact, many require an initial feasibility study to determine whether a more detailed research program is warranted. Any research program to underpin commercial development of the new products discussed in the report would need to cover such issues as market opportunities, production systems, the economics of the enterprise and environmental issues.

Suggestions for Further Research

1. Plants for pharmaceuticals, which could be examined along product lines for the major pharmaceuticals including the primary cardiovascular, anti-infective and CNS market segments. Australian requirements for producing existing plants for these markets need more detailed investigation including for the cardiovascular drug market, *Digitalis* spp. (for digitoxin); *Strophanthus* fratus; *Cinchona* spp (for quinidine); and *Rauwolfia serpentina (*for reserpine*).* A vast list of other plants used in the anti-infective market and CNS drug market should be examined systematically, in partnership with pharmaceutical companies, for their potential to grow and be marketed from Australian farms.

2. Note that medicinal herbs and botanicals supplying this market are often produced through labour intensive production systems. Therefore research should concentrate on measures that are capital and skill intensive.

3. Continue and extend the existing research into garlic, ginkgo/ginseng, Echinacea/golden seal, St. John's Wort and Saw palmetto, which are priorities in view of their market prospects. Meeting the growing demand for improved product efficacy is an issue for all of these products.

4. Initiate or facilitate a series of projects in conjunction with processors to improve the yield and conversion efficiency of agricultural materials used as biomass for ethanol and starch and lactic acid for biopolymers.

5. Review international research, examine and contrast the environmental and health impact of using petroleum and bio-based materials in detergents, paints, herbicides, plastics and pesticides.

6. Identify the crops and their respective agronomic, genetic structure and farm management practices most suitable for meeting the demands of the industrial markets for agrochemicals, packaging materials, energy and fuels, lubricants and waxes, plastics and polymers, resins and adhesives, and solvents.

   Examine, in particular, the following agricultural materials for use in making industrial products:

   a.) Nut shell flours, as an additive to thermosetting resins such as urea formaldehyde.
   b.) Wattle gums, as a thickener, emulsifier, colloidal stabiliser and adhesive.
   c.) Sucrose from cane sugar for sucrose monlaurate, a no-ionic detergent for solubulisation of membrane proteins.
   d.) Mango seeds, a solid fat substitute, used as a food additive or raw material for soap, creams etc.
   e.) Eucalypts (9), belonging to the sub-species *Symphycarpus*, for active metabolytes with potential use in root growth inhibition, anti-bacterial and other medicinal and industrials.
   f.) Neem tree leaves for insecticidal and pesticidal properties.
   g.) Microbiological transformations of readily available terpenoids, such as 1, 8-cineole, to create new products for new markets.

8. Initiate or facilitate a series of projects to enhance production of functional foods – noting that this market could grow to account for 50% of the food market. Note too that Australia is already capable of producing most of the materials for these foods including those with the best prospects, namely: oats, soy, flaxseed, canola, garlic, broccoli (and other cruciferous vegetables), citrus fruits, cranberry, tea, wine and grapes, fish, omega-3 diet eggs, dairy products and beef.

9. Recognise that perennial plants are the main source of plant-based medicinal products and that this should be considered in the selection of tree planting programs. Nevertheless, note also that several of the best plant prospects for medicinal products are weeds, e.g. Devils Claw, St. John's Wort.

10. Examine and validate, if possible, the proposition that increased use of biodegradable products and bio-based chemicals and other bio-based industrial products would have fewer harmful effects on the environment and human health.

11. Investigate the scope for increased use in the Australian wheatbelt of diverse plant species, and plants with joint product potential including, e.g. medicinal products and lignocellulose for ethanol and external benefits from deep-rooted perennials. Perennial plants with prospects for further investigation and commercialisation include Santalum spicatum (Western Australian sandalwood) for bactericides and a group of 9 eucalyptus trees with bioactive metabolites in their leaves.

12 Initiate a series of research monographs on these and the other plants listed in the report, with potential to grow in drier regions and be used for various medicinal, bactericidal, insecticidal and other industrial products.

13. Initiate or facilitate the start of a district pilot program with aboriginal groups and other similar habitat associations to help identify native plants used by Aboriginal people for medicinal, therapeutic, healing and building or industrial purposes. This plant and product database would or could become part of the developing on-line database on Australian native plants.

14. Note the potentially greater role for large-scale foreign owned food and pharmaceutical manufacturers in the new product supply chains and the implications of this for R&D activity and market efficiency.

15. Produce a 'plain English' paper on regulatory procedures for listing and labelling of pharmaceutical, nutraceutical, vitamin and functional food products. This should also cover regulatory procedures in other countries, particularly export markets.

16. Conduct new and improved studies into the economic characteristics of bio-based pharmaceutical, nutraceutical and industrial supply chains. In particular, a full examination and sensitivity analysis of the economics of the supply chain in producing bioplastics, bio-based inks and ethanol from various raw materials with different processing technologies would be useful.

17. Initiate or facilitate a workshop on natural products for new pharmaceutical, nutraceutical, functional foods and industrial products in Australia.

CASE STUDY 1: GOLDEN RICE

PARTNERSHIPS, ALLIANCES, JOINT VENTURES & OTHER FORMS OF SUPPLY CHAIN COLLABORATION WILL BE A SIGNIFICANT FEATURE IN THE FUTURE INSTITUTIONAL STRUCTURE OF BIOTECHNOLOGY

'Golden Rice' is a genetically modified rice with high levels of beta-carotene and other carotenoids, which the body turns into Vitamin A as needed. Vitamin A is a fat–soluble vitamin that is essential for normal vision, mucous membranes, immune system and the skin. The best food sources of Vitamin A are liver, kidney, butter, milk and fish oil. The best sources of beta-carotene, which the body converts to Vitamin A, are carrots and leafy vegetables. Supplements of Vitamin A, however, can have toxic effects on the liver (Hatoff 1982) and may cause birth defects when taken during pregnancy (Rothman 1995). The uniqueness of beta-carotene and other carotenoids is that they are safe to take and are converted to Vitamin A as the body needs it. Vitamin A deficiencies and associated eye problems have been most prevalent in Asia, Africa and Latin America where traditional rice with low levels of Vitamin A has been a large part of the diet.

'Golden Rice' is one example of the positive impact of biotechnology, having the potential to provide massive benefits countering Vitamin A deficiency-related diseases including irreversible blindness. (Zeneca Agrochemicals, 2000).

'Golden Rice' was developed with funding from the Rockefeller Foundation (1991-2002), the Swiss Federal Institute of Technology (1993-1996), the European Union under a European Community Biotechnology Programme (1996-2000) and the Swiss Federal Office for Education and Science. The inventors of 'Golden Rice' are Professor Ingo Potrykus of the Institute for Plant Sciences, Swiss Federal Institute of Technology, Zurich and Dr Peter Beyer of the Centre for Applied Sciences, University of Freiburg, Germany.

In June 2000, the inventors of 'Golden Rice' were joined by Zeneca Agrochemicals [who had also been involved in funding since 1996] and Greenovation to further develop and commercialise the technology. Zeneca Agrochemicals is a subsidiary of UK based AstraZeneca, the 10^{th} largest pharmaceutical company in the world with revenue of $US75 billion/year. Zeneca Agrochemicals accounts for about 4% of revenue. About 11% of Zeneca Agrochemicals' revenue is allocated to R&D. Herbicide sales which account for over 50% of Zeneca Agrochemicals' revenue has been affected adversely by the penetration of genetically modified crops requiring reduced use of herbicides. Zeneca plans to explore the commercial opportunities of 'Golden Rice' for sales into the growing health foods' markets as well as providing regulatory, advisory and research expertise for improving access to developing countries.

Greenovation is a relatively new biotechnology company, founded in 1999, at the University of Freiburg. It performs and funds research and development in plant biotechnology for agricultural and phytopharmaceutical applications. Agribiotech projects focus on metabolic engineering for increasing the nutritional value of plants and their stress tolerance. Greenovation also performs contract research and out-licensing of university research projects to the life science industry.

The institutional structure supporting the discovery and development of 'Golden Rice' illustrates the nature, extent and resources of the supply chain collaborations that are likely to be very influential in the future of biotechnology and the development of agricultural material for the pharmaceutical, nutraceutical and industrial product industries. Pharmaceutical companies, universities, government, philanthropic and specialist R&D bodies are likely to feature in partnerships that extend across several countries with different structures for different stages of development.

CASE STUDY 2

AUSTRALIAN PHARMACEUTICAL COMPANIES USING NATURAL PRODUCTS

ExGenix is an Australian company, established in early 2000 as a spin-off from a subsidiary of the Australian pharmaceutical R&D company AMRAD. The core business of ExGenix is the discovery of novel, pharmaceutically active, leading compounds for development as new medicines. ExGenix acquired AMRAD's Discovery Technologies division, giving it access to a globally competitive natural products drug discovery operation that draws upon the biota of some of the world's most biodiverse regions in Australia and South East Asia, the latter including Sarawak and Papua New Guinea.

ExGenix has an extensive library of vascular and non-vascular plant samples with full taxonomic data from tropical Australia and South East Asia, temperate Australia and exotic or naturalised samples. The library contains around 30,000 plant samples with full taxonomic data.

The natural products screening operation is underpinned by collection agreements with government authorities [including botanical gardens, national parks and aboriginal land councils and trusts], research institutes and regional/district habitat associations.

Through a network of collaborations with four Australian centres of excellence in genetics and molecular biology (The Centre for Molecular and Cellular Biology, University of Queensland; Murdoch Institute; Queensland Institute of Medical research; and Walter and Eliza Hall Institute of Medical Research;) ExGenix has built a portfolio genetic projects aimed at identifying genetic lesions associated with a variety of common human diseases. The Company is aiming to become a market leader in the business of genomics and other proprietary technologies, to discover new compounds for development in-house or in partnership with major multi-national pharmaceutical companies, to develop new drugs for treating diseases. Current pharmaceutical partners include Chiron Corporation, AMRAD and Chugai Pharmaceuticals.

Other pharmaceutical companies in Australia with active natural product exploration, screening and development programs include Zeneca Pharmaceuticals.

1. Introduction

In Brief

This is a scoping paper, with a national focus on the potential over the next decade for Australian agriculture to produce raw materials for the new pharmaceutical, nutraceutical and industrial products that will result from new approaches to plant and livestock breeding. The markets for plant based pharmaceutical and nutraceutical products are experiencing rapid growth and new industrial products are emerging as a new or renewed source of demand for agricultural material.

The terms of reference for the underlying study are extremely wide in the context of scientific discovery and development of genetic material, new products for new markets and a range of social and economic issues that are emerging. A new and even more demanding era for agriculture may be emerging with more segmented markets demanding more differentiated products and services, with tighter quality controls.

We suggest a structure for these industries based around consumer, industrial and service products, instead of commodities, to give emphasis to the different product-driven supply chains and common factors across commodities. That is, there are likely to be more differences within specific commodities such as grain and horticulture than between them, reflecting the demands of the various consumer and industrial product supply chains.

The influential US National Research Council says in its 2000 report for the US Government that '…biological sciences are likely to have the same impact on the formation of new industries in the next [21st century] as the physical and chemical sciences have had on industrial development…' in the last century. Bio-based industrial products are starting to compete with the petroleum-derived products that displaced them through improved processes and increasingly competitive raw material costs.

Pharmaceutical companies are also taking renewed interest in the potential for discovery of new compounds from plants. Nutraceutical manufacturers are looking for herbs and natural product based vitamins to meet the needs of a growing demand for supplementary foods and preventive medicine. And food manufacturers are searching for new ways to enhance the nutritional value of traditional food products. All of these developments are impacting on the demand for raw materials made from plants and to a lesser extent animals, though improved feeds for animals and animal products themselves are equally important for these industries.

The underlying desire for better health, improved quality of life and concern about the availability of non-renewable resources are driving this demand. The quality and content of information about products and processes is likely to have a significant influence on supply and demand.

To illustrate, scientific research suggests that 400-1200 IU of vitamin E per day will contribute to long-term health in significant ways, including reduced heart attacks, diabetic control, better immunity and reduced cancer (Strand 1998). US research results in this area are supported by similar research results from the University of New South Wales (Simons, Konigsmark and Balasubramaniam 1996). This level of intake is 40 times higher than the recommended dietary intake of 10IU (refer to Rogers 1990 for the National Health and Medical Research Council's table of intakes of vitamins).

Some health professionals argue that complete nutrition is best obtained from diet alone and without supplements. Many physicians remain sceptical about the real effect of the whole range of nutritional supplements including vitamins, minerals, amino acids and herbs in particular. The promoters are said to be 'snake oil salesmen and what they're selling is magic,' says Victor Herbert, M.D., Professor of Medicine at Mt. Sinai-New York University Health System (Shelton 2000). [2]But supplement manufacturers claim it is simply not possible to consume the optimal amount of 450 IU of vitamin E through natural foods without upsetting the overall balance of nutrients required. For instance, USANA (March 2000), a large US manufacturer of supplements, claims that to get 450 IU of vitamin

[2] Monash Medical School suggest that doses of 400IU can be toxic (Thomas, BRS-personal communication). This of course, does not disprove the claims of benefits, simply that caution is needed in taking doses.

E you would need to eat one or the other of the following choices which are all leading sources of vitamin E:

- 80 medium sized avocados; or
- 80 mangoes; or
- 900 grams of sunflower seeds; or
- 23 cups of wheat germ; or
- 1.7 litres of corn oil.

The key issue about these claims is that, irrespective of the technical merit of arguments against them, they are having an effect in the market, as evidenced by the growth in consumption of nutraceuticals. For agriculture the implications are significant in terms of the prospective demand for different forms of product and quality of food to supply the raw materials for these nutrients. The way in which agricultural enterprises, processors, R&D bodies and major institutions respond to these opportunities may have a profound effect on the size and structure of the agricultural sector for many years to come. Environmental concerns about the sustainability of the land, water and plant diversity resources add to the complexity of the response. And ethical issues about native plants and their use by aboriginals in medicinal products add one more dimension to the scope of what needs to be considered in design and planning a response.

This research project is an initiative of the Resilient Agricultural Systems Sub-Program within the Future Agricultural Systems Program of RIRDC. It aims to examine in more detail the implications for Australian agriculture of the emerging research showing there may be a greater role for agricultural products than was previously thought possible.

1.1 Background, relevance and potential benefits

New plant and animal breeding technologies including those involving genetic engineering are opening up new roles for agriculture. Genetically engineered crops and microbial processes may yield products such as bio-plastics, anti-cancer agents and food with enhanced nutritional characteristics. Genetically engineered livestock may also deliver products with particular health and nutritional benefits and cosmetic properties. Some of the traditional plants, including the vast Australian native plant resource, have characteristics that are now of increased interest as a source of material for these new uses. And agricultural residues and wastes are finding new uses in bio-plastics and energy conversion.

There are, nevertheless, legitimate community concerns about the use of biotechnology and particularly the longer-term consequences of using GMOs[3]. The Australian government has responded to these concerns and together with New Zealand have introduced amendments to the Food Standards Code requiring all food produced with gene technology to be labelled with that information. This action is designed to provide more information for consumers and is not intended to imply any doubts about the safety of GM foods.

The Australian market for health foods, like that in the USA and Europe, is experiencing very rapid growth of around 15-20%/annum compared to about 5% for traditional grocery products (Mitchell 2000) and this is attracting the interest of major food manufacturers and retailers. In the USA, the food industry has turnover of $US500b/year. It has been estimated that 50% of this could become relevant for what may be described as “functional foods” – if the term is used in its broadest sense.This would include dietary supplements, sugar and fat substitutes, fibre enriched foods, vegetables, fatless meat, skim milk, low calorie diets and similar products (University of Guelph 2000). While natural and organic foods are an integral part of this market it is not clear whether the demand for health food is nutrient based or for the natural or organic attributes. The implications are significant in that high nutrient foods may be produced more efficiently and at a lower cost by genetically modified plants

[3] A recent survey by AC Nielsen found that 45 per cent of respondents did not believe GM foods had any benefits to offer, while only 20% considered they were happy to meet GM foods, believing they do in fact have benefits.

than traditional plants. Ultimately, relative market prices for these various food are likely to sort the market into various segments.

Some of the factors leading to increased consumption of nutraceuticals include the positive research results from nutrient supplements; increased clinical studies being performed to establish the efficacy of natural remedies; increased distribution and promotion by retailers; and growing interest in alternative medicine and self-medication. Nutraceuticals are emerging as an important part of the health care industry, itself in the midst of significant growth. This demand is being fuelled by growing awareness of the role of anti-oxidants in enhancing the quality of life and reducing the prevalence of degenerative diseases. Agricultural plants are the essential source of raw material in the manufacture of anti-oxidants, which typically contain vitamin C, vitamin E and beta-carotene in balanced product formulations. Raw materials used in supplying anti-oxidants range from grains through to horticultural crops such as cabbage, broccoli and grape seeds. Added to this is growing awareness of the need to limit consumption of foods with high levels of saturated fats. This is creating opportunities for plant seeds such as Canola and genetically modified plants with high levels of saturated oil in their natural state such as peanuts.

In addition to the growing demand for nutraceuticals there is increasing consumer and legal pressure for more use of biodegradable packaging materials. This pressure is strongest in the European Union where environmental concerns are high. Biodegradable packaging has the advantage of being able to be composted without contaminating the final product with inert residues. Agricultural plants also have potential to be used on themselves as a natural product for agrochemicals. For instance, certain rice varieties produce weed-controlling compounds in the immediate location of where they grow (Pugh 2000)

1.2 Objectives

This is a scoping paper, with a national focus, on the potential over the next decade for Australian agriculture to produce raw materials for the new pharmaceutical, nutraceutical and industrial products that will result from new approaches to plant and livestock breeding. The study contains:

- A brief review of current pharmaceutical, nutraceutical and industrial products available from agriculture.
- A review of the literature concerned with new products, a review of public and private research nationally and globally on development of new products and a report on planned R&D of private and public organisations.
- Documentation of the results of preliminary production and marketing of new products including management issues, current and projected profitability etc.
- An examination of the implications of the review in terms of opportunities for Australia, including consideration of comparative advantage, suitability of natural resources [including low rainfall regions and associated trees], environmental impacts, suitability of infrastructure, institutional arrangements, public perceptions, appropriate business structures, availability of markets and required managerial capabilities.
- Recommendations for further investigation of Australia’s potential to produce new pharmaceutical, nutraceutical and industrial products.

1.3 Research strategies and methodology

As a scoping study the aim of the project was to identify the broad R&D opportunities for further investigation, research and development by RIRDC, other research funding bodies and research providers. The study involved a broad screening of the product market, its segments and its supply chain from market through to relevant agricultural animals and crops. This involved computer searches of key words, concepts and data held in libraries and commercial databases, government departments, industry organisations and universities. In addition, a number of meetings were held with people in Australia, Europe and the US who had recognised experience in the field. The study team itself comprised people with internationally recognised experience in phytochemistry, pharmacology and nutraceuticals, as well as supply chain economics and research policy development.

More specifically, the study involved three main tasks:

- Identification and examination of the markets for new pharmaceutical, nutraceutical and industrial products that are using agricultural crops and animals as essential raw material inputs.
- Identification and examination of the delivery, processing, managerial, organisational structure and institutional arrangements.
- Review of crops and animals grown and grazed in various Australian climatic regions [including low rainfall tree crops] and which might be used as essential raw material inputs.

Important sources of information for the review also included the database from the Survey of Economic Plants for Arid and Semi-Arid Lands (SEPASAL) at Kew Gardens, UK; International Centre for Research into Forestry, Nairobi; ACIAR; FAO; Australian National and Royal Botanical Gardens and Herbariums [including the Australian seed bank]; Pharmaceutical companies; Lassak and McCarthy's study of Australian medicinal plants; and the main R&D organisations [various CRCs; CSIRO; GRDC; HRDC; DRDC, Sugar R&D and RIRDC itself]. Middlesex University (UK), through Dr John Wilkinson, was an integral part of the research team. Through it we were able to access a significant body of experience and expertise on the subject matter. This included an interactive search on the university's web site, which links with about 1200 scientists around the world. In addition, we received data from Mississippi University about its research activity in the subject area.

To demonstrate the approach of commercial operators in the field we examined several major corporate operations to help our understanding of the supply chains and how they source and interact with agricultural raw material suppliers and research organisations. Commercial information was also obtained on firms involved in the healthcare and pharmaceutical industry in the US. The Venture Capital Association in Australia also provided information, as did the Australian Stock Exchange on the 48 companies in the Healthcare and Biotechnology sector of companies on the ASX.

The study team also met with analysts doing the review of genetically modified plants. Genetically modified plants could have potential to add value to the pharmaceutical, nutraceutical and industrial supply chains by delivering unprocessed products with superior nutritional characteristics and lower costs.

Dr Lassak, a member of the study team, also reviewed and expanded on his previously published work (Lassak and McCarthy 1992) on medicines made from Australian native plants and animals.

Finally, the study examines the case for government intervention and support for research in development of these new products. It is clear that there is significant private activity in the R&D embodied in nutraceuticals and some of the companies involved are major global pharmaceutical and food companies. This raises questions about how and where RIRDC can get leverage in the industry to maximise the return on its investment, the taxpayers that fund it, and the stakeholders, Australian agriculture in particular.

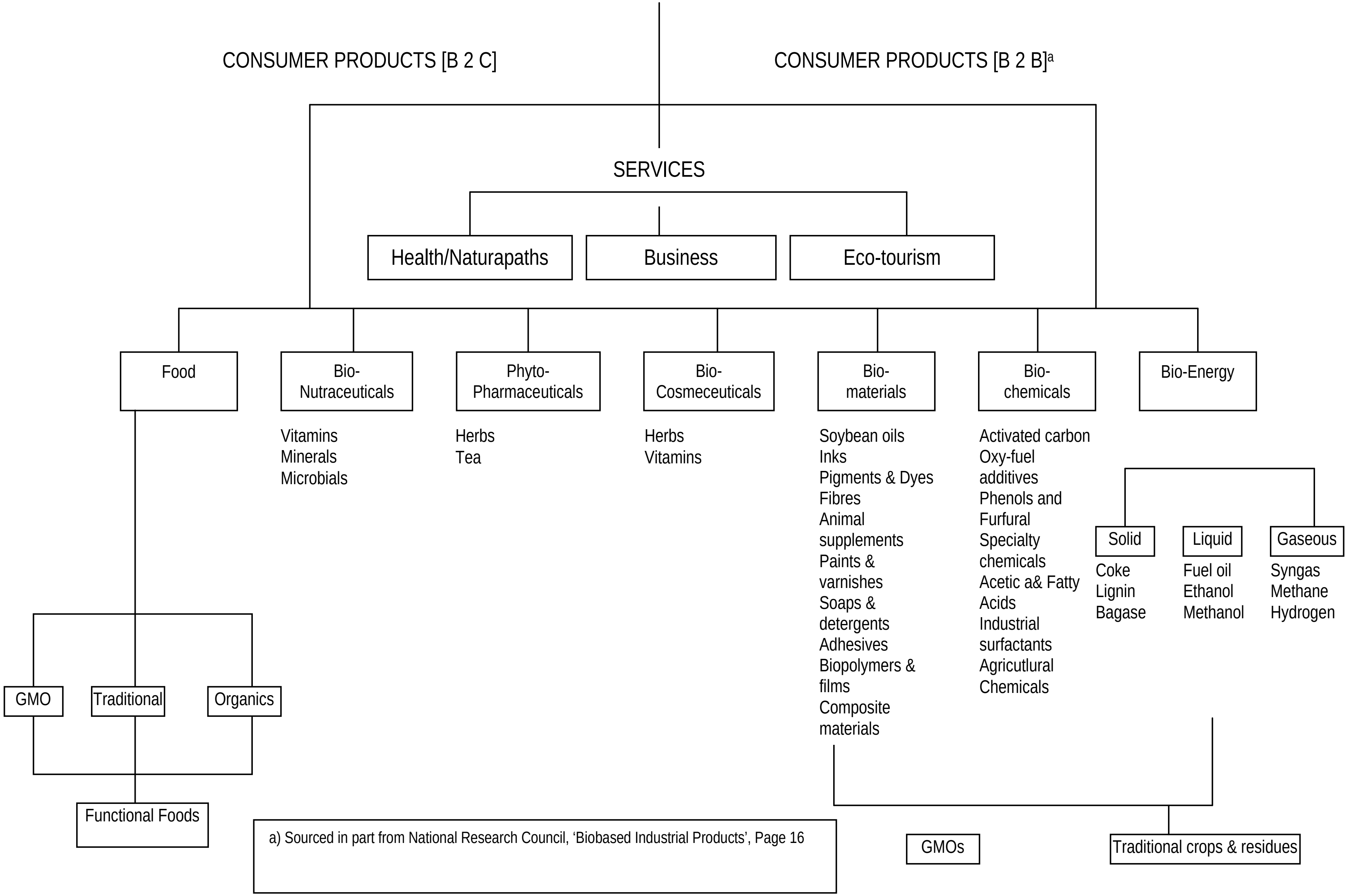
1.4 Outline of the report

The scope of the terms of reference for this study is extremely wide in the context of scientific discovery and development of genetic material, new products for new markets and the range of social and economic issues that are emerging. Much of the growth in nutraceuticals and new pharmaceuticals and bio-industrial products is due to new research results, which are not only scientific breakthroughs but also cover, a range of functional disciplines. In this context we considered it important to identify a structure for analysing these developments and from this, a more focussed way of looking at the R&D opportunities for Australia.

We suggest a product focus for the structure to give emphasis to the end products that are driving the change. Chart 1 sets out three broadly defined product categories – consumer products, industrial products and services. Within each of these categories there is a significant range of sub-categories and specific products that are all affected by the developments in demand and supply of natural products. The inclusion of an industrial product category is intended to provide recognition and emphasis to this source of demand for natural products, which could emerge with a significant market share over the next decade. This report does not deal with services, though it is relevant to note that services in all sectors of the economy typically grow faster than the goods market and food and industrial products are no exception. For instance, the demand for health and naturopath advisory and therapeutic services is a fast growing segment.

Section 2 contains a review of the literature and short description of the history. Here we find in reality there is nothing new about the basic attributes of nutraceuticals. Chinese documents show the use of herbal medicine as long as 7000 years ago (Wilkinson 1998). More recently, the nutritional attributes of food were of great interest to Hippocrates, an originator of medicine research, who considered diet played a large role in the prevention and treatment of disease (Seflin 2000). Section 3 describes the current pharmaceutical, nutraceutical and industrial products available from agriculture. It is necessarily condensed. This is followed in Section 4 with a description of new products. For practical reasons the list is restricted to 20 main product groups spread across three main categories: nutraceuticals; new pharmaceuticals; and new industrial products. The list goes on but these groups are where the study identifies most potential for Australian agriculture. Section 5 discusses the Australian potential in more details after considering its natural resources including infrastructure. Section 6 identifies trees and shrubs, originating from dryland regions, with potential use in the Australian wheatbelt, which is a major land resource with particular strengths and weaknesses. Section 7 examines the implications for Australian research. Recommendations for further investigation are described in Section 8. Throughout the report we make use of case studies to highlight particular themes and issues.

Chart 1: Product Structure: New Age Agriculture



2. Review of the Literature & Research Subjects

In Brief

This section describes, in very brief detail, some of the history and background research issues of the pharmaceutical, nutraceutical and industrial product industries. The history of using animals and plants for these products starts almost from the birth of civilisation and for all but a brief few years in the last century there were only natural products. But it was not really until the Victorian era that scientists began to investigate what made certain plants, or plant extracts, therapeutically beneficial. At the same time this investigation led to increased specialisation, but unfortunately specialisation posed new challenges for coordination and integration of production and processing. These challenges exposed weaknesses in the fragmented production and processing systems that deliver natural products. Then came oil, petrochemicals and a range of products based on them, often manufactured and distributed through highly integrated systems. These systems were able to mobilise and coordinate resources in a more efficient and more commercially focussed way. A top priority for current and future international research into animals and plants for pharmaceutical, nutraceutical and industrial product industries could therefore be more collaboration and effective communication between research groups and commercial and scientific and social disciplines.

There is no shortage of opportunities for natural products. Plant derived anti-microbial agents, antioxidants and industrial products as diverse as plastics, inks and chemicals are of increased interest to markets affected by growing demand for better health, concern about the sustainability of oil-based products and government regulations that favour more use of natural products. Fruit and vegetables, grains, nuts, oils, black grapes, red wine, raspberries, strawberries, fruit skins, tea, tomatoes and citrus fruits are major sources of vitamins.

For industrial products there are just as many opportunities, though the relative price of oil, a key input for fuels and chemicals and plastics, remains the benchmark for cost competitiveness. Bioplastics may emerge as one of the more interesting industrial products with maize, potatoes and canola as the underlying source of material. Genetically modified canola offers the prospect of a lower cost.

There is a significant level of research into these products and industries in Australia, perhaps as high as $200m per year and most of it commercially funded by the pharmaceutical, chemical and food companies. CRCs, Universities and rural R&D corporations are also important sources of funds. Australia is full of ideas and technical skills in biosciences. More important however, is how to implement, how to commercialise and how to remain relevant to a small economy that has many competing demands on its resources and not much tolerance for people and institutions that lack commercial focus. Joint ventures, partnerships, alliances and highly focussed marketing appear to be imperative for a small economy with small firms working in a globalised market where economies of scale and labour productivity are primary sources of competitive advantage.

There are, however, many assumptions behind the optimistic outlook for natural products that need more testing and research including assumptions about:

- *unexploited or idle resources and hidden productivity in agriculture and forestry;*
- *the true biodegradability and environmental impact of natural products;*
- *cost and performance of natural products;*
- *development of novel materials not available from petroleum sources; and*
- *the real impact of production and processing of renewable resources on regional communities.*

In addition, we suggest some research could be initiated into ethnobotanicals, as an activity to both comply with Australia's commitment to the Convention on Biological Diversity and to record and organise the available information on medicinal products used by aboriginals.

2.1 A short history of using animals and plants for pharmaceutical, nutraceutical and industrial purposes

2.1.1 Pharmaceutical uses of plants and animals

The history of man's use of plants and plant products for medicinal purposes dates back many thousands of years, to the time when vegetation was the only available source of therapeutics (Husain, 1991). This reliance on naturally derived treatments persisted through the well developed, documented use of herbal medicines, which gave rise to (naming just a few) the Chinese, Ayurvedic, European, Amerindian and African systems of medicine. Some of these systems, such as those developed in Europe, China and India (Ayurvedic) started the vast Materia Medica, which were recorded as extensive written texts. For example, many of the earliest European Herbals appeared in the Middle Ages, when, during the Sixteenth and Seventeenth Centuries, Banckes (1525), Turner (1551–1568), Gerard (1597) and Culpeper (1652) published their highly influential Herbals. At this time, the disciplines of botany and medicine were intrinsically linked, and many of the doctrines and preparations proposed in these works that remained unchanged for centuries afterwards.

It was not really until the Victorian era that scientists began to investigate what made certain plants, or plant extracts, therapeutically beneficial. This research has continued from that time, and arguably had some of its greatest successes in the 1950's and 1960's. This was when identification and isolation occurred of some of the best known plant-based drugs, such as reserpine (from Rauwolfia spp.; 1952), vinblastine (developed from Catharanthus spp.; 1958), vincristine (also Catharanthus; 1962) and silybin (from Silybin spp.; Wagner et al.1968).

The Catharanthus-derived alkaloids were of particular significance, as their isolation led to an extensive plant-screening programme for additional compounds with anti-tumour activity. Forty thousand specimens were analysed during the 1960's–1980's by the (American) National Cancer Institute (N.C.I.; Drug Research and Development Branch), and this remains the most extensive screening programme of plants to date. Unfortunately, the findings of this programme, in which not a single compound of general therapeutic activity was identified, cannot be accepted as definitive, as there was a lack of integration between the disciplines of chemistry, biology, botany and physiology which were involved in the research (Tyler, 1988). Consequently, many of the plants that were screened should ideally be re-investigated. The N.C.I. programme has also been criticised for its very specific approach resulting in a missed opportunity to instigate a broader spectrum of bioassays, to identify activities other than just anti-tumour effects (Tyler, 1988).

A similar deficiency appears to have occurred in Australia with the 1945 Australian Phytochemical Survey (Lassak 1997 p17), where a large number of plant species were investigated resulting in the isolation and identification of many new compounds. Although the chemical features of the enquiry appear to have been dealt with, the pharmacological and biological testing never quite caught up and as a consequence there is this same lack of integration between the disciplines.

A top priority for current and future international research into medicinal plants could therefore be a more complete collaboration and effective communication between research groups and scientific disciplines (Baker et al. 1995).

2.1.2 Nutraceutical uses of plants and animals

The term "nutraceutical" was only coined in the 1980's, as a marketing label to distinguish certain foods and food ingredients, usually from natural sources, which confer specific health benefits. The term (an amalgamation of "nutrition" and "pharmaceutical") has been used interchangeably with "functional food" or, less commonly, "pharmafood". In 1998, the Australian Food Council defined 'functional foods' as '…those foods which have nutritional, dietary, metabolic or therapeutic roles and potentially have disease prevention, mitigation and control roles, over and above the traditional nutritional sustenance provided…'(Mertens 2000). This definition is similar to that offered by the

Dietary, Supplement Health and Education Act in the US (refer to glossary) though regulations vary significantly between the US and Australia in their application to nutraceuticals.

It is very hard to distinguish nutraceuticals from naturally derived products used for pharmaceutical or medicinal purposes throughout history. This is largely a result of:

- The different systems of medicine practiced today, compared to historical methods. In ancient history, it would be hard to differentiate the use of many plant or animal species for prophylactic or chronic uses from those simply taken as simple nutrients. In many of the written texts from Mediaeval times, it is common to see particular preparations described as general "tonics"– suggesting that they were not necessarily prepared to treat a specific condition, and hence were not true medicines. These preparations would probably be viewed as nutraceuticals today.
- The current overlap between modern nutraceuticals and traditional herbal medicines. A number of modern products, including herbal "teas" and other plant-derived products (such as ginseng) blur the boundary between "alternative medicines" and "functional foods". The difficulty in distinguishing foods and medicines in this context has resulted in a complex regulatory situation. Depending on whether their primary purpose is seen as being nutritional (requiring relatively less regulation) or medicinal (in which case, the controlling guidelines are much stricter, except in the US (Wilkinson 1998)).

Regardless of these difficulties, it is perfectly conceivable that products derived from plants or animals have been used (even if unknowingly) for their indirect health benefits for as long as they have been used as foods or as sources of "true" medicines.

2.1.3 Industrial uses of plants and animals

For the purposes of this paper, the term "industrial product" applies mainly to the higher technology end of this spectrum of uses and will include agrochemicals, inks, dyes, lubricants, plastics and detergents. The use of plant and animal products for industrial products is a vast and diverse subject area, ranging in complexity from use as fuels, as a raw materials for construction, through agricultural applications, to uses such as synthetic intermediates and substrates for biomimetic (imitations) and transformation chemical processes.

Before the 20th century most nonfuel industrial products such as dyes, inks, medicines, chemicals and clothing were made from trees, vegetables or crops (National Research Council 2000). Even the first plastics and synthetic fibres were manufactured from plants as fuels, wood and plant-derived – alcohols, such as ethanol, were dominant. During World War ll, Henry Ford experimented with soybean derived plastics as a substitute for metals, which were at high prices. Only in the last few decades has the emphasis swung away from botanical sources, and towards mineral hydrocarbons, in these areas.

New and rapidly changing materials technology resulted in the replacement of many traditional materials with products such as polymers. This was because of their ease of processing, low density and low and reducing costs with volume (Dagley 2000). Now, however, there is a pronounced swing in interest back towards plastics and other industrial products based on sustainable materials and environmentally sound biodegradable and recyclable residues. Regulations appear to underpin much of this switch, although rising oil prices and new processing technologies using natural materials are also contributing.

For the purposes of this paper, the term "industrial products" will be applied mainly to the higher technology end of this spectrum of uses. It will include areas such as agrochemicals, ethanol, inks, dyes, lubricants, plastics, detergents, and will particularly focus on the potential environmental benefits of using such products (biodegradation, sustainability etc.)

2.2 Research activity

A range of public and private sector institutions undertake research activity and there are many topics, which are the subject of specialised research with applications for the pharmaceutical, nutraceutical, cosmeceutical and agricultural/ industrial fields. The world pharmaceutical market is valued at over $US300 billion, out of which Australia accounts for about 1% of revenue. The leading pharmaceutical manufacturers typically allocate from 15-20% of revenue to R&D. The largest R&D budgets are with Glaxo Welcome, Novartis, Roche, Pfizer and Merck & Co, all exceeding $US1.6 billion. All have a growing interest in nutraceuticals. Governments also fund significant research on pharmaceutical, nutraceutical and new industrial products, particularly in North America and Western Europe. The range of research activity reflects the diverse nature of these subject areas, although certain broad areas, such as the study of plant-derived antioxidants have applications in all of these subject areas (see sections 2.2.2). A selection of these research areas is presented here, and in later sections of the report.

2.2.1 Anti-microbial agents

Plant-derived anti-microbial agents have been largely overlooked since the advent of bacterial and fungal-derived antibiotics in the 1950's. With the limited life span of many antibiotics, and the increasing incidence of multi-drug resistant microorganisms, it is estimated that global spending on anti-infective agents has risen 60% since 1993 (Alper 1998). Globally, a report in 1999 (Evers/Financial Times Pharmaceuticals, 1999) split the market for anti-infective agents between anti-bacterial agents (76%), anti-fungal agents (12%), antivirals (10%) and “others” (2%). In 1998, the anti-fungal market alone was valued at $US2.3 billion (Evers/Financial Times Pharmaceuticals, 1999).

In addition to this pharmaceutical market, approximately 15% of cosmetic consumption in the US and 13% in Western Europe is dedicated to anti-microbials (Hume, 1999). A recent review of plant-based anti-microbial agents, covering established (traditional) remedies and novel plants undergoing laboratory and clinical evaluation in the United States alone, indicates the huge diversity of prospective botanical anti-microbials (refer to Tables 2.1 and 2.2; Cowan, 1999).

Table 2.1: Major classes of anti-microbial compounds from plants

Class	Subclass	Examples	Mechanism
Phenolics	Simple Phenols	Catechol Epicatechin	Substrate deprivation Membrane disruption
	Phenolic acids	Cinnamic acid	
	Quinones	Hypericin	Bind to adhesins, complex with cell wall, inactivate enzymes
	Flavonoids	Chrysin	Bind to adhesins
	Flavones	Abyssinone	Complex with cell wall Inactivate enzymes Inhibit HIV reverse transcriptase
	Flavonols	Totarol	not identified
	Tannins	Egallatannin	Bind to proteins Bind to adhesins Enzyme inhibition Substrate deprivation Complex with cell wall Membrane disruption Metal ion complexation
	Coumarins	Warfarin	Interaction with eucaryotic DNA (antiviral activity)
Terpenoids, Essential oils		Capsaicin	Membrane disruption
Alkaloids		Berberine Piperine	Intercalate into cell wall and/or DNA
Lectins and polypeptides		Mannose-specific agglutinin Fabatin	Block viral fusion or adsorption Form disulfide bridges
Polyacetylenes		8S-Heotadeca-2(Z),9(Z)-diene-4,6-diyne-1,8-diol	Not resolved

Source: Cowan (1999)

Table 2.2: Plants with anti-microbial activity

Common Name	Scientific Name	Compound	Class	Activity [a]	Rel. tox. [b]
Alfalfa	*Medicago sativa*	not identified		Gram-positive organisms	2.3
Allspice	*Pimenta dioica*	Eugenol	Essential oil	General	2.5
Aloe	*Aloe barbadensis, Aloe vera*	Latex	Complex mixture	*Corynebacterium*, *Salmonella*, *Streptococcus*, *Staphylococcus aureus*	2.7
Apple	*Malus sylvestris*	Phloretin	Flavonoid derivative	General	3.0
Ashwagandha	*Withania somnifernum*	Withafarin A	Lactone	Bacteria, fungi	0.0
Aveloz	*Euphorbia tirucalli*	not identified		*S. aureus*	0.0
Bael tree	*Aegle marmelos*	Essential oil	Terpenoid	Fungi	
Balsam pear	*Momordica charantia*	not identified		General	1.0
Barberry	*Berberis vulgaris*	Berberine	Alkaloid	Bacteria, protozoa	2.0
Basil	*Ocimum basilicum*	Essential oils	Terpenoids	*Salmonella*, bacteria	2.5
Bay	*Laurus nobilis*	Essential oils	Terpenoids	Bacteria, fungi	0.7
Betel pepper	*Piper betel*	Catechols, eugenol	Essential oils	General	1.0
Black pepper	*Piper nigrum*	Piperine	Alkaloid	Fungi, *Lactobacillus*, *Micrococcus*, *E. coli*, *E. faecalis*	1.0
Blueberry	*Vaccinium spp.*	Fructose	Monosaccharide	*E. coli*	
Brazilian pepper tree	*Schinus terebinthifolius*	Terebinthone	Terpenoids	General	1.0
Buchu	*Barosma betulina*	Essential oil	Terpenoids	General	2.0
Burdock	*Arctium lappa*	not identified	Polyacetylene, tannins, terpenoids	Bacteria, fungi, viruses	2.3
Buttercup	*Ranunculus bulbosus*	Protoanemonin	Lactone	General	2.0
Caraway	*Carum carvi*		Coumarins	Bacteria, fungi, viruses	
Cascara sagrada	*Rhamnus purshiana*	Tannins	Polyphenols Anthraquinones	Bacteria, fungi, viruses	1.0
Cashew	*Anacardium pulsatilla*	Salicylic acids	Polyphenols	*P. acnes*, bacteria, fungi, general	
Castor bean	*Ricinus communis*	not identified-		General	0.0
Ceylon cinnamon	*Cinnamomum verum*	Essential oils, others	Terpenoids, tannins	*M. tuberculosis*, *S. typhimurium*, *S. aureus*, helminths	2.0
Chamomile	*Matricaria chamomilla*	Anthemic acid	Phenolic acid	Viruses	2.3
Chapparal	*Larrea tridentata*	Nordihydroguaiaretic acid	Lignan	Skin bacteria	2.0
Chilli peppers	*Capsicum annuum*	Capsaicin	Terpenoid	Bacteria	2.0
Clove	*Syzygium aromaticum*	Eugenol	Terpenoid	General	1.7
Coca	*Erythroxylum coca*	Cocaine	Alkaloid	Gram-negative and -positive cocci	0.5
Cockle	*Agrostemma githago*	not identified		General	1.0
Coltsfoot	*Tussilago farfara*	not identified		General	2.0
Coriander	*Coriamdrum sativum*	not identified		Bacteria, fungi	

Table 2.2: Plants with anti-microbial activity (Continued)

Common Name	Scientific Name	Compound	Class	Activity [a]	Rel.Toxicity [b]
Cranberry	*Vaccinium spp.*	Fructose	Monosaccharide	Bacteria	
Dandelion	*Taraxacum officinale*	not identified		*C. albicans*, *S. cerevisiae*	2.7
Dill	*Anethum graveolens*	Essential oil	Terpenoid	Bacteria	3.0
Echinacea	*Echinacea angustifolia*	not identified		General	
Eucalyptus	*Eucalyptus globulus*	Tannin	Polyphenol Terpenoid	Bacteria, viruses	1.5
Fava bean	*Vicia faba*	Fabatin	Thionin	Bacteria	
Gamboge	*Garcinia hanburyi*		Resin	General	0.5
Garlic	*Allium sativum*	Allicin, ajoene	Sulfoxide Sulfated terpenoids	General	
Ginseng	*Panax notoginseng*		Saponins	*E. coli*, *Sporothrix schenckii*, *Staphylococcus*, *Trichophyton*	2.7
Glory lily	*Gloriosa superba*	Colchicine	Alkaloid	General	0.0
Goldenseal	*Hydrastis canadensis*	Berberine, hydrastine	Alkaloids	Bacteria, *Giardia duodenale*, Trypanosomes, Plasmodia	2.0
Gotu Kola	*Centella asiatica*	Asiatocoside	Terpenoid	*M. leprae*	1.7
Grapefruit peel	*Citrus paradisa*		Terpenoid	Fungi	
Green tea	*Camellia sinensis*	Catechin	Flavonoid	General, shigella, *Vibrio*, *S. mutans*, viruses	2.0
Harmel, Rue	*Peganum harmala*	not identified		Bacteria, fungi	1.0
Hemp	*Cannabis sativa*	-Resercyclic acid	Organic acid	Bacteria and viruses	1.0
Henna	*Lawsonia inermis*	Gallic acid	Phenolic	*S. aureus*	1.5
Hops	*Humulus lupulus*	Lupulone, humulone	Phenolic acids (Hemi)terpenoids	General	2.3
Horseradish	*Armoracia rusticana*		Terpenoids	General	
Hyssop	*Hyssopus officinalis*		Terpenoids	Viruses	
(Japanese)herb	*Rabdosia trichocarpa*	Trichorabdal A	Terpene	*Heliobacter pylori*	
Lantana	*Lantana carmara*	not identified		General	1.0
Lawsonia	*Lawsonia*	Lawsone	Quinone	*M. tuberculosis*	
Lavender-cotton	*Santolina chamae-cyparissus*	not identified		Gram-positive bacteria, *Candida*	1.0
Legume(West Africa)	*Millettia thonningii*	Alpinumisoflavone	Flavone	Schistosoma	
Lemon balm	*Melissa officinalis*	Tannins	Polyphenols	Viruses	
Lemon verbena	*Aloysia triphylla*	Essential oil	Terpenoid	Ascaris *E. coli*, *M. tuberculosis*, *S. aureus*	1.5

Table 2.2: Plants with anti-microbial activity [Continued]

Common Name	Scientific Name	Compound	Class	Activity [a]	Relative Toxicity [b]
Licorice	*Glycyrrhiza glabra*	Glabrol	Phenolic alcohol	*M. tuberculosis*, *S. aureus*	2.0
Lucky nut, yellow	*Thevita peruviana*	not identified		Plasmodium	0.0
Mace, Nutmeg	*Myristica fragrans*	not identified		General	1.5
Marigold	*Calendula officinalis*	not identified		Bacteria	2.7
Mesquite	*Prosopis juliflora*	not identified		General	1.5
Mountain tobacco	*Arnica montana*	Helanins	Lactones	General	2.0
Oak	*Quercus rubra*	Tannins Quercetin	Polyphenols Flavonoid		
Olive oil	*Olea europaea*	Hexanal	Aldehyde	General	
Onion	*Allium cepa*	Allicin	Sulfoxide	Bacteria, *Candida*	
Orange peel	*Citrus sinensis*	not identified	Terpenoid	Fungi	
Oregon grape	*Mahonia aquifolia*	Berberine	Alkaloid	*Plasmodium* Trypanosomes, general	2.0
Pao d'arco	*Tabebuia spp.*	Sesquiterpenes	Terpenoid	Fungi	1.0
Papaya	*Carica papaya*	Latex	Mix of terpenoids, organic acids, alkaloids	General	3.0
Pasque-flower	*Anemone pulsatilla*	Anemonins	Lactone	Bacteria	0.5
Peppermint	*Mentha piperita*	Menthol	Terpenoid	General	
Periwinkle	*Vinca minor*	Reserpine	Alkaloid	General	1.5
Peyote	*Lophophora williamsii*	Mescaline	Alkaloid	General	1.5
Poinsettia	*Euphorbia pulcherrima*	not identified		General	0.0
Poppy	*Papaver somniferum*	Opium	Alkaloids and others	General	0.5
Potato	*Solanum tuberosum*	not identified		Bacteria, fungi	2.0
Prostrate knotweed	*Polygonum aviculare*	not identified		General	2.0
Purple prairie clover	*Petalostemum spp.*	Petalostemumol	Flavonol	Bacteria, fungi	
Quinine	*Cinchona spp.*	Quinine	Alkaloid	*Plasmodium* spp.	2.0
Rauvolfia, chandra	*Rauvolfia serpentina*	Reserpine	Alkaloid	General	1.0
Rosemary	*Rosemarinus officinalis*	Essential oil	Terpenoid	General	2.3
Sainfoin	*Onobrychis viciifolia*	Tannins	Polyphenols	Ruminal bacteria	
Sassafras	*Sassafras albidum*	not identified		Helminths	2.0
Savory	*Satureja montana*	Carvacol	Terpenoid	General	2.0
Senna	*Cassia angustifolia*	Rheimn	Anthraquinone	*S. aureus*	2.0

Table 2.2: Plants with anti-microbial activity [Continued]

Common Name	Scientific Name	Compound	Class	Activity [a]	Relative Toxicity [b]
Smooth hydrangea	*Hydrangea arborescens*	not identified		General	2.3
Snakeplant	*Rivea corymbosa*	not identified		General	1.0
St. John's wort	*Hypericum perforatum*	Hypericin, others	Anthraquinone	General	1.7
Sweet flag, calamus	*Acorus calamus*	not identified		Enteric bacteria	0.7
Tansy	*Tanacetum vulgare*	Essential oils	Terpenoid	Helminths, bacteria	2.0
Tarragon	*Artemisia dracunculus*	Caffeic acids		Viruses, helminths	2.5
		Tannins	Polyphenols		
Thyme	*Thymus vulgaris*	Caffeic acid		Viruses, bacteria, fungi	2.5
		Thymol	Phenolic alcohol		
		Tannins	Polyphenols		
			Flavones		
Tree bard	*Podocarpus nagi*	Totarol	Flavonol	*P. acnes*, other gram-positive bacteria	
		Nagilactone	Lactone	Fungi	
Tua-Tua	*Jatropha gossyphiifolia*	not identified		General	0.0
Turmeric	*Curcuma longa*	Curcumin	Terpenoids	Bacteria, protozoa	
Valerian	*Valeriana officinalis*	Essential oil	Terpenoid	General	2.7
Willow	*Salix alba*	Salicin	Phenolic glucoside		
		Tannins	Polyphenols		
		Essential oil	Terpenoid		
Wintergreen	*Gaultheria procumbens*	Tannins	Polyphenols	General	1.0
Woodruff	*Galium odoratum*		Coumarin	General, viruses	3.0
Yarrow	*Achillea millefolium*	not identified		Viruses, helminths	2.3
Yellow dock	*Rumex crispus*	not identified		*E. coli*, *Salmonella*, *Staphylococcus*	1.0

Source: Cowan (1999)

a – 'General' indicates activity against multiple types of organisms (e.g. bacteria, fungi, protozoa)

'bacteria' indicates activity against gram-positive and gram-negative bacteria.

b – 0 = very safe; 3 = very toxic (from Duke, 1985)

2.2.2 Antioxidants

Due to their very wide range of potential applications, ranging from health-care through to cosmeceuticals and industrial potential, there is currently considerable research focused on antioxidants. Phytochemicals, as bioactive components of the diet, are receiving particular attention for their potential protective actions against diseases such as coronary heart disease and some cancers (Rice-Evans *et al*., 1997). As discussed below (Section 3.2.2), coronary heart disease in particular is forecast to become one of the world's leading causes of death. Hence the possibility that diet could positively affect incidence of this disease is of great significance to the nutraceutical and dietary supplement industries.

Table 2.3: Sources of antioxidants

Source	Antioxidant class	Examples
Fruit and vegetables	Vitamins	Vitamin C
Grains, nuts and oils	Vitamins	Vitamin E
Black grapes, red wine	Anthocyanidins	Oenin
	Flavon-3-ols	Quercetin
	Flavan-3-ols	Catechin, epicatechin
Grapes	Anthocyanidins	Cyanidin
White grapes	Hydroxycinnamates	Caffeic acid *p*-coumaric acid
Raspberries, strawberries	Anthocyanidins	Cyanidin
Onions	Flavon-3-ols	Quercetin
	Flavones	Rutin
Fruit skins	Flavones	Chrysin
Black tea	Theaflavanones	Theaflavin and theaflavin gallates
Teas	Flavon-3-ols	Kaempferol
	Flavan-3-ols	Epigallocatechin and epigallocatechin gallates, epicatechin gallate
Tomatoes	Flavon-3-ols	Quercetin glycosides
	Flavanones	Naringenin
	Flavones	Rutin
Citrus fruit	Flavanones	Taxifolin, narirutin, naringenin
Grains	Hydroxycinnamates	Ferulic acid

Modified from Rice-Evans et al. (1997) and Paganga et al. (1999)

In terms of health-care, antioxidants are under investigation for all stages of life, from premature neonates (babies who are poorly able to deal with oxidative stress, contributing to conditions such as broncho-pulmonary dysplasia and necrotizing enterocolitis, Miller *et al*., 1993) through to numerous age-related conditions, such as Alzheimer's Disease (Durany *et al*., 1999) and cataract formation (Giblin, 2000). The significance of antioxidants as a means of preventing a number of acute and chronic conditions, including myocardial infarction (Miller *et al*., 1997) hypercholesterolaemia and hypertension (Abeywardena *et al*., 1996) and cancers (e.g. Simic and Jovanovic, 1994; Hirose *et al*., 1994) has also received considerable attention.

Oligomeric proanthocyanidins (OPC's), found in grape seeds, pine, oak, horse chestnut and numerous other plant species have been singled out for particular attention for their antioxidant potential (Sterling, 2000). An OPC-rich product has recently been shown to increase the antioxidant capacity of blood after oral administration of capsules containing 600mg of grape-derived OPC's, with possible implications in atherosclerosis, particularly in hypercholesterolaemic patients. The study also found that antioxidant capacity of the blood peaked approximately 30 minutes after administration of the OPC product, but that the baseline antioxidant capacity of the blood was not affected by the treatment, indicating that regular dosing with products of this type may be necessary. The authors called for further clinical work to assess the longer-term implications of therapies of this type (Nuttall *et al*., 1998).

In the field of cosmeceuticals, antioxidants are receiving attention for numerous activities, including their protective effects against photo-ageing (e.g. Traber *et al*., 1996) and their ability to stabilise biological membranes, particularly those containing large amounts of polyunsaturated fatty acids (particularly d-alpha-tocopherol form of vitamin E. (Rangarajan and Zatz, 1999). OPC's from grape seed have been demonstrated to protect against UV-induced lipid peroxidation to a similar extent to vitamin E, and prolong the active life of vitamin E (Carini *et al*., 1998). Antioxidant cosmetic products are commonly sold as rejuvenating treatments, or as a method for treating the signs of ageing.

2.2.3 Industrial research activity

Industrially, the applications of antioxidants are also numerous, as outlined below:

Table 2.4: Industrial applications of antioxidants

Application	Details
Elastomers	Prevent oxidative deterioration from heat, light and oxygen. Eases processing, storage and increases quality of end products. Phenolic antioxidants particularly common for latex compounds
Plastics	Many plastics require stabilisation with suitable antioxidants. Use and materials define the amounts required
Petrol	Unprotected petrol can discolour and accumulate gum residues on storage, reducing engine efficiency. Usage currently less widespread, due to changes in petrol composition.
Lubricants	Further examples of petrochemical products requiring stabilisation with antioxidants to prolong/maintain efficacy. Hydraulic fluid can be protected by 1% BHT
Adhesives	Highly dependent on type of adhesive – antioxidant may require thermal stability, permanency and/or minimal/no toxicity
Food	Flavour and odour can easily be adversely affected by oxidation (e.g. rancidity of oils). Toxicity is clearly a key feature of antioxidants selected for the food industry.

Kroschwitz, 1978

Although petroleum based industrial products replaced most bio-based products over the last century there continued to be research into several areas such as improving the efficiency with which biomass can be converted to ethanol (refer, for instance, to Energy Research Development and Information Centre, UNSW). The presence of occasional oil price spikes gave considerable momentum to this research. Europeans, encouraged by growing environmental regulations in favour of biodegradable products, have continued to do research into the use of biological materials for bioplastics (Bioplastics 1999). ICI, for instance, launched bio-based Biopol ® resin in 1990 (CPL Scietific 1999).

This was developed from a biodegradable polyester comprising copolymers of poly-hydroxy-butyrate/valerate (PHB/V) and is produced by the bacterium *Alcaligenes eutrophus* in a fermentation process using sugar as the base material. Further development and product launches followed after the business was taken over by Zeneca Ltd and, in turn, by Monsanto, which then started investigation into whether or not plants such as switchgrass, sugar or corn could be genetically modified to improve efficiency of the conversion process.

Biodegradable polymers have encountered continuing problems with cost competitiveness, but recently there are reports of successful results from genetic modification of *Arabidopsis thaliana* – a relative of canola (rikilt 2000). More recently, Bachmann *et al*. (2000) predicts the raw material costs of biopolymers produced from plants will fall below that of petropolymers made from oil. fermentation technology will enable the costs reductions but biopolymers will also be in a position to generate price premiums from biodegradability attributes. Bachmann *et al.* suggest biotech products may account for as much as 50 % of the polymer market and 15% of the basic chemical markets within 10 years.

2.2.4 Australian research programmes and projects

The Australian pharmaceutical industry allocated $254m to R&D in 1995-96, equivalent to 5.5% of industry revenue, and this was estimated to be approaching $300m in 1999-2000. About 42% of this R&D expenditure was allocated to clinical research. Out of 10,862 R&D projects in 1998 there were 1222 involving biotechnology. We estimate that the R&D budget allocation from Australian-based pharmaceutical companies and spent in Australia on nutraceuticals and plant based pharmaceuticals could be around $30m/year.

The level of private research undertaken in Australia by health food manufacturers accounts for less than 1% of revenue (equivalent to $8m in 2000) and is confined largely to clinical research. This reflects the fact that the manufacture of most raw material and product development takes place offshore in Europe and the USA.

The Australian food industry also invests in functional food R&D. Like health food manufacturers, about 1% of food industry revenue is invested in R&D. This amounts to about $500m/year. An increasing proportion of food manufacturers' R&D budgets is being allocated to what could be termed R&D on functional foods. We estimate that at least 20% of the R&D budgets of food manufacturers, equivalent to $100m, would be described as functional foods R&D. This includes, for instance, the expenditure by Goodman Fielder Limited on Hi-maize, which increases the fibre content of food without changing its taste or texture. It includes $4m/year of expenditure by a newly created Bioscience Division at Bonlac Foods on natural, health enhancing ingredients in foods, confectionery and beverages. Arnotts is examining the viability of including vitamins and herbs in biscuits.

The rural commodity based R&D corporations and RIRDC also allocate expenditure to the new products. GRDC has the largest commitment to biotechnology through a strategic alliance with AWB Limited and CSIRO and which has resulted in the formation of Graingene, a programme to capture intellectual property through new generation plant biotechnology.

Several CRCs are involved in specific disciplines of research that may be considered inputs or have indirect linkages to the new products [Table 2.5]. The CRC for Food Industry Innovation involves a joint venture between the University of NSW, CSIRO, Arnotts Biscuits and GFW and has a budget of about $34.5m. Its largest program is for Probiotic and Pre-probiotic foods, which are part of the functional food markets. Other major CRC programmes on the subject matter include the CRC for International Food Manufacture & Packaging Science (budget of $30.3m, almost 20% of which is derived from contributions by the Horticultural Research and Development Corporation (HRDC)); the CRC for Tropical Plant Protection; the CRC for Polymers. The CRC for International Food Manufacture & Packaging Science is currently doing research into oilseeds and other natural extracts as sources of materials for bio-plastics.

Further funding for R&D into biotechnology is planned by the State Governments of Victoria ($300m over five years) and Queensland ($155m over 10 years) (Kumar 2000). These funds will be distributed mainly through the Victoria Institute for Biotechnology and the Institute of Molecular Science at the University of Queensland.

Table 2.5: Cooperative Research Centres: dealing with pharmaceutical, nutraceutical and/or industrial products from natural materials

	Grant Period	Total Budget [$m]	Features
CRC for Polymers	1992-2000	20.7	Polymer blends, plastic materials
CRC for Industrial Plant Biopolymers	1992-2000	27.8	Biopolymers from plant cells for thickening products such as yoghurts
CRC for International Food Manufacture & Packaging Science	1995-2003	50.3	Microbiology and bacterial molecular genetics
CRC for Plant Science	1991-1999	42.9	Enhancing plant growth and performance characteristics
CRC for Food Industry Innovation	1993-2000	34.5	Improved and novel natural food ingredients
CRC for Sustainable Sugar Production	1995-2003	44.1	Sugar production orientation
CRC for Quality Wheat Products and Processes	1995-2003	78.4	Molecular basis for wheat functionality
CRC for Molecular Plant Breeding	1997-2005	69.2	Genetic engineering
CRC for Sustainable Rice Production	1997-2005	52.2	Improved genotypes with better adaptation to saline conditions.
CRC for Biological Control of Vertebrate Pest Populations	1992-2000	49.6	Biological control of pests.
CRC for Biopharmaceutical Research	1992-2000	39.3	Tissue culture engineering.

The largest overall R&D resource allocations appear to be in functional foods (accounting, by our estimates, for about 60% of current R&D expenditure on the subject areas in Australia). This reflects the relative size of the food industry and the presence of significant local manufacturing. The most neglected research area is for industrial products and this reflects the low level of local manufacturing in bio-materials, biochemicals and ethanol. The Cooperative Research Centre for International Food Manufacture and Packaging Science has developed a proposal to undertake research into starch-based biodegradable packaging. The Department of Biotechnology at the University of NSW is developing strains of bacteria that can increase the efficiency of converting biomass to ethanol. This includes the use of genetically modified bacteria to improve conversion efficiency. The CRC for Polymers is examining new technologies for recycling of polymers including biodegradable polymers.

Australia imports more than $10 billion of chemical and related materials and products (incl. Organic chemicals; medicinal and pharmaceutical products; plastics; dying, tanning and colouring materials etc.), manufactures $1.1 billion and exports $3.3 billion. There is, however, increasing research being undertaken by power generating companies into the use of alternative sources of energy including the use of by-products, wastes and residues of agricultural and horticultural activities which are suitable for energy conversion, including straw, stubble, stalks, leaves, trash, husks, hulls, shells, pips, leaves etc.

From the above specific allocations we have compiled an estimate of the R&D expenditures in Australia on new pharmaceuticals, nutraceuticals and new industrial products [Table 2.6].

Table 2.6: Australian research and development on new pharmaceuticals, nutraceuticals, functional foods and new industrial products: 2000 [$m]

Private Pharmaceutical Companies on Nutraceuticals	$30m
Private Health Food Companies	8m
Food Manufactures R&D on Functional Foods	100m
CRCs, R&D not included elsewhere	20m
Rural R&D Corporations	5m[a]
State & Commonwealth Government Departments	10m
TOTAL	173m

a.) the estimated expenditure by the various rural R&D corporations is a general estimate compiled from field discussions. A number of research projects are undertaken that could be seen as indirectly affecting nutraceutical, pharmaceutical and industrial products. For instance, we estimate that about 8.5% or more of RIRDC's budget could be seen as research of this nature, implying a major share of the rural R&D expenditure.

2.3 Institutional and business issues

2.3.1 Drivers of structure

There are five defining features of the institutional structure and location of the industries involved in pharmaceutical, nutraceutical and new bio-based industrial products and the agricultural industries that supply them:

1. Economies of scale, which are strong and persist across most processing activities.
2. Strategic alliances, joint ventures and partnerships to integrate and capture the benefits of research and gain access to markets and capital.
3. Relative labour costs and productivity of labour, which influences the location of production and processing.
4. Government intervention, which is common in both regulation of products and activities as well as in support for R&D.
5. Management expertise and venture capital support.

The health and personal care sector of the global Morgan Stanley Capital International (MSCI) stock indexes – a $US20 trillion index of listings of the world's leading companies – is the fourth largest industry sector in the world with an estimated value of around $US2.2 trillion. The top 10 companies in this sector account for 50% of its value. Two companies, CSL and Fauldings, are the only Australian firms to make the list of 58, and they account for just 0.1% of the value of the market (BT Funds Management). Although different firms lead the Australian market[4] there is still significant concentration, with the top two accounting for about 30% of pharmaceutical sales.

[4] In 1998 Astra was the leading pharmaceutical manufacturer in Australia with a five per cent share, just ahead of Merck, Sharp and Dohme and Glaxo Welcome (Australian Pharmaceutical Manufacturers Association 2000). In contrast, Pfizer, Merk, Johnson & Johnson, Glaxo and Bristol Myers Squibb lead the global market.

Market concentration is even more severe in the vitamin, herbal and botanical raw materials market. For example, in the US, eight firms hold 73 per cent of the vitamin raw material market; and 36 per cent of the herbal and botanical raw material market (US Food and Drug Administration Centre for Food Safety and Applied Nutrition 1999). Nearly all vitamin E, in particular, is sourced from one raw material supplier. In Australia, the top four firms hold over 75 per cent of the vitamin market (Foodweek 1999). The Australian Competition and Consumer Commission is currently investigating practices of a cartel of four major pharmaceutical companies (F Hoffman-La Roche, BASF, Rhone Poulenc) that dominate the supply of vitamins for animal food purposes in Australia.

Market concentration is also evident in the industrial market for lysine where Australia has continued to be a substantial importer, having no local processing. Nevertheless, a feasibility study undertaken in the early 1990s indicated that it was commercially feasible to establish a new lysine plant in Australia. (Rogers 2000), but unfortunately resources could not be mobilised to undertake the investment. Recent prices for lysine suggest such a plant would have been even more profitable than the original feasibility study indicated.

This suggests management and access to venture capital may have been a limiting factor at that time. Other factors affecting adversely the lysine plant's profitability were the cost of raw material as low cost cassava was proving to be an effective substitute for maize – the raw material proposed to be used for the Australian plant.

Standard and Poor (1994), in a review of the Australian pharmaceutical and nutraceutical industries identified five critical success factors for businesses to remain viable:

1. Product innovation. A constant flow of new products is required and this depends, in part, on substantial investment in R&D. On average, pharmaceutical companies' investment in R&D accounts for about 15% of sales revenue.
2. Product life-cycle management. To take advantage of patent protection and initially high prices, new products have to be developed and released quickly. Delays in the development and release of new products have a severe negative effect on value.
3. Effective marketing through product differentiation and compliance with regulations.
4. Alliances with other pharmaceutical companies. This facilitates economies of scale and lower costs. Mergers, joint ventures, partnerships and strategic alliances are common in the industry.
5. Niche marketing. This is of particular importance for the typically small companies that exist in Australia. They need to focus on tightly defined markets and products to remain viable.

Although economies of scale are strong in the industry, local companies such as Blackmores and Fauldings have demonstrated that with very focussed marketing and sound sourcing practices there is a position for small companies. Blackmores is focussed on the herbal and nutritional supplement areas. Revenue for the company has increased from $40m to $70m over the last decade and exports now account for 15% of revenue.

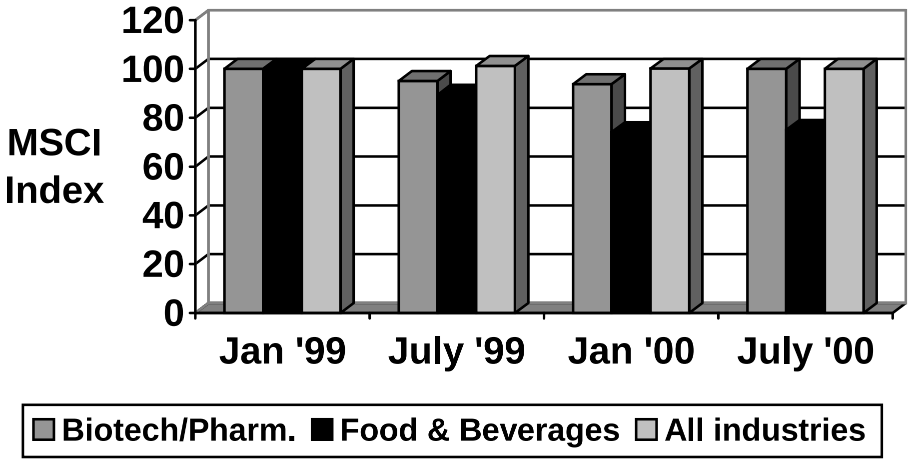
It is understood, however, that Blackmores relies largely on imported materials for its inputs. The company is essentially an assembler of raw materials manufactured elsewhere, largely in the US and Western Europe. R&D for the company represents less than 0.5% of revenue and most of this research is of a clinical nature.

Labour costs and the productivity of labour are key factors in production and processing, particularly in view of the imports from countries with low labour costs. The labour intensity of horticultural enterprises including, for instance, herb growing is recognised (RIRDC Publication No. 98/76). In these enterprises, mechanical harvesting is an important means of improving labour productivity providing quality is maintained. Labour productivity is also an important factor in processing profitability, though this depends largely on the intensity of processing activity undertaken.[5]

2.3.2 Corporate profitability

To improve our general understanding of relative profitability in the biotechnology and pharmaceutical and food industries we extracted and examined data from the MSCI world index of stock market prices. Over the 18-month period from December 1998 to May 2000 there was a significant difference in both stock market returns and risk of the food and pharmaceutical indexes, with the latter clearly outperforming the former on both performance measures. Although this is a relatively short period it does convey some insights about the extent of change happening in these industries and which sectors are attracting and struggling to retain resources (Chart 2.1). More generally, however, we expect to see over the long-term relatively high volatility in the biotechnology stocks, reflecting the high risk of this sector.

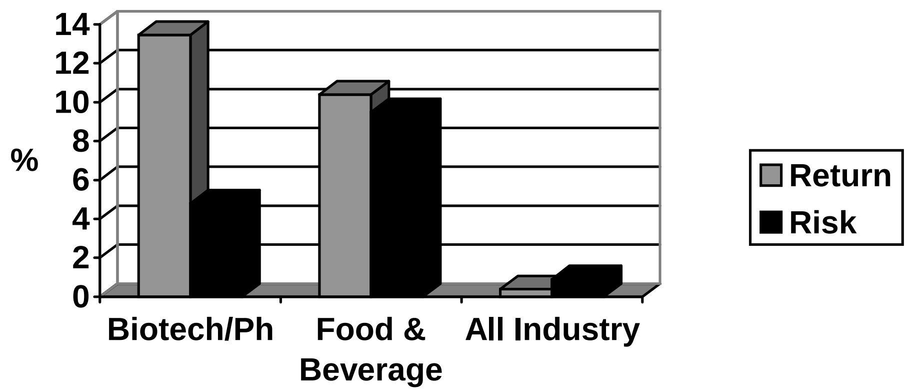
Chart 2.1: Movements in World Stock Market Indexes: Jan. 99 to July '00



Although biotechnology stocks have performed well in terms of risk over the last couple of years (Chart 2.2) they have had a fairly ordinary performance over the past 20 years. The paybacks to R&D are risky and drawn out over many years. This reflects the fact that their R&D is often involved with cutting edge technology, almost bordering on what might traditionally have been termed “basic research”. The risk and return performance of biotechnology stocks shown in Chart 2.2 may not be repeated in the next five years, although the number of new stock listings and expanded R&D expenditure in this sector suggests there will be continued, if volatile, interest.

[5] Wages, salaries and supplements represent about 20% of revenue and 58% of value added by Blackmores, where the cost of materials [including taxes on inputs] represents over 65% of revenue.

Chart 2.2: Risk & Return: Selected Industries: '99-'00



Source: Morgan Stanley Corp. International (MSCI)

The Deloitte Biotech Index, an Australian index, is based on 32 shares listed on the Australian Stock Exchange, three (CSL, Cochlear and Resmed) of which account for almost 75% of the value of the index. This means sectoral performance is very much governed by what happens with these three stocks which are more closely focussed on the human health end of biotechnology. Among the listed companies in the index with more direct and closer links to agricultural production there is Clover Corporation (manufacture and supply of natural long chain polyunsaturated oils derived from tuna, evening and primrose) and Amrad (incl. ExGenix with research into active compounds from Australian native plants). Planned listings include Gropep Pty Limited, a private company (owned jointly by Dairy Research and Development Corporation and CSIRO) that develops and manufactures a range of insulin-like growth factors.

Another grouping of stocks is emerging with some interest to capital markets groups. They measure those firms with firm practices and policies on environmental sustainability (Martin 2000). It appears to be outperforming the overall market in terms of returns. Environmental sustainability may emerge as an attribute that will attract capital in the future, in which case firms would benefit by adopting good management practices in this area.

2.3.3 Regulations

The regulation of pharmaceutical and complementary medicines is designed essentially to protect public health and safety, while simultaneously encouraging market-based solutions to stimulate investment and industry growth. In Australia the objective of the Therapeutic Goods Act 1989 is to provide a framework for the regulation of therapeutic goods in Australia and to ensure their quality, safety and efficacy. The Therapeutic Goods Administration (TGA) office executes the Act. Any product for which a therapeutic claim is made must be entered in the Australian Register of Therapeutic Goods [ARTG] before the product can be presented to a market in Australia. Implementation of the TGA is given effect through three main processes (Peachy 2000):

- pre-market assessments, during which products are assessed as being either higher risk (e.g. prescription medicines) or lower risk (e.g. most complementary medicines [6]). Once approved

[6] Complementary medicines can be either 'listed' or 'registered' on the ARTG, depending on their ingredients and claims made. For some products the effect of ingredients is not confirmed or in dispute. St John's Wort (*Hypericum perforatum*) for instance, an ingredient in many complementary medicines, is under review because of reports of interactions which may lead to loss of therapeutic effect of the prescribed medicine. (Therapeutic Goods Administration 1999).

"higher risk" products are included in the ARTG as registered products and "lower risk" products included as "listed products";

- licensing of manufacturers, which requires Australian manufacturers to comply with the principles of Good Manufacturing Practice [GMP]; and
- post-market vigilance, a monitoring process to ensure compliance with the legislation and regulations.

Over the last three years there have been significant changes to the regulation of complementary medicines which, in keeping with their relatively lower risk status, are now seen to be placed in a relatively less regulated environment.

Compliance with regulations can add significantly to costs of development, administration, advertising and labour generally. These costs can become a significant entry barrier, particularly to small firms. Differing regulations between countries can produce different industry structures, with regulatory costs having the potential to affect export orientation. For example, in the US, exports seeking listing with the Food & Drug Administration (FDA) may need to go through a lengthy and costly series of pre-clinical testings and trials (refer to Chart 7.1) that may require significant resources.

That's not however, always the case. Indeed US regulations on some nutraceuticals are less stringent than in Australia, though in the final analyses it all depends upon the claim that is being made. The recent growth in use of medicinal products in the US is attributed in part to the Dietary Supplement Health and Education Act of 1994 which relaxed regulations through the new category of "dietary supplements" (Etkin and Johns 1998). Under this Act dietary supplements can go to the market without testing for efficacy or safety or complying with manufacturing standards. Dietary supplements cannot by this law make claims about treatment of specific illnesses. The bigger the claim and promotion of that claim then the greater is likely to be the onus of proof.

Pharmaceutical regulations also have great potential to create extended benefits for those firms protected by the regulation (refer to Case Study 3 on Taxol).

2.4 Ethnobotanical issues [flora and fauna used by indigenous people]

There is a significant, but far from fully documented, history on the use of fauna and flora by indigenous people for the purpose of preparing medicinal products and in what is in effect an indigenous version of functional foods. Lassak and McCarthy identify and describe a number of aboriginal medicinal and nutritional products formulated from native fauna and flora for use as tonics, narcotics, painkillers and digestive relief. Isaacs (1987) refers to aboriginal herbal medicinal knowledge being gleaned through the best scientific methods – '… extensive trial, and presumably error, and observation of the results, not on animals in test laboratories but on human patients over thousands of years…' There are over 40,000 species of plants in Australia, of which 90 per cent are native to the country (Blakeney 1997). But as Lassak notes, '…while the use of plant remedies by the early white settlers is on the whole well documented, most Aboriginal uses have been communicated by word of mouth…' leaving the information incomplete and prone to error and mistaken identity.

The potential for discovery of new compounds in the Australian native plant resource remains significant. Webb notes in 1969 that some 500 alkaloids were discovered in Australian plants from 1949 to 1969, 40 per cent of which were identified as new. Since that time there has been a steady accumulation of data by both public researchers and companies. The use of native plants by Australian aborigines in Central Australia alone includes about 70 species such as *Isotoma petraea* and *Crotolaria cunninghamii*. Others are too numerous to mention but include *Duboisia leichhardtii, Tylophora, Solanum aviculare, S. laciniatum, Piper novae-hollandiae and Castanospermum* (Department of the Environment 2000).

In bio-prospecting for bioactive ingredients it became efficient to search those plants and animals and their extracts which had been used by indigenous groups. This can sometimes, but not always, save substantially on investment in exploratory research, pre-screening and testing. It is recognised that there is often a significant body of accumulated knowledge embodied in indigenous medicinal products and various nutritional foods. Farnsworth (1996) refers to an international study, which surveyed 119 commercially useful plant-based drugs to find that 74 per cent of the sample were previously known and used in traditional medicine (Janke 1998). Despite this recognition, it is not an easy process to compensate the owners of the knowledge in the same way that contemporary holders of patents and plant breeding rights are rewarded for their knowledge. Technical difficulties exist in applying these measures of property right protection to traditional knowledge embodied in aboriginal medicinal products.

From an economic perspective, the key issue on this subject is about the ultimate effect on the incentive of aboriginal people and communities to invest in further development and release of their knowledge about the medicinal properties of fauna and flora. There are flow-on effects from this response and further questions about the effect on biodiversity of plant and animal resources and associated cultural and social diversity. Without effective incentives it seems reasonable to expect the owners of that knowledge to either not release it to the public domain or attach a lower priority to it and the plants and animals from which it is derived. Moreover, with this diminution of incentive may come a new threat to biological diversity.

The international Convention on Biological Diversity (CBD), an agreement reached at the 1992 United Nations Conference on Environment and Development (UNCED) and which Australia ratified in 1993, has been developed to both protect the rights of indigenous people to their knowledge, while simultaneously conserving biological diversity. The CBD is the single most important agreement that sets out the guidelines for effective recognition and protection of aboriginal knowledge of flora and fauna. The CBD (Article 8) encourages countries, ‘subject to national legislation’, to:

> …respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant to the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilisation of such knowledge, innovations and practices.

Article 10 states the Contracting Parties:

> …shall, as far as possible and as appropriate … protect and encourage customary use of biological resources in accordance with traditional cultural practices that are compatible with conservation of sustainable use requirements…’

Davis (1999), in a study for IP Australia, refers to the limitations of the CBD in that it encourages, but does not oblige signatories to ‘…respect and preserve indigenous knowledge…’ through their national legislation. The main concern here is that ad-hoc Commonwealth, State and Territory laws may override the recognition and protection of aboriginal knowledge. The most prominent example of the problem is illustrated in the case of smokebush, sp. *Conospermum,* a plant that is quite widespread in Western Australia. Smokebush was used by aboriginal people for “old peoples” disease such as rheumatism and lumbago. In the 1960s the US National Cancer Institute, under license from the Western Australian State Government, tested smokebush for possible anti-cancer chemicals but this was unsuccessful.

More recently, however, a substance called *Conocurvone* was isolated from smokebush and found to counter HIV virus in low concentrations (Blakeney 1999). The Western Australian Government then granted a license to pharmaceutical company Amrad (now owned by Amrad associate, ExGenix) to develop the patent for the anti-AIDS smokebush product. Amrad is reported to have paid $1.5m to the

State Government to gain access rights to smokebush and related species[7]. The Western Australian State Government's action is facilitated by the Conservation and Land Management Act 1984, which was amended in 1993 to include a clause giving the state control over biological resources. The smokebush case highlights the potential for conflict between Commonwealth and State legislation when it comes to application of the CBD.

In 1996 the Commonwealth, State and Territory governments endorsed a *National Strategy for the Conservation of Australia's Biological Diversity* (Department of the Parliamentary Library 1997-98). Action 1.8.2 of the Strategy is to:

> '…ensure that the use of traditional biological knowledge in the scientific, commercial and public domain proceeds only with the cooperation and control of the traditional owners of that knowledge and ensure that the use and collection of such knowledge results in social and economic benefits to the traditional owners. This will include:
>
> (a.) encouraging and supporting the development and use of collaborative agreements safeguarding the use of traditional knowledge of biodiversity, taking into account existing intellectual property rights; and
>
> (b.) establishing a royalty payments system from commercial development of products resulting at least in part, from the use of traditional knowledge…'

A full examination of the mechanisms for protecting aboriginal knowledge is beyond the scope of this study. But clearly the CBD and the National Strategy for the Conservation of Australia's Biological Diversity provide guidelines that may impact on the design of research projects involving Australian flora and fauna and aboriginal communities that use them. Contractual arrangements, agreements and licenses for the sharing of revenue from research and development projects may be affected by the commitments to the CBD.

Moreover, the intent and objectives of the CBD raise even more fundamental issues about biodiversity, food variety and what Walqvist (1998) calls 'Eco-nutrition'. In this study, evidence is shown that the survival of traditional aboriginal societies depended upon access to a diverse range of phytochemicals in native plants. Without this diversity and variety of foods survival was threatened, hence the long history of interest by aboriginals in native flora and fauna. Walqvist's point, we understand, is that lack of food variety may be the cause of many of today's health problems and that we may only find a sustainable solution through biodiversity which is the source of food variety.

Resolving the ethno-botanical property rights problem, however, is no simple task because of the advances in automated rapid screening technologies, which enable simulation and screening of thousands of samples in a few hours. Moreover, many of the diseases and nutritional disorders that were the original target of aboriginal medicines are of reduced prevalence in the year 2000.

In our view, and consistent with the CBD, it would be appropriate to initiate a small pilot project to encourage the collection of information about medicinal products developed and used by aboriginals. This could be done in conjunction with an aboriginal community.

[7] It is worth noting that the value of smokebush is perceived to be considerably higher by those who own the resource than those with an interest in developing it, the result of which is likely to be delayed research and development, if any.

2.5 Environmental issues

2.5.1 Sustainable plant production for natural consumer products

Endorsement of the principles of the CBD has raised further questions about the impact on biodiversity of more intensive prospecting for genetic and biochemical resources. If the first-round effect of the CBD is to encourage increased prospecting for plants with medicinal product potential then this may place further pressure on the available supply. Out of concerns for the environment, Sarah Laird (1995) describes how agreements for biodiversity prospecting need to incorporate activities that promote local capacity and incentives to preserve genetic diversity among natural plants. *People and Plants* is a joint initiative of the WWF, UNESCO and the Royal Botanical Gardens, Kew, UK to promote agreements at the project, regional and national level to protect and enhance biodiversity in the context of more intensive bio-prospecting activity.

The survival of native plants may be threatened by a sharp lift in demand for the products made from them. For instance, *Devil's Claw*, a native African plant with a tuber used for the treatment of arthritis and rheumatism and as an anti-inflammatory product, has been harvested intensively enough to threaten its survival in natural conditions. Clearly, not all plants are subject to this threat and sometimes even a modest market incentive generates a huge supply response, particularly if that plant is capable of being produced in a mechanised plantation system. Australian tea tree is an example of extreme supply response with inadequate market support and a substantial fall in prices.[8]

Returning a system to sustainable production after a period of excess demand may be achieved through intensification of supply or decreasing demand, the latter achieved normally in a market economy through increased price, which in turn can be expected to stimulate supply. A market based solution, in these circumstances leads to at least some attempts to convert the system from one of natural or unsustainable wild production to more sustainable cultivated production. In turn, this may raise questions about the impact on biodiversity if the cultivated agricultural or forestry system is designed to promote, by protection, survival of just a few plant species.

Wills and Lipsey (1999), in a report for the Forest Renewal Program in British Columbia, recommended a series of government incentives to encourage more diversity in the products from forestry systems. Agro-forestry for instance, would '… involve not merely the gathering of non-timber forest species which naturally grow in a setting…' but the cultivation and enhancement of these products in forest settings to improve their quantity, quality and sustainability. It may also involve the introduction and tending of understorey species into a new area (for example, injecting mushroom spores into logs)…' Elsewhere, Walqvivist proposes the '…regeneration of ecological niches which allow annual biomass fixation and associated biodiversity to be optimised…' Non-timber forest products, if managed effectively, are seen as offering the base for a production system that meets environmental objectives concerned with the conservation of forests, watersheds and biological diversity. Several of RIRDC's programs are focussed on the derivation of environmentally sustainable farm programs. For instance, the objective of the Agroforestry and Farm Forestry program is to integrate sustainable and productive agroforestry within Australian forestry systems.

Wills and Lipsey suggest that non-timber forest resources and native plants in British Columbia are an untapped resource and very much part of that province's comparative advantage. With support, they estimated the revenue from non-timber forest products could account for in excess of one-third of total forest revenue in the next 8-10 years. At the same time, the presence of such products was seen to add diversity to the whole production system, including the plant genetic resources and income.

Non-timber forest products account for a much higher proportion, often the full amount, of total forest income in forests with low timber potential (Wilkinson and Elevitch 2000). The FAO estimates that 80

[8] Production of tea-tree oil from *Melaleuca alternifola* has increased from 10-12 tonnes at the start of the 1990s to around 60 tonnes in the mid-1990s and 400-500 tonnes in 1999-2000. Meanwhile, global consumption has risen to only about 200 tonnes, which has lead to a collapse in prices from about $A60/kg to less than $20/kg and often there is no market at all (Bolt, C 2000).

per cent of the population of the developing world use non-timber forest products to meet part of their nutritional needs.

Thomas and Schumann (1993), writing for the USDA, add their support for the exploration and development of non-timber forest resources, noting they have the potential to provide extra income as well as better and more sustainable use of existing resources. They suggest this type of enterprise should be undertaken only after a thorough evaluation including a feasibility study and comprehensive business plan.

2.5.2 Sustainable plant production for industrial products

A number of bio-based industrial products have emerged over the past decade, including liquid fuels, chemicals, fibres, lubricants, plastics, building materials. Bio-based industrial products are seen by the influential USA's National Research Council as having potential to improve significantly the sustainability of natural resources, environmental quality and national security (National Research Council 2000).

'… agricultural and forest crops may serve as alternative feedstock to fossil fuels in order to moderate price and supply disruptions in international petroleum markets and help diversify feedstock sources that support the nation's industrial base. Bio-based products may be more environmentally friendly because they are produced by less polluting analogous processes than in the petrochemical industry. Some rural areas should be well positioned to support regional processing facilities dependent on locally grown crops. As a renewable energy source, biomass does not contribute to carbon dioxide in the atmosphere, in contrast to fossil fuels. The committee believes that these benefits of bio-based products are real. However, these and other benefits listed below have not, in most cases, undergone a rigorous analysis to demonstrate their validity:

- use of currently unexploited productivity in agriculture and forestry;
- reliance on products and industrial processes that are more biodegradable, create less pollution, and generally has fewer harmful environmental impacts;
- development of less expensive and better performing products;
- development of novel materials not available from petroleum sources;
- exploitation of US capacities in the field of molecular biology to selectively modify raw materials and reduce costs of raw material production and processing;
- revitalization of rural economies by production and processing of renewable resources in smaller communities;
- reduction of the potential for disruption of the US economy due to dependence on imported fuel;
- countering of oligopoly pricing on world petroleum markets; and
- mitigation of projected global climatic change through reduction of buildup of atmospheric carbon dioxide…' (National Research Council, USA).

Similar benefit claims are made in Australia and again, often, without the support of "rigorous analysis".

There is increasing consumer and legal pressure in the European Union for more use of biodegradable packaging materials [bioplastics]. These are seen to have the advantage that they can be composted without contaminating the final product with inert residues, while the discarded material will decay rather than be preserved as a semi-permanent litter.(nf-2000). But often the claims for biodegradability have not been fully evaluated. Researchers from the Universities of Gent, Stuttgart, Bolgna and Munich and a private company, Organic Waste Systems of Belgium have been evaluating methods for biorecycling of bioplastic wastes. They have found that the term bioplastics is applied to many plastics of varying chemical composition and biological stability with equally varying demands on the local ecology.

In Australia, the Cooperative Research Centre for Polymers is involved in the development of biodegradable polymers (Dagley 2000). Cargill Dow Polymers has developed a cost-effective process for producing a biodegradable polymer (polylactide) from maize.

The Sustainable Energy Development Authority (SEDA), a NSW Government agency, is committed to reducing the level of greenhouse gas emissions in NSW by investing in the commercialisation and use of sustainable energy technologies. The programs being used by SEDA include biomass, hydro-electricity, wind and solar generation technologies. "Dry" by-products (eg. husks, hulls, shells, pips, leaves), wastes and residues of agricultural and horticultural activities (eg. straw, stubble, stalks, leaves, and trash). SEDA is currently examining the viability of using these materials to generate electricity at a competitive cost of $60/MWh including the benefits of reduced CO_2 emissions. In a similar vein to SEDA, the CSIRO is examining the viability of using biomass to produce ethanol and methanol as replacements for traditional oil-based fuel and feedstock (Foran and Mardon 1999). The Cooperative Research Centre for International Food Manufacture and Packaging Science has, among other things, patented bio-processes using enzymes rather than established chemical processes to produce recycled paper pulp from waste paper.

More generally, most of the evidence about the shift to bio-based materials and resurgence of interest and use in natural food products is associated with a belief that the products are environmentally friendly. Nevertheless, as the US National Research Council states, there are a number of untested assumptions behind these beliefs, several of which are listed above. For Australia in particular, the assumption of unexploited productivity in agriculture and forestry needs detailed examination because of the fragile nature of the soils and the relatively low rainfall over much of the country. Harvesting of crop residues, for instance, as biomass for ethanol may in this environment create a new set of problems.

3. Current Pharmaceutical, Nutraceutical and Industrial Products Available from Agriculture

In Brief

About 25% of the active components of pharmaceutical drugs have their origin in flowering plants and this share is expected to increase to around 30% over the next five years. The pharmaceutical companies are increasing their R&D allocations to these products. Drugs based on fungi account for a further 10% of this market. The global market for plant derived drugs is growing by over 6%/year and expected to reach $US31 billion within the next two years.

Collaboration between leading pharmaceutical, universities and research institutes is growing to accommodate the demands for more commercialised research.

The herbal remedies with continued growth and large market share include ginkgo, ginseng and garlic.

The functional foods market may, however, represent the best medium-term prospect for Australia because of the large size of the traditional food market on which it is based.

Further out there appears to be good prospects for botanical extractive materials and industrial products.

3.1 Pharmaceuticals

3.1.1 The global pharmaceutical product categories

The main categories of disease, in terms of sales are drugs for cardiovascular conditions, alimentary or metabolic disorders, the central nervous system (CNS), respiratory problems and infections. These broad categories can be further sub-divided, as follows:

Cardiovascular drugs

Drugs for myocardial infection had a global market of $US8 billion in 1996, divided between lipid-lowering drugs ($US6 billion), antithrombolytics ($US1.4 billion) and anticoagulants ($US700 million). Drugs for hypertension had a global market of $US22 billion in the same year, which could be broken down into ACR inhibitors ($US7.5 billion) calcium antagonists ($US7 billion), beta-blockers ($US3 billion) and diuretics ($US1.5 billion).

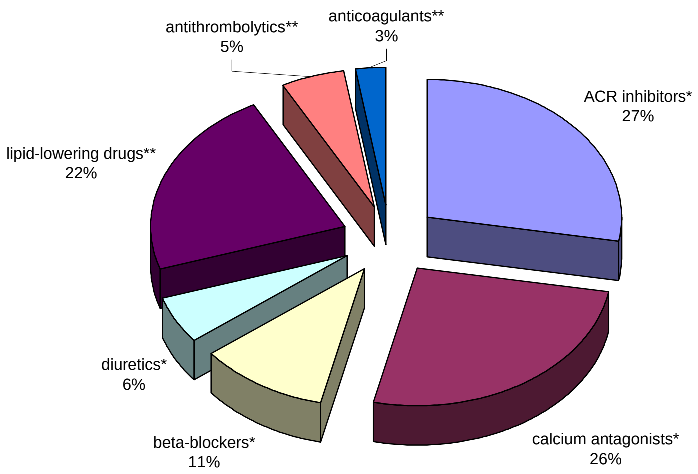
Alimentary/metabolism drugs

The two major classes of disease within this therapeutic area, in terms of drug sales, are Diabetes mellitus, treated with either insulin ($US2.4 billion) or oral hypoglycaemic agents ($US2.35billion).

CNS drugs

The key disease within the CNS area is that of senile dementia and Alzheimer's Disease, which, despite their high prevalence in society have relatively low shares of the global pharmaceutical product market. In 1996, sales of CNS drugs were approximately $US975 million, but this has been predicted to fall at about 1% per year to approximately $US800 in 2001.

Chart 3.1: Global cardiovascular drugs market shares: 1997



Respiratory drugs

The major respiratory condition, in terms of drug sales, is asthma, which can be allergic, non-allergic or exercise-induced in nature. The major drug class for this condition is the bronchodilators, accounting for approximately 50-55% of the market (approximately $US1.9 billionn in 1996), and including beta$_2$-agonists such as Ventalin ($US734 million) and Serevent ($US544 million), catecholamines including Terbutaline ($US194 million) and Xanthines, such as theophylline ($US67 million). The other main drug class for asthmatic conditions are the steroids (approximately $US1.8 billion annual sales in 1996).

Anti-infectives

The two main anti-infective targets are antibiotics (for bacterial infections) and anti-virals. Antibiotics, including quinolones, cephalosporins, broad-spectrum penicillins (with and without β-lactamase inhibitors) and macrolides had a combined market value of over $US8 billion in 1996. Anti-virals can be represented by drugs developed for the treatment of HIV, such as reverse-transcriptase inhibitors (approximately $US1 billion) and protease inhibitors (approximately $US300 million).

3.1.2 Plant-derived pharmaceutical drugs

A number of reviews of the literature indicate that approximately 25 % of the active components of drugs prescribed in 1996 had their origins in higher (flowering) plants, with an additional 10% derived from fungi. A comprehensive review of plant-derived drugs identified a total of 119 drugs, obtained from fewer than 90 plant species (Farnsworth *et al*., 1985), including the examples listed in Table 3.1.

The drugs with botanical origins, which are available today, can be divided into a number of categories. These include long-known products, which still remain the drug of choice today, such as the cardiotonic digitoxin, and newer drugs, such as the taxoids from *Taxus* spp. and artemisinin, and its derivatives from *Artemisia* spp. As there is growing demand for natural-based medicines, there is considerable evidence that these medicines will take an increasing proportion of the existing (largely synthetic) drug markets (up to 30% market penetration; (Wilkinson, 2000).

The pharmaceutical industry’s attitude to medicinal plants and natural products has changed dramatically over the past twenty years of so. This is very much in line with the increased awareness and interest in medicinal plants and natural treatments, in both the general public (especially in the area of self-medication and functional cosmetic/food ingredients) and in the scientific community. As a reflection of this, in 1980, none of the top 250 pharmaceutical companies had research activities involving higher plants, but by the early 1990's, more than half of them had introduced such programs (Anon., 1994).

Reflecting the strong commercial precedence for drugs derived from natural products, there are a number of companies specialising specifically in centering their technology platforms on active pharmaceutical ingredients derived from natural products (Scheraga, 1998). These products range from fungal systems (e.g. inhibitors of P-glycoprotein and plasminogen activator under development by Xenova) to higher plants, including cancer treatments and fungal inhibitors from Phytera, advanced-stage cancer treatments from Oxigene and immuno-modulators from Pharmagenesis (Table 3.2).

Table 3.1: Classic plant drugs obtained from higher plants

Drug	Clinical action or use	Primary botanical origin
Atropine	Anticholinergic	*Atropa belladonna*
Caffeine	CNS stimulant	*Camellia sinensis*
Camphor	Rubefacient	*Cinamomum camphora*
Chymopapain *	Chemonucleolysis	*Carica papaya*
Cocaine	Local anaesthetic	*Erythroxylum coca*
Codeine	Analgesic/anti-tussive	*Papaver somniferum*
Colchicine	Anti-gout	*Colchicum autumnale*
Digitoxin	Cardiotonic	*Digitalis purpurea*
Digoxin	Cardiotonic	*Digitalis lanata*
Emetine	Amoebicide	*Cephaelis ipecacuanha*
Ephedrine	Sympathomimetic	*Ephedra sinica*
Galanthamine *	Cholinesterase inhibitor	*Lycoris squamigera*
Gossypol	Male contraceptive	*Gossipium* spp.
Hyoscamine	Anticholinergic	*Hyoscamus niger*
Kawain	Tranquiliser	*Piper methysticum*
Levodopa *	Anti-Parkinsonian	*Mucuna deeringiana*
Menthol *	Rubefacient	*Mentha* spp.
Methoxsalen	Psoriasis/vitiligo	*Ammi majus*
Methyl salicylate *	Rubefacient	*Gaultheria procumbens*
Morphine	Analgesic	*Papaver somniferum*
Nordihydroguaiaretic acid *	Antioxidant	*Larrea divaricata*
Noscapine	Anti-tussive	*Papaver somniferum*
Ouabain	Cardiotonic	*Strophanthus fratus*
Physostigmine	Cholinesterase inhibitor	*Physostigma venenosum*
Pilocarpine	Parasympathomimetic	*Pilocarpus jaborandi*
Podophyllotoxin	Topical treatment for condylomata acuminata	*Podophyllum peltatum*
Quinidine *	Anti-arrhythmic	*Cinchona ledgeriana*
Quinine	Anti-malarial	*Cinchona ledgeriana*
Reserpine	Antihypertensive	*Rauwolfia serpentina*
Scopolamine	Sedative	*Datura metel*
Sennosides A and B	Laxative	*Cassia* spp.
Tetrahydrocannabinol	Antiemetic	*Cannabis sativa*
Theophylline	Bronchodilator	*Camellia sinensis*
Tubocurarine	Muscle relaxant	*Chondodendron tomentosum*
Vinblastine *	Anticancer	*Catharanthus roseus*
Vincristine *	Anticancer	*Catharanthus roseus*
Yohimbine	Aphrodisiac	*Pausinystalia yohimbe*

** Clinical action not correlated to traditional use*

A common feature of many of these developments is that the companies involved enter into commercial partnerships with larger pharmaceutical companies, as shown below. It has been observed that, 'Collaborations are an important part of natural products research, and many of the top pharmaceutical companies have long-standing agreements with academia, government and other companies to access natural products sources' (Ortega, 1998).

Table 3.2: Selected drug candidates and therapeutic indications for companies involved in development of drugs from natural origins

Company	Partner	Product	Therapeutic indication
Xenova		XR9576 (piperazinedione derivatives; Ashworth *et al*., 1999)	P-glycoprotein inhibitor; possible applications in modulating multi-drug resistance
	Eli Lilly & Co., MetaXen LLC	PAI-1	Plasminogen activator inhibitors; antithrombotic action Rheumatoid arthritis, infectious disease, respiratory, neurological and auto-immune disorders
Phytera		Marinovir (Cyclomarin A from marine actinomycetes; Pazoles and Siegel, 1998).	Herpes therapy; anti-viral and anti-inflammatory
		Sunillin	Anti-fungal activity; also potential against inflammation, cancer, diabetes, allergies, cardiovascular and neurological disorders
	Expand, Umarine, NeuroSearch A/S		Potassium ion channel interactions; potential in memory, depression, asthma and diabetes therapies
Oxigene	Bristol-Myers Squibb	Combrestatin (from *Combretum caffrum*; e.g. Pettit, 1996)	Angiogenesis inhibition; cancer therapies
Pharmagenesis	President Pharmaceutical Corp.	PG2	Immunomodulator; stimulates haematopoeisis in cancer patients
Pharmagenesis		PG490-88	Immunosuppressant; reduction of bone marrow transplant rejection
Pharmagenesis	Eli Lilly & Co.		Antifungal agents

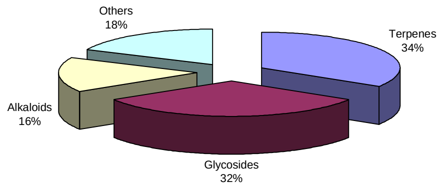
In addition to the direct use of plant-derived compounds, another class of botanically derived drugs are those used as "molecular templates". An example is the development of atracurium from the alkaloids isolated from curare, obtained from *Chondrodendron tomentosum*, or as feedstocks (e.g. the production of oral contraceptives from yams [*Dioscorea* spp.] and sisal [*Agave* spp.]).

In a 1997 market survey, the global market for sales of plant-derived drugs was estimated at $US22.6 billion, increasing by 6.3% annually to reach $US30.7 billion by 2002 (Business Communications Co.; cited in Ortega, 1998). This amount is split approximately evenly between single entities sold under prescription, and non-prescribed herbal remedies. Within the market for plant-derived drugs, there are four major categories (terpenes, glycosides, alkaloids and "others"), illustrated below (Chart 3.2), in terms of their market share and predicted demand growth rates.

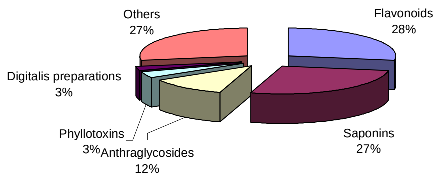
Chart 3.2: Market share of major plant-derived drug categories (A) and glycosides (B)

Total market sizes (1997): $US22.6 billion; glycoside market size: $US7.3 billion

A. Plant Derived Drug Market Shares

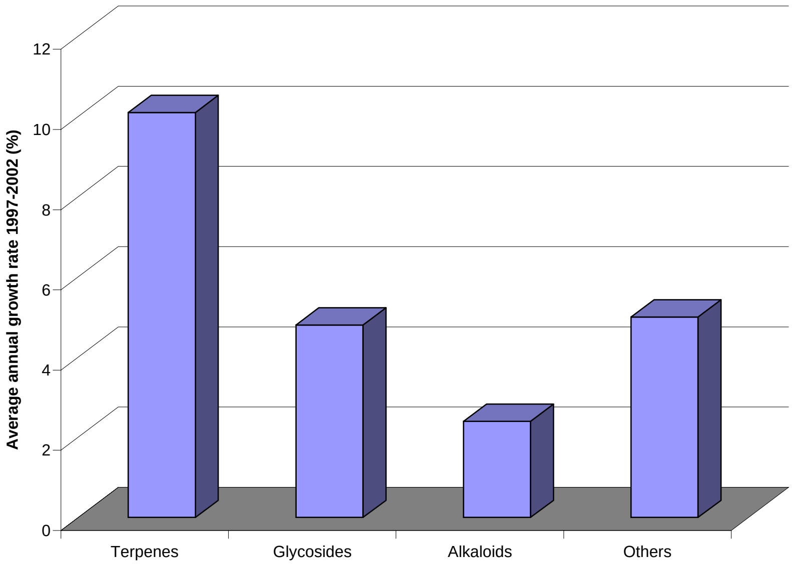


B. Glycoside Market Shares



Source: Business Communications Co., cited in Ortega, 1998

Chart 3.3: Forecasted average annual growth rates for major plant-derived drug categories, 1997-2002



Source: Business Communications Co., cited in Ortega, 1998

3.1.3 Licenced botanical medicines

In Europe, the market for licenced herbal medicines stands at more than 500 million Euros (approx. $US475 million), and is dominated, in terms of sales, by products based on *Ginkgo biloba*, which account for the three top selling preparations. In Germany, where the herbal medicines market is particularly well developed, sales of *Gingko* have dropped during the last 10 years (from 9.9 million sales in 1993 to 8.5 million in 1997). But sales of other herbs, such as St John's Wort (*Hypericum perforatum*) increased sharply over the same period from 2.6 to 8.5 million units (Mertens, 2000).

Table 3.3: Licensed herbal medicines: revenue: Europe: 1992-98

Rank		Brand	Manufacturer	Herb	Sales (million $US)*	
1992	1998				1992	1998
1	1	Tanakin	Beaufour	*Ginkgo biloba*	82.7	85.6
3	2	Ginkor	Beaufour	*Ginkgo biloba*	51.3	57.1
2	3	Tebonin	Schwabe	*Ginkgo biloba*	79.9	44.7
4	4	Endotelon	Sanofi	Grapeseed	41.8	40.9
5	5	Permixon	Fabre	Saw palmetto	33.3	37.1
6	6	Ultra levure	Biocodex	Yeast	15.2	21.9
4	7	Tadenan	Fournier/Debat	*Pygeum africanum*	34.2	22.8
-	8	Jarsin	Lichtwer	St John's Wort	2.9	24.7
10	7	Sinupret	Bionorica	Gentian, Sambuca...	17.1	22.8
9	10	Kwai	Lichtwer	Garlic	20.0	19.0
-	10	Gingium	Hexal	*Ginkgo biloba*	5.7	19.0
-	13	Roekan	Intersan	*Ginkgo biloba*	4.6	18.1
-	14	Gelomyrtol	Pohl	Peppermint	18.1	16.2
11	10	Ginkgobil	Ratiopharm	*Ginkgo biloba*	13.3	19.0
8	16	Venostasin	Klinge	Horse chestnut	20.9	15.2
-	14	Hepar SL forte	Serturner	Artichoke	1.0	16.2
7	17	Klosterfrau melissengeist	Klosterfrau	Balm mint	21.9	10.5
-	17	Euphytose	Roche	*Passiflora*, *Valerian*, Kola...	7.6	14.3

Source: Mertens/Financial Times Healthcare, 2000
** Converted from Euros at June 2000 rate*

The interest in phytomedicines by "conventional" pharmaceutical companies is likely to continue in the near future, as evidenced by the growing acquisitions of companies specialising in phytomedicines (Table 3.4).

Table 3.4: Recent phytomedicine company acquisitions

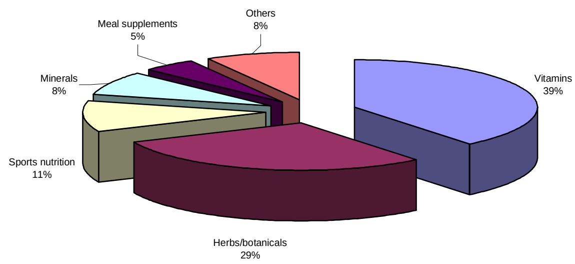
Multinational	Phytomedicine company acquired
American Home products	Dr. Much
Boehringer Ingelheim	Pharmaton, Quest
Boots	Kanold
Bausch & Lomb	Dr. Mann
Degussa	Asta Medica
Fujisawa	Klinge
Johnson & Johnson/Merck	Woelm Pharma
Pfizer	Mack
Rhone Poulenc	Natterman
Sanofi	Plantorgan
Searle	Heumann
SmithKline Beecham	Fink
Solvay	Kali

Source: study data

3.1.4 Unlicensed botanical medicines

Accurate market figures for unlicensed herbal products are harder to locate than those for the more fully regulated licenced market. However, the herbal/botanical market has been described as a leading sector within both the dietary supplement (Sauer, 1999a) and over-the-counter (OTC; Wilhelm, 2000) markets. In the dietary supplement market, predicted growth rates are inversely related to the development of the market. In Germany and France, with their relatively well established history of using herbal supplements, annual rates are forecast to rise at approximately 5%, whereas in the UK and Scandinavia, where the market is less well established, growth rates of more than 10% are predicted (Joerg Gruenwald; cited in Wilhelm, 2000).

Chart 3.4: US dietary supplement market: 1999
(Total market size: $US14.7 billion)



Source: Nutrition Business Journal, 1999

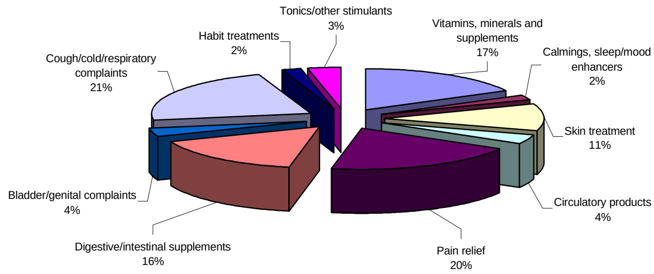
In the $45.07 billion global OTC market, herbal supplements and vitamins were the strongest-performing sector in 1998-99, reflecting the 'increasing world-wide interest in self-medication that goes beyond traditional cold remedies and pain relievers.' (Sauer, 1999a). This is indicated below (Table 3.5), demonstrating that, although not the largest category of OTC products (Chart 3.5), vitamins, minerals and supplements showed year-over-year growth more than 8% greater than any other category of OTC product in 1998.

Table 3.5: Leading self-medication markets (1998 audited sales only): growth rates

Category	Year-over-year growth (%)
Vitamins, minerals and supplements	+16
'Calmings', sleep/mood enhancers	+8
Skin treatment	+6
Circulatory products	+6
Pain relief	+4
Digestive/intestinal supplements	+4
Bladder/genital complaints	+4
Cough/cold/respiratory complaints	+2
Habit treatments	+2
Tonics/other stimulants	-2

Source: IMS Health, cited in Sauer, 1999a

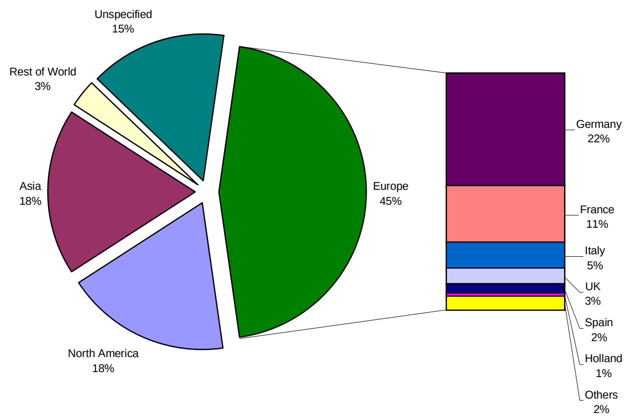
Chart 3.5: Leading self-medication markets (1998 audited sales only): market shares



Source: IMS Health, cited in Sauer, 1999a

The European market for herbal remedies accounts for 45% (Chart 3.6) of the global market, and stood at $US7.5 billion in 1997. As mentioned above, Germany and France are the most established markets, followed by Italy, the UK, Spain and Holland.

Chart 3.6: Global distribution of herbal remedies market, 1997



Source: PhytoPharm Consulting, cited in Scimone and Scimone, 1999

Rapid growth rates of 50-100% in 1998-99 and 20-25% in 2000-2001 have been forecast for the North American market (PhytoPharm Consulting, cited in Scimone and Scimone, 1999), again reflecting the relatively poorly developed market there. In 1998, the US market for herbal remedies stood at $US4 billion, based on a 20% growth from the 1997 value of $US3.24 billion. Of this, between $US1.6 and $US3.0 billion was accounted for by (unlicenced) herbal supplements (Herbal Research Foundation, cited in Scimone and Scimone, 1999). In many ways, the situation in the United States, which is a relatively "immature" market for herbal remedies, could be extended to Australia.

It has been observed that many of the top-selling herbs in the US market are "crossover" products, similar to those that have been successful in the European (and specifically German) markets (Scimone and Scimone, 1999). Based on this, it has been predicted that the next major selling herbs in the USA will be those which are relatively well established in the European market, but which have not yet been commercialised fully in the USA.

A survey of American companies involved in the herbal business (Scimone and Scimone, 1999) indicates that market leading herbs are predicted to include black cohosh rhizomes, artichoke leaves, nettle root, devil's claw root, kava root and herb, isoflavonoids from soy and red clover, neem products and hawthorn leaves/flowers (Table 3.6).

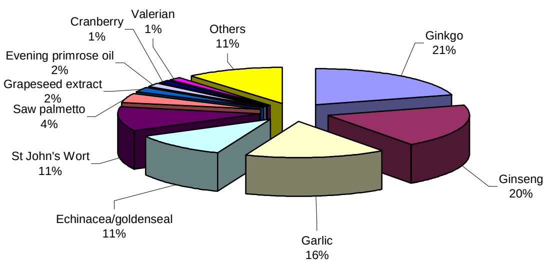
Table 3.6: Herbs with predicted potential in the US herbal remedy market

Herb	Plant part	Indication
Black cohosh (*Cimicifuga racemosa*)	Rhizomes	Pre-menstrual syndrome, menopausal conditions
Artichoke (*Cynara* spp.)	Leaves	Aids digestion, lowers cholesterol
Nettle (*Urtica dioica*)	Root	Benign prostatic hyperplasia
Devil's claw (*Harpagophytum procumbens)*	Root	Arthritis
Kava (*Piper methysticum*)	Root (and herb)	Sedative, anti-depressant
Soy and Red clover	Isoflavonoids	Cancer prevention
Hawthorn (*Crataegus* spp.)	Leaves and flowers	Cardiovascular degeneration
Neem (*Azadirachta indica*)	Herb, oil, resin	Infections and infestations

Source: Adapted from Scimone and Scimone, 1999

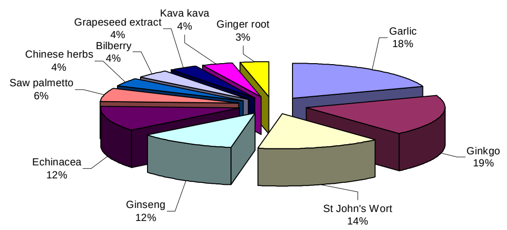
In the US, many of the top-selling herbal remedies are similar to those in Europe, headed by ginkgo, ginseng and garlic, as shown below. Herbal formulas also showed very healthy growth rates in the United States, reaching 25.1% in the year to April 1998 (Spence Information Services, cited in Scimone and Scimone, 1999) and 17.0% in the following year (SPINS and A.C. Nielsen, cited in Sauer, 1999b). The strongest growth within this sector was shown by formulas containing St John's Wort (>1000% annual growth rate), with a number of other formula types also showing more than 30% growth rates (Chart 3.7).

Chart 3.7a: Leading herbal remedies market shares in the United States, 1996-7
(total market size $US440 million*)



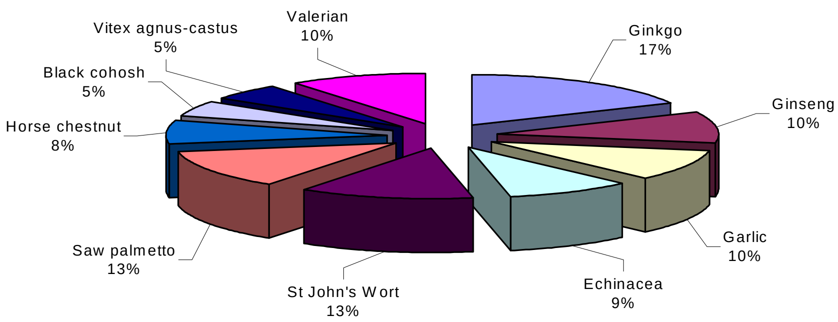
* Information from sales in mass market, food and drug stores only.
Source: Information Resources Inc., cited in Scimone and Scimone, 1999.

Chart 3.7b: Leading herbal remedies market shares in the United States, 1998-99



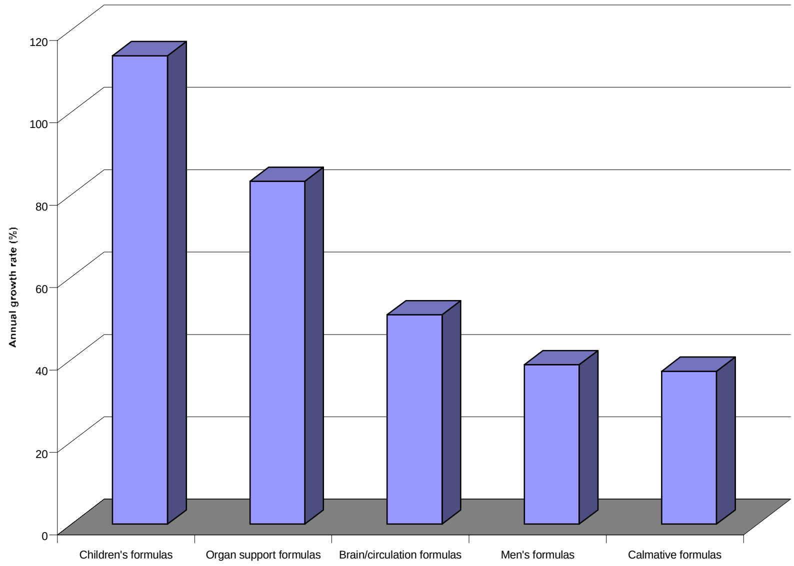
Source: The Hartman Group, cited in Sauer, 1999b

Chart 3.7c: Leading Herbal Remedies Market Shares: Europe: 1997



Source: PhytoPharm Consulting., cited in Scimone and Scimone, 1999.

Chart 3.8: Annual growth rates for herbal formulas in the United States (year ending April 1998)



Although the major herbs discussed above are mainly from the Western tradition of herbal medicine, other systems of herbal medicine are being accepted into the Western marketplace. For example, the most popular Ayurvedic herbs, and their normal uses in the United States are given below:

Table 3.7: Alternative herbal plants

Herb	Use
Amalaki (*Emblica officinalis*)	Very rich source of vitamin C. Used to treat inflammation, fever, infections, and to normalise cholesterol
Ardhrakam (*Zingiber officinale*)	Used to treat nausea, colds and to improve digestion. May also prevent diarrhoea, arthritis and ulcers
Arishta (*Azadirachta indica*)	Used to boost immune system, relieve allergies and inflammation. Heals skin conditions
Ashwagandha (*Withania somnifera*)	Used to promote energy and vitality, to combat weakness and to treat respiratory problems, and as a sedative.
Brahmi (*Bacopa monniera*)	Used to stimulate mental function, and as a non-stupefying sedative.
Guggul (*Commiphora mukul*)	Used as antiseptic and astringent, anti-inflammatory and to normalise blood cholesterol levels
Haritaki (*Terminalia chebula*)	Used to relieve constipation, fight infections and cleanse the colon. May be antibacterial against *Salmonella*.
Mandukaparni (*Centella asiatica*)	Used to treat wounds, jaundice, high pressure, rheumatoid arthritis. Also treats nervous disorders, and improves emotional and cognitive function
Shatavari (*Asparagus racemosus*)	Used to cleanse the blood and as a tonic, especially for the female reproduction organs, especially post-menopausal.
Yashtimadha (*Glycyrrhiza glabra*)	Used to combat stomach ulcers and intestinal irritation, urinary and respiratory problems. Can also ease eczema, dermatitis and psoriasis.

Anon, 2000

3.2 Nutraceuticals

Three main product categories make up the nutraceutical group: minerals and nutrients, vitamins and herbal extracts.

3.2.1 The global nutraceutical market

Nutraceuticals can be seen as the latest in a succession of health foods, the evolution of which can be summarised as follows (Table 3.8).

Table 3.8: Evolution of nutraceutical market

Era	Food-health concept/ Catalyst for change	Effect on/ Product types
1950's-1960's	"Refined"	Fibre Cod liver oil
1970's	"Green"	"Natural" ingredients Pesticide-free
1980's	"Low" and "Lite"	Calorie intake Fat/salt/sugar Fish oils Cholesterol
1990's	"Nutraceuticals"	Dietary fibres Oligosaccharides Polyunsaturated fatty acids Cholines/phospholipids Glycosides Dietary vitamins/minerals Peptides Lactic acid bacteria
Until 2010	Disease-fighting foods	Genetically engineered plants and fruits: e.g. bananas to give paediatric vaccines Tomatoes with elevated nicotine content to aid smoking cessation
	Health-optimising foods	Foods with disease prevention function, studies on modes of action and benefits. e.g. terpenes, carotenes, limonoids, xanthophylls, phytosterols, isoflavones, oligosaccharides and vitamin-enriched foods

Source: Mertens/Financial Times Healthcare, 2000

Some of the broad categories of functional foods possible through modification of food composition are listed below (Table 3.9).

Table 3.9: Emerging functional foods

Food modification	Examples of possible functionality
Addition of phytochemicals	Antioxidant activity, lowered risk of cardiovascular heart disease, lowered risk of cancer, reduced blood pressure
Addition of pre/pro biotics	Improved GI function, enhanced immune system, reduced risk of colon cancer, reduced risk of allergies
Addition of bioactive peptides/proteins	Enhanced immune function, increased bioavailability of minerals
Additional of dietary fibre	Prevention of constipation, reduced risk of colon cancer, reduced blood pressure
Addition of n-3 polyunsaturated fatty acids	Reduced risk of heart attacks and some cancers, enhanced immune system
Removal of allergens	Reduced/eliminated risk of specific food allergies

Source: Mertens/Financial Times Healthcare, 2000

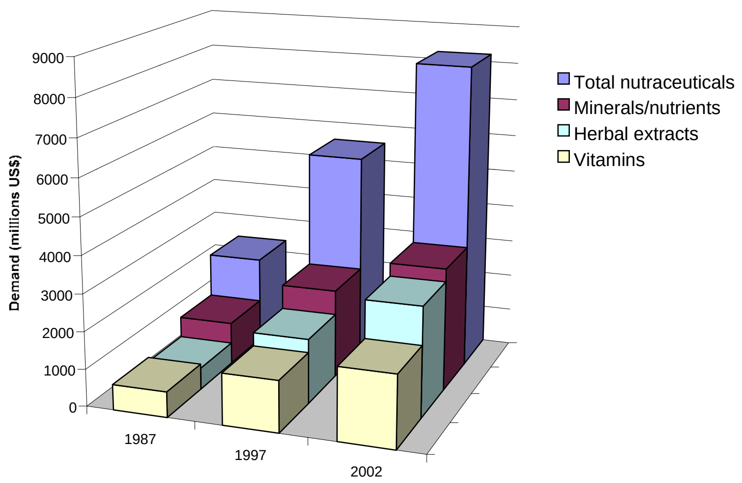
In 1997, the global nutraceutical market was valued at $US5.5 billion, more than double the value from 10 years earlier. By 2002, the market is predicted to stand at $US8.2 billion, rising at 8.3% per annum (Freedonia Group, 1998). As shown in Table 3.10, it is predicted that herbal extracts will generate the fastest growth in worldwide demand among all nutraceuticals, reflecting their widely perceived health advantages, increased validation and increasing support among medical practitioners.

Table 3.10: World nutraceuticals demand and growth, 1987-2002 in $USmillion

Item	1987	1997	2002	Annual growth 87/97	97/02
Nutraceutical demand					
Minerals & nutrients	1,139	2,385	3,305	7.7	6.7
Vitamins	686	1,380	1,935	7.2	7.0
Herbal extracts & others	517	1,735	2,960	12.9	11.3
TOTAL	2,342	5,500	8,200	8.9	8.3

Source: Freedonia Group, Inc., 1998

Chart 3.9: Global nutraceuticals demand 1987-2002



Source: Freedonia Group, Inc., 1998

Table 3.11: US bulk nutraceuticals demand and growth, 1987-2001 in $US m

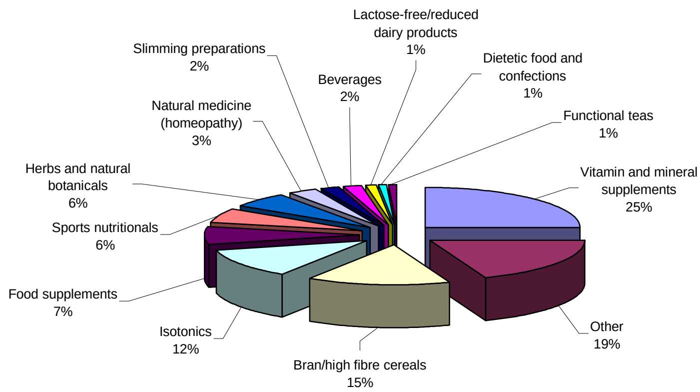
Item	1987	1996	2001	Annual growth % (1996-2001)
Nutraceutical demand				
Vitamins	288	485	650	6.0
Essential nutrients	236	410	555	6.2
Minerals	242	395	515	5.4
Herbal extracts	32	320	650	15.2
Others	78	125	160	5.1
TOTAL	876	1735	2530	7.8

Source: Freedonia Group, Inc., 1997, cited in Theodore, 1997

The precise market value for nutraceuticals however, is not clear, reflecting the difficulty with which the market is defined. Depending on exactly what is included within the broad definition of "nutraceuticals" or "functional foods", the figures from the Freedonia Group market review can look very conservative indeed. For example, a 1997 review put the market for functional foods in the United States alone at $US14.7 billion, rising to $US91.7 billion for a "broader" nutraceutical market, including natural/organic foods, foods consumed primarily for health benefits, and "lesser-evil" foods. The same report valued the US supplements market at $US12.7 billion (Nutrition Business Journal, 1997, cited in James, 1999).

If the term "nutraceutical" is taken in its broadest sense, including health foods, dietary supplements and natural foods, the global market has been put at $US504 billion (cited in James, 1999). $US500billion of this market is split equally between the US and Europe. This contrasts with another study, valuing the market for functional foods at $US32 billion in 1997, rising to $US45 billion by 2002, divided primarily between Japan ($US14 billion rising to $US19.5 billion), the US ($US10.5 billion rising to $US15 billion) and Europe ($US7.5 billion rising to $US10.5 billion). A separate report by Novartis International puts the global market at $US10 billion, rising to $US23 billion by 2002 (cited in James, 1999). A final report on the US nutraceutical market puts the total value of this market at $US8.1 billion, with vitamin and mineral supplements and bran and high fibre cereals having the leading shares.

Chart 3.10: US nutraceutical market, by sector: 1997
(Total market size: $US8,075 million)



Source: Shear/Kershman Laboratories Inc., cited in Theodore, 1997

The market for nutraceutical beverages is difficult to categorise, as it ranges from sports drinks, through fortified juices to herbal teas. As shown above, functional teas occupy a relatively small market share (annual sales approx. $US75 million). Fortified juices (such as calcium- or vitamin-enriched orange juice) accounted for approx. $US200 million sales in 1997, whilst isotonic sports drinks sales in the same year came to $US1.2 billion (Shear/Kershman Laboratories Inc., cited in Theodore, 1997). Celestial Seasonings, one of the largest producers of herbal drinks has recently been acquired by the Hain Food Group for $US390 million, to form the largest natural foods company in the United States. The resulting Hain Celestial Group Inc. expects total sales of $US1 billion by 2002 (Plank, 2000).

The leading companies in the global market for functional foods are shown in Table 3.12 below. A number of these companies may well be interested in contract growing of raw materials for their produce, due to the scale of their operations.

Table 3.12: World's leading functional foods companies, by turnover, in $US billion 1997-99

Company	Year	Total turnover (US$ billion)	Functional foods turnover (US$ billion)
Novartis International (Switzerland)	1998	21.30	2.40
Yakult Honsha (Japan)	1998	1.27	1.27
Abbott Laboratories (US)	1998	12.48	1.26
Kellogg Company (US)	1998	6.76	0.90
Unilever (UK/Netherlands)	1998	43.89	0.80
SmithKline Beecham (UK)	1998	12.96	0.76
Otsuka Pharmaceutical (Japan)	1998	3.13	0.59
Campina Melkunie (Netherlands)	1998	3.90	0.55
Groupe Danone (France)	1998	14.10	0.50
Calpis Co. (Japan)	1997	0.80	0.48
Meiji Milk Products (Japan)	1998	3.80	0.41
Snow Brand Milk Products (Japan)	1998	4.64	0.33
Suntory (Japan)	1998	6.70	0.30
Weider Nutrition International (US)	1998	0.25	0.25
General Mills (US)	1999	7.07	0.20
Nestlé (Switzerland)	1998	51.99	0.20
MD Foods (Denmark)	1998	3.60	0.18
Molkerei Alois Möller (Germany)	1998	1.20	0.18
Sanitarium (Australia)	1998	0.18	0.18
Groupe Lactalis (France)	1998	5.00	0.17
Groupe Distriborg (France)	1998	0.25	0.16
Parmalat (Italy)	1998	5.50	0.11
Tropicana Products (US)	1998	2.00	0.10
Takara Shuzo (Japan)	1998	1.60	0.09
Balance Bar Company (US)	1998	0.08	0.08
Toni (Switzerland)	1997	1.13	0.06
McNeil Consumer Healthcare (US)	1999	n/a	n/a
Raisio Group (Finland)	1998	0.90	0.05
Vandemoortele (Belgium)	1998	0.85	0.05
Cooke Pharma (US)	1999	0.05	0.05
Skånemejerier/Skåne Dairy (Sweden)	1998	0.30	0.02
GumTech International (US)	1998	0.01	0.01
Ehrmann (Germany)	1998	0.32	n/a

Source: James/Leatherhead Food Research Association, 1999

The largest Australian-owned food manufacturing company, Goodman Fielder, had a total turnover of around $US2.2 billion in 1998-99, with perhaps 10% of this being classified as functional foods. The total value of turnover of the top 60 Australian food manufacturers was about $33 billion.

Minerals and nutrients

Demand for minerals and nutrients is forecast to rise by 6.7% annually to reach a global market size of $US3.3 billion by 2002 (Freedonia Group, 1998). The strongest growth areas are expected to come from liquid meal substitutes, energy-boosting shakes, sports drinks and fortified foods, which will meet consumers preferences to obtain nutritional requirements thorough dietary means. The most favourable opportunities for the mineral market are predicted to come from calcium and magnesium (Freedonia Group, 1998).

Vitamins

Vitamins A, C and E are expected to provide the best prospects in this sector of the nutraceutical market, at least partly due to their antioxidant activity, with allied health benefits (see later). Fortified foods and beverages are expected to fuel this demand for vitamins, increasing global demand (Freedonia Group, 1998).

Herbal extracts

Herbal extracts are predicted to show the fastest global growth in the nutraceutical field, largely due to their perceived health benefits, but also reflecting the relatively less stringent regulations in place in many countries (Freedonia Group, 1998a).

3.2.2 Underlying drivers of the demand for nutraceuticals

Disease conditions and company priorities

According to a recent survey (Leatherhead Food RA, 1999, cited in Sloan, 2000), heart disease was ranked first in terms of diseases which would affect the future development of the nutraceutical market, with 49% of European nutraceutical manufacturers saying that this condition would have "very great influence" on the market. This reflects the prediction that early this century, coronary vascular disease will overtake infectious diseases as the world's leading cause of death and disability (Sloan, 2000). Other diseases, together with their perceived influence on the future nutraceutical market, are given below.

Table 3.13: **Influence of disease conditions on nutraceuticals in the next 5 years**

Disease [a]	%
Heart disease	49
Cancer	37
Obesity	37
Osteoporosis	27
Gut health	21
Immune system	17
Bowel function	11
Neural tube defects	8
Mood/cognitive performance	7
Arthritis	3
Urinary tract infections	0

Source: Leatherhead Food R.A. (1999), cited in Sloan (2000).

a.) Figures indicate percentage of European Nutraceutical manufacturers stating that the disease will be "very influential" on future developments.

Disease conditions and public priorities

In the US, a recent consumer survey (Peet 1999) has been conducted to determine the key disease areas, showing many similarities to the diseases identified as important by nutraceutical manufacturers (Table 3.13), and to the most desirable health claims in Europe (Table 3.15). These results are summarised in Table 3.14.

Table 3.14: Consumer health issues (US)

Disease/therapeutic area	Percentage "concerned" with condition
Cardiovascular disease/obesity	70
Osteoporosis/arthritis	65
Cancer	60
General health	60
Metabolic conditions/diabetes	30
Age-related conditions	30
Immune system	25
Adolescent health	15

Source: Peet, 1999

Desirable health claims

Market research in Europe indicates that products which "give energy" are highly desirable in the UK, France and Germany. Other popular claims, given in the top five health benefits in two out of these three countries, include "lowers cholesterol" (UK and France), "promotes healthy bones" (UK and Germany) and "boosts immune system" (Germany and France). The most desirable claims for nutritional/ nutraceutical products are shown in more detail at a country level in Table 3.15.

Table 3.15: Most desirable health claims for products in The UK, France and Germany

	UK		FRANCE		GERMANY
1	Gives energy	1	Gives energy	1	Boosts immune system
2	Promotes healthy bones	2	Lowers cholesterol	2	Promotes health bones
3	Promotes healthy teeth	3	Increase disease resistance	3	Promotes health teeth
4	Reduced risk of breast cancer	4	Boosts immune system	4	Gives energy
5	Lowers cholesterol	5	Prevents constipation	5	Promotes healthy gut

Source: Leatherhead Food R.A. (1999), cited in Sloan (2000).

The concerns and therapeutic targets outlined above are reflected in future market projections for functional products, foods and beverages. By 2002, it has been forecast that 47% of the $3.96 billion global market will be dedicated to products giving energy or improving mental function, closely followed by 37.9% dedicated to cardiovascular disease (Kroll 1997).

The market is not without potential difficulties, however. The Kellogg Company chose to withdraw its "Ensemble" range of products, aimed at reducing cholesterol, following disappointing sales in the trial product launch in the US. The company has not abandoned the nutraceutical marketplace, however, as they acquired the Worthington Foods company (which specialise in natural, vegetarian and soy-based foods) for $307 million in November 1999. Both Campbell Soup and The Hain Food Group have also recently withdrawn soup style supplements (Gregory, 2000).

Table 3.16: US sales projections of functional products: by disease treated: 2002

Disease/therapeutic area	Percentage of market	Market value ($US billion)
Energy/mental function	47.0	1.87
Heart disease	37.9	1.50
Laxatives & detoxification	5.1	0.20
Arthritis & joint pain	2.2	0.09
Cancer	2.1	0.08
Intestine & digestive system	1.7	0.07
Diabetes	1.3	0.05
Other	1.0	0.04
Immune boosting	0.9	0.03
Teeth & gums	0.8	0.03

Source: Kroll/Business Communications Co., Inc. (1997)

A similar situation exists for the highly developed Japanese nutraceutical market, which in 1998 was valued at ¥1,300 billion (PROMAR International, 1999), as shown below.

Table 3.17: Japanese nutraceutical market share: by function: 1998

Function	Market share (%)
Energy	44
Intestinal regulation	16
Strengthen bones	12
Skin care	6
Vitamin/mineral balance	4.8
Nutritional balance	4.1
Tooth decay reduction	3.3
Weight control	3.3
Reduce throat irritation	2.6
Prevent halitosis	1.8
Other	2.5

Source: PROMAR International, 1999

Research indicates that every major food and pharmaceutical company interviewed by Business Communications Co., Inc was interested in functional foods. Food marketing/processing companies were generally more likely to be interested than pharmaceutical companies, as consumers generally see foods primarily as “tasteful” items, rather than functional. Pharmaceutical companies, in general were more likely to develop patent-protected prescription products than patented functional food ingredients (Kroll, 1997).

In regard to the functional food market, as distinct from the whole functional product market (including beverages), the spread of therapeutic targets is simpler, with cardiovascular conditions accounting for 85% of the $1.66 billion annual projected functional food market in the US in 2002.

Table 3.18: US sales projections of functional foods, by disease, 2002

Disease/therapeutic area	Percentage of market	Market value ($ billion)
Heart disease	85.0	1.40
Cancer	5.0	0.08
Energy/mental function	3.9	0.07
Diabetes	3.1	0.05
Teeth & gums	2.0	0.03
Other	1.0	0.01

Source: Kroll/Business Communications Co., Inc. (1997)

3.2.3 Growing availability and access to herbal products

Existing products

There is a huge diversity of herbal products offered globally for self-medication covering a wide range of complaints. For the purposes of this paper, a selection of the best selling plant species used in herbal preparations is presented.

Garlic
Garlic (*Allium sativum*) is primarily used to combat infections, reduce cholesterol levels, and treat circulatory disorders, including high blood pressure and high blood sugar levels. Garlic sales accounted for 10% of the European herbal remedies market (Scimone and Scimone, 1999) and 16-18% of the US market during 1996-1999 (Scimone and Scimone, 1999, Sauer, 1999b). Approximately 1000 tonnes of fresh garlic are required annually for the production of Kwai® N by Lichtwer Pharma AG – this material is sourced exclusively from China (Lichtwer Pharma, 2000). China is one of the world's leading producers of garlic, exporting almost 25,000 tonnes to the United States in 1993 alone (Lumpkin, 1996). In Australia China is the major supplier to the domestic market.

Ginkgo
Ginkgo (*Ginkgo biloba*) is taken to improve microcirculation, especially to the brain and central nervous system, with the aim of improving mental function and concentration, especially in cases of dementia and Alzheimer's disease. In many market surveys, Ginkgo is commonly the single most popular herbal remedy, reflecting the public concern over maintaining cerebral function. Ginkgo accounts for 17% of herb sales in Europe, and 19-21% of sales in the United States (Scimone and Scimone, 1999; Sauer, 1999b).

Ginseng
Ginseng (*Panax ginseng*) is most commonly taken as a general tonic, an adaptogen (helping the body to combat stress, fatigue and cold) and stimulant. Ginseng is frequently in the top three most commonly purchased herbs, accounting for 10% (Europe) to 12-20% (United States) of the herbal market between 1996 and 1999 (Scimone and Scimone, 1999). In 1992, the global production of ginseng stood at 6,900 tonnes, rising at 6% annually. In 1992, cultivated ginseng sold for $32 per lb. Wild-collected roots sold for $81 per lb, although wild harvesting of this species is increasingly uncommon (Wahab and Clark, 1993).

Spirulina
Spirulina (*Spirulina platensis*) is a microalga, containing high concentrations of gamma-linolenic acid, Vitamins B12 and E, provitamin A (beta-carotene) and protein. Claims made for Spirulina include immunostimulant activity, stabilisation of blood sugar, anti-allergen, appetite suppressant and cancer preventative. Global production of spirulina was put at approximately 2,000 tonnes in 1996 (Fox, 1996).

Chamomile
German Chamomile (*Chamomilla recutita*, syn. *Matricaria recutita*) and Roman Chamomile (*Chamaemelum nobile*, syn. *Anthemis nobilis*) are used largely interchangeably to treat digestive problems, combat tension and reduce irritation (such as sore skin and eczema). The herb is cultivated widely in temperate areas, and global large-scale farm production in 1998 was estimated to be 1,000 tonnes (Fletcher, 1999).

St John's Wort
A European native, St John's Wort (*Hypericum perforatum*) is amongst the most extensively studied plants used in herbal medicine. It is mainly taken to counter depression, and has been used as a natural alternative to synthetic anxiolytics, such as Prozac. Recently, St John's Wort has been transferred to the pharmacy-only sales list in Ireland, which may affect future sales of this herb. This herb accounted for between 11-14% of herbal sales in Europe and the United States between 1996 and 1999 (Scimone and Scimone, 1999, Sauer, 1999b).

Echinacea

Echinacea (mainly *Echinacea purpurea*, but also *E. angustifolia* and *E. pallida*) is widely used as an immunomodulator, for treatment and prevention of upper respiratory tract infections. Sales of Echinacea have been estimated at 9% of the European herbal market in 1997 and approximately 12% in the United States (Scimone and Scimone, 1999, Sauer, 1999b).

Saw palmetto

The primary claim made for Saw Palmetto (*Serenoa repens*) is for treatment of benign prostatic hyperplasia (BPH), a condition likely to increase in incidence with the general ageing of the population. Sales of Saw Palmetto range from 4-6% of the total herbal market in the United States to 13% in Europe (Scimone and Scimone, 1999, Sauer, 1999b).

Goldenseal

Goldenseal (Hydrastis canadensis) is a traditional North American "cure all", mainly used today to treat mucous membrane disorders, digestive problems and to counter infections. It is commonly used in conjunction with *Echinacea* for treatment and prevention of upper respiratory tract infections. This combination of herbs accounted for 11% of herbal sales in the United States in 1996-7.

Valerian

Valerian (*Valeriana officinalis*) is classic sedative and relaxant used for centuries. Today, the herb is mainly taken to encourage sleep, improve quality of sleep, lower blood pressure and relieve anxiety. The plant is widely cultivated in Western Europe, where the roots and rhizome of 2-year old plants are harvested for processing. In Europe, Valerian accounted for 10% of the herbal market in 1997, but is a much less popular herb in the USA, with 1% or less of the market there (Scimone and Scimone, 1999, Sauer, 1999b).

Cranberry

Cranberry juice has been strongly promoted as an answer to urinary tract infections. Cultivation is expanding rapidly in North America and Canada, with a 51% increase in area "farmed" in Canada in 1997-8 (2021 ha; Pearen *et al*., 1999), producing 32,906 metric tonnes with an estimated farm value of $55.4 million (Vandenberg and Parent, 1999). In the USA, approximately 15,000 ha are dedicated to cranberry production in 1999, yielding approximately 250,000 metric tonnes of cranberries (Anon, 1999a).

Grapeseed extract

Extracts of grapeseed (*Vitis vinifera*) are primarily taken today as a rich source of antioxidant compounds (oligomeric proanthocyanidins). In the United States, grapeseed extracts account for 2-4% of the herbal sales market between 1996 and 1999 (Scimone and Scimone, 1999, Sauer, 1999b).

Evening primrose

Evening primrose (*Oenothera biennis*) oil is a rich source of essential fatty acids, especially cis-linoleic and cis-gamma linoleic acids, and is commonly taken for pre-menstrual problems including bloating and tension, for eczema, breast tenderness and to reduce blood pressure. Multiple sclerosis and rheumatoid arthritis are also claimed to benefit for the oil. In the USA in 1996-7, 2% of herbal remedies sold were based on evening primrose oil (Scimone and Scimone, 1999).

Kava kava

Kava kava (*Piper methysticum*) accounted for 4% of herbal sales in the USA in 1998-9 (Sauer, 1999b). The plant is primarily taken as a tonic and stimulant, to combat anxiety, and to promote sleep.

Future trends in herbal products

It has been forecast that herbal products for reducing blood pressure and/or cholesterol, enhancing physical and/or mental stimulation, stimulating the immune system, combating depression or prostate problems will benefit considerably from the evolving morbidity patterns in developed countries. This is expected to lead to good sales in the future (Freedonia Group, 1998). Plants which are already marketed for these conditions include those shown below:

Table 3.19: Herbal plant species with good growth forecast for future sales

Therapeutic target	"Established" plant used for treatment
Cholesterol/blood pressure	Garlic
Physical/mental stimulation	Ginkgo/Ginseng
Immune system	Echinacea/Goldenseal
Depression	St John's Wort
Prostate problems	Saw palmetto

3.3 Raw materials

The US market for botanical extract raw materials is estimated to be approximately $US500 million (Health Business Partners, cited in Boswell, 1999), which is equivalent to about 25% of the global market. iGround or crushed crude herbs take up the remaining market share . The extract market is forecast to grow to $US1.5 billion within 5 years. More importantly, the proportion of this market accounted for by extracts, rather than crude herbs, is forecast to rise to as much as 75%, reflecting the increased demand for product consistency and quality (May Yamada, cited in Boswell, 1999).

Other estimates for the extractive industry valued the total market for plant-derived chemicals at $US1.89 billion in 1998, with growth rates over 9%/year (Marley/Freedonia Group, 1999). Within this market, the four main categories identified were essential oils ($US625 million), botanical extracts ($US560 million), gums, gels & polymers ($US392 million) and “others” ($US313 million). These chemicals often compete with petroleum or animal-derived products. Although raw materials for production of plant-derived products are often relatively cheap, harvesting and processing costs, combined with relatively low yields can reduce cost competitiveness against petroleum-based products. Nevertheless, the popularity of plant-derived chemicals with consumers provides a marketing edge (Marley and Thomas, 1999).

Table 3.20: Plant-derived chemicals: Projected demand [Marley/Freedonia Group (1999)]

Item	1993	1998	2003	2008	Annual growth (%)	
					98/93	03/98
Plant-derived chemicals (million lb)	370	535	740	995	7.7	6.7
$US/lb	3.2	3.53	3.97	4.52	2.0	2.3
Plant-derived chemicals demand [$USm]	1185	1890	2935	4495	9.8	9.2
Essential oils [$USm]	465	625	820	1054	6.1	5.6
Botanical extracts [$USm]	268	560	1120	1990	15.9	14.9
Gums, gels and polymers [$USm]	274	392	500	660	7.4	5.0
Others [$USm]	178	313	495	791	11.9	9.6

In parallel to this increase in demand, the whole market for companies involved in supplying botanical extracts is seen to be moving into a more “mature” phase. Numerous mergers are occurring (for example Hauser merging with several units of Zuellig Group NA, Folexco taking over East Earth Herb to form A.M. Todd Botanicals and large operators such as American Home Products acquiring Solgar). It has been estimated that, for a company to survive in the US market place, it now needs to have annual sales in excess of $US20 million (Dave Wilson, cited in Boswell, 1999). As shown below (Table 3.21), many of the largest companies in the botanical supplies industry have sales well in excess of this amount.

As the international market for herbal ingredients for ultimate use in pharmaceuticals, nutraceuticals and cosmetics grows, the sourcing of raw plant materials is set to broaden simultaneously, both in terms of increased harvests of existing crops, and development of new crops and varieties. This has put companies involved with supplying botanical raw materials and extracts under increased pressure, through sourcing of new supplies (including negotiating increasingly complex intellectual property and biodiversity-related issues; see Baker *et al*., 1996, for indications of the measures taken by Australia in this field) and establishing new cultivation programs.

This strain on the supply industry is compounded by the entry into the market of major pharmaceutical companies, with their demands for large volumes of extracts and botanical raw materials (Thurston, 1998). This increased demand, accompanied by an increased requirement for consistent quality, has resulted in a radical shift away from wild-crafted plant materials (Wilkinson 2000e) towards cultivated crops. Indena USA, for example, (which has an exclusive supply arrangement with Bristol-Myers Squibb for supply of 10-DAB, a precursor for Taxol® and with the Bayer Corp. for supply of IDN 5109, a semi-synthetic compound derived from *Taxus wallachiana* due for development as an anti-cancer agent) sourced 25-30% of its botanical raw materials from cultivated sources in 1996. By 1998, this had risen to approximately 60% (Thurston, 1998).

Table 3.21: Leading botanical suppliers (raw materials)

(Data at April, 1999)

Company	US sales ($ million)
Hauser/Botanical International	>100
Indena	>50
Henkel	30-50
Optipure (Chemco)	30-50
Flachsmann	30-50
Martin Bauer/Muggenberg Extrakt	30-50
Folexco/East Earth Herb	30-50
Botanicals International Powders	30-50
Schweizerhall	15-20
Euromed (Madaus)	15-20
Mafco Worldwide Corp.	15-20
Triarco Industries	15-20
Sabinsa	15-20
MW International	10-15
AYSL	10-15
Quality Botanicals International	10-15
SKW Trostberg	10-15
PureWorld (Madis).	10-15
Technical Sourcing International	10-15
Arkopharma	10-15
Starwest Botanicals	10-15
Amway/Trout Lake Farm	10-15

Source: Nutrition Business Journal and Health Business Partners estimates, cited in Boswell, 1999

Currently, the supply of plant-derived chemicals, especially unusual extracts for medicinal applications, comes from a small number of growers, and is often produced in relatively small geographical areas. Consequently, prices and availability of such products is extremely volatile, as supply can be drastically affected by political, agricultural and environmental factors (e.g. global carnauba wax prices almost doubled with a two week period in 1998, following storms in the primary growing areas in North-eastern Brazil; Marley and Thomas, 1999).

The industry for supply of plant-derived chemicals is highly fragmented. Many companies are small, privately owned niche players, almost traders, with limited product lines and annual sales of less than $50 million. These distribution positions, placed as they between the growers of the raw materials and the end-product (food/cosmetic/pharmaceutical) manufacturer, are likely to come under increased cost competiton from more vertically integrated structures. It has been forecast that, with the increasing interest in plant-derived products, major chemical and pharmaceutical companies will enter this marketplace directly with more competitive structures arising from economies of scale in both production and distribution. These firms are expected to account for increased market share (Marley and Thomas, 1999). For the future of this industry, 'the challenge for marketers of plant-derived chemicals will be to maintain access to reliable sources of raw materials, to control or reduce production costs effectively and to compete aggressively with the growing number of synthetic alternatives' (Marley and Thomas, 1999).

Sourcing of different components from plants for pharmaceutical, cosmeceutical or nutraceutical purposes, can be a very time-consuming and specialist undertaking, especially if the plants in question are non-commercialised. A small number of institutes have specialist, centralised libraries of plant extracts available for screening and investigation, which can make the sourcing/screening process much quicker and easier for pharmaceutical/ cosmeceutical/nutraceutical companies. Middlesex University, for example, has a collection of more than 7000 species available for these purposes. Similar sized collections exist in Australia with private companies such as ExGenix, CSIRO and botanical gardens. For countries outside of Australia, access to the country's biological resources, especially for economically-driven research can be extremely difficult indeed, due to the country's strict export regulations (initially outlined in Baker *et al*., 1996). By restricting foreign access in this way, Australia effectively has a strong advantage for future commercialisation of Australian native species, which could be further developed and exploited.

3.4 Industrial products

A report from the European Commission in 1997 identified the following plant species for various industrial end-uses (Table 3.22).

Potato and maize also have significant potential as low cost sources of starch for producing polymers and genetically modified canola, and as noted above, is showing promising results as a low cost material for bioplastics.

Table 3.22: Examples of non-food crops, classified by end-use

Industrial Product	Plant Source
Agrochemicals	Spurge (*Euphorbia* spp.) Pyrethrum (*Tanacetum cinerariifolium*) Annual wormwood (*Artemisia annua*) Caraway (*Caraway*) Quinoa (*Chenopodium quinoa*)
Board, composites, building and insulation materials	Hemp (*Cannabis sativa*) Flax (*Linum usitatissimum*) Kenaf (*Hibiscus cannabinus*) Cotton (*Gossypium* spp.) Common reed (*Phragmites* spp.) Elephant grass (*Miscanthus* spp.) Sunflower (*Helianthus annuus*)
Cordage and sacking	Hemp (*Linum usitatissimum*) Kenaf (*Hibiscus cannabinus*) Nettle (*Urtica dioica*)
Dyes	Woad (*Isatis tinctoria*) Madder (*Rubia tinctoria*) Safflower (*Carthamus tinctorius*)
Energy and fuels	Oilseed rape (*Brassica napus*) Sunflower (*Helianthus annuus*) Willow (*Salix* spp.) Elephant grass (*Miscanthus* spp.) Poplar (*Populus* spp.) Common reed (*Phragmites* spp.) Spurge (*Euphorbia* spp.) Cordgrass (*Spartina* spp.)
Industrial raw materials	Oilseed rape (*Brassica napus*) Sunflower (*Helianthus annuus*) Castor (*Ricinus communis*) Chicory (*Cichorium* spp.) Crambe (*Crambe* spp.) Kenaf (*Hibiscus cannabinus*)
Lubricants and waxes	Oilseed rape (*Brassica napus*) Linseed (*Linum usitatissimum*) Spurge (*Euphorbia* spp.) Rain daisy (*Dimorphotheca pluvialis*) Honesty (*Lunaria biennis*) Meadowfoam (*Limnanthes alba*)
Industrial Product	**Plant Source**
Paper and pulp	Hemp (*Cannabis sativa*) Flax (*Linum usitatissimum*) Kenaf (*Hibiscus cannabinus*) Elephant grass (*Miscanthus* spp.)
Plastics and polymers	Honesty (*Lunaria biennis*) Castor (*Ricinus communis*) Meadowfoam (*Limnanthes alba*)
Resins and adhesives	Rain daisy (*Dimorphotheca pluvialis*) Stokes aster (*Stokesia laevis*)
Soaps, detergents, surfactants, solvents and emulsifiers	Coriander (*Coriandrum sativum*) Hemp (*Cannabis sativa*) Spurge (*Euphorbia* spp.) Cuphea (*Cuphea* spp.) Poppy (*Papaver somniferum*) Gold of pleasure (*Camelina sativa*) Castor (*Ricinus communis*) Quinoa (*Chenopodium quinoa*)
Textiles	Hemp (*Cannabis sativa*) Flax (*Linum usitatissimum*) Nettle (*Urtica dioica*)

Source: European Commission, 1997

Gums, gels and polymers

Inulin, a polymer of fructose is found in high concentrations in the tubers of Jerusalem artichoke (*Helianthus tuberosus*) and Chicory (*Cichorium intybus*). In its raw form, inulin can be used as a low-calorie sweetener, and the fructose-rich syrups derived from it have potential as feedstocks for fermentation processes and chemical transformations, with a wide range of possible applications. Glucomannan is another plant-derived polymer being researched in Europe for its unique functional properties (viscosifying action and synergy with other natural gums). It is hydrocolloidal in nature, containing mannose and glucose, and can be obtained from yams of the genus *Amorphophallus*. Currently, the supply of this substance is from Asia, but product quality and consistency is frequently inadequate from the large number of small plots and inefficient distribution systems. Improved quality and standardisation of product for use as a food ingredient/additive is being investigated (De Braeckelaer *et al*., 2000).

Dyes

In 1989, 5% of the inks used in the US were of plant origin (Palmieri and Venturi, 1999), but by 1999 the market share had increased to 22% (National Soy Ink Information Centre 2000). Soybean oil for ink production has also risen sharply in Asia and Japan in particular where the two largest printers are switching to soy inks. Plants used for dyes on commercial or experimental purposes include woad (*Isatis tinctoria*, also used as a source of wood preservatives in areas of Germany) and safflower (*Carthamus tinctorius*, also grown for its seed oil, which has applications in varnishes and paints). Similarly, the oil from the rain daisy (*Dimorphotheca pluvialis*) is receiving interest for its high content of dimorphecolic acid – an unusual fatty acid with possible applications in urethane resins, paints, varnishes, lubricants, and cosmetics (NF-2000). In the United Kingdom, the Ministry of Agriculture, Fisheries and Food (MAFF) is funding research to produce environmentally friendly ink-jet inks, with possible further applications in textile dyeing and paper colouring and paints, from woad, madder (*Rubia tinctoria*) and weld (*Reseda luteola*).

Oils and surfactants

Key vegetable oils include coconut, soybean, palm, linseed, canola, sunflower and castor oil (see table). Linseed is used to improve the adhesion qualities of latex-based paints, and, in its epoxidised form, is a common plasticiser or stabiliser for vinyl plastics (Salunkhe *et al*., 1992). Its production is now supported by the common agricultural policy (CAP) in Europe. Soybean, because of its large scale availability and low cost, is widely used for a range of industrial products, while castor oil is also used in an array of different applications, from as a lubricant to as a fungistat, a cosmetic ingredient and as a plasticiser.

The seed oil from honesty (*Lunaria biennis*) is receiving commercial interest, due to its high content of nervonic and erucic acids, making it appropriate for high- temperature lubricants and engineering nylons, and also some pharmaceutical preparations (NF-2000). Seed oils from *Crambe* species are also being investigated as good sources of erucic acid. Although some varieties of canola also produce this compound in large amounts, these can be “unstable”, as they are cross-fertilised with low-erucic acid producing varieties, whereas Crambe species do not have this potential problem (Tittonel *et al*., 2000). Borage has been described as an “established minor crop” in parts of Europe (NF-2000), cultivated for the high gamma-linoleic acid content of its seed oil, and its resulting applications in nutritional supplements and pharmaceuticals.

Table 3.23: Annual global oil production (1997 data)

Oil	Annual production (million tonnes)
Soybean	20.8
Palm	17.6
Rapeseed	11.8
Sunflower	9.3
Palm kernel/coconut	5.6
Others	14.7

Source: Hill, 1998

Oils such as coconut and palm kernel oils have been of particular interest, because of their high concentration of fatty acids with a medium chain length (C_{12-14}), making them particularly suitable for further processing to surfactants for washing and cleansing agents, as well as cosmetics. Oils from palm, sunflower and rapeseed contain many longer-chain fatty acids (C_{18}), and can be readily used as industrial lubricants. Other oils receiving commercial interest include hazelnut (*Corylus* spp.), grapeseed (*Vitis vinifera*), avocado (*Persea americana*), nettle (*Urtica dioica*) and hemp (*Cannabis sativa*).

Other agricultural products

The residual solid materials from production of linseed oil (see above) forms a valuable livestock feedstuff (NF-2000). In addition to its pharmacological and perfumery uses, the oil from caraway (*Carum carvi*), and specifically, one of its major components, carvone, is receiving interest as an insect repellent, a suppressant of sprouting in stored potatoes, and for inhibiting the growth of some fungi (NF-2000). Pyrethrum (*Pyrethrum cinerariaefolium*) is cultivated extensively in Kenya, and also increasingly in Australia (via for instance, Bureau of Rural Science) for the insecticidal compounds found in its flower heads. Fermentation products of Stevia (*Stevia rebaudiana*) are currently being investigated as fodder for livestock, particularly sheep and goats (Calvo *et al*., 2000). Certain varieties of rice are being investigated for their potential to produce weed-controlling compounds (Pugh 2000).

4. New pharmaceutical, nutraceutical and industrial products available from agriculture

In Brief

Driving the demand for better health is increased prevalence of disease and, at least in the case of the US, evidence of diminished quality of life associated with those diseases. Cancer, cardiovascular disease and diabetes are shown to have the most deleterious effect on the quality of life, hence the level of interest of any measures that might alleviate the prevalence. Industrial products are meeting with renewed interest as the price of oil based substitutes continues to rise.

There is a growing demand from consumers for natural-based medicines, and there is considerable evidence to show that medicines of this type will account for an increasingly large proportion of the pharmaceutical markets currently dominated by synthetic drugs. This includes the cardiovascular drug market; the anti-infective drug market; and the CNS drug market.

Garlic, Ginkgo and Ginseng are already positioned in the market to meet this increasing demand. Ginkgo products such as Tanakin and Ginkor (Beaufour) and Tebonin (Schwabe) already dominate the European market for herbal medicines, with annual sales in excess of $US180 million in 1998. The anxiolytic market has been estimated to stand at $US2.5 – 4 billion. Plant-derived drugs with tranquillising or sedative actions are likely to continue to be popular, and the demand for herbal products, such as valerian (Valeriana officinalis), St John's Wort (Hypericum perforatum) hops (Humulus lupulus), passionflower (Passiflora spp.) and kava (Piper methysticum) with these activities is set to continue. The increasing demand for this type of product can be seen in the case of Jarsin, a licenced product based on St John's Wort, which saw sales rise from $US2.9 million in 1992 to $US24.7 million in 1998 (see section 3.1.3). If as much as 30% of the synthetic pharmaceutical market is to be penetrated by high quality "herbal pharmaceuticals" (Wilkinson, 2000), it can be seen that there is still great scope for anxiolytic herbs, which could ultimately have global sales approaching $1 billion.

The undeveloped nature of the herbal/nutraceutical market in Australia suggests there is considerable potential for rapid growth. Similarly, the market for self-medication treatments for coughs, colds and respiratory complaints is now approximately $US9 billion, growing at 2% annually. The most dominant herbal remedies for this indication are those based on Echinacea spp, which accounts for 9% of herbal sales in Europe, 12% in the US and about 10% in Australia

Cancer is another condition often cited as a cause for future concern, which is likely to affect increasing numbers of people as the world's ageing population grows. Compounds from Catharanthus spp (including vinblastine and vincristine), as well as yew (Taxus spp.)-derived chemicals such as Taxol® will continue to be important drugs. With a move towards natural – and self-medications, there is likely to be an increasing shift to products which may have some potential for cancer prevention. Antioxidants again are a key class of compounds in this area, and are likely to see massive growth in the future for their potential ability to reduce the risk of developing cancers

With an ageing population, conditions such as benign prostatic hyperplasia (BPH) and menopause-related complaints such as osteoporosis are likely to affect increasing numbers of people. Herbs such as saw palmetto (Serenoa repens) and pygeum (Prunus africana) are effective treatments for BPH, whilst chasteberry (Vitex agnus-castus) is used by many women during the menopause. Sales of these herbs are likely to grow to meet increasing demand over the next few years.

4.1 Pharmaceuticals

4.1.1 Herbal medicines

The introduction of new "phytopharmaceuticals" is expected to lead to increased demand for new crop species, which is positively encouraged in the European Union, as a result of overproduction of food crops (Houghton, 1995; Wilkinson, 1996). The cultivation of plants specifically for use in the pharmaceutical (as well as the nutraceutical and cosmetic) industries is likely to increase, given the trends in demand for these products described elsewhere in this report. A key demand on these cultivated crops will be one of quality and lack of toxicity – possible evidence for adverse reactions, interactions or simple toxicity may be sufficient to result in the cessation of demand for any particular species (Wilkinson, 200d). In this regard, the current situation with St John's Wort (*Hypericum perforatum*), and its continuing OTC availability in parts of Europe will be of particular interest following recent reports of adverse reactions and interactions with conventional drugs (Wilkinson 200g).

The herbs with greatest potential are those which are easily marketed due to their existing food (regulation) status, those which serve the greatest need (ie. which can be used most widely), and those which give the greatest possibility of new discoveries. Of the ten "top herbs" considered, only garlic fitted all three criteria:

Table 4.1: Herbs with greatest potential for future development

Herb	**Ease of marketing**	**Greatest need**	**Possible novelty**
Chamomile	•		
Garlic	•	•	•
Ginger	•		
Echinacea		•	
Feverfew		•	
Ginkgo		•	
Hawthorn		•	
Saw palmetto		•	
Milk thistle			•
Valerian			•

Source: Tyler, 1988

Other plants singled out by Tyler for future research and development include:

- Black cohosh (*Cimicifuga racemosa*) for dysmenorrhoea, PMS and menopausal problems,
- Yohimbe (*Pausinystalia yohimba*) for erectile dysfunction in males – more safety and efficacy data are required, but the market potential for this herb is described as "enormous",
- Guggul (*Commiphora mukul*) for lowering cholesterol and triglycerides,
- Nettle root (*Urtica dioica*) for benign prostatic hyperplasia,
- Hops (*Humulus lupulus*) as a sedative,
- Horehound (*Marrubium vulgare*) as an expectorant
- Yerba santa (*Eriodictyon californicum*) to improve palatability of drugs
- St John's Wort (*Hypericum perforatum*) as an anti-depressant
- Ginseng (*Panax ginseng* and *P. quinquefolius*) to enhance performance/endurance
- Neem (*Azadirachta indica*) as a treatment for periodontal diseases.

To this list, the following could also be added:

- Kava (Piper methysticum) as a sleep-promoter, anti-depressant or sedative
- African potato (*Hypoxis hemerocallidea*) as an immune-stimulant
- Cat's claw (*Uncaria tomentosa*) as an immune-stimulant, anti-inflammatory
- Astragalus (*Astragalus membranaceous*) as a treatment for high blood pressure and as an immune stimulant
- Sage (*Salvia* spp.) as cholinesterase inhibitors and antioxidants

As stated previously, certain parallels can probably be drawn between the market potential for herbal products in the United States and Australia, based on the relatively under-developed status of the markets in these countries, compared to leading European countries, such as Germany. The following herbs have been highlighted by the Executive Director of the American Botanical Council as herbs, which will probably become popular in the United States over the next 12 months (Table 4.2).

Table 4.2: Emerging herbs in the United States market place

Herb	Activity/potential
American ginseng (*Panax quiquefolius*)	Immunomodulation, with specific potential against upper respiratory tract infections. Evidence for possible synergistic enhancement of conventional breast cancer drug activities.
Andrographis (*Andrographis paniculata*)	Immunostimulant, with specific potential against colds and influenza Possible potential for AIDS and HIV patients
Ginger (*Zingiber officinale*)	Treatment of nausea (motion sickness and morning sickness possible specific indications)
Hawthorn leaf and flower (*Crataegus* spp.)	Cardiac conditions (e.g. increasing heart output and contractility)
Horse chestnut seed (*Aesculus hippocastanum*)	Treatment for chronic venous insufficiency
Red clover (*Trifolium pratense*)	Improved artery elasticity (post-menopausal)
Sangre de Drago (*Croton lecheri*)	Wound healing, treatment of viral disease-associated diarrhoea.
Schisandra (*Schisandra chinensis*)	General tonic/adaptogen, possibility for hepatoprotection

Blumenthal, 2000

4.1.2 Plant-derived products

The possibility of discovering another highly significant plant-derived compound such as Taxol can never be ruled out, given that the proportion of plants screened for biological activities is such a small fraction of the global flora. Other compounds, such as artemisinin and galanthamine are also key examples of compounds relatively recently obtained from plant sources. Future developments in this field are almost impossible to predict, given the range of therapeutic targets and the sheer diversity of plant life. Future work in this field would almost certainly have to be conducted in collaboration with industry and/or academia, where the necessary primary novel research is being undertaken. As funding for such research can often be at a premium, especially in the academic sector, governmental involvement with such work could be a cost-effective approach to future developments.

4.2 Nutraceuticals

4.2.1 Herbal products

Herbal teas are forecast to be an area of particularly rapid growth in the next few years. According to Business Communications Co., Inc., the global market for functional foods and beverages will rise at approximately 12.4% per annum to reach $314.1 million by 2002 (Kroll, 1997a). Functional beverages accounted for 53% of this market in 1997 ($92.7 million). Within the functional beverage sector, "powder to mix" products (mainly protein and/fibre based products, accounting for 40% of the functional beverage sector) and teas in bags (37%) were dominant, with cultured drinks responsible for less than 10% of the sector. Critically, however, annual increases in sales were predicted at 3.3% for powder-to-mix products, just 1.3% for cultured drinks (it has been stated that there is a "limited market for cultured milk and yoghurt drinks"), but a much larger 27% increase per annum for teas in bags (Kroll, 1997a).

The demand for functional foods and food supplements is certain to grow, and it has been predicted that 'virtually all foods will have a functional form', in the same way that most foods today have a "diet" or "low fat" form today (Kroll, 1997). Key areas for future research will include:

- Phytochemicals – especially for use in the treatment/prevention of common conditions, such as heart disease and cancer. Particular interest is likely to focus on grains and fibre, herbs, spices, fruits and vegetables, and beverages, such as green and black teas, wine and grape juice, cranberry juice and blueberry juice, and the phytochemicals they contain
- Oils and fatty acids – for example omega-3 oils (such as docosahexaenoic acid, DHA), usually obtained from fish, but also present in nuts, seeds and plants.
- Fructo-oligosaccharides – natural carbohydrates, which act as dietary fibre, improving intestinal function.
- Stanol esters – such as those found in pine extracts, used for lowering blood cholesterol
- Guarana – as energising product for use in soft drinks and teas.

Plants such as Stevia (*Stevia rebaudiana*) and Japanese quince (*Chaenomeles japonica*) are also receiving increased interest for their multiple potential applications. Stevia is best known as a source of the natural sweetener, stevioside. But it can also be used as a rich source of chlorophyll (for use in medicines and oral hygiene products) and phytosterols (with potential applications in the production of oral contraceptives, cholesterol-regulating products and anti-cancer agents; Calvo *et al*., 2000). As mentioned previously, fermentation products from Stevia can also be used to make a valuable livestock feed. Japanese quince is currently being investigated in parts of Europe as a source of novel juice, flavour and fragrance products, as well as pectin, dietary fibre and a novel seed oil (Trajkovski, 2000).

4.2.2 Plant-derived products

Antioxidants form an important part of the nutraceutical market. Currently vitamins A, C, and E, carotenoids and flavonoids are the leading antioxidant phytochemicals.

Current leading antioxidants

The value of the natural vitamin C market for 1998 was $314.2 million showing a 9% increase on the previous year. Antioxidant/carotenoid formulas showed an even larger increase of 11.4% from 1997 to 1998 with sales totalling $96.8 million, while sales of natural vitamin A, D and K increased by 16.1% to $11.5 million. The largest per centage increase occurred in the market for natural vitamin E single supplements, which increased by 24.8% to $323.9 million from 1997 to 1998 (Kane 1999).

Emerging products

Lycopene, an acyclic carotenoid found mainly in tomatoes (and also red peppers and red cabbage), is one of the major carotenoids in Western diets. It has the potential to become a major player in the nutraceutical market if studies continue to show it to be anti-carcinogenic. The anti-carcinogenic activity is thought to arise from the antioxidant properties of the carotenoid, which decrease oxidative damage to DNA. Currently the only supplier of lycopene to the nutraceutical market is the Israeli company LycoRed Natural Products, which is a subsidiary of Makhteshim-Agan Industries.

Another emerging antioxidant is resveratrol (3,5,4'-trihydroxystilbene) which is found in green vegetables, citrus fruit and in particular in red wines, the latter being the main source of resveratrol in the diet. Resveratrol may be responsible for the health benefits attributed to drinking red wine as it has been shown to have antioxidant effects as well as anti-carcinogenic and anti-inflammatory effects.

Limonene, a monocyclic monoterpene, is found in many essential oils. An alcohol of limonene, perillyl alcohol, which may be isolated from lavender, had shown activity against various cancers in animal studies. It is currently being studied in phase 1 trials in Europe and the US (Kane 1999).

Other plant products being studied

There are many further examples of plant extracts, which are being studied for their antioxidant properties. Thus, for example, licorice extract has been shown to inhibit LDL oxidation by a mechanism which involves the scavenging of free radicals (Craig, 1999). Also herbs such as Oregano and Rosemary have been found to contain compounds which are effective antioxidants. Herbs are thought to be important targets in the search for natural antioxidants from the point of view of safety (Nakatini, 1993). Extracts of sunflowers have been shown to have an antioxidant capacity comparable to that of the synthetic antioxidants BHT and BHA (Yoshiaki and Koji, 1994).

Potential applications of antioxidants

The potential applications of antioxidants appear to be almost limitless. As discussed above antioxidants exert and anti-carcinogenic effect. Since cancer is such a cause for concern in modern life there is a great interest in products, which may be able to prevent the onset of this disease. Antioxidants are also indicated in the prevention of artherosclerosis by preventing the oxidation of LDL and are indicated for the prevention of cardiovascular problems. Free-radical damage caused by the by-products of oxygen metabolism is known to cause premature ageing of the body. Thus antioxidants may be marketed for use in products designed to maintain general good health. They are also used in skin care products to prevent premature ageing of the skin. Antioxidants are also used to prevent food spoilage, in particular the degradation of lipids. There is a great interest in the use of natural antioxidants for this purpose because concerns have been voiced about the safety of the synthetic antioxidants currently being used.

4.3 Industrial products

4.3.1 Biotechnology

The possibilities arising from the use of genetic manipulation of plants is almost limitless, ranging from the manufacture of biodegradable plastics through to production of pharmaceutically-relevant antibodies. As the whole issue surrounding genetically-modified organisms (GMO's) remains highly sensitive at present, it would be appropriate to construct scenarios for planning research. If the development and/or medium to large scale planting of GM plants faces regulatory constraints then the pay-offs to research in this area will be constrained. Conversely, the pay-offs may be substantial in a more liberal environment.

In the United States, the biotech industry employed over 150,000 people in 1997, with annual sales of $13.4 billion (see below). Agricultural biotechnology product sales accounted for $875 million in this year, an increase of 54% over 1994 (Anon, 1999b).

Table 4.3: US biotech industry totals, 1997

	1997	1996	Per cent change
Financial			
Sales	13.4	11.5	+17
Revenues	18.6	16.1	+16
R&D expense	9.9	8.5	+16
Net loss	5.1	3.4	+50
Industry			
Market capitalisation	97.0	93.0	+4
Number of companies	1,283	1,274	+1
Employees	153,000	140,000	+9

Source: Morrison and Giovannetti (1999).

The recent Cartegena Protocol on Biosafety, agreed to in Montreal in January 2000 (CBD, 2000) potentially creates the first global regulatory structure specifically centred on biotechnological issues. As this protocol is expected to take up to two years to ratify, a certain amount of the language currently involved is ‘vague and flexible’ (Mahoney, 2000). Nevertheless, there are sections of the protocol, which could have potential for future agricultural biotechnological advances. For instance, the final regulatory restrictions, which could affect biotechnological projects and products, will not apply to pharmaceutical products. Critically, the protocol ‘Recognises that modern biotechnology has great potential for human well-being, if developed and used with adequate safety measures for the environment and human health.’ (Annex to decision Em-I/3, p. 42 CBD 2000).

4.3.2 Conventional technologies

Predictions for the continued increase in production of plastics will generate the need for additives, especially plasticisers and stabilisers that can be derived from vegetable oils. Strong adhesives and coating which reduce fabrication and maintenance costs, as well as liquid surfactants for the emulsion polymerisation process and textile processing will also be in strong demand (Salunkhe *et al*., 1992), and could be met through non-food vegetable oils. Such oils and their derived products will be increasingly in demand in the future for reasons of ecological compatibility, and the use of renewable resources will be an important criterion in the development of new products (Hill, 1998).

In a recent review of the industrial uses of vegetable oils (Palmieri and Venturi, 1999), a key area for future developments in this area was seen as substituting oil-derived (petrochemical) products with a “green” alternative fatty product from plants. Although the economics of this substitution are not yet seen to be viable on their own, there are a number of additional advantages to be gained from vegetable oils products. These include:

- Renewability of raw materials
- The possibility of widening the number of crops in any given rotation program
- Very high levels of biodegradability
- Low ecotoxicology
- Improved fire resistance characteristics
- Easier disposal, with the possibility of recycling
- Non-contribution to atmospheric CO_2 levels on combustion as the carbon contained in such oils is of relatively short-term photosynthetic origin.

Innovative products, derived from fatty alcohols, fatty acids or glycerides, including alkyl polyglycoside, fatty alcohol sulphate, cocomonoglyceride sulphate and protein-fatty acid condensates will also find applications in the surfactant and cosmetic industries.

4.4 Others

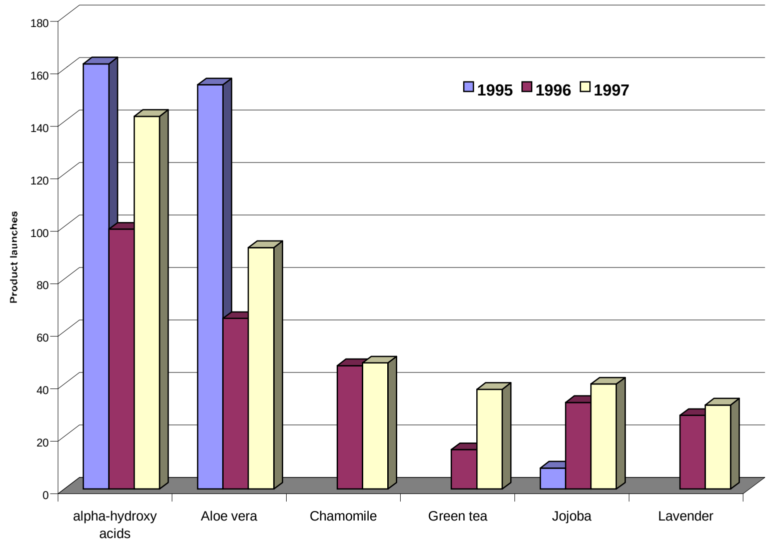
4.4.1 Cosmeceuticals

In a very similar manner to the acceptance of nutraceuticals as a valid sector of the food industry, products containing natural products are finding an increasingly receptive audience in cosmetic and personal care products. Cosmeceuticals are effectively products, which are on the boundary between drugs, and cosmetics – essentially they are products, which exert desirable physiological activity, such as skin healing, antioxidant activity, smoothing or conditioning properties.

In the United States, the market for cosmeceuticals in 1998 was estimated at $2.5 billion (Decision Resources, cited in Brown, 1998), with the key markets within this category being anti-wrinkle treatments, products to promote microcirculation, sunscreens, analgesics, and products to promote hair growth. Globally, the market for cosmeceuticals has been put at $10 billion, with the fastest growing sector in this market being anti-ageing products (Ouellette, 1998).

Some of the more popular cosmeceutical ingredients are given in the figure below, showing that -hydroxy acids (AHA's) and aloe vera are among the most frequently used ingredients, in terms of product launches in the United States. After 1997, demand for AHA’s has levelled off slightly, reflecting concerns over possible irritancy and UV damage concerns (Ouellette 1998). Despite this, AHA’s (including lactic, tartaric, malic and citrus acids) had annual US sales of $500 million in 1996, predicted to rise to $600 million by 2000 (Ouellette, 1998). -hydroxy acids are predicted to become a major component of cosmeceuticals in the near future – both produce exfoliation, but BHA’s, including salicylic and citric acids, being lipid soluble, are able to penetrate to the thicker sub-epidermal skin layers. Generally, BHA's are both more active and less likely to cause irritation than AHA’s. Specific BHA’s, such as salicylic acid, also have additional desirable properties, such as anti-microbial and anti-inflammatory actions.

Chart 4.1: New US botanical cosmeceutical skin-care product launches: 1995-97



Source: Marketing Intelligence Service, cited in Brown, 1998

Another product class receiving increasing interest are enzymes, which have potential application by affecting collagen and elastin (the skin's "support" matrix), modulating skin lipid and oil production and regulating cellular turnover. Such products are not without drawbacks – allergic reactions can be common in sensitive individuals, and the enzymes tend to be highly unstable, and prone to breakdown, making formulation difficult. Collaborative Labs in the USA are trialing a product containing immobilised papain (derived from Papaya) for use as an alternative exfoliator to AHA.

Table 4.4: Selected botanical cosmeceutical ingredients and claimed activities

Plant/Product	Company	Product claim
Oats	Pierre Fabre, Aubrey Organics	Anti-irritating, anti-inflammatory
Echinacea	Bioelements	Reduces lines and wrinkles, improved skin elasticity
Kalaya oil	Janet Sartin Inc.	Reduced wrinkles
Phytoplenolin	Bio-Botanica	Anti-inflammatory, cellular renewal, sunscreen
Olive leaf	Bio-Botanica	Antifungal, antiviral
Aloe	Univera Phytochemicals	Skin bleaching
Mullein	Nu Skin International	Anti-inflammatory, analgesic
Aloe	Univera Phytochemicals	Skin bleaching
Rumex	Fytokem Products	Skin toning (tyrosinase inhibitor)
Willowherb	Fytokem Products	Anti-irritant
Canola (Oilseed rape)	Fytokem Products	Skin conditioner

Indena, one of the world's largest botanical extract suppliers, has a range of extracts with cosmetic potential in a number of the key and emerging cosmeceutical therapeutic areas.

Table 4.5: Indena cosmeceuticals

Therapeutic Remedy	Product
Soothing of Irritated Skin	Chamomile dry extract Marigold dry extract St John’s Wort dry extract Silymarin
Anti-ageing	*Echinacea* dry extract Pygeum purified soft extract Soybean saponins Silymarin
Free radical scavaging	Bilberry dry extract Ginkgo biloba dry extract
Seboregulation	Pumpkin seed lipophilic extract *Serenoa repens* purified extract Hawthorn
“Orange peel” skin	Bladderwrack dry extract Butcher's broom dry extract Ivy soft extract (A)escin
Microcirculation stimulation	*Ginkgo biloba* dry extract
Stimulation of collagen synthesis	*Centella asiatica*
Microcapillary protection	Melilot dry extract
Stimulation of hair scalp	Peruvian bark fluid extract

Source: Indena (cited in Brown, 1999)

Therapeutic skincare products and sun care products underpin the growth in the US skincare market up to its 1997 value of $5.7 billion, and functional cosmetics have been described as a “natural extension” of these products (Bucalo and Rummell, 1999). In the US, the market for botanical ingredients for use in cosmetics and toiletries stood at $345 million in 1998, and was forecast to increase at 7.9% annually, to reach $505 million by 2003 (Freedonia Group, 1998b). A breakdown of projected demands within this botanical sector is given below in Table 4.6.

Table 4.6: Botanical extracts in cosmetic and toiletries (C&T) 1989-2008

Item	1989	1993	1998	2003	2008
C&T shipments (mill $)	20950	22025	28565	31755	35250
lb botanical / 000$ C&T	1.43	1.59	1.93	2.39	2.84
Botanical extract (mill lb.)	30	35	55	76	100
$/lb	6.00	6.57	6.27	6.64	7.20
Botanical extract demand (mill $)	180	230	345	505	720
Essential oils	101	113	150	200	258
Plant acids/enzymes	19	37	65	106	173
Aloe vera	38	46	63	86	115
Others	22	34	67	113	174
% botanical	67.9	66.7	65.7	65.6	65.2
Natural products demand	265	345	525	770	1105

Source: Freedonia Group, 1998b

Multifunctional products such as those containing botanical extracts, antioxidants and sun protectants typify modern therapeutic cosmetics.. Sun care, in particular is forecast to grow most rapidly in the skincare and makeup sectors of the market, with a compound annual growth rate of 2.8% between 1998 and 2002 (Bucalo and Rummell, 1999). Previous studies have indicated that inclusion of certain botanical extracts, as well as lending their own desirable biological activity, can synergistically enhance the sun protection factor (SPF) of synthetic sunscreening products, and so their inclusion can be desirable for two separate effects (Ramos *et al*., 1996; Wilkinson and Brown 1999).

Novel plant oils also represent an underdeveloped source of new beneficial cosmeceutical ingredients. For example, meadowfoam seed oil (*Limnanthes alba*) is currently being promoted for a range of applications, including lubricating oils, synthetic rubbers and polymers, but its potential applications in personal care products are probably most attractive. The oil has the highest C_{20}-C_{22} fatty acid content of any commercially available seed oil, giving it high stability and resistance to oxidation and rancidity. When added to other oils, it can also increase their stability, and increases heat resistance. Selling at less than $7 per pound, the oil is competitive with other speciality vegetable oils, such as Jojoba, and has applications as an emollient in lipsticks, makeup, hand lotions and skin creams, as well as in shampoos and conditioners (Harvilicz, 2000). Other oils suitable for cosmeceutical development include avocado (*Persea americana*), almond (*Amygdalus communis*) and Jojoba (*Simmondsia chinensis*).

4.4.2 Fragrance/flavour compounds

Essential oils have the potential for both the flavour/fragrance markets, and also as active constituents of commercial products – such as the antimicrobial activity of Tea Tree (*Melaleuca alternifolia*), which is now found in a wide range of cosmetic and non-licenced products. Australian Kesom oil (*Persicaria odoratum,* syn. *Polygonum odoratum*) is being promoted as a novel essential oil, with an unusually high content of aliphatic aldehydes. As synthetic aliphatic aldehydes are used in the production of flavour and fragrance ingredients, this oil may be a potential source of natural versions of these compounds, which are currently highly expensive, and have limited availability (Hunter, 1996).

4.5 Conclusions and general discussions

Driving the demand for better health is increased prevalance of disease and, at least in the case of the US, evidence of diminished quality of life associated with those diseases. For example, Cutler and Richardson (1999) identified nine conditions that are consistently reported as affecting severely the health status of an individual in that country: amputation, arthritis, blindness, other vision problems, cardiovascular disease, diabetes, hearing problems, orthopedic problems, and paralysis. Significant increases were reported in the prevalence of arthritis, cancer, cardiovascular disease and diabetes over the decade ended 1990. Cancer, cardiovascular disease and diabetes are shown to have the most deleterious effect on the quality of life, hence the level of interest of any measures that might alleviate the prevalance.

4.5.1 Pharmaceutical products

There is a growing demand from consumers for natural-based medicines, and there is considerable evidence that medicines of this type will account for an increasingly large proportion of the markets currently dominated by synthetic drugs. It has been predicted that market penetration by pharmaceutical versions of herbal medicines, which are produced to high standards (for example those complying with GMP standards, or backed by clinical efficacy studies) could be as high as 30% of the market (Wilkinson, 1999b, 2000a).

Cardiovascular drug market

The global market for cardiovascular drugs stood at approximately $30 billion in 1996. Existing plant-derived drugs for this therapeutic category include digitoxin and digoxin (from *Digitalis* spp.), ouabain (from *Strophanthus fratus*), quinidine (from C*inchona* spp.) and reserpine (from *Rauwolfia serpentina*).

The dominant herbal products used to treat cardiovascular problems are those based on hawthorn (*Crataegus* spp.). Other potential herbs, which have some reputation for this indication, include *Panax pseudo-ginseng*, Horehound (*Marrubium vulgare*).

Anti-infective drug market

As shown in section 2.2.1, there are numerous plant species, which have received attention as potential antimicrobial agents. Many of these species would be appropriate for cultivation in Australia, and so it may be appropriate to concentrate on those plants, which have joint products. Examples here would be chaparral (*Larrea tridentata*), which also has potential as an anti-cancer treatment (see section 2.2.1) or rosemary (*Rosemarinus officinalis*) which is widely used in the perfumery industry. Alternatively, plants that are already widely available in Australia, such as *Eucalyptus* spp., could be further developed commercially, with antimicrobial products giving these species added value.

Of particular value would be antibiotics proven to be effective against MRSA (Methicillin or Multiple Resistant *Staphylococcus aureus*). Essential oils from some Australasian species (including Tea Tree; *Melaleuca alternifolia*) have been shown to have such activity (Carson *et al*., 1995; Harkenthal *et al*., 1999). If this was properly validated and exploited, these species should become more valuable and present potential for overcoming the existing over-supply problem. Interestingly, manuka honey has also been shown to have activity against *Helicobacter pylori* (al Somal *et al*., 1994), which is the probable cause of dyspepsia, is associated with gastritis and implicated in gastric and duodenal ulcers and gastric cancer.

CNS drug market

The market for CNS drugs can be divided between drugs affecting memory function and those used as anxiolytics.

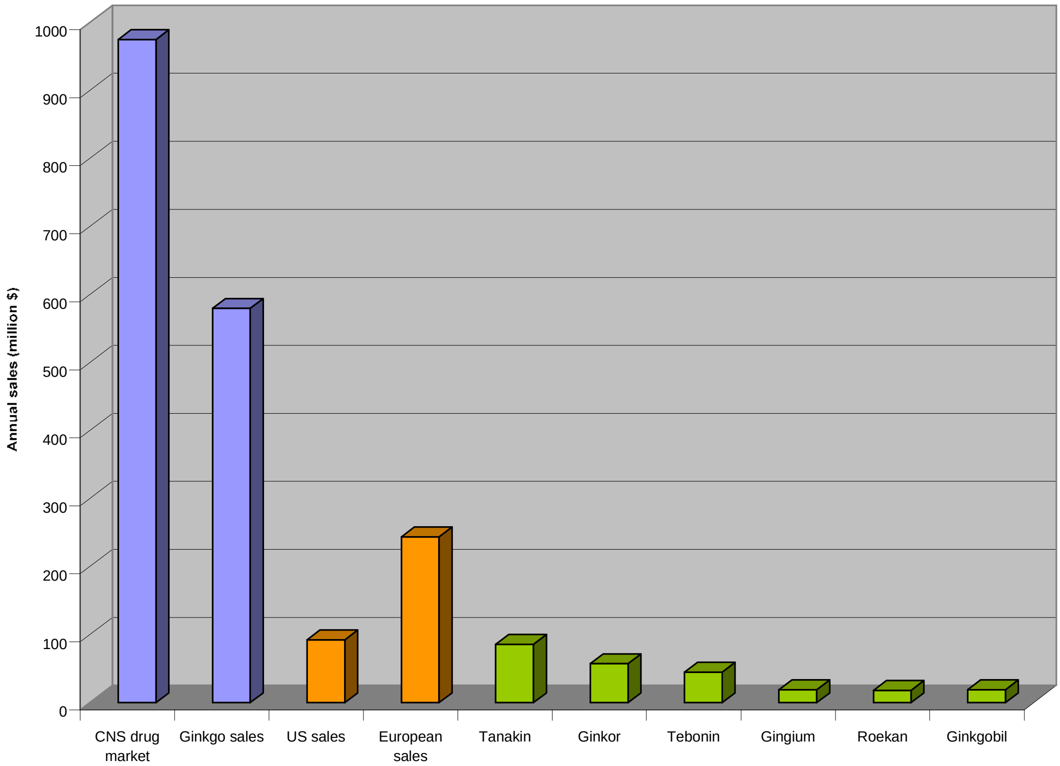
The drug market for treatment of degenerative diseases such as Alzheimer's Disease stood at approximately $1 billion in 1997 and, although the market for such drugs has been predicted to decline slowly (Evers, 1998), memory function has been cited as a growth market for functional products in the US. This may well indicate a progressive movement away from conventional pharmaceuticals to a more self-medication/preventative approach to treatment of memory dysfunction in the future. Therefore, demand for plants with memory-boosting activity is likely to account for increasing amounts of the $1 billion market for memory function drugs.

Plant-derived drugs including galanthamine (from Galanthus spp.), levodopa (from Mucuna spp.) and physostigmine (from Physostigma spp.) may see a resurgence in popularity in the near future. Herbal products based on plants such as Ginkgo and Ginseng are also likely to grow rapidly to meet this increasing demand. Ginkgo products such as Tanakin and Ginkor (Beaufour) and Tebonin (Schwabe) already dominate the European market for herbal medicines, with annual sales in excess of $180 million in 1998.

Sage (*Salvia* spp.) is another candidate for development as a treatment for Alzheimer's Disease, as a result of its inhibitory activity against the enzyme acetylcholinesterase. This enzyme is critical in regulating the levels of the neurotransmitter, acetylcholine, in the brain. As low levels of this compound in the brain have been associated with Alzheimer's Disease (e.g. Wenk *et al*., 2000), sage preparations which inhibit acetylcholinesterase, which is responsible for breaking the neurotransmitter down, are currently being investigated (Wilkinson, 2000e and 2000i). As Alzheimer's Disease is estimated to affect 2% of the Western population aged over 55, sales of pharmaceutical treatments for the condition have been forecast to rise from $362 million in 1998 to $2.0-2.5 billion in 2005 (Datamonitor, 1998).

The anxiolytic market has been estimated to stand at $2.5 - 4 billion (Pharmaprojects, 1994; Barclays de Zoete Webb, 1992 – both cited in Steiner 1996), divided between serotonergic compounds and drugs active at the $GABA_A$ receptor. Plant-derived drugs with tranquillising or sedative actions are likely to continue to be popular, and the demand for herbal products, such as valerian (*Valeriana officinalis),* St John's Wort (*Hypericum perforatum*) hops (*Humulus lupulus*), passionflower (*Passiflora* spp.) and kava (*Piper methysticum*) with these activities is set to continue. The increasing demand for this type of product can be seen in the case of Jarsin, a licenced product based on St John's Wort. Its sales rose from $2.9 million in 1992 to $24.7 million in 1998 (see section 3.1.3). If as much as 30% of the synthetic pharmaceutical market is to be penetrated by high quality "herbal pharmaceuticals" (Wilkinson, 2000), it can be seen that there is still great scope for anxiolytic herbs, which could ultimately have global sales approaching $1 billion.

Chart 4.2: Comparison of global sales of synthetic CNS drugs and herbal products based on *Gingko biloba*.



CNS drug market: synthetic anti-dementia drugs (Evers, 1998)
"Ginkgo sales": combined US and European
US sales (1996-7 mass market, food and drug store sales only; Scimone & Scimone, '99,)
European sales of licensed herbal medicines (1998 sales; Mertens, 2000)

4.5.2 Nutraceutical products
Some of the markets which will be of particular importance include:

Herbal supplements
In 1998, herbal supplements were part of the fastest growing sector of the $US45 billion global OTC market, with annual growth rates of 16%. Similarly, herbal/botanical products took up 29% of the US dietary supplements market in 1999. Although Europe dominates the global market for herbal remedies, with 45% of total sales, the areas of most rapid annual growth (between 50 and 100%) are predicted to come from those countries where the herbal market is relatively poorly developed.

Although the United States is often cited as an example of such an "underdeveloped" market, the situation in Australia is very similar, as it has been stated that 'In Australia, the functional foods market by strict definition is relatively undeveloped by the standards of the US, Japan and Europe…' (James 1999). This suggests there is considerable potential for further growth in the herbal/nutraceutical market in Australia.

Treatments for coughs, colds and respiratory complaints

In 1999, the market for self-medication treatments for coughs, colds and respiratory complaints stood at approximately $US9 billion, growing at 2% annually (see section 3.1.4). The most dominant herbal remedies for this market are those based on *Echinacea* spp (*E. purpurea*, *E. pallida* and *E. angustifolia*), which account for 9% of herbal sales in Europe and 12% in the United States. Total annual sales of *Echinacea* products in the United States alone in 1999 have been put at between $US71 and $US109 million (Aarts, 2000, Brevoort, 2000), but there is still considerable potential for commercial development of plants from this genus. If high-quality herbal products could account for approximately 30% of this market, as has been predicted for pharmaceutical companies (Wilkinson, 2000a), the future potential for herbs for coughs and colds could be as high as $US3 billion.

Other herbs which can be used to combat coughs and colds, or which function as immunomodulators ("Increasing disease resistance" and "boosting the immune system"), and which could also be developed commercially, include garlic (*Allium sativum*), goldenseal (*Hydrastis canadensis*) and the African potato (*Hypoxis hemerocallidea*).

Cardiovascular disease preventatives

Cardiovascular disease is frequently cited as a key health issue, both by consumers and by manufacturers of functional foods. As outlined above, herbs such as hawthorn, horehound and Panax spp. are likely to dominate the herbal treatments for this market. Closely related are herbs to lower cholesterol, such as artichoke and garlic. Lichtwer's Kwai, a licensed product based on garlic, has annual sales in Europe of $20 million in 1998 (see section 3.1.3). Unlicensed garlic products accounted for 10% of European herbal sales in 1997, and 16-18% of sales in the United States between 1996-1999. Considering the emphasis put on cardiovascular disease as a therapeutic target, these values are very likely to increase over the next few years.

Weight control

Grouped with cardiovascular disease in a recent survey, obesity was cited as a key health concern in 70% of the people polled in the United States. Globally, the market for weight control sales has been put at $US64.1 billion in 1997 (Peet 1999). "Diet" or "healthy" foods accounted for the large share of this (91%) with 2% being OTC dietary aids. Due to the size of the market, this small sector of the market is still worth over $1 billion. Herbs such as *Garcinia* spp. have some potential for development as weight-loss aids, through their potential to alter lipid metabolism. Other herbs, such as *Ephedra* have stimulatory activity on the CNS, which may aid weight loss, whilst alga of the genus *Spirulina* are also promoted as weight loss aids, through either actions on the appetite centre of the brain or on blood sugar levels. With all these products, more research is needed to prove both their efficacy and safety, but if developed, their potential market could easily run to hundreds of millions of dollars.

Antioxidants

The future potential for antioxidants is vast, in the fields of pharmaceutical, nutraceutical and industrial products. Plants with considerable antioxidant potential, which would be suitable as crop species in Australia include Tea (*Camellia sinensis*), tomato (*Lycopersicon esculentum*, as extracts, or a source of lycopene and related compounds) and Vines (*Vitis vinifera*, as, for example grapeseed extracts, or a source of antioxidants such as resveratrol).

Anticancer compounds

Cancer is another condition often cited as a cause for future concern, which is likely to affect increasing numbers of people as the world's ageing population grows. Compounds from *Catharanthus* spp (including vinblastine and vincristine), as well as yew (*Taxus* spp.)-derived chemicals such as Taxol® will continue to be important drugs. With a move towards natural and selfmedications, there is likely to be an increasing shift to products that may have some potential for cancer prevention. Antioxidants again are a key class of compounds in this area, and are likely to see massive growth in the future for their potential ability to reduce the risk of developing cancers. Plants such as the desert shrub chaparral (*Larrea tridentata*) have been proposed as treatments for breast cancer, with the activity possibly coming from the potent antioxidant nordihydroguaiaretic acid (NDGA). Further research would be required on this plant, to confirm its efficacy, and study the potential hepatotoxicity, which may be associated with the plant.

Urino-genital conditions

With an ageing population, conditions such as benign prostatic hyperplasia (BPH) and menopause-related complaints such as osteoporosis are likely to affect increasing numbers of people. Herbs such as saw palmetto (*Serenoa repens*) and pygeum (*Prunus africana*) are effective treatments for BPH, whilst chasteberry (*Vitex agnus-castus*) is used by many women during the menopause. Sales of these herbs are likely to grow to meet increasing demand over the next few years.

It has been observed that ‘drug companies have already capitalised on the ageing trend by introducing drugs that are used by people as they age such as Viagra, which is a temporary relief from impotence.’ (US Business Reporter, 2000). Global sales of Viagra stood at $193 million for the first quarter of 1999 (CNN, 1999). There is therefore also considerable potential for “herbal Viagras”, whether they act simply as aphrodisiacs or have some more physiologically-based activity, such as treatment of erectile dysfunction. There are numerous herbs which are said to have aphrodisiac functions, including damiana (*Turnera diffusa*), yohimbine (*Coryanthe/Pausinystalia yohimbe*, also isolated from *Rauwolfia serpentina*) Gotu kola (*Centella asiatica*) and Muira puama (*Ptychopetalum* spp.).

Many of these herbs have had some scientific investigation for their aphrodisiac/erectile dysfunction activity, but more work would be required if products containing these plants were to achieve significant market shares. Yohimbine, for example, has been shown to have some benefits in treating erectile dysfunction, but not sufficient for the FDA to allow its promotion for treatment of impotence. Emu oil and egg shells are animal products with rumoured potential to supply the aphrodisiac market.

CASE STUDY 3: Taxus for Taxol

Taxol was discovered by a prospecting venture in the 1960s involving the USDA and US National Cancer Institute. The Pacific yew tree (*Taxus brevifolio*) was found to contain in extracts from its bark an active compound that proved effective for arresting the development of human cancer cells, especially ovarian, breast, head, neck and throat cancers.

The discovery, once proven, met with immediate and increasing demand, but there is a supply constraint because the bark is only found in low concentrations on old growth (100 years) yew trees. About 0.5 grams of compound are contained in every 12 kg of bark and a 100-year-old tree yields 3kg of bark and when the bark is removed the tree dies. By 1991 harvest of the yew bark was around 425,000 kg, which would have needed about 100,000 trees (Colorado State 1996). Clearly the position was unsustainable.

Researchers then identified a semi-synthetic solution in the form of the needles of various Taxus species and the US Food and Drug Administration now approves the semi-synthetic Taxol. Bristol Myers Squibb (BMS) has an exclusive license to produce the drug and has supply contracts with several nurseries to provide a renewable supply of the needles (Purdue 1996). The needle source of taxanes, however, is understood to be less stable than that from the bark.

Researchers continue to investigate ways of enhancing the productivity of Taxus through various methods including plant cell cultures and complete synthesis of taxol, but in 25 years of research it has still not been possible to effectively reproduce the compound.

There is considerable controversy about the position of BMS with Taxol, the origin of which was Palcitaxel which was developed by various research institutes, universities and government departments (Pharmaceutical policy 2000). BMS acquired exclusive world-wide rights over the clinical trial data of Taxol, without payment of any royalties to the US government and although it signed a reasonable pricing clause on acquisition of the rights the wholesale price is about 20 times the cost of bulk production. Revenue for BMS is estimated to be about $US1.5 billion/year from sales of Taxol.

Despite the widespread demand for Taxol, the economics of producing *Taxus brevifolio* are constrained severely by the low yield and long maturity and the prospect of new synthetic discoveries. But one option that is meeting with success is production of Taxus for ornamental purposes. The US nursery industry has taken a special interest in various Taxus cultivars and hybrids. Taxus nursery production includes plants for sale to retailers and wholesalers for landscape and gardening purposes. It is understood that this household industry is growing rapidly in value with increased needle clippings and eventually bark harvesting. The joint product or ornamental use value of the Taxus facilitates viability.

5. Discussion of Australian Opportunities

In Brief

Australia has a significant opportunity to meet and nurture the growing demand for new pharmaceutical, nutraceutical and industrial products made from natural materials. The largest and most immediate prospect is for functional foods that can be produced most readily for a number of crops and animal products already produced in Australia. These include oats, soybeans, canola, flaxseed, tomatoes, garlic, broccoli and other cruciferous vegetables, citrus fruits, cranberry, teas, wine and grapes, fish, dairy products (probiotics in particular), omega-3 eggs, medicinal honey, kangaroo meat and beef. There may also be significant development potential in sea plants.

The best prospects for medicinal herbs are garlic, ginkgo/ginseng, echinacea/golden seal, St. John's Wort and Saw palmetto. The labour intensity of producing some of these crops such as garlic poses challenges to local producers and researchers to come up with more strategic solutions that might improve labour productivity and not simply increase yield. Mechanical harvesting, quality control and improved safety and labelling standards are essential for improved competitiveness.

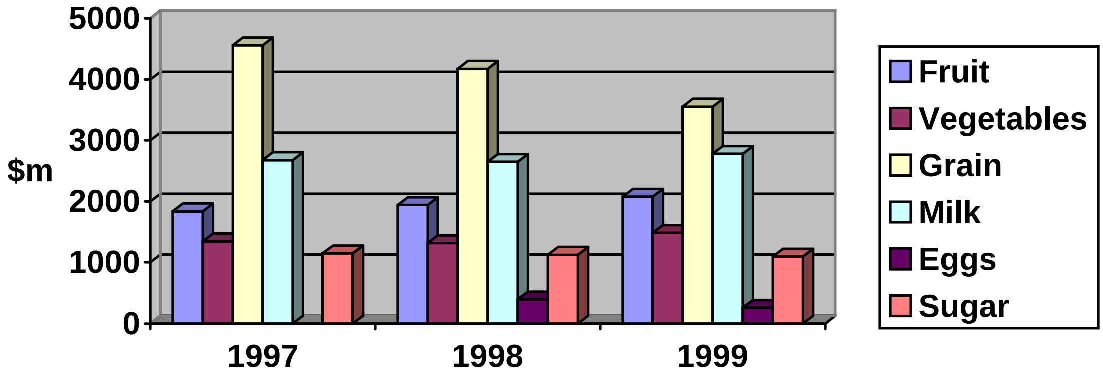
Food manufacturers now in Australia (foreign and locally owned) are capable of developing a competitive supply of functional foods. Local manufacturing limitations, however, constrain the prospects for developing a local market for agricultural materials used in making vitamin supplements, pharmaceuticals and industrials such as bioplastics. Biomass from crop residues and forests for energy have a largely natural advantage, assuming competitiveness against oil in particular. A particular challenge exists in establishing a competitive presence in local manufacturing of vitamins, including those used in feed for animals. Bioplastics also have significant potential because of the continued growth in consumption of polymers and the fast growing demand for biodegradable plastics. In these industries the solutions appear to rest with development of effective incentives and partnerships and alliances with large globally oriented pharmaceutical and chemical companies.

5.1 The Australian market situation for existing consumer goods

In 1997-98, the turnover by Australian manufacturers of medicinal and pharmaceutical products was estimated by ABS to be $4.6 billion, increasing to more than $6 billion over the last financial year (Australian Pharmaceutical Manufacturers Association). Turnover in this industry has grown at a compound rate of more than 15%/year over the last 10 years, making it a leading growth sector in the Australian economy. Prescription and specific pharmacist sales account for about 56% of turnover. Australia is a net importer of medicinal and pharmaceutical products and essential oils and perfume materials, though in each of these product groups exports are growing strongly. A significant part of the inputs into these exports are imported.

There are six major crops and livestock products that supply or have potential to supply the demand for functional foods, new pharmaceutical, nutraceutical and industrial products. It is estimated (refer to Section 1.1) that up to 50% of the food market could eventually take the form of functional foods. This woulkd require the definition to be used broadly to include dietary supplements, sugar and fat substitutes, fibre enriched foods, vegetables, fatless meat, skim milk, low caloried diets and similar products. At the farm level grain is the leading raw material (Chart 5.1) available to meet the growing demand for functional foods. At the manufacturing level, food is clearly the major consumer category in terms of current value. Table 5.1 shows the current trade, production and apparent consumption of the main products involved in functional foods, pharmaceutical and medicinal and nutraceutical products.

Chart 5.1: Farm Sales: Selected Crops & Products used in Functional Foods



Source: Data derived from ABS, Agricultural Industries: Financial Statistics: 1998-99, Cat. 7506

Table 5.1: Production and trade in selected potential functional foods, medicinal & pharmaceutical products: Australia 1997-98 [$m]

Industry	Production	Exports	Imports	Apparent Consumption
Food manufacturing	38,945	16,045	3,460	26,360
Beverages & Tobacco	8,674	1,059	575	8,190
Medicinal & Pharmaceutical	4,594	1,144	2,544	5,994
Essential oils, perfumes etc.	875	291	750	1334

Source: Australian Bureau of Statistics, 'Manufacturing Industry: 1997-98', Catalogue 8221: 'International Merchandise Trade: 1997-98', Catalogue 5422.

If 50% of Australian food consumption eventually became categorised as functional then the apparent local consumption would exceed $13 billion/year.

The Australian vitamin market at the retail level is valued at about $769 million, equivalent to about $425 million at the ex-factory level. These products are contained partly in each of the four sub-categories shown in Table 5.1.

We examined Australian exports of selected manufactured food and pharmaceutical and nutraceutical products in the context of the general food division potentially containing what may be termed functional foods. Cereals and cereal preparations are the major category (Chart 5.2), but the fastest growing exports are medicinal and pharmaceutical products (Chart 5.3).

Chart 5.2: Exports of Selected Processed Functional Food, Medicinal & Pharmaceutical Products: '88 to '98

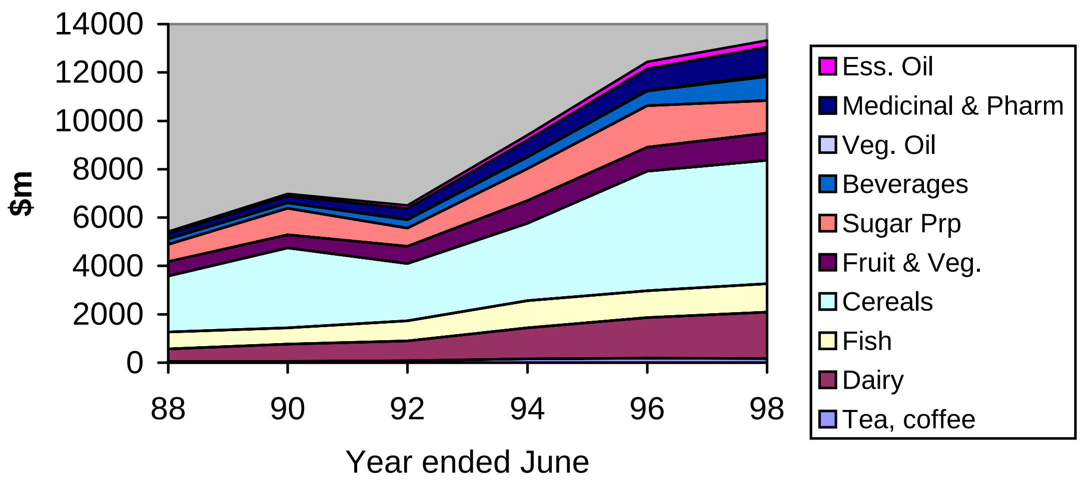
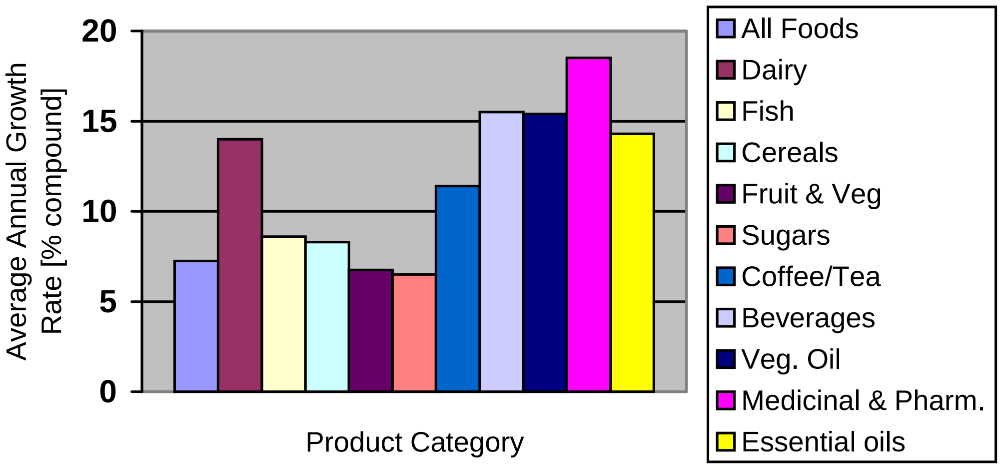


Chart 5.3: Export Growth Rates : Processed Products: 1987-88 to '97-98



We defined a food as functional if it has a beneficial effect on target functions in the body, beyond adequate nutritional effects, in a way that is relevant to health and well-being and/or reduction in disease. An expert US panel on functional foods identified several key plant and animal foods with potential to meet the requirements of the functional food tag (Hasler 1998) (Table 5.2). The main feature of interest about this functional food list is that each and every product can be grown, competitively, now in Australia. A few more can be added including, for instance, canola, Omega-3 diet eggs and kangaroo meat (Constance 2000). As noted earlier, functional foods is where the biggest potential for Australia lies because of the potential size of the market, perhaps accounting for 50% of the total food market.

Because the nutraceutical industry contains a vast number of diverse products it is not within the scope of this report to describe a detailed situational analysis for each product. Instead we provide more aggregated data and make reference to detailed studies done elsewhere. These include for instance, a July 2000 report for RIRDC (Publication 00/51) by Keane International Marketing and a 1999 US FDA report on the dietary supplement industry in that country, as well as numerous reports commissioned by RIRDC on specific products.

Market growth in medicinal herbs and botanicals is likely to continue at its present rate of around 10-20%/year in both Australia and the US; vitamins at 6-7%; minerals at 7-8%; and specialty supplements at 10%. Growth rates reflect typically market size with small segments having higher growth rates than large segments. The best prospects for medicinal herb and botanical growth (Table 3.19) are garlic, ginkgo/ginseng, echinacea/golden seal, St. John's Wort and Saw palmetto.

This priority list is broadly similar to the 'primary list' of Keane International but different in some key products in the inclusion of garlic and ginkgo, which we believe still have scope for inclusion in Australian research. Garlic faces severe competition from imports sourced from China, which has extremely low labour costs, which provide an advantage for a labour intensive enterprise. Research should therefore concentrate on capital and skill intensive activities such as mechanical harvesting, quality control and branding. If all that research can do is increase yields then we would agree with Keane International that there are probably higher priorities.

TABLE 5.2: Agricultural products with functional food potential

Product Category	Species	Role in Disease Prevention
Plants	Oats	Cardiovascular – reduces lipoprotein cholesterol, via ∃-glucan
	Soybean	Cardiovascular via isoflavones and cancer via protease inhibitors
	Flaxseed	Cancer, via ∀-linolenic acid and cardiovascular
	Tomatoes	Cancer, via lycopene.
	Garlic	Cancer, anti-infectives, and cardiovascular
	Broccoli and other cruciferous vegetables (sp. Cabbage, cauliflower and brussels sprouts)	Cancer, via glucosinolates
	Citrus fruits	Cancer, Vitamin C, folate and fibre
	Cranberry	Anti-infective, via fructose and nondialyzable polymeric compounds
	Tea	Cancer, via polyphenolic catchins
	Wine (red in particular) and grapes	Cardiovascular, via flavonoids and phenolic content of red wines
Animals	Fish (sp. Shark cartilage [a])	Cardiovascular and cancer, via Omega-3(n-3) fatty acids
	Fish (2)	Chitin, from carapaces of crabs and prawns as a polymer of acetylated glucosamine.
	Dairy Products	Osteoporosis, via calcium and colon cancer, via microbial probiotics
	Kangaroo meat	Cardiovascular, low fat, high iron
	Beef	Cancer, via conjugated linoleic acid, an anticarcinogenic fatty acid. Also, beef cattle cartilage with potential in treatment of cancer.

Source: Derived from Hasler 1998 (Note a): from our records)

In regard to ginkgo we consider the fact that it is grown competitively in a high labour cost country such as Germany is encouraging for Australia which has similar resource constraints, but generally a competitive edge in adapting to market requirements. Australian has shown it is able to compete against West European food producers in most areas and ginkgo may not, indeed, is unlikely to be an exception. The sheer size of the garlic, ginkgo and ginseng markets in Europe, North America and locally places them in a priority position for further research.

Australia imports about 65% of its requirements for medicinal herbs and botanicals, though the locally produced share of the market is increasing for some products and decreasing for others (eg echinacea and garlic).

In regard to vitamins, Australia imports most of its raw material requirements, some of which are used in exports. While there is significant existing capacity to supply the fruits and vegetables used to manufacture vitamins there is limited local processing of ingredients. Most ingredients are sourced from the US and Western Europe. Vitamins are distributed to the market through conventional food, dietary supplements and fortified or functional foods. According to US data, about 30% of vitamin consumption is accounted for by human supplements, 20 % by fortified foods and 50% by animal feed industries. The three human consumption groups are to some extent imperfect substitutes with each other and to some extent complements. The US FDA believes that '…while consumers can get all the nutrients they require from foods the opposite is not true, they cannot get all the nutrients they require from supplements…' Supplement manufacturers argue (refer to Section 1), however, that it is not possible to get all the vitamins required to prevent diseases and stay healthy in a modern society. The contest between supplement manufacturers, conventional foods and functional or fortified foods is one with significant implications for the Australian food industry because the same manufacturers that supply vitamins to the dietary supplement industry also supply ingredients for fortified /functional foods. Without an effective local vitamin ingredient manufacturing presence there is likely to be continued growth in imports. Economies of scale in manufacturing, however, present a serious entry barrier for local start-up businesses.

The human dietary supplementary product segment shares by value in Australia are lead by Vitamin C [21.5%], Vitamin B [18%], Multi-vitamins [14%], Herbals [13%], Vitamin E [7%] and Minerals [6%]. Major raw material sources for Vitamin A are citrus fruits and leafy green vegetables [sp. Broccoli]. For Vitamin B they are whole grains, fish, red meat [sp liver], chicken; for multi-vitamins/anti-oxidants they include all of the above and cruciferous-broccoli extracts, green tea and bilberry extracts. For Vitamin E the richest sources are polyunsaturated seed oils [canola, safflower, sunflower, cottonseed, corn, cottonseed and soybeans]. Australian bush foods such as yams, wild desert oranges and Arnhem Land plum are shown to have high levels of Vitamin C.

We estimate the total Australian human consumption vitamin market in 2000 will be valued at close to $800m at the retail level. Over 90% of the raw materials for this market will be imported. Australia is the 10th largest importer of vitamins in the world and also imports significant quantities of proteins for use as human and animal dietary supplements. Using US market shares the value of vitamin supplements for animal feed could be as high as $667 million and for fortified foods around $267 million/year.[9] The total value of the vitamin market in Australia is therefore around $1,734 million.

In Australia, in 1998 the human vitamin market in the grocery channel was valued at $92.0m with growth at 12%/annum (Foodweek 1999). The main corporate market shares are held by Fauldings (29%); Roche (18%), Herron (15%), Blackmores (13%), Health Minders (7%) and Bayer (6%). Cenovis is the main brand (35%).

There are four main distribution channels for nutraceuticals:

- Grocery Stores: (15% share)
- Pharmacies (30% share)
- Health food stores (20%)
- Multi-level Marketing (21%)
- Direct mail (9%)
- Direct sales (3%)
- Practitioner sales (2%)

[9] US data (US Food and Drug Administration 1999) indicates animal feed vitamin supplements account for 50% of total vitamin sales in that country. If we assume that the unit value of vitamins for feed is 50% of that for humans at the retail level and the volume of the feed market is 66% higher than that for human consumption then the total value of vitamins for feed in Australia would be $A667 million. With similar reasoning the market for vitamins in fortified food is estimated to be $267 million.

5.2 New plant product possibilities

As part of this study we identified a range of new plant possibilities. Some of these are included in the next chapter on dryland agriculture. But the vast range of plant possibilities for pharmaceuticals, nutraceuticals and industrial products have their origin in plants from tropical and sub-tropical areas and they come in various forms, ranging from trees to shrubs and vines and herbs. These untried plants are described in Annex 4. These are plants that have potential to grow in Australia in various climates, including dryland, and could be examined in more detail. They are untried. They have been identified on the basis of their chemical activity.

Some of these plants have quite exotic possibilities. Paddy melon (*Citrullus colocynthis*), for instance, is a serious summer weed in the wheatbelt, but it contains triterpenoid glycosides and is known to have been used to treat tinea and ringworm. The Neem tree (*Azadirachta indica*), from South and Central America, produces limonoids with anti-inflammatory and anti-malarial properties. However, no product is currently registered in Australia. Devils Claw (*Harpogophytum procumbens*), from the edge of the Kalahari desert, is almost facing extinction because of unprecedented demand in Europe for its properties in treating arthritis and rheumatism, but it is also a potentially dangerous weed.

We also identify a number of potential by-products that could generate additional revenue for existing enterprises. These include nut shell flours (from walnut shell and macadamia shell that could be used as fillers in plastics), lipids from mango kernals (which could be used in the fast growing functional food and cosmeceutical industries), chitin from prawns and lobster carapaces (as a polymer of acetylated glucosamine), beef cattle cartilage (as an anti-cancer treatment) and tung oil (from *Aleurites fordii*).

5.3 The Australian market situation for existing industrial goods

There is significant potential for agricultural materials to be used in production of commodity chemicals and fuels such as ethanol and biodiesel; intermediate specialty chemicals such as ethylene and acetic acid; and bio-based materials such as bioplastics and vegetable based inks. These bio-based products are produced either directly (via physical or chemical processing of biomass materials such as cellulose, starch, oils, protein, lignin etc) or indirectly (via microbial and enzymatic processes). Although petroleum replaced bio-based materials steadily throughout the last century there has been in Europe and North America a shift towards more use of bio-based materials. For example, in 1995 in the US, fermentation ethanol gained a 1% share of the domestic transport fuel market; vegetable oil based inks gained an 8% share of the US domestic ink market; and fatty acids gained an 8% share of the domestic market. According to the US Soy Ink Information Centre soy based inks will capture almost 25% of the US ink market in 2000. In 1996-97 the USDA estimated that 12m tonnes of US corn, equivalent to 5% of US corn production, was used in producing five billion litres of ethanol fuel.

Table 5.3 shows the estimated production and trade in selected industrial products that have potential to use bio-based materials. The present use of bio-based materials in these products in Australia is negligible. Green power (using a range of sustainable raw materials such as solar, wind, timber waste and agricultural waste) at a current 30% price premium has the potential for a 3-4% market share of the electricity market. (Crawford-Smith 1998). There is a range of activity in other industry groups such as plastics, but the share of the overall markets is small. For example, EcoEarth Technologies has developed a range of starch derived plastics to make pots, plastic bags and other containers.

TABLE 5.3: Production and trade in selected industrial products : Australia 1997-98 [$m]

Industry	Production	Exports	Imports	Apparent Cons.
Electricity power generation		0	0	
Petroleum, coal & diesel	8,451	13,433	4362	
Organic Chemical	992	137	2135	2,990
Inorganic Chemicals	1,438	327	678	1,789
Synthetic resin	1,937			
Plastics in primary form		277	1005	
Plastics in non-primary form		161	808	
Paint	1,633			
Pesticide	1,146			
Vitamin supplements for animal feeds [a]	0		667	667
Diesel Fuel				
Petroleum				
Ink	220		750	

Source: Australian Bureau of Statistics, 'Manufacturing Industry: 1997-98', Catalogue 8221; 'International Merchandise Trade: 1997-98', Catalogue 5422.
Note a) Study estimate –refer to previous page footnote

Ultimately, it is the relative cost of producing petroleum and ethanol and methanol that determines the profitability of converting land to a biomass plantation for ethanol. Mardon estimates that wheat straw and wheat grain are relatively efficient sources of material for producing methanol and ethanol, but none of the source materials are viable at current oil prices. [Refer to Table 6.5 in Chapter 6].

Manildra Energy Australia is building a commercial scale fuel ethanol plant at Nowra (NSW). Using wheat as a feedstock, the plant will have the capacity to produce 700 million litres of blended ethanol fuel. The viability of producing ethanol is extremely sensitive to the source of material and plant size. In the US, a case study of a large scale (1.5 billion litres/year) ethanol processing plant using corn residue as the raw material found the unsubsidised cost of production ($US0.58/gallon, equivalent to about $A0.23/litre) to be cost competitive with petrol. With current ethanol processing technology the most viable options are based on annual crop residues, the harvesting of which may, but not always, present new problems and costs for sustaining soil fertility and structure.

In Australia, in August 2000, even with oil at $US32.50/barrel, there remains a significant cost disadvantage of about 10 cents/litre in using ethanol from the lowest cost material (wheat straw in Table 6.5). Ethanol reduces fuel efficiency by about 2% when used in the standard 10% blending proportion with unleaded petrol (National Research Council). The cost disadvantage for ethanol could be reduced through improved processing efficiency (larger processing plant); higher oil prices; or favourable tax treatment. The cost disadvantage would widen with lower oil prices and/or an appreciating Australian dollar.

Bachmann *et al.* have recently presented a very optimistic outlook for the use of agricultural materials in polymers and basic chemicals with projections that biopolymers could account for 50% of this market within 10 years. New fermentation technologies underpin the outlook.

5.4 The natural resource base

5.4.1 Large land mass for mainly extensive agriculture

The total land area of Australia is 7.69 million km^2, more than 40% of which is classified as unsuitable for agricultural or grazing activities other than nomadic hunting activities. The Australian agricultural land resource comprises 36.5 million hectares (365,000 km^2 or 5% of the total) which is allocated typically to about 17.1m hectares of pasture and 19.4m hectares of cropland (Table 5.4). It is from about 10% of the total Australian landmass that over 95% of the value of agriculture and forestry products are generated.

5.4.2 Relatively small land area but high value for intensive agriculture

The horticultural industries along with grain (section 5.1) have much of the potential to supply the needs of a growing demand for pharmaceutical, nutraceutical and new industrial products. There is about 330,000 hectares of land used for horticulture in Australia, 39% of which is used for fruit; 36% for vegetables; 22% for viticulture; and 3% for nurseries. Although representing less than 2% of the total cropland resource, the gross value of horticultural production now exceeds $4.5 billion, equivalent to 25% of the gross value of all crop production. There appears to be scope to expand horticultural production providing markets can be accessed, water supplies secured, and producers can meet the demands of a more discerning consumer seeking fresh, safe, convenient and reliable supplies.

5.4.3 Forests, mainly for timber products

Australia's forest resource is dominated by natural forests including eucalypts, mixed with a variety of acacia species, cyprus pine (*Callitris* spp.) and paperbark (*Melaleuca* spp.). In total there are eight broad native forest communities in Australia, comprising eucalypt, acacia, melaleuca, rainforest, casuarina, mangrove, callitris and others.

Table 5.4: The Australian land resource: by state: by land use ['000 ha]

	Land for Grazing & Cropping	Total Pasture	Planted or Improved Pasture	Crop Use	Forestry	Total Land Resource
NSW	61,009	10,810	3,687	4,757	21,057	80,072
Victoria	12,768	5,237	3,936	2,445	7,501	22,777
Queensland	149,748	22,232	2,543	2,495	49,226	173,031
South Australia	56,901	4,663	2,008	3,219	5,602	98,409
Western Australia	114,521	12,709	4,272	6,419	34,930	252,752
Tasmania	1,949	928	612	75	3,038	6,796
Northern Territory	68,276	16,899	19	4	35,389	134,802
A.C.T	50	21	13	0	135	235
TOTAL	465,221	73,500	17,090	19,415	156,877	768,874

*Source: **1**. Foran, B. and Mardon, C. (1999), 'Beyond 2025: Transition to a Biomass-Alcohol Economy Using Ethanol and Methanol,' CSIRO Wildlife and Ecology. **2.** Bureau of Rural Science, 'National Forest Inventory: Australia'*

Plantation forests comprise mainly radiata pine and eucalyptus. They represent less than 1% of Australia's forest area but account for more than 50% of the wood used by processors (ABARE 1999). Over 90% of the plantation area is covered by softwood but the growth in hardwood plantations (18%/year) is double that of softwood. The total value of forest products produced by Australia's forest industries is about $6 billion (1996-97), 65% of which is derived from plantation wood. Australia is a net importer of forest products ($2.7 billion of imports and $1.2 billion of exports in 1997-98).

5.4.4 Forests, may have significant non-timber product potential

Honey, beeswax, essential oils, tea tree oil, mushrooms and barks are Australia's most important non-wood forest products, but the value of output represents a relatively small proportion of the value of wood from forests. A recent report for the province of British Columbia in Canada (ABARE 1999) estimates that non-timber forest products have the potential to account for more than one third of total forest revenues in that country (Wills and Lipsey 1999). Many of the non-timber forest products identified for British Colombia are grown or could be grown in Australia as part of an integrated forest enterprise. These products include:

- wild food mushrooms
- nutraceutical and medicinal mushrooms (mycromedicinals) and fungi
- nutraceuticals and pharmaceuticals from plants, bark, lichens, insects, soil organisms and wood waste
- biocides (non-toxic insecticides) from the same sources
- anti-phytovirals (medicines for plants)
- floral greenery
- eco-tourism

Like British Columbia the potential to grow these and other products within Australian forests appears to be significant and unexploited. There is some significant activity with honey in particular. Using the British Columbian projection, however, of one third of forest revenue coming from non-timber products then the value in Australia would exceed $2 billion. Even one half of this level would make a major industry.

5.4.5 Vast sea resource, but not that many wild fish

There is also a vast sea resource in Australia, featuring one of the longest coastlines, 40,000km, of any country in the world and, with 10,000 km^2, the third largest fishing zone in the world. Despite the size of this sea resource, the Australia fish catch is relatively low and ranked about 54^{th} in the world. Low levels of sea nutrients explain the gap. A detailed examination of the sea resource is outside the scope of this project, other than to note that certain fish products such as shark cartilage, fish oil, sea minerals and sea vegetables have significant potential to be developed into higher valued nutraceutical products. The principal components in fish oil are omega-3-fatty acids, eicosapentanoic acid and docosahexanoic acid. Oil fish such as salmon, mackeral and sardines contain relatively high levels of omega-3. Consumption of omega-3- fatty acids is shown to be associated with improved cardiovascular health and reduced incidence of Alzheimer disease (Colgan 1995 p148).

In addition to fish, the large seaweed resource (brown and red in particular) also contains omega-3-acids (RIRDC Project DAV-87A).

A list of sea products and their purported medicinal benefits is shown below (Table 5.5). Australia, through Betatene Ltd (a subsidiary of Henkel Corporation), produces over 80% of the world's natural ∃-carotene (Curtain 2000). This is extracted from open brine pond cultures of alga near Whyalla (Sth Australia) and Esperance (Western Australia).

CASE STUDY 4:
ARE WE EXPLOITING THE FULL POTENTIAL OF NON-TIMBER PRODUCTS FROM FORESTS?

Commercialisation of Nutraceutical and Pharmaceutical Products Derived from Nature

Forbes Medi-Tech Inc. is a Vancouver based diversified health science company focussed on research, development and commercialisation of innovative nutraceutical and pharmaceutical products derived from nature. The Company effort is focussed mostly on the cholesterol lowering; pharmaceutical steroids; and cardiovascular markets. It is extracting plant sterols from forestry pulping by-products that are then used to develop cholesterol lowering agents to be used both as functional food ingredients and pharmaceutical therapeutics for the cholesterol lowering markets. The Company has also developed fermentation technology that converts plant sterols into pharmaceutical fine chemicals, essential in the production of various pharmaceutical steroids such as contraceptives and anti-inflammatories.

Investment activity by the Company includes manufacturing initiatives and accumulation of raw material inventory to support the commercialisation of *Phytrol,* a cholesterol-lowering functional food ingredient, and Androstenedione (AD) and Androstadienedione (ADD), which are fine chemical intermediates used to produce various steroid based products.

Forbes Medi-Tech announced recently the results of pre-clinical trials of its novel cardiovascular pharmaceutical compound FM-VP4 which was found to reduce cholesterol levels by 75 per cent, decrease blood fat (tryglyceride) levels by 44 per cent and reduce atherosclerotic lesions by 75 per cent in apolipoprotein E-deficient mice. The Company anticipates completing pre-clinical trials of FM-VP4 by the end of calendar 2000 and applying to the US FDA for approval to proceed to Phase 1 human studies by early 2001. The Company is currently carrying out Phase ll clinical trials of CardioRex™, a cholesterol lowering pharmaceutical product and plans to complete these trials by the end of calendar 2000.

Forbes Medi-Tech was listed on the NASDAQ market in March 2000 with a capital raising of $US27m and reached a price of $11.00/share, before falling to $5.88 in mid July. The Company is seen as having significant potential but has been caught in the general worldwide volatility of high risk internet and biotechnogy stocks. The movements in the stock price highlight the risk and sensitivity of the biotechnology market.

The Company has strategic alliances and licensing agreements with Novartis Consumer Health, a subsidiary of the major Swiss parent pharmaceutical company Novartis AG with turnover in excess of $US101 billion/year. It also has agreements with Cargill, a major international food company with sales of $US50 billion/year and Quaker Oats.

The use and application of forestry by-products for higher value health purposes would appear to have the potential to add considerable value to forest industries. The extent to which high valued by-products exist in Australian forests is a matter for further research and beyond the scope of this study.

Source: Forbes Medi-tech, various news releases, Bioscience Securities

Table 5.5: Sea products and possible health benefits

Product	Possible Health Benefit
Shark cartilage	Calcium supplement & inhibits blood flow to tumours
Shark liver oil	Anti-cancer, anti-wrinkles cosmeceutical
Squalene	Shark liver oil concentrate, for reducing cholesterol and fatigue, improving vision & blood circulation
Spirulina (blue green algae)	Amino acid, for muscle building
DHA	Fish oil, used for heart disease-softens arteries
Beta carotene	Converted to Vitamin A by liver, helps vision
Glucosamine chondroitan (from shelfish)	Strengthens bones
Salmon oil	High in Omega 3
Sea cucumber	Treats arthritis
Cod liver oil	Rich in Vitamins A and D
Seaweed beverage	Magnesium nutritional supplement
Other sea vegetables (arame, bladderwrack, dulse, hijiki, kelp, kombu, nori, sea palm, wakame)	Carotenes, iodine, Vitamin B12

Source: Kopple, D. – http://www.contentmail.com *Sep. 25 2000*

5.4.6 Questions raised about sustainability of the land resource

A recent report by CSIRO (Foran and Mardon 1999) discusses the sustainability of present agricultural and grazing practices. The report suggests '…10m-40m hectares of more intensively used land is expected to have declining capacity because of dryland salinity, soil acidification, nutrient and structural depletion and fragmentation of biodiversity…' This represents up to 10% of the agricultural and grazing resource. A summary of the land and water biodiversity resource damage, according to Foran and Mardon, is shown in Table 5.6.

Foran and Mardon propose the conversion of between 12 and 31 million hectares of vulnerable higher rainfall pasture and croplands to managed perennial trees and shrubs. They believe this would correct simultaneously the problems of salinity and soil acidification and general problems of depletion. In addition, it is seen to provide the biomass materials for ethanol and methanol production and reduced carbon dioxide emissions. Bioenergy Australia, a group of 34 Australian government and private sector energy and service companies, promotes the development of biomass energy in Australia using a range of materials including wood and wood wastes, crop residues and purpose grown energy crops. The proposals by Foran and Mardon would seem to fit within the approach of Bioenergy Australia.

The proposals by Foran and Mardon, if implemented, are projected by them, subject to certain assumptions, to generate employment in rural Australia (160,000 direct jobs), reduce carbon dioxide emissions (by more than 300m tonnes/year) and provide the material for ethanol, methanol and power generation.

Table 5.6: The Australian land, water & biodiversity resource: state of sustainability: by resource

a.) The Land Resource	Soil acidification		Dryland salinity	Soil fertility & soil loss	
Area currently affected	24m ha		2.5m ha	3m ha	
Area affected in future 25 years	43m ha		15m ha	10m ha	
b.) The River Resource	33% extremely poor			40% with clear signs of degradation	
c.) The Vegetation Resource	Forests	Woodland	Open woodland	Shrub-land	Grassland
Area in 1788 as % of total	9%	21%	21%	14%	7%
Area in 1993 as % of total	5%	14%	14%	17%	16%
Remaining original vegetation	Less than 10% in many areas				
d.) Biodiversity Resource	Mammals	Birds	Reptiles	Amphibians	Freshwater fish
Declining trend	23%	9%	7%	16%	
Endangered species	33%	32%	13%	12%	10%
Vulnerable species	16%	50%	41%	2%	8%

Source: Foran and Mardon, 1999

There would be significant and widespread ecological, economic and sociological effects from the Foran and Mardon proposals, which are not without their own specific risks including assumed shadow prices for oil. In addition, more fundamental questions about the use of trees to lower the water table have been raised by Jones (2000) who suggests a balance of native grasses, trees and shrubs would provide a more effective understory than trees and shrubs alone. The proposals by Foran and Mardon do line up with the recommendations prepared by the US National Research Council for a major diversion of US land resources (14m hectares) into bio-based materials. There is one major difference between the Australian proposal and that of the National Research Council. The NRC sees the materials as coming mainly from annual crop residues whereas Foran and Mardon view perennial plants as a more favourable source of material because of environmental effects.

5.5 Biotechnology industry in Australia

The percentage of genetically modified crops grown in Australia (less than 1% of the land area) is relatively low compared to the USA (72%), Argentia (17%) and Canada (10%) (Bureau of Rural Science 2000). BRS estimates there were about 40 million hectares of genetically modified crops grown in 1999. Herbicide resistant soybeans and canola and insect resistant cotton and maize make up a large proportion of these plantings. Cotton and canola are the most common transgenic crops in Australia.

There are complex issues involved in the development and management of transgenic crops and these are not part of this study. For the purposes of this study, however, we view the benefits, subject to appropriate safeguards, as having significant potential to transform agriculture and position it with a capability to supply the growing opportunities for new pharmaecutcial, nutraceutical and industrial crops. The potential benefits include:

- Reduced use of herbicides and insecticides.
- Transgenic crops may be 100 times more effective in building up anti-cancer defences (Enriquez and Goldberg 2000).
- New uses for old crops, e.g. conversion of sugar into polyester.
- Improved nutrient crops, e.g. high vitamin A rice and high lysine maize.
- Production of biopolymers (refer to Chemical section below).

Bioengineered medicines are expected to grow at 13% or more/year (Freedonia Group 1999). Retention and development of Australia's capacity in transgenic crop production is critical to creating a capacity to exploit the growing possibilities for new pharmaceutical, nutraceutical and industrial products.

It is the market that will make the final judgements about transgenic, traditional and organic crops and animals. Traditional crops and animals will clearly continue to play a major role in agriculture and one of the key challenges will be in enabling these competing production systems to co-exist with each other in a sustainable way.

A recent survey of the biotechnology industry estimates there are 151 dedicated biotechnology enterprises and 150 other companies with significant commitments to biotechnology in Australia (Fayle, D., Hopper, K. and Dawes, J 2000). About 43% of the dedicated biotechnology companies are focussed on health with significant activity in agricultural materials and food. This study identifies food biotechnology and complementary medicine as areas of particular strength in dedicated Australian biotechnology enterprises. Australian enterprises are, however, much smaller than their US counterparts (revenue of $US5.5m/year compared to $US14.5m in the US) and they allocate a relatively small proportion of revenue to R&D. (Table 5.7).

Table 5.7: Biotechnology company features: Australia and selected countries: 1998-99

Item	Canada [1998]	Australia [1999]	USA [1998]	Europe [1999]
Average Revenue ($USm)	3.0	5.5	14.5	3.7
Average R&D Expenditure ($Usm)	1.5	1.3	7.7	2.3
R&D Expenditure/Sales %	50	24	53	62

Source: Fayle et al. 2000

Although venture capital raisings have increased substantially over the past decade [10] funding for innovative ideas and scientific breakthroughs remains a difficult task in Australia.

During 1998-99 75 companies received venture capital funding, two of which were in pharmaceutical, two in biotechnology and one in agriculture. Venture capital raisings for pharmaceutical, biotechnology and agriculture are estimated to have been around $25m, equivalent to about 10% of venture capital raised for new investment.

The Australian venture capital industry has, in the past, been recognised more for its failures than success. For example, Biota Holdings' anti-flu drug 'Relenza' failed to find local venture capital support for a product that has major sales potential of $100m/year out of which Biota receives a 7-10% royalty from Glaxo Wellcome who ultimately came to its rescue[11]. A decade ago, the Department of Biotechnology at the University of NSW demonstrated a lysine processing operation was feasible, viable and an opportunity for a major market player in Australia. Funding could not be mobilised and Australia now imports about 7,000 mt at a cost of around $50m/year. Meanwhile, the world lysine market has expanded to about $1 billion/year (National Research Council p56). There is a long list of rejections for projects that have good science and technical backgrounds but limited access to local capital which itself is a scarce commodity.

[10] The 1999 Yearbook of the Australian Venture Capital Association indicated that new venture capital investments have increased from $90 million in 1993 to $343 million in 1999 and the number of venture capital funds from 4 to 16 over the same period. Venture capital represents about 0.5% of the total value of investment in Australia and is equivalent to less than 4% of foreign investment inflows.

[11] Refer to Australian Financial Review, 'Biotechnology: bitter pill', date unknown, authored by John Davidson.

Venture capital raisings in Australia account for 0.62% of GDP compared to 2.7% in the US and 4.9% in Europe (Australian Financial Review 2000). Australia is a net importer of capital and the economy is small. The cost of capital is higher here, particularly for small companies. A risk averse superannuation sector, which has a significant influence on the supply of capital in the country, is not really interested in investing in small high-risk companies, unless accompanied by significant government subsidies, a totally unsustainable situation whatever the short merit. For instance, Colonial First State presents its ‘Global Health and Biotechnology Fund’ as an entry vehicle to the ‘next global investment revolution’ with an exposure to Australian biotechnology stocks, but a preference for more established international companies (Baker 2000).

The ultimate effect of the presentation of a local venture capital market standing ready to fund innovative biotechnology ideas is that it diverts attention from the only real source of capital which is foreign investment, and the large global pharmaceutical and food companies in particular. There are numerous case studies to support this conclusion, including Biota Holdings and Betatene Ltd, which were both saved from oblivion by foreign multi-national pharmaceutical companies.

The most effective way of helping mobilise resources for investment in Australian biotechnology would be to improve skills and competency in business planning and procedures for creating alliances with larger pharmaceutical companies. These firms ultimately have the capital, global networks and market access to extract most out of a new idea and develop a new product for a global market. Business planning and risk management skills are also imperative for producers entering new markets and engaging in the development of products for the pharmaceutical, nutraceutical and industrial markets.

5.6 Australia’s chemical industry

Australia’s chemical industry has a long history of association with agriculture, developing in the 1960s to manufacture phosphate fertiliser. During the 19th century a rapidly growing domestic market encouraged the development of pharmaceuticals using eucalyptus oil and vegetable products (Acted Consultants 2000). F.H. Faulding and Drug Houses of Australia were established at that time. There was little activity in the pharmaceutical industry until the World War Two and after this point an increase in tariffs on imports provided protection from low cost competition. As with most protected industries an inefficient structure emerged, a reflection of small enterprises with large product ranges and lack of specialisation. When tariffs were reduced in the mid-1970s the whole sector fell away from representing almost 3% of GDP to less than 1.5% in the 1990s.

One of the fastest growing chemical markets is that for polymers, rising globally from virtually zero in the early-1950s to 160m tonnes by 1998 for the global market (Dagley 2000). All plastics are polymers and polyethylene is the key material used in soft drink and milk bottles, shopping and dry-cleaning bags, food takeaway and storage containers. Growth in polymer trade is expected to be at least 5%/year for the next five years, with increasing interest in biodegradable polymer. Cargill Dow Polymers is producing biodegradable polymer from corn. DuPont aims to derive 25% of their revenue from sustainable resources by the year 2010 (Holliday). Australia has a significant deficit in polymer trade with imports of $2.5 billion in 1996 and exports of $628 million. There appear to be significant opportunities for Australia to move into manufacturing of biodegradable polymers, providing it can meet the challenges of economies of scale and access to capital. Again, the solutions seem to rest with one or more of the large foreign-owned pharmaceutical, chemical or food companies. Bachmann *et Al.* note that with some new technologies there is a significant (tenfold, in some cases) reduction in the size of the most efficient plant. This is an important feature for Australia to examine in more detail because the manufacturing sector generally, and chemical industry in particular, has faced a problem in the past in competing with large-scale plants.

One of the more exotic potential advantages of bioplastics is based on reports that link polyvinyl chloride with reproductive disorders. Phthalates, the plasticiser that imparts flexible functionality in plastics, have been shown to cause reproductive disorders in rats and mice. These results have been coupled with evidence of declining fertility in humans and declining sperm counts in particular (Vines 2000). Were more conclusive evidence to emerge about a positive link between phthalates and fertility it would seem to create immense possibilities for bioplastics as a substitute material, irrespective of the cost disadvantage. Exploitation of this possibility would, in turn, depend upon the composition of the plants used in making bioplastics because plants themselves also contain the oestrogen mimics that are thought to be the source of the disorders. Again, this would seem to create further possibilities for transgenics to remove or dilute the oestrogen mimics.

5.7 Comparative advantage for Australia

Australia's resource base for the purpose of supplying raw materials for the new pharmaceutical, nutraceutical and industrial products has the following features, some of which are positive and others which act as constraints:

- An efficient and highly competitive agricultural sector which can compete with negligible government assistance on major world agricultural commodity markets for grain, fruit, vegetables, sugar, timber and dairy.
- A capacity to respond at the production level to changing market, technology and economic conditions. This is a major asset in a changing world. It exists mainly with the larger efficient producers of the commodities listed above, though it remains a problem with smaller producers. It is a bigger problem for producers in the UK and Europe who have occasionally, not always, been insulated from the forces of marketing and technological change. That said, despite the somewhat generous levels of government assistance made available for agriculture in North America and Europe, the large producers in these countries are extremely efficient with ready access to technology and markets.
- Growing export culture.
- Increased competency in auditable quality control production, storage and distribution systems, particularly in horticulture.[12]
- Access to competitive infrastructure in the form of roads, ports, air transport and communication facilities.
- A relatively large supply of land, most of which is not very fertile and most of which has an arid to semi-arid climate, but still there is a significant area with sufficient rainfall and soil to produce major crops and forests.
- Increased evidence and growing awareness that a proportion of the agricultural land resource is threatened by degraded soils, deteriorating water quality and declining biodiversity (Nix 2000; Williams 2000).
- A small and high cost, but generally highly skilled labour force in production, distribution and technology. This should enable high levels of labour productivity to be achieved and it should attract the interest of large foreign owned pharmaceutical, chemical and food manufacturers with capital.
- An active and diverse R&D presence in biotechnology and pharmaceuticals.
- A diverse range of native plants (that accounts for 10% of the world's plant species), some of which have potential for medicinal products, but a large proportion of which have not been fully examined in terms of their chemical composition.
- A manufacturing sector with economies of scale problems that constrain competitiveness in the more intensively processed food sector (Silva 2000) and pharmaceutical sector, although the latter is starting to experience higher export growth. Foreign owned manufacturers are shown to have superior export performance than locally owned firms (Wondu 2000).
- A local venture capital industry that, despite recent growth, remains small, undeveloped and uncommitted to relatively higher risk investments. It is largely irrelevant to the needs of the industry for the next 5-10 years.

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[12] The Tasmanian government, for example, has developed *Tasmanian Quality Vegetables* to facility quality control of vegetables for processing and major retailers, Coles and Woolworths, insist that fresh vegetable suppliers implement externally auditable HACCP (Hazard Analysis Critical Control Point) risk assessment systems.

- The presence of a number of leading multi-national pharmaceutical, chemical and food manufacturing companies that have global distribution networks, access to markets, access to capital, significant R&D budgets and significant skills in managing large enterprises.
- Relatively high access to information and communication technology. This attribute is potentially significant in view of the potential for e-commerce to improve the efficiency of pharmaceutical supply chains (National Office for the Information Economy 2000).

Like every country there is a mix of positive and negative factors in the landscape of comparative advantage. The fundamental feature of Australia which governs many of the relative strengths and weaknesses of industries is size and population. It is a small economy with less than 20m people. This feature diminishes its appeal to many global companies, though recent efforts to position Australia as a stable entry point to Asia are finding a more interested audience. From a strategic perspective this approach could be extended more vigorously to the pharmaceutical and food manufacturing and chemical companies that dominate the supply chains for pharmaceuticals, nutraceuticals and industrial products. Many of the companies are already here and that is a major institutional asset. It would be useful to have them source more of their raw materials from Australia.

A key positive factor is Australia’s competitiveness at the farm production level, although there are no grounds for complacency and productivity and skill levels will need to improve constantly to be able to meet the requirements of these new markets. There are particular challenges in capturing benefits at the farm gate though, like most other industries, there will be large producers with the resources, technology and skills to be able to meet the demands of the more vertically linked pharmaceutical supply chains. Negotiation skills will also be important for producers in holding their competitive positions against the clearly larger processors involved. There may be competition policy issues (eg collusive pricing) that need to be dealt with from time to time and through the ACCC, the institutional vehicle exists.

In regard to encouraging expansion of manufacturing this is an area of potentially greater concern because of the more vertically integrated supply chains. Questions of location for globally oriented companies are typically complex (Shapiro 1982) with macro-economic factors such as taxation, inflation, interest rates and exchange rates being important influences, as well as skill levels and access to raw materials. Companies do manage, from time to time, to extract concessions from governments to locate in particular countries. Although sectoral policies are generally out of fashion in the more liberal trade environment there is always scope to attract the interest of large globally-oriented firms by simply making them more aware of the economic environment, resources and quality of materials available in Australia.

Clearly, any expansion of local manufacturing would have to be built around exports which means the plants have to be of an efficient size, the raw materials of high quality and the labour capable of high productivity. The recent research by Bachmann *et al*., indicating a substantial downward shift in the minimum sized plant for certain chemicals, is a matter that deserves detailed examination in Australia.

CASE STUDY 5
BIODEGRADABLE PLASTICS

There is increasing acceptance of biodegradable plastics, particularly in those regions where conventional petrochemical-based materials have ecological disdavantages. In 1994 bioplastics comprised about 5 per cent of the total polymer, plastics and resin markets in industrial countries (National Research Council 2000). We expect this share of the market has increased but probably not in Australia where local manufacturing is limited.

Novamont is one of the largest manufacturers of biodegradable polymers and distributes a range of corn and potato starch based polymers to Australia through a Melbourne based company, Pastral Fidene. These polymers are completely biodegradable to carbon dioxide, water and carbon based humus. They are designed to replace hydrocarbon-based polymers such as polyethylene, polystyrene and polypropylene. In conjunction with a Canadian company, Publicite Ad Factory, Novamont has recently created a line of almost renewable biodegradable pens and pencils. The 'Flower Pen'', which is made of biodegradable plastic contains a cache of seeds in the cap which germinate as the casing degrades when the pen is discarded and finds its way to the rubbish tip.

Other major bioplastic manufacturers are Bayer, Cargill-Dow Polymers, Biotec, Eastman Chemicals, Monsanto, Union Carbide and DuPont. Dupont is reported to have a long-term objective to derive 25% of its revenue from non-depletable resources by 2010 (Holliday 1999).

The feedstocks for producing biodegradable polymer include corn, wheat and other cereals, potatoes, sugar beet, whey, oilseeds and sugar cane.

Polymer consumption in Australia is growing at about 8%/year (Dagley 2000). Australia is a major importer of polymers and polymer products with about $3.0 billion in 1999 and the growth rate is likely to persist with increasing substitution of polymer for steel in many industrial processes including motor vehicle manufacturing. Biodegradable polymers are relatively expensive and more than double the cost of traditional material which is around $3.00/kg. But a joint venture between Dow Chemicals and Dupont to produce bioploymers is expected to reduce costs substantially, with projections that the cost of biopolymers made from maize will soon become cheaper than those made from oil. Plant based polymers may, within 10 years, become the source of a new and even more highly competitive polyester fibre industry.

For the Sydney Olympics, bioplastic waste collection bags made from imported materials were used for collecting compostable food scraps and bioplastic disposable cutlery wasused, with the waste including the cutlery and bags being composted at nearby Homebush. These products are made from Matter-Bi polymers, produced and distributed by Novamont and Plastral Fidene. They are designed to biodegrade in about 30-40 days.

Australia has some research activity in polymers at the CRC for Polymers at Monash University in Melbourne and a strategic alliance between DuPont and CSIRO Molecular Science. The CRC for International Food Manufacture and Packaging Science also plans to establish a starch-based biodegradable packaging facility. Collaborative and multi-disciplinary research is recognized as the most effective way of accelerating discovery, development and commercialisation of new technologies in the industry.

6. Trees and shrubs for the Australian wheatbelt

In Brief

Perennial woody plants are viewed as one of the solutions to the problems of salinity and a rising water table. In the context of this study, these plants offer also the prospect of revenue from the supply of raw materials for industrial and medicinal products. Perennial plants tend to be the source material of a large proportion of natural based medicinal and industrial products. This section points to three groups of plants with potential for the Australian wheatbelt: those that already grow somewhere in dryland agro- forestry situations with medicinal products as a by-product; those with potential to be grown for medicinal products; and those with potential for industrial products. Only those plants originating from drier climates are considered.

Perennial plants with prospects for further investigation and commercialisation include Santalum spicatum (Western Australian sandalwood) for bactericides; and a group of nine eucalyptus trees with bioactive metabolites in their leaves.

Industrial product potential exists in the form of energy from eucalypt plantations. Processing technologies are improving the competitiveness of bio-fuels such as ethanol so that at the current high price levels they may become competitive with oil. The cost of raw material in bio-based fuels is a key factor in competitiveness and at present wood is a less competitive material than many others, including, for example, wheat straw.

Wattles also have potential to supply the material for various chemical products such as emulsifiers and adhesives. The very adaptable and versatile Neem tree, a source material for fuels, lubricants, insecticides and medicinal products, is also identified as a species for further research into its adaptability to Australian dryland climates.

This section also identifies a product transformation process for the growing supplies of terpenoid 1, 8-cineole and which could be evaluated further with the aim of developing new cosmeceutical products.

The plant and product development ideas presented here are relatively new and therefore carry the normal high risk of failure associated with new ideas and potentially high returns. Moreover, it is important to recognise that nearly all plants grow better with higher rainfall, warmer temperature and fertile soils. The plants identified here are unlikely to be an exception. Genetic modification of plants to improve their adaptability to saline and dry climates may open the way for a greater range of woody perennials that would grow in dryland regions.

The wheatbelt is one of Australia’s most valuable agricultural assets, the source of some 30 million tonnes of grain in normal seasonal conditions, accounting for more than 60% of gross farm income. The wheat industry is a leader in the key economic performance indicator, growth in productivity, which averaged 4.6%/year from 1977-78 to 1993-94 compared to 2.7% for all Australian agriculture (Knopke and Mullen 1995). The regions in which the Australian wheatbelt is located account for almost 80% of the total land under crop in Australia and almost 50% of the planted pasture.

The wheatbelt region of Australia is an area of particular interest in the context of its large area, value in extensive crop production and growing use of perennial woody plants for the purpose of lowering the water table and alleviating salinity and soil degradation problems. The Australian wheatbelt resource, which typically has about 15 million hectares under crop each year, is shown on a regional level in Table 6.1. Products from woody plants grown to address salinity problems, can generate cash and revenue from these woody plants, thus providing an incentive for further investment.

Table 6.1: The Australian wheatbelt regional resource: state of sustainability: by resource

Statistical Division	Total Land ['000 ha]	Farm Land ['000 ha]	Total Pasture ['000 ha]	Planted Pasture ['000 ha]	Total Crop ['000 ha]	Dryland salinity rating
Northern NSW	9,810	7,318	1,693	602	1,190	2
North Western NSW	19,950	16,627	2,271	428	1,036	3
Central West-NSW	6,304	4,780	1,342	800	848	2
Victorian Wimmera	3,058	2,292	680	537	806	3
Victorian Mallee	4,082	2,576	457	318	1,035	3
QLD Darling Downs	9,008	7,964	1,080	301	1,151	2
QLD Wide Bay-Burnet	5,228	3,864	841	154	147	4
Sth Aust. Yorke & Lower Nth	1,852	1,699	328	181	785	2
Sth Aust Murray Lands	4,779	3,372	651	442	654	2
Sth Aust.Eyre	7,235	4,522	683	289	1,083	2
W.A. Lower Gt. Sthn	3,892	2,830	1,160	927	662	4
WA Upper Gt. Sthn	4,442	3,415	1,096	852	1,202	8
WA Midlands	11,042	7,205	1,345	935	2,789	6
WA Sth East	61,176	17,466	1,407	677	483	2
WA Central	76,356	43,337	2,443	392	1,224	4
Total	**228,214**	**129,267**	**17,477**	**7,835**	**15,095**	

Source: Derived from Foran and Mardon, 1999

Given the current state of knowledge about commercial production from woody plants, the most profitable whole farm plans for the wheatbelt are likely to be dominated by grain enterprises with activities to reduce the water table being treated as cost recovery cells, rather than profit centres. This is because of the comparative advantage of the region in grain production. Therefore, it is a question of what is the least-cost solution to reducing the water table. Part of that least-cost solution may include marginal revenue from a perennial plant with, for instance, medicinal or industrial products. The whole farm plan needs to consider all objectives, options and the linkages between the enterprises. Ideally, woody plants may emerge to provide products that are cost competitive with wheat.

This section of the report deals only with trees and shrubs for the wheatbelt and those trees and shrubs that have their primary origin in low rainfall regions. In our judgement, however, there are other plants that may be of interest to wheatbelt researchers wanting to examine the full range of plants available including those from higher rainfall and tropical climates and non-woody plants. There are numerous plants that have adapted to climates and soil conditions that are quite different to their primary source of origin.

These include, for instance, Tea Tree (*Melaleuca alternifolia*), originating from the north coast of NSW and now growing commercially in the wheatbelt at West Wyalong and *Eucalyptus olida*, a native of the highlands of New England (NSW), that produces methyl cinnamate, and which now grows commercially at West Wyalong. There are many others.

Nevertheless, as Hall (1998) states: 'dryland tree resources will remain <u>mainly</u> indigenous'. The full list of non-dryland woody and non-woody plants that we identified and which may still have application in the wheatbelt in terms of their medicinal product potential is shown in Annex 4. We make no judgement about the relative risks associated with investment into further research into these plants.

6.1 Trees and shrubs now producing medicinal products in drier regions

Two on-line databases (SEPASAL and ICRAF) and various written records were examined for trees and shrubs capable of growing in Australia's semi-arid conditions, including salt affected land (though growing in salt affected land was not a matter of priority). The International Centre for Agroforestry (ICRAF) database contains a global listing of trees that are known to have been used in agro-forestry in various countries. The database identifies 97 species that are grown or are known to have been grown for agroforestry purposes in Australia. From this list, 20 species are known to have produced products for medicinal purposes and within this group there are 12 growing in rainfalls of up to 700mm but not less than 300mm per year. (Table 6.2). Two of these species (*Acacia nilotica* and *Calotropis procera*) have potential to become a weed.

Out of the list of 12 agroforestry trees with medicinal product potential (shown in Table 6.2) there were 2 (*Prosopis juliflora* and *Schinus molle*) that have both salt tolerance and recognised capacity to grow in semi-arid regions. (The trees identified here were not screened for salt tolerance, we simply note this as a feature of the trees selected for growing in dryland regions). *P. juliflora* tends to grow in warmer sub-tropical regions, while *S.molle* is more tolerant of frosts. *P. juliflora*, is a further example of a plant growing well outside of its origin in Central and South America.

Agricultural land in Australia is technically capable of producing almost all of the raw materials used in manufacturing nutraceuticals, herbals and new pharmaceuticals. But, as with most agricultural enterprises, favourable climatic and soil conditions enhance yield and potential viability. As discussed, the viability of growing plants with the capability of producing medicinal products on marginal land in Australia is likely to depend on the generation of external benefits for other crops on nearby land including the lowering of the watertable.

6.2 Trees and shrubs with potential to produce medicinal products in drier regions

There are numerous other plants, not now used in agroforestry, which may grow in Australia's drier regions and produce medicinal products. The Royal Botanic Gardens at Kew, UK, manages a major database of useful plants of tropical and sub-tropical drylands (compiled from the Survey of Economic Plants for Arid and Semi-Arid Lands (SEPASAL). Out of 6000 records there are 1210 species with medicinal product uses.

Several trees and shrubs with medicinal, bactericide and other medicinal product potential have been identified, some of which are in the SEPASAL database and others from our own sources, and the ones that look most interesting are described in this section. These are plants that have potential to grow in variously dry regions of Australia, including the wheatbelt, but not necessarily the saline parts of it. The plants listed in Table 6.3 could be examined further in specific research projects. They have been classified according to potential product use.

TABLE 6.2: Selected[a] agroforestry trees with medicinal product potential in Australia				
Species	**Rainfall**	**Altitude**	**Salt Tolerant**	**Medicinal Product**
Acacia nilotica subsp nilotica[b]	200-1270mm	0-1340m	n.a., thrives on alluvial soils, tolerates poor quality	Bark used by Zulus for influenza Wide range of treatments including cancer, ulcer, TB
Barrington racemosa	500	0-300	No	Anti-malaria, cough, asthma
Calotropis procera[b]	300-400	0-1300	Sandy, no evidence of salt tolerance	Asclepin and mudarin
Eucalyptus camaldulensis	250-2500	0-1500	No evidence	Oils for influenza; & Bactericide; & antiseptic
Eucalyptus citreodora	650-1600	0-1600	No evidence	Oils for influenza, bactericides, & antiseptics
Juniperus procera	400-1200	1100-3500	No	Yes
Melia azedarach	350-2000	0-1800	No	Antihelminthic, antimalarial & more
Prosopis juliflora	50-1200	0-1500	Yes, tolerant to high salinity	Syrup and tea for weight deficiency & retarded motor development
Santalum album	450-3000	600-1200	No	Valuable oil.
Schinus molle	300-600	0-2400	Yes, tolerates salinity & alkalinity	Leaf juice for opthalmia Various other uses for bark and leaf.
Sclerocarya birrea ssp. Caffra	200-1370	500-800	No evidence	Bark used for boils, diarrhoea & many other uses
Ziziphus mauritiana	120-2200	0-1500	Yes	Various

a.) Selected according to origin from a dryland climate and evidence of growing in rainfall below 700 mm/annum
b.) High potential to be a weed without strict control.

Source: Extracted from ICRAF

The plants listed in Table 6.3 may be also grown in agroforestry production systems, but we do not have information on this. We used six basic pre-screening criteria in the search:

Plants containing compounds showing activity against certain difficult to treat conditions

Tinea, ringworm and similar fungal skin infections are often difficult to treat and novel cures for more effective treatments are always being explored. *Cassia notabilis* (Cockroach bush) is a small shrub growing in arid to semi-arid areas and with decoction of the leaves to produce anti-fungal products. *Santalum acuminatum* (Native peach or quondong) already grows in the West Australian wheatbelt and the seed has potential as a wound dressing.

Of growing importance is the search for anti-malarial plants (as malaria, and in particular cerebral malaria, is on the increase), anti-cancer and anti-tumour and more recently, anti-HIV/AIDS plants. As noted in Chapters 3 and 4, the markets for treatment and prevention of these conditions are significant. The bark of *Nauclea orientalis* has potential as an anti-malarial agent. *Conospermum species* have potential and are still being evaluated by the US National Cancer Institute (although from our discussion with pharmaceutical companies this potential has been downgraded).

Plants promoting health

Tonics fall typically within the functional food category, and are aimed at promotion of health and prevention of disease. *Alstonia constricta,* with habitat ranging from rainforest to dry inland regions including the wheatbelt, is a source material for alcoholic infusions. The plant families with nerve tonic potential include Apocynaceae, Convolvulaceae, Euphorbiacea, Loganiaceae, Malphigiaceae and Rubiaceae and they tend to often originate from tropical regions (Elisabetsky and Siquerira 1998).

Plants with existing markets

These plants include those which may be used for the treatment of diabetes, those containing anti-inflammatory and hypotensive constituents, as well as some anti-malarial plants (*Artemisia annua* is probably the most important source of the anti-malarial compound artemisinin, but it is again of tropical origin), including the very versatile ‘neem’ (*Azadirachta indica*). Neem is a source material for both antimalarial and anti-inflammatory product, in addition to having insecticidal properties.

TABLE 6.3 : SELECTED POTENTIALLY USEFUL MEDICINAL PLANTS FOR FURTHER INVESTIGATION

Plants Species	Synonyms	Family	Habit	Habitat	Mode of application	Chemical Constituents	Existing Market
1. Plants Used to Treat Tinea and Ringworm							
Cassia notabilis Cockroach bush	*Senna notabilis*	Caesalpiniaceae (Leguminosae)	small shrub	arid to semi-arid tropical areas	decoction from leaves and twigs applied to skin	Saponins & anthraquinones	
Cassia venusta	*Senna venusta*	Caesalpiniaceae (Leguminosae)	shrub	tropics, wet as well as arid	decoction from fresh, new leaves, applied to skin	Saponins & probably anthraquinones in closely related species	
Santalum acuminatum Sweet quondong; Native peach	*Fusanus acuminatus Eucarya acuminata*	Santalaceae	tree	semi-arid subtropics	ground seed kernels applied to lesions	probably acetylenic esters present in kernel oil	
2. Plants Used As Tonics							
Alstonia constricta Bitter bark; quinine bark		Apocynaceae	tree	rainforest to dry inland (but not arid) in tropical and subtropical climates	infusion of bark in alcohol	alkaloids	
Exocarpos cupressiformis Native cherry; native ballart		Santalaceae	shrub to small tree	coastal as well as inland areas	twigs used	flavonoid glycosides; triterpenoids	
Isopogon ceratophyllus		Proteaceae	shrub	temperate areas	bark		
Nauclea orientalis Leichhardt tree	*Sarcocephalus coadunatus S. cordatus*	Rubiaceae	tree	dry tropics	alcoholic bark infusion	bitter principle	
Catha edulis Khat		Celastraceae	tree	arid & semi-arid	leaves chewed	alkaloids	
3. Plants With Bactericidal Uses							
Santalum acuminatum Sweet quondong; native peach	*Fusanus acuminatus Eucarya acuminata*	Santalaceae	tree	semi-arid sub-tropics subtropics	fruit used against ‘golden staph’	acetylenic lipids	

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
Santalum spicatum Western Australian sandalwood	*Fusanus spicatus* *Eucarya spicata*	Santalaceae	tree	semi-arid subtropics	volatile oil is bactericidal	sesquiterpenoid alcohols	yes
4. Plants Used In The Treatment Of Diabetes							
Prosopis juliflora		Fabaceae	tree	marginal soils; drought tolerant	a flour made from cotyledons and embryos is suitable for diabetics		yes
5. Antimalarial Plants							
Nauclea orientalis	*Sarcocephalus coadunatus S. cordatus*	Rubiaceae	tree	dry tropics	bark infusion		
Azadirachta indica Neem		Meliaceae	tree	warm and not too dry climates	as a tea from the leaves or as an alcoholic extract	limonoids	yes
6. Plants With Anti-Inflammatory Properties							
Azadirachta indica Neem		Meliaceae	tree	warm and not too dry climates		limonoids	
7. Anti-Aids/Hiv Plants							
Conospermum species Smoke bush		Proteaceae	bush	semi-arid subtropical climates	source of conocurvone, the active principle		
8. Plants With Anti-Cancer And Anti-Tumour Properties							
Cassia senna Alexandrian senna	*Cassia acutifolia* *Senna alexandrina*	Fabaceae	shrub	tropics semi-arid regions	source of a polysaccharide which inhibits certain tumours	polysaccharides	yes (but only as a laxative)

Plants and other organisms used commercially on a large scale and which yield potentially valuable, but as yet unexploited, joint or by-products

There are several eucalypts, including for example *E. globulus*, with potential to extract small amounts of very active metabolites that have potential in medical product formulations. The following list shows 12 of these eucalypts, all belonging to the sub-genus *Symphyocarpus*, could grow in dryland Australia. The metabolites are contained in the leaves and could be a useful by-product for those trees grown for other purposes such as biomass or even watertable reduction. Some of these species, such *E. robusta*, grow more vigorously on wetter sites and the wetter end of the wheatbelt which has around 500-700mm of annual rainfall.

Species	**Type of bioactive metabolite**
Eucalyptus amplifolia	Macrocarpals; euglobals
Eucalyptus blakelyi	Euglobals
Eucalyptus globulus	Marcocarpals; euglobals
Eucalyptus grandis	Grandinol; grandinal; G-factors; sideroxylonals; euglobals
Eucalyptus incrassata	Euglobals
Eucalyptus macrocarpa	Macrocarpals
Eucalyptus resinifera	Resinosides
Eucalyptus robusta	Robustadials; phenones
Eucalyptus rubida	Stilbenes
Eucalyptus sideroxylon	Sideroxylonals
Eucalyptus tereticornis	Euglobals
Eucalyptus viminalis	Macrocarpals

With the exception of stilbenes (*E. rubida*) (variously substituted 1, 2-diphenyl-ethenes) all these numerous and structurally very diverse metabolites are acylphloroglucinols. Their bioactivities are shown in Table 6.4. Further research could be undertaken into the following groups with priority given to those where there is an existing or growing supply of the tree for other purposes, *E.globulus* being one option.

All macrocarpals are strongly antibacterial against gram-positive bacteria (but inactive against gram-negative bacteria, yeasts and fungi) whilst some, macrocarpals A,B,E, am-1 and H, inhibit “blue mussel” *(Mytilus edulis galloprovincialis)* attachment[13]. Macrocarpals A,B,D and

G inhibit aldose reductase and may find applications in the treatment of complications resulting from diabetes; several macrocarpalus are inhibitors of HIV-Rtase.

[13] “Blue mussel”, like the barnacle in Europe, is a problem for boat operators. It causes rapid deterioration and depreciation. Materials that slow down or prevent the attachment of barnacles and “blue mussel” have value to owners. These materials are typically painted on to the boat surface.

Table 6.4: Selected eucalypts with active metabolites: by bioactive function

	Blue mussel attachment inhibition	Root growth inhibition	Anti - bacterial anti -viral (anti - fungal)	Anti - malerial	Anti - tumour	Diabetes treatment	Other
Euglobals					X		
G-factors (peroxide)		X	X				
Grandinal	X						
Grandinol		X	X				
Marcocarpals	X		X			X	X
Resinosides	X						
Robustadials				X			
Sideroxylona ls	X		X				
Stilbenes	X						
Phenones							X

Many euglobals show strong inhibition of Epstein-Barr virus (EBV) activation induced by 12-O-tetradecanoylphorbol-13-acetate – a tumour promoting substance – and thus have antitumour potential.

Of all “blue mussel”attachment inhibitors, sideroxylonal A is the most powerful one known at present. Two acylphenones from *Eucalyptus robusta* exhibit phosphodiesterase-inhibiting activity.

Plant derived substances capable of being transformed to useful end products

We have not been able to identify any new medicinal substances from woody plants now grown in dryland areas. The next section describes several potential new industrial products that might be developed from the growing supplies of 1, 8-cineole.

6.3 Trees and shrubs with potential to produce industrial products in drier regions of Australia

6.3.1 Energy from mallee and bluegum ?

Woody perennials have potential to generate various forms of energy (electrical and heat, liquid and gas fuels and charcoals) through biomass and a range of other more specialised industrial products including polymers and specialty chemicals. There are three factors driving renewed interest in biomass for these products:

- The Commonwealth Government target of having 2% of energy from renewable resources, a carbon dioxide sequestration measure;
- Increased availability of biomass from, for instance, large-scale plantings of eucalypts (mallees and bluegum) for other purposes including eucalyptus oil and watertable management; and
- New processing technology that is, for instance, improving the yield of methanol and ethanol from even low quality wood material (Gravitis et al 2000)

Foran and Mardon (1999) propose three options for the conversion of land to perennial plant-based biofuel production systems which would help lower watertables and prevent the salinity problem as well as generate returns from biomass materials:

- Allocation of all of the more intensively managed pasture land to biomass perennial plantations.
- Within each State, allocate 60% of the planted pasture land and 40% of the crop land to deep-rooted biomass perennial plantations.
- Within statistical divisions of each state, allocate all crop and pasture land in those areas that have a rating of more than four (4) in terms of dryland salinity problems.

With Option 2 applied to the Australian wheatbelt, an area of 4.7m hectares of planted pasture (60% of 7.8m ha) and 6m hectares of crop land (40% of 15.1m hectares) would be converted to biomass plantations. These would aim to (1) alleviate salinity problems and (2) create the biomass for energy production. The cost of feedstock in energy materials such as ethanol remains a critical factor in viability.

Foran and Mardon found that with a wood-based material used as feedstock, at a cost of $164/t DW, the cost of feedstock accounted for 57% of the total cost of ethanol. They estimated this cost to be $1.91/litre, compared with current unleaded wholesale pre-tax petrol costs of less than $0.40/litre. The cost of wood-based ethanol can be reduced substantially with large-scale plants, but is still uncompetitive even with massive plant sizes and substantial reductions in the cost of the material (Table 6.5). Wheat straw and other grain residues remain among the most cost competitive materials for ethanol. But they still fail to match the cost of petrol made from oil, noting also that ethanol is less efficient than petrol and therefore has to be about 2% cheaper to achieve the same performance. The amount of wheat straw available for ethanol production would need to be supplemented by specialised woody crop production to achieve volume and economies of scale.

Table 6.5: Cost estimates for ethanol and methanol: 1999

Fuel Output	Feedstock	Scale '000 tonnes /year	(PJ per year)	Capital Cost ($m)	Labour Required	Raw Material Cost [$/tonne)	Operating Cost [$/tonne]	Capital Charges [$/t]	Total Cost [$/tonne]	Cents/litre
Methanol	Wood	100	2.24	172	248	426.4	256.6	344.4	1027.4	81.3
Methanol	Wood	16.5	0.37	30	38	328	237.9	361.8	927.7	73.4
Methanol	Wheat Straw	100	2.24	152	225	114.3	226.4	305	645.8	51.1
Ethanol	Wood	115	3.37	387	277	1390.7	360.3	673.1	2424.1	191
Ethanol	Wheat Grain	120	3.52	161	274	543.8	211.9	267.9	1023.6	80.8
Ethanol	Sugar Cane	119	3.49	216	274	508	245.1	363.9	1117	88
Micro-EtOH	Sugar Beet1(a)	0.47	0.014	1.1	9	883.7	742.9	457.8	2084.3	165
Micro-EtOH	Sugar Beet2 (b)	0.47	0.014	1.1	9	1378.2	742.9	457.8	2578.8	204
Micro-EtOH	Sugar Beet1 (a)	1.19	0.035	1.7	10	883.7	347.1	279.4	1510.2	119
Micro-EtOH	Sugar Beet 2 (b)	1.19	0.035	1.7	10	1378.2	347.1	279.4	2004.8	158

Note: 1 Based on irrigated area, beet yield 70t/ha roots, tops used as cattle feed.
2 Based on non-irrigated area, beet yield 50t/ha roots, no value for tops.

Source: Chris Mardon

CASE STUDY 5

PERENNIAL PLANTS WITH MEDICINAL PRODUCTS IN THE CONTEXT OF ENTERPRISE OPTIONS & WHOLE FARM PLANNING FOR WHEATBELT FARMS

In North America the percentage of perennial plants (19%) used for producing medicinal products is about twice as high as that of annuals (9.5%).(Moerman 1998). Within the perennials, large plants (trees and shrubs) are more likely to have been used for medicinal products than vines and smaller plants. In addition, medicinal plants tend to be more dispersed and found over a wider region than annuals. And medicinal plants are also judged to be more visible, recognisable and showy. All of these features appear to make them attractive for planting in the Australian wheatbelt.

The benefits and commercial viability of planting perennials in the Australian wheatbelt for watertable and salinity control may be enhanced through selection of trees and shrubs that have the potential to produce a range of products, extending through timber, oil, medicinal products and residues for biomass. A diverse range of products with various harvest lead times is likely to improve cash flow, reduce risk (particularly from price fluctuations) and the overall value of the enterprise. The prospect of short-term cash flow from medicinal products would also enhance adoption of perennials as part of the whole farm system. In addition, the showy nature of perennials that produce medicinal products would enhance their value for laneways and windbreaks.

John et al. (2000) presents enterprise selection and management options for salinity management in the wheatbelt with a strategic and tactical or short-run perspective. Perennials are currently seen only as a strategic solution because of negative short-term cash flows generated. Medicinal and/or industrial products from these perennials may have potential, through improved cash flow, to shift perennials into the tactical option category.

6.3.2 Adhesives from wattles

Gum Arabic, the dried exudate of *Acacia senegal* is widely used as a thickener, emulsifier, colloidal stabiliser and adhesive in a variety of industries: pharmaceutical, food, etc.

Australian *Acacia* gums are darker in colour than Arabic gum owing to the presence of small amounts of polyphenolic substances and tannin. The polyphenol/tannin content results in better adhesive properties and as a result the gums of several Australian wattles (*Acacia dealbata* and possibly *Acacia microbotrya*) have been used in the manufacture of superior brands of water colours.

Acacia dealbata is a very common tree in the highlands of eastern Australia. It is a prolific producer of a water-soluble gum, which might be useful in the manufacture of watercolours, etc. The flowers of this species are the source of the highly prized "mimosa absolute" used in perfumery and lately also in the food flavouring industry. To date, all mimosa absolute is produced in France from trees, which originated in Australia. The French mimosa industry is centred along the Mediterranean coast near the towns of Cannes and Grasse.

6.3.3 Agrochemicals from "neem"

The neem tree (*Azadirachta indica)* is a tall, spreading and very leafy tree. It will grow in a variety of situations, from the moist tropics with moderate rainfall (400 – 1200 mm/annum) to semi-desert areas where it will withstand temperatures up to and above 50 degrees C. It does not tolerate freezing conditions or lengthy periods of cold weather. It grows well on dry and infertile sites as well as on some acid soils (National Research Council 1992).

The fruits resemble olives. However, neem seed will remain viable, under normal conditions, for only a few weeks. The most useful property of neem is it ability to control insects. Extracts from its leaves and seeds are particularly potent insecticides.

Its insecticidal and pesticidal properties are due to a number of limonoids: azadirachtin (the most potent of them), meliantriol, salannin, nimbin and nimbidin and others.

The ripe Neem fruit contains a triglyceridic fatty oil, which is useful as:

- Fuel;
- a raw material for soap manufacture; and
- lubricant

While a lot is known about this tree, it would be useful to investigate:

- its application in the Australian landscape and wheatbelt economy;
- how the tree could best be adapted to our dryland farming enterprises; and
- how chemical industries could use the output.

It is also noted that despite being available for a long period, neem oil or azadirachtin-based products have not captured any significant share of the world personal health care, pesticide or veterinary markets, and no product is currently registered in Australia. Registration would logically make a difference to the market size in Australia and it is to this process that we now turn. It is understand that the principal reason azadirachtin is not currently registered in Australia is the uncertainty as to the potential toxicity of some of the metabolites that may be derived from the products. Efforts on registration are continuing (Chudleigh, in press).

6.3.4 Other issues

Product transformations – microbiological transformations of readily available terpenoids

1, 8-cineole is one of the most readily available terpenoids here in Australia. It is the major constituent of several eucalyptus oils produced commercially in Australia. These include *Eucalyptus polybractea, E. dives* var. C, E.*radiata* subsp. *Radiata* (cineole form), as well as several *eucalyptus mallee* species (*E. kochi, E. plenissima, E. loxophleba [Sub.sp. pissiphloia]), E. plenissima, E. polyblactia*) which are being planted on a very large scale in Western Australia. The present world demand for this type of oil is about 3000 – 4000 tonnes per annum and this is adequately supplied by present world production.

In order to be able to sell the huge additional quantities of cineole rich oils, particularly from Western Australia, new uses will have to be found for 1,8-cineole in particular.

A potentially environmentally friendly process for a chemical modification of cineole would be the use of microorganisms rather than of environment polluting chemicals. R. M. Carman and associates at the University of Queensland have transformed 1,8-cineole to a large variety of oxidation products by the microorganisms present in the digestive system of the brushtail possum and by *Pseudomonas flava*[14]. The products generated include:

2a-hydroxy-1,8-cineole
2*B*-hydroxy-1,8-cineole
2-keto-1,8-cineole
9-hydroxy-1,8-cineole
1,8-cineole-9-oic acid
7-hydroxy-1,8-cineole
(1R,2R,4S)-2*a*-hydroxy-1,8-cineole
2*a*,9-dihyrdoxy-1,8-cineole
2*a*,10-dihydroxy-1,8-cineole
2*a*-hydroxy-1,8-cineole
(1R,2R,4R)-2*a*,4-dihydroxy-1,8-cineole
7,9-dihydroxy-1,8-cineole
(1S,2R,4S)-2*a*, 7-dihydroxy-1,8-cineole

It would be useful to evaluate the pharmacological activity of these compounds and whether they could be used as starting materials for the production of fragrances, etc.

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[14] References for Microbial Transformations of Cineole via Microorganisms:

1. I.C.McRae et al., *Aust. J. Chem.*, **32.,** 917 (1979)
2. R.M.Carman et al., *Aust.J.Chem.*,**39.,** 1739 (1986)
3. T.M.Flynn et al., *Aust.J. Chem.*,**32,** 2093 (1979)
4. R.M.Carman et al., *Aust.J. Chem.*, **45.,** 651 (1992)
5. S.D.Bull et al., *Aust. J. Chem.*, **46**., 441 (1993)
6. R.M.Carman et al., *Aust,.J. Chem.*, **47**., 1509 (1994)
7. R.M.Carman et al., *Aust.J.Chem.*, **47.,** 2087 (1994)
8. R.M.Carman et al., *Aust.J. Chem.*, **49.,** 1 (1996)
9. R.M.Carman et al., *Aust.J. Chem.*, **49.,** 741 (1996)
10. E.V.Lassak et al., *Aust.J. Chem.*, **26.,** 845 (1973)

Laeva – piperitone is another readily available terpenoid which is unable to be micro biologically modified. Chemical transformation to piperitol followed by esterification could result in perfumery compounds.

Whilst this kind of research is very speculative, it might lead to commercially useful products. If successful, it would benefit the essential oils industry in a very significant way.

Transgenic plants

Genetic modification of plants to improve drought and salinity resistance is a subject of widespread interest. Genetic modification may also enable increased yields from wood in ethanol production. Increased drought tolerance could open the way for a range of woody perennials with medicinal and industrial product potential and which currently grow only in tropical and sub-tropical regions. The subject matter is beyond the terms of reference for this study, other than to note the potential benefits. Kleter et al. (2000) reviewed a number of developments in crop production biotechnology including salinity and drought tolerance.

6.4 Concluding comments

Perennial shrubs and trees have potential to be an important part of the whole farm plan for the typical Australian wheat farm. They offer both direct and indirect benefits and the potential for a more sustainable wheat farming system. When the whole farm plan considers all objectives, options and the linkages between enterprises the position of perennial plants is enhanced. The external benefits on lowering water tables are generally recognised. There is also a growing market for several of these plants as source material for natural based medicinal and industrial products.

This section identifies a range of plants for further investigation. The major challenge ahead is likely to be in identifying optimal whole-farm systems in the wheatbelt which incorporate the right mix of perennial and annual crop enterprises in the context of viable supply chains. The wheat industry has been very successful in developing highly competitive supply chains for grains based on large-scale, competitive farm systems. If these same features can be extended to some of the perennial crops for industrial and medicinal products there would be significant benefits for the region.

7. Implications for Australian Research

In Brief

The conventional justification for government involvement in rural research and development is that without some form of intervention there would be market failure and less than the optimal level of resources allocated to R&D activities. Pharmaceutical and food manufacturing companies, however, are extremely active in R&D for those products where there are established markets and where patents and other similar discovery incentives work. This includes pharmaceuticals, nutraceuticals and functional foods. The research budgets of the firms involved with these products are substantial and a significant multiple of all government backed R&D on the subject. Their R&D expenditure on natural products is growing and it is efficient and effective to encourage and facilitate this growth. They are also positioned to capture benefits of R&D because of their market dominance.

The question, and the challenge, for a public R&D organisation is how best to work with these privately owned, very profit driven, often foreign controlled and vertically organised structures. R&D organisations may take on a greater facilitating role with objective of generating more relevant R&D. The question of how the benefits of R&D can be captured at the farm gate will remain an on-going challenge. There is also the challenge of undertaking research to encourage more local manufacturing to take advantage of the significant opportunities emerging for bio-based materials. The opportunities appear to be significant for those R&D organisations with capacity in business development and partnerships and alliances. It may require a change in culture to work in these alliances.

Another major challenge for the R&D organisation will be in working with and facilitating the coexistence of farm production systems built around the supply of organic foods, genetically modified crops and traditional production systems. They each have their markets, all with sound prospects for efficient producers.

There is widespread evidence of a significant outward shift in demand for bio-based materials for industrial production, natural foods and foods and cosmetics with improved health and nutritional efficacy. From our observations this growing demand is derived from three main underlying influences:

- Growing awareness and interest in the quality of life, what contributes to good health and measures, including better diets, to beat the aging process;
- Renewed concern about sustainability, purity of resources and environmental quality; and
- Government regulations and targets for a range of environmental performance indicators such as carbon emissions, regeneration of land and water and biodegradability of used products.

The shift in demand is accompanied, coincidently or otherwise, by significant technological change that is affecting processing and raw material production costs. As a consequence of these shifts in supply and demand the production of pharmaceutical, nutraceutical and new industrial products made from bio-based materials is in the midst of a period of unprecedented change. This period may ultimately be recognised as being just as significant as the industrial revolution some 200 years ago. It is likely to be as significant as the Internet revolution and to have a major impact on all consumers, producers and processors, including those who seek to ignore it.

Responses to this biological revolution will not be easy because of the inherent instability in supply and demand. Technological breakthroughs in, for instance, genetically engineered plants may reduce production costs for those who embrace and adopt the improvement, but they may face simultaneously a reduced or more segmented market if consumers reject the technology. The Kyoto Protocol may be revised, strengthened, downgraded or re-enforced, driving the demand for carbon credits, forest plantings and renewable biomass material with it. Consumers may have severe doubts about the benefits of GMOs now, but in five years time a genetically modified plant could be released with proven beneficial effects on, for instance, cancer. Will those doubts remain or will they change over time with improved information?

One way of dealing with this emerging period of increased uncertainty would be to start to construct various scenarios that may unfold for the future. The CSIRO has recently completed for the Department of Immigration and Multicultural Affairs a series of Future Options to the year 2050. This approach appears to have potential value for R&D organisations in that it enables the different scenarios to be constructed and diverse research programs and projects built around each and all scenarios. Among the most obvious scenarios to be examined are the economic features associated with different crude oil prices which have increased by more than 100% in the last year with reasonable probability (October 2000) of a further price spike developing over 2000-01 as Middle East conflict intensifies.

But then again, this might be the last gasp for OPEC and oil with the price increase leading to a massive and permanent shift into alternative energy sources such as fuel cells for motor vehicles. Other extreme scenarios exist with consumer response to GMOs; a technology breakthrough in conversion efficiency of biomass to ethanol; another breakthrough in fermentation technologies for polymers; and a shift in government regulations on minimum levels of biodegradable products from any one factory. The possibility that petro-chemical based plastics could be associated with infertility also presents possibilities for bioplastics.

7.1 The case for government support

In addressing the scope for research into this subject we considered it was important to examine the case for government intervention, including support for research programs and projects. The case for or against government involvement governs the conclusions about future research and recommendations for programs and projects and the balance of research resources in private and public research (Items 4 and 5 of the Terms of Reference). If there is, for example, private sector activity in exploring for active compounds in native Australian plants then it might be counterproductive for certain government backed research to be initiated unless it facilitates further activity by the private sector.

More generally, the case for government intervention is based typically on evidence of market failure. This is a necessary, but not sufficient, condition for intervention. It is also necessary to demonstrate the economic benefits of the intervention and in particular that the benefits of, for instance research, will outweigh the costs.

There are four potential sources of market failure:

- The presence of *private or public good* characteristics (Mansfield 1975)
- The presence of *externalities*
- *Moral hazard*
- *Economies of scale*

From our examination of the subject industries we have found widespread evidence of both extreme commercial competition and market failure. Pharmaceutical and food manufacturing companies in particular are extremely active in R&D for those products where there are established markets and where patents work. This includes pharmaceuticals, nutraceuticals and functional foods. The research budgets of the firms involved with these products are substantial, growing and a significant multiple of all government backed R&D on the subject. It is efficient and effective to encourage this growth. The question for a public R&D organisation is how best to work with these private organisations and facilitate more and better R&D to overcome constraints that may be limiting their activity.

The opportunities appear to be significant for those R&D organisations with capacity in business development and partnerships and alliances. They will have to contend, however, with large and sometimes market-dominant organisations that are shown to be willing to exert their influence on prices. It may therefore be a challenge to capture benefits of jointly-funded research at the farm gate.

Regulations under the Therapeutic Goods Act are designed essentially to overcome the problem of **moral hazard** which exists when there is some asymmetry of information between the producer and consumer of, for example, pharmaceutical and/or nutraceutical goods. The 'moral hazard' problem arises when the quality of a good or service is not readily or materially evident, which may be a problem with foods and pharmaceuticals that make claim to certain health attributes and efficacy has not been established. Similar issues are involved with genetically modified plants when the Office of the Gene Technology Regulator is involved with gene regulation.

The role for Rural R&D Corporations in these regulatory areas needs to recognise that there is already a significant regulatory framework in place and industry organisations are involved at a senior level with administration of the regulations. For example, the Australia New Zealand Food Authority (ANZFA) is responsible for maintaining food standards in Australia and New Zealand, coordination of food surveillance, development of codes of practice and provision of research support including adequate information to enable consumers to make informed choices. Particular gaps exist, however, in improving the efficacy of products that make claim to particular health benefits and this is likely to be more of a problem for new and exotic products that may be developed, for example, from Australian animals and plants.

There would be benefits in RIRDC funding a small project that sets out in plain English the distinctively different regulatory arrangements for therapeutic goods, complementary medicines, cosmeceuticals, gene technology and food. There are several different regulatory bodies and standards involved and there is an increasingly blurred demarcation line between them, which is even further confused by the different treatment of imported goods and exports. There are also different regulations between countries and it would be useful, particularly for exporters, to have a document that sets out the different procedures in the US, UK, Germany etc. Good quality information and effective communication of that information is essential for overcoming problems of moral hazard.

Externalities are present and potentially significant in some regions, particularly in the context of dry-land salinity, soil degradation and water contamination. Recent research in Western Australia, however, indicates that at least in that state the costs and benefits of dealing with salinity may be more internal than previously thought (John, Pannell and Kingwell 2000). If this is the case, then the solutions may rest more at a local level with improvements to whole-farm management practices and skills in dealing with the optimal balance of cash crops and deep-rooted perennials to lower on-farm watertables. By planting trees and shrubs that produce medicinal products there is the prospect of generating short-term cash from an enterprise that was previously considered only for its long-term effect on the watertable, an external benefit. It is evident that whole farm planning in the Australian wheatbelt, particularly where there is a salinity problem, is emerging as a complex task in dealing with the short and long-term enterprise cash flows to come up with the right mix of annual and perennial crops that will not only keep salinity at bay, but also preserve cash flow.

External effects may also exist in the management of GMO crops that, without appropriate management arrangements and safeguards may have adverse effects on surrounding vegetation and other farming systems.

Economies of scale have acted as a significant entry barrier to effective competition in pharmaceuticals in particular and in the supply of ingredients for vitamins as well as many chemical products. Large scale has been a particular problem for Australian manufacturing which has had problems in accessing markets beyond the relatively small Australian market. Economies of scale may lead eventually to concentration of industry ownership and then to inefficient price setting behaviour. The Australian Competition and Consumer Commission is investigating price fixing by several companies supplying vitamins for animal feeds in Australia. Similar investigations have occurred in the US and Europe into vitamins for human consumption.

The lack of effective local manufacturing is a potentially serious barrier to Australian suppliers of raw material for pharmaceutical, nutraceutical and industrial products because there is often limited scope for supplying the raw material to manufacturers in other countries. For instance, it is difficult to envisage Cargill Dow Polymers sourcing corn or potatoes for starch from Australia for a large-scale biodegradable polymer plant in the US, the output from which may well end up in Australia as material for local polymer products. Not all products are affected in the same way by the presence of economies of scale as some processed products such as power generation are non-tradeable goods and there is often a significant natural cost advantage in using locally sourced materials.

There is no simple solution to the economies of scale problem. The best prospects may rest with new technology, which may change the shape of the processing cost curves and perhaps improve the competitiveness of small enterprises. The recent research by Bachmann *et al*. indicating a reduction of the minimum sized fermentation plant for biopolymers is a matter of considerable interest in the context of the need for more local manufacturing to fully exploit the markets identified here. Again, however, the large globally oriented pharmaceutical, nutraceutical and chemical companies may be the main operators of any effective local manufacturing presence because they have the capital and access to markets. Continued scrutiny by the ACCC appears to be necessary to improve the competitive state of the market.

The main justification for intervention in research is that it is largely a **public good** (Watson 1992). But particular care is needed in the interpretation of this conclusion for pharmaceutical, nutraceutical and bio-based industrial goods because firms are often able to capture the benefits of the research through patents, data exclusivity rights, marketing exclusivity licenses and closely held information practices. The protection and incentive offered by some of these arrangements could be very significant (Refer to the Case Study on Taxol).

One of the most pressing areas for further research and information is in the area of nutritional information about food products. For example, a recent survey shows that while 56 per cent of consumers are aware that nutrition is important to them, only 26 per cent feel they have a nutritious diet, partly because they did not understand health claims and terms such as anti-oxidant or Omega 3. Provision of this information is clearly a public good. A *public good* is accepted generally to be one in which either the consumption by an individual or entity does not reduce its availability for others or it is not possible to exclude others from consuming it. Independent and objective information about the health and nutritional content of food and nutraceutical products would be generally accepted as a public good. Improved information in this area can be expected to increase demand for functional foods and nutraceuticals that meet key performance levels.

7.2 Role of the private sector & strategic alliances

The private sector plays the leading role in development and production of pharmaceutical, nutraceutical and new industrial products. The pharmaceutical sector is Australia’s largest source of funds for medical research with expenditure of almost $300m/year, representing more than 5% of revenue compared to 1% for manufacturing generally. We estimate about 10% of this R&D is allocated to nutraceuticals. Food manufacturers also allocate significant resources to R&D into functional foods and improved nutritional quality of food. (Table 2.6).

A key feature of R&D into pharmaceuticals is the presence of strategic alliances, partnerships and joint ventures. A 1996 survey of 14 pharmaceutical companies revealed that these companies alone had 571 relationships with 261 different organisations (APMA 1999). The need for specialised expertise and coordination of that expertise underpins this institutional structure. Alliances and partnerships require expertise in themselves if they are to be successful in sharing the risks and rewards and tasks in a way that produces benefits and generates sustained motivation for all parties involved. **Private firms are typically the leaders in these strategic alliances and often they will contribute most of the capital, be exposed to most of the risk and receive most of the benefits**. The reality is that large multi-national enterprises are best placed to contribute capital and to provide the crucial linkages between research and commercialisation. These organisations also have high levels of competency in R&D and information management.

As noted elsewhere in this report, the **supply chains for the new pharmaceutical, nutraceutical and industrial products are likely to be more vertically integrated through direct ownership or contractual relationships that facilitate quality control**. These supply chains will place more pressure on traditional rural R&D organisations to do research that is relevant to the major player(s) in that supply chain. Therefore, initiation of research into improving the yield of, for instance, cranberry may be irrelevant to the supply chain if it doesn't deal simultaneously with the product specificity and efficacy required by the supply chain to meet the demands of its end consumers and the TGA. This applies particularly if health claims are to be made about the product. In these circumstances **there will be more demands placed on R&D organisations to participate in strategic alliances with major supply chain participants if they are to remain relevant.**

This raises the question of how a relatively small government/grower funded R&D organisation can form an effective alliance with a global pharmaceutical, chemical or food company that seems to have so many resources at its disposal. Solutions to this critical question are beyond the scope of this study, other than to note that it will require pre-feasibility, feasibility assessments, business planning and negotiation skills of a high level. Local R&D organisations may have an edge in knowledge of the local environment and links to local producers and this could be one reason for a large multi-national company being interested in forming a strategic alliance with a relatively small government/grower funded R&D organisation.

7.3 The benefits and beneficiaries

There are some key features about the structure of the pharmaceutical, nutraceutical and industrial enterprises that affect the level and distribution of benefits. First, the concentrated nature of many processing activities in pharmaceutical, nutraceutical and industrial enterprises means **that a large part of the benefits of research may be captured by the processor**, presuming the processor exists at all and providing there is some patentable feature of the process or product[15].

Hence the growing interest in gene technology and plant variety rights. An electricity utility enterprise wanting to derive more of its energy from biomass or other green sources is in a strong position to capture the benefits of research into agricultural plants and processes that will reduce the costs of its inputs. In these circumstances there appear to be potential benefits in jointly funding research with processors as well as through the normal levy collection arrangements with growers. It is relevant to ask why growers would want to fund the research at all if the processor is going to capture the benefit. One reason is that, through patents and licenses, which we expect as an outcome of the research, growers would be able to appropriate some of the benefits even though they flow through the processor.

A second feature of processing is that it does not always happen in Australia. Most of the ingredients for vitamins are imported and therefore research that increased, for instance, the yields and productivity of a vegetable destined for vitamin production may end up embodied in an imported product or a product for the fresh market.

A third feature is that **agricultural supply for some plants, herbs in particular, is severely limited by labour intensity**. In these circumstances, research that simply increased the yield of a particular plant may accentuate the labour cost problem and not generate benefits unless accompanied by an improvement in labour productivity, perhaps by improved mechanisation of harvesting. Improving the yield of a plant that is grown with labour intensive practices may actually result in increased imports if the technology is made available to the low labour cost country because it will gain a relatively greater benefit and then be able to increase its production and exports. The relatively high level of labour intensity in producing a number of horticultural products is a key issue for R&D organisations to

[15] More specifically, the distribution of research benefits flows to those groups in the supply chain that are least responsive to price changes. (Freebairn, Davis and Edwards 1982).

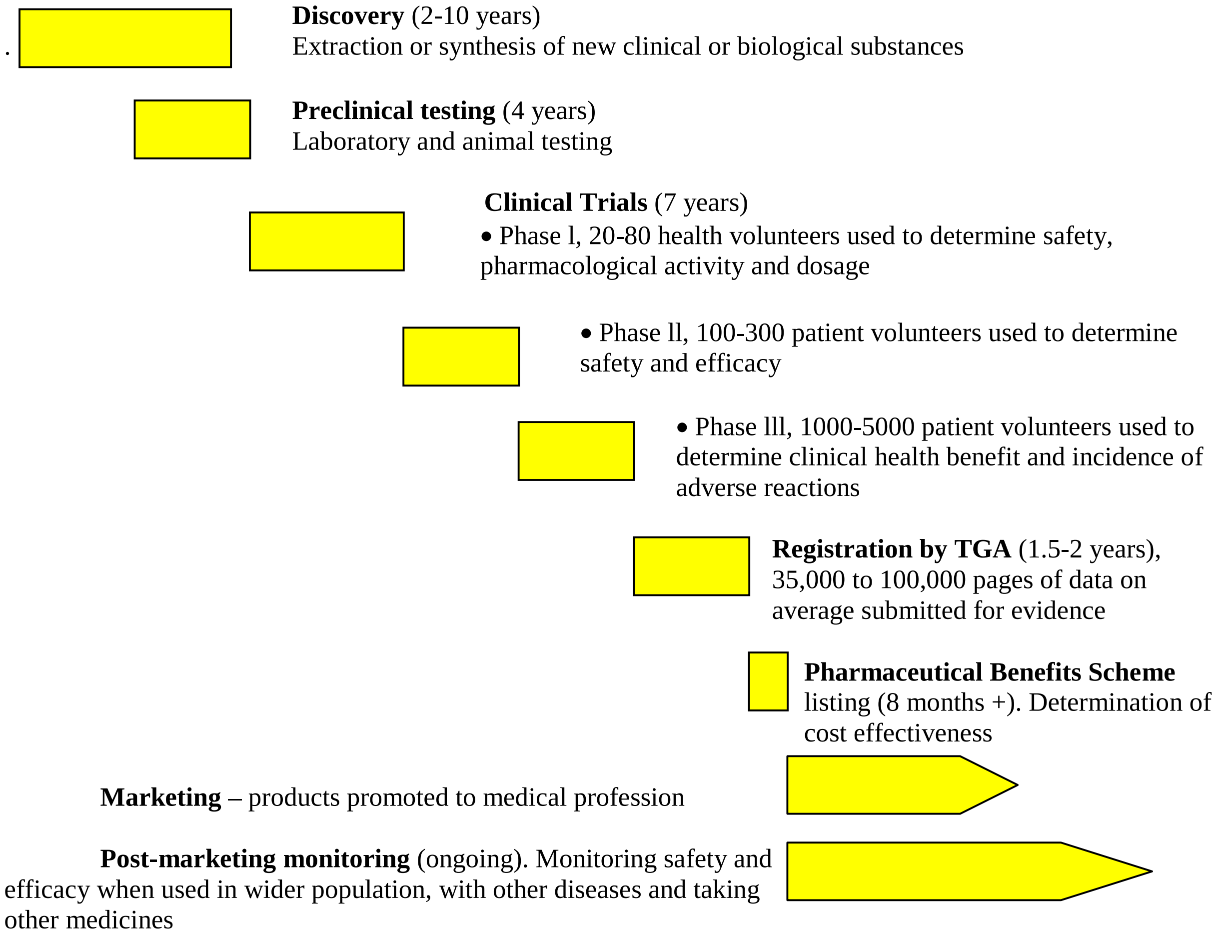
consider. To improve the competitiveness of these enterprises there needs to be more priority given to measures that increase capital and skill intensity and labour productivity.

In regard to the level of benefits from research there is a significant lead-time in developing new products for medicinal purposes. For the average registered pharmaceutical it takes 15 years to take a product from discovery through to marketing (Chart 7.1). There are significant and changing risks, costs and rewards over this 15-year time period.

Clearly, **only those organisations or groups with significant capital can take a product through the full discovery, development and marketing stages**. There are, however, emerging opportunities to reduce the lead times for discovery and development with automated rapid screening technologies, which enable thousands of samples to be screened each day. And the lead-time can be reduced substantially by focussing on non-medicinal, health products where regulatory costs and delays are lower.

Moreover, returns to investment at the early stage of development can be very high even though a royalty may represent only a small percentage of end product sales value. For example, Forbes Medi-Tech, a small Vancouver based biotechnology company has developed Phytrol, a proprietary, phytosterol-based cholesterol-lowering composition, licensed the rights to Novartis (6^{th} largest pharmaceutical in the world with revenue of $US101 billion) for use as a functional food ingredient, dietary supplement and over-the–counter sales. It is understood Forbes will receive 1.5% of gross revenues for a 20-year period for those products, which are derived or developed from the technology. It is the sheer size of the functional food market that creates value from this type of arrangement.

Chart 7.1: Stages in development of medicinal products



Source: APMA Facts Book 1999 p 17

CASE STUDY 6

MECHANISED HARVESTING IS IMPORTANT FOR IMPROVING THE PRODUCTIVITY OF LABOUR, PARTICULARLY IN COUNTRIES LIKE AUSTALIA WITH RELATIVELY HIGH LABOUR COSTS

Garlic (*Allium sativum*) is a product identified earlier in the report as having potential for continued growth as a consequence of its medicinal properties and access to markets where there is also a relatively high state of awareness of its attributes. Australian consumption is about 5,500 tonnes/year, with about 80% supplied by imports from China, New Zealand, South Africa, Taiwan, USA and Mexico.

Garlic requires a temperate climate, light, well drained soils and plenty of water, which, in Australia, means irrigation. The main growing areas in Australia are the Riverland region of South Australia, Sunraysia region of Victoria and Central NSW. There is a significant area of land in Australia that is capable of growing garlic.

A major limiting factor for garlic production in Australia is that it requires a significant investment in labour of between 1000 and 1500 hours per hectare to produce and market a high quality crop that might produce 10 tonnes/ha valued at $23,000 (Knoxfield 2000). Harvesting accounts for a major share of the labour hours and this creates a competitive advantage for countries with low unit labour costs. Mechanised harvesting appears to be essential if the garlic industry is going to be able to compete against low priced imports from low labour cost countries (Salmons 2000).

RIRDC research (Project No.: BIO-1A) has identified a selection of high yielding (20 tonnes/ha), virus tested garlic seed stock with high alliin content. While use of the new seed would treble seed costs the extra yield more than compensates for this and gross margins are expected to increase by about 50%. But labour costs (representing more than 70% of total costs) also increase substantially, in line with the extra harvest volume. As a result, the effect on competitiveness is not as great as it could be with a mechanised harvesting system. Moreover, if the yield improving technology is available to a country with low cost labour there may actually be an increase in imports as enterprise profits in these countries will increase by more than those in high labour cost countries.

Many of the herbal plants that produce pharmaceuticals and nutraceuticals are labour intensive and are grown competitively in developing countries. For high labour cost countries like Australia there would be benefits in doing more research into mechanised harvesting and other capital and skill intensive techniques that would enhance competitiveness against low priced imports from labour intensive countries. Quality assurance, for instance, in production, distribution and processing would enhance competitiveness against these imports.

8. Conclusions and Recommendations for Further Investigation

There is significant evidence to show that each of the emerging markets for new pharmaceutical, nutraceutical, functional foods and industrial products made from natural materials may transform the whole structure of traditional agricultural supply chains. They offer new markets for new products and often with new technologies and the support of new institutions and new regulations. There will be varying responses from producers, commodity marketing organisations, R&D organisations and governments. Where there is resistance to change it may often be based on genuine concerns about safety, the environment and sustainability. These concerns need to be addressed and dealt with in well-designed and comprehensive R&D programmes.

The R&D tasks of the new pharmaceutical, nutraceutical, functional foods and industrial products are interdependent (spread across many functions, skills, organisations and existing programs) and potentially complex (with joint products, potential for new discoveries and externalities ever present). The outcomes are uncertain (reflecting the increased pace of technological change in the biological sciences and lagging clinical studies to ascertain the full effect of these breakthroughs).
The agricultural raw materials to be used in development of the new pharmaceutical, nutraceutical, functional foods and industrial products may be sourced from a range of different traditional industries, but the demands on suppliers in terms of product specificity, efficacy and availability will be higher.

It is quite possible that there will be more differences within commodities than between them. Common interests between commodities will emerge in identifying ways of improving quality, product specificity and product efficacy; in dealing with more vertically integrated supply chains and large and influential pharmaceutical, chemical and food manufacturing companies; and capturing benefits at the farm gate. Sharper differences will exist between supply chains within commodities for traditional markets; GMOs; organic foods; pharmaceuticals; functional foods; industrial products etc.

The demand for specialised expertise in doing R&D on new pharmaceutical, nutraceutical, functional foods and industrial products is significant, multi-functional and rarely resides in one organisation or one country. For this reason we suggest alliances, partnerships and joint research projects should be encouraged. We expect there could be greater levels of private participation in these research projects than with others because of the presence of significant globally-oriented pharmaceutical, chemical and food companies in the respective health and industrial products. Patents, trade marks, brands, licensing and other tradeable mechanisms are likely to play a more significant role in the funding of research and development.

Targets are being set by governments in North America *(USA, in particular)* and Western Europe *(EU members)* to enable them to move progressively to a bio-based economy that is less reliant on fossil fuels. Like their decisions a decade ago to embrace the information and communication technological revolutions, the early adoption of a broad natural product strategy, with deliberate targets to be achieved, is likely to give them leadership in a global economy that is attaching more and more value to the environment and sustainable use of resources.

While government regulations currently underpin the development of renewable energy sources there is increasing evidence that capital markets are starting to find favour with firms that have clear commitments towards renewable energy, natural products and sustainable management practices (Martin 2000; Hill 2000). The Australian Government currently has a commitment, as part of its greenhouse gas abatement policy, to a 2% target for renewable electricity generation by 2010. An important policy question for Australia is whether there would be benefits in a broader use of such targets, given the approach in America and Western Europe.

Suggestions for further research

In this section attention is drawn to several key findings of the study and several matters that could be examined further.

Pharmaceutical products

1. Plants for pharmaceuticals, which could be examined along product lines for the major pharmaceuticals including the primary cardiovascular, anti-infective and CNS market segments. Australian requirements for producing existing plants for these markets need more detailed investigation including for the cardiovascular drug market, *Digitalis* spp. (for digitoxin); *Strophanthus* fratus; *Cinchona* spp (for quinidine); and *Rauwolfia serpentina (*for reserpine*).* A vast list of other plants used in the anti-infective market and CNS drug market should be examined systematically, in partnership with pharmaceutical companies, for their potential to grow and be marketed from Australian farms.

Nutraceutical materials

2. Note that medicinal herbs and botanicals supplying this market are often produced through labour intensive production systems. Therefore research should concentrate on measures that are capital and skill intensive.

3. Continue and extend the existing research into garlic, ginkgo/ginseng, Echinacea/golden seal, St. John's Wort and Saw palmetto, which are priorities in view of their market prospects. Meeting the growing demand for improved product efficacy is an issue for all of these products.

Industrial product recommendations

4. Initiate or facilitate a series of projects in conjunction with processors to improve the yield and conversion efficiency of agricultural materials used as biomass for ethanol and starch and lactic acid for biopolymers.

5. Review international research, examine and contrast the environmental and health impact of using petroleum and bio-based materials in detergents, paints, herbicides, plastics and pesticides.

6. Identify the crops and their respective agronomic, genetic structure and farm management practices most suitable for meeting the demands of the industrial markets for agrochemicals, packaging materials, energy and fuels, lubricants and waxes, plastics and polymers, resins and adhesives, and solvents.

7. Examine, in particular, the following agricultural materials for use in making industrial products:

- Nut shell flours, as an additive to thermosetting resins such as urea formaldehyde.
- Wattle gums, as a thickener, emulsifier, colloidal stabiliser and adhesive.
- Sucrose from cane sugar for sucrose monlaurate, a no-ionic detergent for solubulisation of membrane proteins.
- Mango seeds, a solid fat substitute, used as a food additive or raw material for soap, creams etc.
- Eucalypts (9), belonging to the sub-species *Symphycarpus*, for active metabolytes with potential use in root growth inhibition, anti-bacterial and other medicinal and industrials.
- Neem tree leaves for insecticidal and pesticidal properties.
- Microbiological transformations of readily available terpenoids, such as 1, 8-cineole, to create new products for new markets.

Functional foods

8. Initiate or facilitate a series of projects to enhance production of functional foods, noting that this market could grow to account for 50% of the food market. Note too Australia is already capable of producing most of the materials for these foods including those with the best prospects, namely: oats, soy, flaxseed, canola, garlic, broccoli (and other cruciferous vegetables), citrus fruits, cranberry, tea, wine and grapes, fish, omega-3 diet eggs, dairy products and beef.

Environmental issues

9. Recognise that perennial plants are the main source of plant based medicinal products and that this should be considered in the selection of tree planting programmes. Nevertheless, note also that several of the best plant prospects for medicinal products are weeds.e.g. Devils Claw, St. John’s Wort.

10. Examine and validate, if possible, the proposition that increased use of biodegradable products and bio-based chemicals and other bio-based industrial products would have fewer harmful effects on the environment and human health.

Plants for the drier wheatbelt region

11. Investigate the scope for increased use in the Australian wheatbelt of diverse plant species, and plants with joint product potential including, for example, medicinal products and lignocellulose for ethanol and external benefits from deep-rooted perennials. Perennial plants with prospects for further investigation and commercialisation include Santalum spicatum (Western Australian sandalwood) for bactericides and a group of 9 eucalyptus trees with bioactive metabolites in their leaves.

12 Initiate a series of research monographs on these and the other plants listed in the report, with potential to grow in drier regions and be used for various medicinal, bactericidal, insecticidal and other industrial products.

Institutional issues

13. Initiate or facilitate the initiation of a district pilot program with aboriginal groups and other similar habitat associations to help identify native plants used by Aboriginal people for medicinal, therapeutic, healing and building or industrial purposes. This plant and product database would or could become part of the developing on-line database on Australian native plants.

14. Note the potentially greater role for large-scale foreign owned food and pharmaceutical manufacturers in the supply chains of the new products and the implications of this for R&D activity and market efficiency.

Infrastructure

15. Produce a ‘plain English’ paper on regulatory procedures for listing and labelling of pharmaceutical, nutraceutical, vitamin and functional food products. This should also cover regulatory procedures in other countries and export markets in particular.

16. Conduct new and improved studies into the economic characteristics of bio-based pharmaceutical, nutraceutical and industrial supply chains. In particular, a full examination and sensitivity analysis of the economics of the supply chain in producing bioplastics, bio-based inks and ethanol from various raw materials with different processing technologies would be useful.

17. Initiate or facilitate a workshop on Natural Products for New Pharmaceutical, Nutraceutical, Functional Foods and Industrial products in Australia.

9. Appendices

9.1 APPENDIX 1. Terms of Reference

This is a scoping paper, with a national focus, on the potential over the next decade for Australian agriculture to produce raw materials for the new pharmaceutical, nutraceutical and industrial products that will result from new approaches to plant and livestock breeding. The focus of the scoping paper should be at the broad national level.

The specific terms of reference to be addressed by the paper are:

1. Brief review of current pharmaceutical, nutraceutical and industrial products available from agriculture.
2. Provide a review of the literature concerned with new products, a review of public and private research nationally and globally on development of new products and report on planned R&D of private and public organisations.
3. Documentation of the results of preliminary production and marketing of new products including management issues, current and projected profitability etc.
4. Relate the outcomes of the above activities to the most applicable opportunities for Australia, including consideration of comparative advantage, suitability of natural resources, environmental impacts, suitability of infrastructure, institutional arrangements, public perceptions, appropriate business structures, availability of markets and required managerial capabilities.
5. Provide recommendations for further investigation on Australia's potential to produce the new products.

The study is expected to deliver:

1. A draft report to be reviewed by a reference panel of stakeholders.
2. A final camera-ready document suitable for public distribution to farmers, processors, marketers, farmer organisations, educators and policy makers.

Other Considerations:

The consultant will be required to liaise with the RIRDC communications section to assist in the preparation of media releases and articles for popular rural journals.

The consultant will be expected to access overseas information either through travel or subcontracting. The consultant will be expected to coordinate this information with the RIRDC project on a *Review of the farm and resource management issues relating to genetically modified plants.*

9.2 APPENDIX 2. List of Persons and Organisations Consulted

In the course of the study researchers contacted a number of individuals and organisation to improve understanding about the level of research activity and product development occurring. Eight basic groups were identified:

A. The Australian Agricultural Research and Development Corporations
B. Australian Universities
C. Offshore Universities
D. Specialist research organisations with programs in the subject area.
E. Cooperative Research Centres
F. Industry Associations
G. General Organisations
H. Commercial Companies

The following organisations are representative of those contacted about the research project. Middlesex University contacts are not included here, but are available from the author.

Aboriginal and Torres Strait Islander Commission, Canberra, Australia	Michael Davis – Tel. 02 6121 4000
Astrazeneca, Sydney, Australia	Tel. 02 9635 3275
Australian Biotechnology Association, Melbourne, Australia	Tel. 03 9596 8879
Australian Venture Capital Association, Sydney, Australia	Tel. 02 9232 1055
ACIAR, Canberra, Australia	Dr Ian Bevege – Tel. 02 6217 0500
Australian Pharmaceutical Manufacturers Association, Sydney, Australia	Tel. 02 9922 2699
Biota Holdings Limited, Melbourne, Australia	Tel. 03 9529 2311
Biotechnology Australia, Canberra	Tel. 02 6213 6367
Blackmores Limited	Phillip Daffy – Tel. 02 9951 0111
Bureau of Rural Sciences	Craig Pearson/Sandra Thomas
Centuris, Sydney, Australia	Julie-Anne White. Tel. 02 4342 7478
Cooperative Research Centre (CRC) for Food Industry Innovation	Prof. Noel Dunn. Tel. 02 9385 1014
CRC for International Food Manufacture and Packaging Science	Dr Roger Edwards and Allan Foster, Tel. 03 9214 8576
CRC for Industrial Plant Biopolymers	Dr Doug Hawley – Tel. 03 9706 9730
CRC for Polymers, Melbourne, Australia	Dr Ian Dagley – Tel. 03 9558 8111
CRC for Tropical Plant Protection, Brisbane, Australia	Prof. John Irwin – Tel. 07 3365 2790
CSIRO, Sydney, Australia	Dr Chris Mallett – Tel. 02 9490 8250
CSIRO Wildlife, Canberra, Australia	Barney Foran – Tel 02 6242 1600
Deloitte, Sydney, Australia	Glen Sanford – Tel. 02 9840 7000
Dairy Research & Development Corporation, Melbourne, Australia	Joe Sullivan – Tel. 03 9602 5300
Everen Securities, Chicago, Australia	Tel. 312 574 6000
ExGenix Operations Limited, Melbourne, Australia	Howard Wildman – Tel. 03 9208 4023
Faulding Pharmaceuticals	
Fisheries Research and Development Corporation, Canberra, Australia	Patrick Hone – Tel. 02 6285 4485
Food Science Australia, Sydney	Michael Eyles – Tel. 9490 8341
Grains Research and Development Corporation	Tel. 02 6272 5525
Herbal Medicines Research and Education Centre	Dr George Li – Tel. 02 9351 4435
Horticultural Research and Development Corporation, Sydney, Australia	Les Baxter, Russell Soderland – Tel. 02 9418 1352
International Centre for Research into Agroforestry, Nairobi, Kenya	Ian Dawson
Mediherb, Brisbane, Australia	Lee Carroll – Tel. 07 4661 0700
Monash University, Melbourne, Australia	Prof. Mark Wahlqvist – Tel. 03 9905 8145
Olsen & Vickery, Perth, Australia	Graham Olsen – Tel. 08 9530 4604
Paramount Plastics, Melbourne, Australia	P. McWilliam – Tel. 03 9359 3888
Pig Research and Development Corporation, Canberra, Australia	I. Johnson – 02 6272 5139
Plastics and Chemicals Industries Association	Tel. 03 9699 6299
Phytex, Sydney, Australia	Reg Smith - Tel. 02 9533 1324
Plastral Fidene, Melbourne, Australia	Warwick Hall – Tel. 02 9481 1166
Promega, Sydney, Australia	Dr Noel Chambers – Tel. 02 9565 1100
Queensland Dept. Primary Industries, Brisbane, Australia	Craig Davis – Tel. 07 3406 8611
Rural Industries Research and Development Corporation, Canberra, Australia	Dr David Evans – Tel. 02 4454 3039
RIRDC (RIRDC) (Essential Oils and Plant Extracts)	Tony Byrne – 02 6272 5472
RIRDC (New Animal Products)	Peter McInnnes – 08 8556 7331
RIRDC (Honeybee, rice)	Jeff Davis – 02 6272 4152
RIRDC (Organic produce)	Ewan Colquhoun -
Royal Botanic Gardens, Kew, UK	Steve Davis – 0 20 8332 6772
Sugar Research and Development Corporation, Bundaberg, Australia	Ian Jones – Tel. 07-32100495
Therapeutic Goods Administration, Canberra, Australia	Fay O'Connor. Tel. 02 6232 8474
University of Newcastle, Newcastle, Australia	Prof. Ron Wills – Tel. 02 4348 4140
University of New South Wales, Sydney, Australia	Dr Peter Rogers – Tel. 02 9385 3896
University of Mississipi, Mississipi, USA	Dr Alice Clark
University of Southern Cross, Lismore, Australia	Prof. Peter Waterman & David Leach
USANA Limited, Salt Lake City, USA	Tel. 801 954 7100

9.3 APPENDIX 3. Research into Natural Products: Case Studies of Australia & USA

A3.1 University of Southern Cross

Meeting with Prof. Peter Waterman, ATTORI (Australian Tea Tree Oil Research Institute) Professor of Chemistry; Assoc. Professor David Leach, Research Manager (Chemistry) of ATTORI; and Dr. Luigino Doimo, Postdoctorate Researcher at ATTORI.

Background

The CENTRE FOR PHYTOCHEMISTRY, of which Peter Waterman is the Director, opened recently on 25th February 2000. There are about 25 scientists working at the Institute (this includes about four higher degree research students of the University of the Southern Cross). ATTORI has close links with the University (on whose land it is situated) and with other Institutes sharing the University Campus, in particular the Centre for Plant Conservation Genetics, the Australian Agriculture Research Institute and the Environmental Analysis Laboratory.

Attached to the University Campus is the Cellulose Valley Technology Park, a more recent University of Southern Cross project. Its aim is to encourage local natural product based industries to establish their research facilities in Cellulose Valley in close proximity to the research facilities offered by the University and thus to make northern NSW the hub of a natural product industry. The Cellulose Valley Technology Park is in its early stages of development and a number of companies have expressed an intension to establish some kind of presence there. At present there is Mediherb Pty Ltd and Blackmores Pty. The New Zealand company SCENZ (Supercritical Extraction New Zealand Limited) is planning to locate.

Research Programmes

Current projects cover celcy oil, ginger extracts, Backhousia citriodora leaf oil, melaleuca alternifolia oil, and various subtropical and tropical eucalypts.

Plants with medicinal properties and which could have application in the acidic and semi arid Australian environment, include some woody plants (shrubs, trees). But the problem is that few plants will grow well and fast under such conditions. It was felt that resin producing plants, usually belonging to the family Burseraceae (genera Commiphora, Canarium, Bosswellia), could be useful as they yield the commercially sought after resins such as myrrh, olibanum, frankincense as well as essential oils. Some Acacia exudates might also be useful. Other plants which might be useful are species of Pygeum (used in the Cameroons for prostate cancer), Stevia species (sweeteners for diabetics), valerian (sedative: the active principles are according to recent work by Argentinian workers not the valepotriaites but some as yet unidentified constituents) and possibly the Ethiopian Khata edulis (contains alkaloids with tonic properties; a general pepping-up drug).

Resources, Services and Information Management

In addition to standard laboratory equipment the Research Institute has the following: very advanced gas-liquid chromatography – mass spectrometry equipment, high resolution gas liquid chromatography, liquid chromatography, liquid chromatography – mass spectrometry, nuclear magnetic resonance etc. There are also facilities for pilot-scale industrial development such as supercritical fluid extraction, spray and freeze drying equipment, constant temperature rooms for ageing experiments etc.

Since its establishment some four years ago, ATTORI has expanded from being a purely tTea Tree oil oriented laboratory into applied phytochemical research aimed at the production of value-added products based on natural extracts.

Commercialisation

The University of the Southern Cross searches for suitable industrial partners for any industry-oriented research projects. It views closer collaboration between scientists and industry as increasing the likelihood of a successful and thus profitable outcome.

A3.2 University of Mississippi [National Centre for the Development of Natural Products] [NCNPR]

Background

Based at the University of Mississippi, NCNPR is housed in a new research centre, which opened in July of 1995 with 80 – 100 scientists and support personnel. The state-of-the-art facility is equipped with specialised laboratories for plant extraction, biological screening, isolation and analytical chemistry, synthetic chemistry, molecular modelling, biochemistry/cell biology, pharmacology/toxicology, agronomics, and plant tissue culture work. The Research Core groups, facilities, and resources that are seen to comprise the infrastructure necessary to conduct natural products research support these laboratories. The Research Core groups include a Plant Collection and Medicinal Plant Garden, Biological Testing, Analytical Testing, Lead Optimisation and Development, and Database and Compound Library cores.

NCNPR believe natural products offer a vast and virtually unlimited source of new agents for both the pharmaceutical and agrochemical industries. NCNPR was created to bring together an alliance of academia, government, and the pharmaceutical and agrochemical industries to integrate research, development, and commercialisation of potentially useful natural products. It is the USA's only university-affiliated research centre devoted to improving human health and agricultural productivity through the discovery, development, and commercialisation of pharmaceuticals and agrochemicals derived from natural products. The NCNPR conducts basic and applied multi-disciplinary research to discover and develop natural products for use as pharmaceuticals, dietary supplements and agrochemicals, and to understand the biological and chemical properties of medicinal plants. Research focuses on discovering new drugs for unsatisfied therapeutic needs to treat degenerative diseases such as cancer and infectious diseases, improving the quality and safety of dietary supplements, and discovering new, effective agrochemicals that will not harm the environment. To complement in-house biological screening capabilities, there is a repository of several thousand natural product extracts that are available for screening by collaborators working in other therapeutic areas. The NCNPR also conducts research on medicinal plants so that they may be developed as crops for US farmers.

Discovery and early development of bio-active natural products as prototype pharmaceuticals has been a priority in the School of Pharmacy for almost 30 years. It involves researchers in the Department of Pharmacognosy, the Department of Medicinal Chemistry, the Department of Pharmaceutics, the Department of Pharmacology, and the Research Institute of Pharmaceutical Sciences.

USDA's Natural Products Utilisation Research Unit is located at NCNPR and brings expertise, experience and linkages in natural products research related to agriculture. The NCNPR faculty and staff also have a large number of collaborations with scientists working in other government agencies, academic organisations, research institutes and industry.

Research is focussed on using leading edge knowledge and technology to discover bio-active natural products, develop novel technologies or processes that facilitate the discovery of bio-active natural products, and provide research-based information on plant-derived products with medicinal or agricultural applications. The multi-disciplinary program is conducted in two major research areas: the Natural Product Discovery and Development Program, and the Medicinal Plant Research Program.

The NCNPR is staffed with 55 research faculty and support staff, a 22 person academic faculty of the School of Pharmacy who hold joint appointments in the Centre, and 21 research scientists and staff of the USDA/ARS Natural Products Utilisation Research Unit. There are also a number of undergraduate and graduate students and postdoctoral scientists.

Research Programs

1. Natural Product Discovery and Development-Program

The Natural Product Discovery and Development Program is divided into two major areas of research: the Drug Discovery and Development Program and the Agrochemical Discovery and Development Program.

Drug Discovery and Development Program
The goal of the Drug Discovery and Development Program is to discover single entity and multi-component bioactive natural products that may serve as leads for the development of new pharmaceuticals that address unsatisfied therapeutic needs. Emphasis is on agents that control certain infectious diseases, cancer and immune disorders. Chemical constituents responsible for biological effects are identified and then either isolated and purified in the search for new single entity pharmaceutical ingredients or characterised and standardised in the search for new multi-component botanical products. Main strengths of this program are in the areas of:

- Sourcing, acquisition and sample preparation
- Biological evaluation in contemporary and relevant targets
- Isolation and structure elucidation

The discovery program starts with the collection of natural products from worldwide sources. Sources of natural products include plants, marine organisms and microorganisms. The sourcing, acquisition, and sample preparation are built upon a well-documented track record of unique strengths, including:

- Experience in collecting and processing higher plants, marine organisms and microbes for biological evaluation
- Expertise to develop novel and unique sourcing strategies
- Maintenance of a unique, bio-diverse extract and. compound library
- Expertise in microbial and semi-synthetic transformations
- Capability to follow-up on active leads

The biological evaluation conducted at the NCNPR is aimed at supporting the discovery of promising lead compounds by using a combination of mechanism-blind and mechanism-specific biological assays to detect agents that show novel activity against selected infectious diseases, cancer, and immunological targets. There is also significant collaboration with many academic, government and private sector laboratories in the US that run complementary biological assays in support of the discovery program.

With a strong critical mass of expertise, the Centre is particularly well suited to undertake the bioassay directed fractionation of plant, marine, and microbial extracts that exhibit promising biological activities. Promising leads are then developed either as single chemical entities or as multi-component botanical ingredients. In the case of single chemical entities, analogies are synthesised using computer-aided design, and structure activity relationship (SAR) studies. Molecular modelling is used to optimise the desired pharmacological properties. Selected lead compounds are then progressed into an early development program where preclinical, chemical development, analytical, pre-formulation, formulation and stability studies necessary for the successful filing of an Investigation New Drug Application (IND) are completed. These activities are done in collaboration with academic or private sector laboratories. In cases where a natural product sample contains several components that may act through different mechanisms of action within the body, and therefore act additively or synergistically to exert a therapeutic effect, early development work is based on standardisation of the multicomponent mixture rather than isolation of individual constituents.

Current projects within this Program include the discovery and development of antifungal agents for life-threatening infections; anticancer agents that target specific critical processes in the cancer cell; antibiotics effective against bacteria that are resistant to many current antibiotics; new drugs for tuberculosis, malaria and other tropical parasitic diseases; antioxidants for cancer prevention; immunostimulatory botanicals; anti-inflammatory botanicals; immunomodulatory natural products; and the development of Dronabinol Hemisuccinate (THC) suppositories to control nausea due to chemotherapy and for pain management. Research is also conducted on the optimisation of yields of desirable bioactive constituents in plants.

Agrochemical Discovery and Development Program

The goal of the Agrochemical Discovery and Development Program is to identify lead compounds for the development of environmentally benign and toxicologically-safe pest management agents. This program is done in collaboration with scientists in the Natural Products Utilisation Research Unit of the USDA Agricultural Research Service. Emphasis is on the discovery and development of agents useful in the control of pests affecting small niche crops.

2. Medicinal Plant Research

The Medicinal Plant Research Program has two major areas of research: Botanicals and Human Health and Medicinal Plants as Alternative Crops.

Botanicals and Human Health Program

The goal of the Botanicals and Human Health Program is to identify botanical products with the potential to improve human health and to enable the safe, effective and proper use of high-quality botanical products by informed professionals and consumers. Consumer health products based directly on plant and minimally-processed plant products, known as herbal products, botanicals, dietary supplements, phyto-medicines, or nutraceuticals have recently shown a rapid sales growth in the US. NCNPR considers the quality of the products that are on the marketplace to be highly variable with neither the consumer nor the health-care professional able to distinguish between high and low quality products. The NCNPR scientists believe that good science is needed to provide information required by the public to make good decisions concerning the proper use of these products.

The Botanicals and Human Health Program includes both research and educational activities. Research projects focus on enhancing product quality and safety through botanical, pharmacological, chemical and agronomic characterisation of botanical products, and the discovery of new botanical products.

Current projects that focus on enhancing product quality and safety, include working with the Food and Drug Administration to develop a model for the development of botanicals as drug products; developing analytical methods for bio-active constituents, degradation products, and contaminants; and working with USDA on the use of genetic profiling to certify authenticity of seeds and plant specimens.

The NCNPR's approach for the development of new botanical products relies on traditional use/ethnobotanical information to identify leads, a battery of biological assays (cellular, biochemical and molecular) to detect biological activity and chemical standardisation technologies. The research program starts with gathering, assessing, and organising literature regarding traditional uses of botanicals throughout the world. This information is reviewed to identify lead candidates for new product research. Much of the controversy surrounding existing literature on botanicals results from inadequate research aimed at ensuring quality plant material that has been authenticated botanically and characterised chemically and pharmacologically. The research program includes sample authentication, analytical and biological characterisation, and standardisation activities. Research is also conducted on the optimisation of yields of desirable bioactive constituents in plants. Current projects include identification and development of botanicals with antioxidant, immunostimulatory and anti-inflammatory activities.

Educational activities include providing practical information on botanical products to health-care professionals, government officials and consumers. Market research studies are coinducted to understand what health-care professionals and consumers know and don't know about botanical products, how health-care professionals and consumers use botanical products, and to identify supply chain issues that are unique to manufacturing and distributing botanical products. Scientists in the NCNPR and the academic departments of the School of Pharmacy are involved in continuing education programs for pharmacists, physicians and other health-care professionals, and serve on advisory committees to the FDA, the National Institutes of Health (NIH), the United States Pharmacopoeia (USP) and industry trade associations.

Medicinal Plants as Alternative Crops Program

The goal of the Medicinal Plants as Alternative Crops Program is to conduct research that can be used to develop medicinal plants as high value alternative crops for U.S. farmers. Research focusses on identifying medicinal plants that are viable economic opportunities for farmers and on correlating cultivation, harvesting and agronomic conditions to the plant's ability to produce the desired chemical and pharmacological profile. Environmental chambers are used to simulate different growing conditions and experimental plots are grown at the Centre's Medicinal Plant Garden. Other research activities include determining the optimal post-harvest processes to maximise desirable properties, genetic engineering, crop improvement studies, and translational research and marketing research.

Current projects within this Program include economical production of podophyllotoxin, an important intermediate in the synthesis of anticancer agents; evaluation of agronomic potential of medicinal plants in Mississippi; value-added development of botanicals through harvest; post-harvest and storage practices; and market research to quantify commercial potential.

3. Development of Products and Technologies

In partnership with the Department of Medicinal Chemistry, the Department of Pharmacology, the Department of Pharmacognosy, and the Department of Pharmaceutics in the School of Pharmacy; and with external collaborators, the NCNPR, has the expertise to complete the studies required in the US to file an Investigational New Drug (IND) application for a new pharmaceutical product. And it can complete the early development activities for a new agrochemical product or a botanical dietary supplement. The development capabilities of the Centre include:

- Medicinal Chemistry, Structure-Activity Relationship Studies, Computer-Aided Drug Design, and Molecular Modelling Analytical Methods Development, Preformulation and Formulation Development
- Biochemical Studies and Mechanism of Action Determination
- Efficacy and Safety Assessments
- Greenhouse Studies
- Optimisation of Extraction Processes

Externally sourced grants and contracts provide funding for development activities. The NCNPR actively seeks collaborations with specific academic and industrial partners to accelerate the development programs.

Resources, Services and Information Management

The NCNPR research program is supported by significant resources including:

- A repository and database containing over 10,000 natural product specimens, derived extracts, and pure compounds
- A 10-hectare Medicinal Plant Garden for medicinal plant cultivation and experimentation
- Central Instrumentation Laboratory housing 500, 400, and 300 MHz NMRS; HR-MS; FF-IR; LC-CD/ORD
- Molecular Modelling Laboratory with nine Silicon Graphics work-stations and supporting software
- Technical Literature Services with on-line search capabilities
- Natural Products Analytical Laboratory with state-of~the-art instrumentation
- Integrated Science Library housing over 65,000 volumes
- Central Animal Facility (to be completed in 2000)

Commercialisation

The primary responsibility of the School of Pharmacy's Office of Technology Commercialisation and Business Development is to facilitate the commercialisation of the products, technologies, and information discovered and developed by the NCNPR. The NCNPR is committed to the commercialisation of its discoveries so that such discoveries can positively impact society. By meeting its objectives of providing focussed leadership in natural products research, culminating in the discovery, development and commercialisation of new pharmaceuticals and agrochemicals, the NCNPR meets its mission of improving human health and agricultural productivity. As a result, the US is seen to achieve improved competitiveness in the global pharmaceutical and agrochemical market. An additional benefit will be the identification of potential alternative cash crops for U.S. farmers, and the demonstration of the benefits of global biodiversity conservation.

9.4 APPENDIX 4. : Potentially Useful Plants for Medicinal & Industrial Purposes

This section identifies and describes briefly a number of plants from various climates that have chemical constituents of potential value for medicinal and industrial products. Some of these plants, which originate from dry regions, have been extracted from the list for the specific requirements of Chapter 6. These are plants requiring further research to evaluate their application in Australia in various regions.

9.4: APPENDIX 4: Potentially Useful Medicinal Plants for Further Investigation: all Habitats

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
1. Plants Used to Treat Tinea and Ringworm							
Barringtonia macrostachya	*B. cylindrostachya*	Lecythidaceae	tree	Tropics		saponins	
Cassia alata	*Senna alata*	Caesalpiniaceae (Leguminosae)	tall shrub	tropical coastal areas	crushed leaves rubbed on skin	anthraquinones in the leaves	Yes, limited
Cassia notabilis Cockroach bush	*Senna notabilis*	Caesalpiniaceae (Leguminosae)	small shrub	arid to semi-arid tropical areas	decoction from leaves and twigs applied to skin	saponins & probably anthraquinones in closely related species	
Cassia venusta	*Senna venusta*	Caesalpiniaceae (Leguminosae)	shrub	tropics, wet as well as arid	decoction from fresh, new leaves, applied to skin	saponins & probably anthraquinones in closely related species	
Citrullus colocynthis Paddy melon		Cucurbitaceae	vine	all regions, particularly dry inland	single application of juice on affected part of body	the ripe fruits contain triterpenoid glycosides	
Crinum angustifolium Onion lily		Amaryllidaceae (Liliaceae)	herb	flood plains in the tropics	decoction or infusion from bulbs and/or leaves applied to skin	alkaloids in the bulbs	
Crinum uniflorum		Amaryllidaceae (Liliaceae)	herb	flood plains in the tropics	crushed bulb applied to skin	alkaloids in the bulbs	
Diospyros maritima		Ebenaceae	tree	tropical coast	heated fruit is ground to paste & applied to lesion	naphthoquinones in the fruits	
Corymbia gummifera	*Eucalyptus gummifera*	Myrtaceae	tree	coastal areas in the subtropics	crushed fruit rubbed on skin	kino contains phenolic compounds and flavonoids	
Ficus opposita Sandpaper fig		Moraceae	tree	wet tropics	latex applied to lesion	the latex contains triterpenoid esters	
Gyrocarpus americanus Propeller tree; stinkwood		Hernandiaceae	tree	tropics	infusion of roots applied to lesions	bark contains alkaloids	
Myristica insipida Queensland nutmeg		Myristicaceae	tree	tropical coastal areas	resin applied to skin	probably tannins present in the resin	
Passiflora foetida Wild passionfruit		Passifloraceae	vine	tropics	the skin is bruised first, then covered with mashed leaves	cyanogenic glycosides in the leaves	

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
Santalum acuminatum Sweet quondong; Native peach	*Fusanus acuminatus Eucarya acuminata*	Santalaceae	tree	semi-arid subtropics	ground seed kernels applied to lesions	probably acetylenic esters present in kernel oil	
OR Elaeocarpus grandis		Elaeocarpaceae	tree				
Scaevola taccada Sea lettuce tree; native cabbage		Goodeniaceae	shrub	coastal areas in tropics	crushed fruit rubbed on skin	fruits, possible glycosides	
2. Plants Used as Tonics							
Alstonia constricta Bitter bark; quinine bark		Apocynaceae	tree	rainforest to dry inland (but not arid) in tropical and subtropical climates	infusion of bark in alcohol	alkaloids	
A. scholaris	*A.cuneata* Echites scholaris	Apocynaceae	tree	tropical rainforest	as a general tonic	alkaloids	
A. vitiensis var. vitiensis	*A. villosa*	Apocynaceae	tree	moist tropics	decoction of leaves	alkaloids	
A. vitiensis var. novo-ebudica		Apoeynaceae	tree	moist tropics	leaves used	alkaloids	
Bacopa monniera	*Bramia indica*	Scrophulariaceae	creeper	coastal tropical and subtropical regions	whole plant	alkaloids triterpenoid saponins	
Caesalpinia bonduc	*Guilandina bonduc Guilandina bonducella Caesalpinia bonducella*	Caesalpiniaceae (Leguminosae)	shrub	coastal tropics	seeds and roots as well as bonducin as such	Bonducin (= guilandin)	
Centaurium spicatum Centaury	*Erythraea australis Centaurium australe*	Gentianaceae	herb	pastures, grasslands	decoction of whole plant	erythrocentaurin (a glycoside)	
Croton insularis Queensland cascarilla		Euphorbiaceae	shrub to tree	tropical rainforest	powdered bark as well as bark infusion		

Plants Species	Synonyms	Family	Habit	Habitat	Mode of application	Chemical Constituents	Existing Market
Croton phebaliodes Native cascarilla		Euphorbiaceae	small tree	tropical rainforest	bark	a bitter substance	
Eclipta prostrata	*Eclipta alba*	Asteraceae	herb	tropical and subtropical coastal areas	roots/whole plant	wedelolactone; nicotine	
Exocarpos cupressiformis Native cherry; native ballart		Santalaceae	shrub to small tree	coastal as well as inland areas	twigs used	Flavonoid glycosides; triterpenoids	
Isopogon ceratophyllus		Proteaceae	shrub	temperate areas	bark		
Morinda citrifolia Indian mulberry	*Morinda quadrangularis*	Rubiaceae	tree to shrub	coastal tropics	leaves	probably alkaloids	
Nauclea orientalis Leichhardt tree	*Sarcocephalus coadunatus S. cordatus*	Rubiaceae	tree	dry tropics	alcoholic bark infusion	bitter principle	
Piper novae-hollandiae		Piperaceae	climber	rainforest in tropical and subtropical areas		probably alkaloids	
Sebaea ovata Yellow centaury	*Exacum ovatum*	Gentianaceae	herb	coastal areas, all types of climate	herb	bitter principles, probably lactones & lactone glycosides	
Smilax australis		Smilacaceae	climber	humid subtropics	whole herb		
Smilax glyciphylla Native sarsaparilla		Smilacaceae	climber	humid coastal subtropics	herb	glyciphyllin(a glycoside)	
Wedelia calendulacea		Asteraceac	herb	coastal tropics		wedelolactone	
Harpagophytum procumbens		Pedaliaceae	herb to small shrub	tropics and subtropics	as a tea from its tuber-like roots	iridoid glycoside	yes
Astragalus membranaceus as well as some related	*Astragalus propinquus*	Fabaceae	herb	temperate to cold climates in mountainous areas	root powdered or as extracts; also as tea	triterpenoid glycosides, polysaccharides, flavonoids etc	yes

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
Saussurea lappa	*Aucklandia costus*	Asteraceae	herb	tropics	root	essential oil containing sesquiterpenoid lactones	yes, for oil only
Ligustrum lucidum Glossy privet		Oleaceae	shrub	distributed world wide	as herbal tea	triterpenoids (free and as glycosides); essential oil	yes
Catha edulis Khat		Celastraceae	tree	arid & semi-arid region	leaves chewed	alkaloids	
3. Plants With Bactericidal Uses							
Artemisia vulgaris		Asteraceae	herb		leaves used to treat ulcers	sesquiterpenoid lactones	
Bryophyllum calycinum	*Kalanchoe pinnata*	Crassulaceae	herb	dry, warm areas	leaves used for the treatment of shingles	isocitric acid	
Centella asiatica Indian pennywort	*Hydrocotyle asiatica*	Apiaceae	herb	moist areas in temperate to tropical climates	herb used for the treatment of ulcers and wounds	triterpenoid glycosides	yes
Eucalyptus *species* (refer also to Chapter 6)							
Ipomoea brasiliensis	*I. Pes-caprae* ssp. brasiliensis	Convolvulaceae	woody climber	moist areas in the tropics and sub-tropics	leaves used to treat boils, abscesses and sores		
Jasminum grandiflorum		Oleaceae	shrub	tropical coastal areas	leaves used for the treatment of mouth ulcers		
Santalum acuminatum Sweet quondong; native peach	*Fusanus acuminatus* Eucarya acuminata	Santalaceae	tree	semi-arid subtropics	fruit used against'golden staph'	acetylenic lipids	
Santalum spicatum Western Australian sandalwood	*Fusanus spicatus* *Eucarya spicata*	Santalaceae	tree	semi-arid subtropics	volatile oil is bactericidal	sesquiterpenoid alcohols	yes

Plants Species	Synonyms	Family	Habit	Habitat	Mode of application	Chemical Constituents	Existing Market
Sida rhombifolia Paddy's lucerne; jelly leaf	*S. retusa*	Malvaceae	shrubby herb	tropics and subtropics	leaves used for the treatment of sores and ulcers	the plant contains ephedrine	
Vigna radiata	*Phaseolus radiatus*	Fabaceae	herb		beans used for the treatment shingles		
4. Plants Used In The Treatment Of Diabetes							
Astragalus membranaceus as well as some related A. species	*A. propinquus*	Fabaceae	herb		high doses of dried root (up to 60g)	triterpenoid glycosides polysaccharides and flavonoids etc.	yes
Prosopis juliflora		Fabaceae	tree	marginal soils; drought tolerant	a flour made from cotyledons and embryos is suitable for diabetics		Yes
Pueraria lobata Kudzu root and *Pueraria thomsonii*	*P. montana var. lobata* *P. thunbergiana* *P. pseudohirsuta* *Dolichos lobatus*	Fabaceae	climbing vine	worldwide	root contains hypotensive constituents	puerarin and other isoflavonoids	yes
Scoparia dulcis scoparia		Scrophulariaceae	shrub	tropics, in coastal areas	the plant contains an antidiabetic compound; the plant has not been used for this condition by the aborigines	amellin`, which is said to be the active constituent; triterpenes	
Stevia rebaudiana Sweet herb; stevia	*Eupatorium rebaudianum*	Asteraceae	herb	semi-tropical highlands	leaves are sweet but hypoglycaemic activity is doubtful	stevioside (a mixture of diterpenoid glycosides)	yes
Syzygium cumini	*Eugenia cumini* *Eugenia jambolana* *Syzygium jambolanum*	Myrtaceae	tree	tropics and subtropics, mountainous areas	bark and seeds are used		yes?

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
Vaccinium myrtillus bilberry		Ericaceae	shrub	temperate and subalpine of a gallic acid derivative Climates	leaves as a tea	neomyrtillin, a glycoside	yes?
5. Plants With Insecticidal/Pesticidal Uses							
Annona reticulata Bullock's heart		Annonaceae	tree	tropics	seeds as well as roots are effective against aphids; stems and leaves too		
Corymbia citriodora Lemon scented gum	*Eucalyptus citriodora*	Myrtaceae	tree	coastal tropical and subtropical regions	mosquito repellent	3,8-p-menthane diols are the active constituents	
Annona muricata Custard apple		Annonaceae	tree	tropics	seeds, root and leaves contain an insecticidal substance		
Annona squamosa Sugar apple		Annonaceae	tree	tropics	leaves and roots are insecticidal		
Azadirachta indica ('Neem')		Meliaceae	tree	warm and not too dry climates	seed and leaf extracts sprayed on crops	limonoids	Yes
6. Antimalarial Plants							
Caesalpinia bonduc	Guilandina bonduc *G. bonducalla Caesalpinia bonducella*	Caesalpiniaceae	shrub	coastal areas in the tropics		bonducin (=guilandinin)	
Carica papaya Paw-paw		Caricaceae	tree	moist tropics	flowers infused as a tea(very bitter) usually in combination with other plants		

Plants Species	**Synonyms**	**Family**	**Habit**	**Habitat**	**Mode of application**	**Chemical Constituents**	**Existing Market**
Nauclea orientalis	*Sarcocephalus coadunatus* *S. cordatus*	Rubiaceae	tree	dry tropics	bark infusion		
Artemisia annua		Asteraceae	woody herb	tropics	pure artemisinin taken orally	artemisinin	yes?
Eucalyptus robusta	*E. multiflora*	Myrtaceae	tree	wet tropics and subtropics	source of robustadials	robustadials A and B	
Azadirachta indica Neem		Meliaceae	tree	warm and not too dry climates	as a tea from the leaves or as an alcoholic extract	limonoids	yes
7. Plants With Anti-Inflammatory Properties							
Ananas comosus ('pineapple')	*Ananas sativus* *Bromelia comosa* *Bromelia ananas*	Bromeliaceae		tropics	the mixture of enzymes obtained from the fruit juice is used	Bromelain (a mixture of enzymes)	
Azadirachta indica Neem		Meliaceae	tree	warm and not too dry climates		limonoids	
Callitris intratropica Northern cypress pine		Cupressaceae	tree	tropics; rocky, sandy soils	essential oil from heartwood	azulenes etc.	yes
Croton arnhemicus		Euphorbiaceae	shrub	tropics, both coastal as well as inland	inner bark	triterpenoid saponins	
Elytrigia repens	*Agropyron repens* *Triticum repens*	Poaceae	herb	temperate to cold climates	treatment of inflammatory disease of the urinary tract using an aqueous decoction or an alcoholic extract of the plant	various sugars, and an essential oil rich in agropyrene which exhibits antibiotic properties	
Gyrocarpus americanus Propeller tree; stinkwood	*Gyrocarpus jacquinii*	Hernandiaceae	tree	tropics	roots and young shoots rubbed on the body parts affected	alkaloids	

Plants Species	Synonyms	Family	Habit	Habitat	Mode of application	Chemical Constituents	Existing Market
Harpagophytum procumbens Devil's claw		Pedaliaceae	herb	arid tropics	aqueous extract of the roots (tubers)	iridoid glycosides,etc.	yes
Curcuma longa	*Curcuma domestica*	Zingiberaceae	herb	tropics	a fraction of the essential oil	possibly sesquiterpenoids	yes
Strychnos lucida Strychnine tree		Loganiaceae	shrub to tree	tropics	decoction of fruit or bark applied to affected part of body	alkaloids	
Centella asiatica Indian pennywort	*Hydrocotyle asiatica*	Apiaceae	herb	moist areas in temperate to tropical climates	leaves eaten	triterpenoid glycosides	yes
8. Plants With Hypotensive Properties							
Morinda citrifolia	*Morinda quadrangularis*	Rubiaceae	tree to shrub	coastal tropics	a drug from the roots and the trunk	morindin (a glycoside), anthraquinones	yes?
Saussurea lappa	Aucklandia costus	Asteraceae	herb	tropics	fractions of the essential oil (costus oil)	12-hydroxycostunolida and the delactonised oil are the most potent hypotensive fractions of the oil	yes?
Pueraria lobata Kudzu root and *Pueraria thomsonii*	*Pueraria montana Var. lobata; P. thunbergiana; P. pseudohirsuta*; *Dolichos lobatus*	Fabaceae	vine	worldwide	roots (tubers)	isoflavonoids, flavonoids, coumarins; puerarin is the main isoflavonoid	yes
9. Anti-Aids/Hiv Plants							
Ancistrocladus sp. related to *A. abbreviatus*			vine	tropical rainforest	source of alkaloids; michellamine B appears to be the most active		
Conospermum species Smoke bush		Proteaceae	bush	semi-arid subtropical climates	source of conocurvone, the active principle		

Plants Species	Synonyms	Family	Habit	Habitat	Mode of application	Chemical Constituents	Existing Market
10. Plants With Anthelmintic Properties							
Carica papaya Paw-paw		Caricaceae	tree	humid tropics	latex, probably taken orally	papain (a proteolytic enzyme which kills intestinal parasites)	
11. Plants With Anti-Cancer And Anti-Tumour Properties							
Bauerella simplicifolia	*Acronychia baueri* *Acronychia simplicifolia*	Rutaceae	shrub to small tree	dry rainforest in tropical to subtropical areas	Source of alkaloids	acronycine etc,	
Pygeum africanum (?)	*Prunus africana*	Rosaceae	shrub	tropics	prostate cancer		
Serenoa repens (‘Saw palmetto’)	*Serenoa serrulata* *Sabal serrulata*	Palmaceae	shrubby palm	tropics	prostate cancer – for relief of symptoms only	fatty acids, triterpenoids, polysaccharides etc.	
Cassia senna Alexandrian senna	*Cassia acutifolia* *Senna alexandrina*	Fabaceae	shrub	tropics - semi-arid regions	source of a polysaccharide which inhibits certain tumours	polysaccharides	yes (but only as a laxative)
Cassia angustifolia Indian senna	*Senna alexandrina*	Fabaceae	shrub	tropics			yes (but only as a laxative)

10. Glossary

ACE inhibitors	Treatment for elevated blood pressure. Acts by inhibiting the release of angiotension II, which constricts arteries. (ACE: Angiotensin-converting enzyme)
Acute	Rapid onset, sever symptoms and brief duration (of diseases)
Adhesin	Bacterial surface proteins associated with the attachment of the bacterium to the host cell; a primary stage of infection
AHA	Alpha hydroxy acids
Alimentary	The entire passage through which food passes, from mouth to anus
Alkaloid	Nitrogen containing, basic organic compounds occurring in plants
Allylic	Sulphides associated with reduced prevalence of cancer (onions,garlic)
Allergic reaction	Hypersensitive reactions of the body to foreign bodies (antigens), usually including cellular damage and inflammation
Alzheimer's Disease	A progressive degeneration of mental function and memory occurring in middle age
Amoebicide	A compound able to kill amoebae (single-celled animals)
Analgesic	A medication that reduces or eliminates pain
Angiogenesis	Development of blood vessels in a tissue
Anti-arrhythmic	A substance used to treat cardiac arrhythmia (any abnormality of heart rate and/or rhythm)
Antibiotics	Substances that can destroy or inhibit the growth of other micro-organisms. Widely used in the prevention and treatment of infectious diseases
Anticholinergic	Inhibiting or blocking the physiological action of acetylcholine at a receptor site
Anticoagulants	A substance that prevents the clotting of blood
Antiemetic	A drug that prevents or alleviates nausea and vomiting
Antihypertensive	Reducing or controlling high blood pressure
Antimicrobial	Capable of destroying or inhibiting the growth of micro-organisms
Antioxidant capacity	The total antioxidant potential of a system (such as blood)
Antioxidants	A chemical compound or substance that inhibits oxidation
Anti-Parkinsonian	Used to treat Parkinson's Disease, a degenerative disorder of the central nervous system characterised by tremor and impaired muscular coordination
Anti-thrombolytics	Able to inhibit the break-down of blood clots
Anti-thrombotic	Able to inhibit the formation of blood clots
Anti-tussive	Able to reduce coughing
Astringent	Substances that cause cell shrinkage- often used to protect skin or reduce bleeding.
Atherosclerosis	A form of arteriosclerosis characterised by the deposition of plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.
Ayurvedic	India's traditional, natural system of medicine that has been practiced for more than 5,000 years
Agonist	A drug which acts on receptors in the same manner as the body's own chemical messenger(s)
Antagonist	A drug which acts on receptors in the opposite manner to the body's own chemical messenger(s)
Benign prostatic hyperplasia	A benign (non-cancerous) enlargement of the prostate gland – usually begins after age of 50 years – can pinch off the urethra making urination difficult or impossible if significant enlargement occurs
Beta-carotene	Antioxidant with relatively high level of vitamin A(sources include carrots, peaches, spirulina, alfalfa, spinach and other green foods)
Beta-blockers	A drug that opposes the excitatory effects of norepinephrine (noradrenaline) at beta-receptors, used for the treatment of angina, hypertension, arrhythmia, and migraine
BHT	Butylated hydroxy toluene – a strong antioxidant, often used as a reference compound for testing antioxidant activity of natural compounds/extracts
Bioassays	Tests used to determine the biological activity of a substance by comparing its effects with those of a standard preparation on a test organism
Biodegradation	Capable of being decomposed by biological agents, especially bacteria
Bioplastic	A biodegradable packaging polymer which may be based on intermediate input of lactic acid, made from by-products fermentations of, for example, whey – Cargill Dow Polymers and Matibai are manufacturing polylactic acid from corn and sugar beet – alternatively, microbially formed polyhyrdoxyalkanoates [PHA] offer potential
Biotechnology	Important enabling technologies based on the application of biological processes [Biotechnology Australia]
Bronchodilator	A drug that widens the air passages of the lungs and eases breathing by relaxing bronchial smooth muscle
Broncho-pulmonary dysplasia	Abnormal development or growth of tissues, organs, or cells in the lungs or airways
Cardiotonic	An agent used to restore/protect the normal tone of the heart
Cataract	Opacity of the lens or capsule of the eye, causing impairment of vision or blindness
Chemonucleolysis	Dissolving of the nucleus pulposus (the pulpy cushioning substance between the vertebrae), usually by chemical means that breaks down the protein structure
Cholinesterase	An enzyme found chiefly at nerve terminals that breaks down the neurotransmitter, acetylcholine
Chronic venous insufficiency	A condition in which the flow of blood in the veins is inadequate. Most often seen in the veins of the lower extremities
CNS	Central Nervous System (brain and spinal cord)
Collagen	The fibrous protein constituent of bone, cartilage, tendon, and other connective tissue
Complementary Medicines	Include, in Australia, the following products: vitamins, mineral, plant or herbal, naturopathic and/or homeopathic preparations and nutritional supplements
Condylomata acuminata	A type of genital wart
Cosmeceutical	Cosmetic products that make claim to have medicinal or drug like benefits with capacity to treat a disease, ailment or

	defect of the human body – a traditional cosmetic product labelled and presented explicitly as a cosmetic product only would not in Australia come within the coverage of the TGA or require listing in the ARTG
Diabetes mellitus	A disorder of carbohydrate metabolism, which can ultimately result in coma – can be insulin dependent or insulin independent
Dietary supplements:	Products (other than tobacco) intended to supplement the diet, containing one or more of the following: a vitamin, mineral, herb or other botanical; an amino acid or metabolite; an extract; or any combination of the previously mentioned items – according to U.S. Food and Drug Administration (FDA) regulations, a dietary supplement may be marketed in food form if it is not "represented" as a conventional food and is clearly labelled as a dietary supplement – specific health or structure/function claims are allowed on dietary supplements provided the FDA deems adequate scientific substantiation exists for the claim
Disulphide bridge	A chemical bond formed between two sulphide-containing moieties (often in amino acids)
Diuretics	A substance or drug that tends to increase the discharge of urine
Duodenal ulcer	An ulcer formed in the uppermost section of the small intestine
Dysmenorrhoea	Painful menstruation
Dyspepsia	Disturbed digestion; indigestion
Elastin	A protein similar to collagen that is the principal structural component of elastic fibres
Elastomers	A polymer having the elastic properties of natural rubber
Enzyme	Proteins or conjugated proteins produced by living organisms and functioning as biochemical catalysts
Ethnobotanicals	Flora and fauna used by indigenous persons for food and medicinal purposes
Eucaryotic	Having cells with membrane-bound nuclei
Exfoliation	Removal in flakes or scales; peel (as in skin)
Expectorant	A substance which promotes the secretion or expulsion of phlegm, mucus, or other matter from the respiratory tract
Fortified foods	Foods enriched with vitamins and minerals, usually at a range up to 100 per cent of the Dietary Reference Intake (DRI, formally called the Recommended Daily Allowance or RDA) for that nutrient – often, these foods are mandated by law to be fortified to a level that replaces nutrients lost during processing
Functional Foods:	UK medical journal Lancet describes a food as functional if it has beneficial effects on target functions in the body, beyond adequate nutritional effects, in a way that is relevant to health and well-being and/or reduction in disease (Lancet. Vol 354. September 4 1999, p794) – in Australia it remains unclear whether or not functional foods will be regulated by the Therapeutic Goods Act or by the Food Standards code administered by the Australia New Zealand Food Authority – in the US deregulation of health claims means that functional foods do not require approval of the FDA
Fungistat	A substance that inhibits the growth of fungi
GABA	Gamma-aminobutyric acid
Gastric ulcer	An ulcer formed in the stomach
Genistein	An isoflavone or plant oestrogen, found in soy foods. Research indicates genistein inhibits the growth of cancer cells.
Gout	A disturbance of uric acid metabolism occurring predominantly in males, characterized by painful inflammation of the joints, especially of the feet and hands.
Gram-positive	A class of bacteria microscopically distinguishable by their responses to Gram's stain.
Haematopoeisis	The process of production of blood cells and platelets
Hepatoprotection	The ability to protect the liver from chemical damage
HIV	A retrovirus that causes AIDS (Acquired Immune Deficiency Syndrome)
Hydrocolloid	A substance that forms a gel with water
Hypercholesterolaemia	Having an elevated level of the fat-like substance, cholesterol, in the bloodstream
Hypertension	Abnormally elevated blood pressure
Hypoglycaemic agent	Oral medications used to treat diabetes by lowering blood sugar levels
Immunomodulator	A drug that alters, suppresses or strengthens the body's immune system.
Immunosuppressant	A drug that suppresses the body's immune system; often used in organ transplants
Insulin	A hormone functioning in the regulation of the metabolism of carbohydrates and fats, especially the conversion of glucose to glycogen, which lowers the blood glucose level
Jaundice	Yellowish discoloration of the whites of the eyes, skin, and mucous membranes caused by deposition of bile salts in these tissues
Laxative	A food or drug that stimulates evacuation of the bowels
Lipid peroxidation	Oxidation of biological molecules, (such as fats and waxes) by the peroxidase enzyme
-lactamase	A bacterial enzyme which can inactivate the -lactam moiety of certain antibiotics, conferring resistance to that antibiotic. Combinations of antibiotics and compounds with inhibitors of -lactamase are widely used to combat resistance.
Lutein	Along with another carotenoid, zeaxanthin, lutein appears to protect the macula of the eye. Plant sources include spinach, kale and broccoli.
Lycopene	A caratenoid, shown to be a potent anti-oxidant. Recent research suggests lycopene rich products may lower the risk of prostate cancer. Main food sources are tomatoes, watermelon, red peppers.
Materia Medica	Substances used in the preparation of medicinal drugs.
Medical foods	Foods formulated to be consumed or administered internally while under the supervision of a physician – the food product is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements are established by medical evaluation – medical foods may be used to treat diabetes, obesity or heart disease, for example, and may carry specific claims, but in a strict sense are sold through physicians and not through conventional retail outlets
Myocardial infarction	Tissue death in the heart resulting from interrupted blood supply
Necrotizing enterocolitis	An acute inflammatory disease in the intestines of premature infants; intestinal tissue death may follow
Neonates	A new-born infant, especially one less than four weeks old

Neural tube	A tubular structure in the embryo which differentiates into the brain and spinal cord
Nutraceutical	Nutraceuticals are often defined synonymously with functional foods in the media and literature. In fact, the term nutraceutical, as coined by Stephen DeFelice, M.D., founder of the Foundation for Innovation in Medicine in Cranford, N.J., covers dietary supplements, those fortified foods that are enriched with nutrients not natural to the food such as orange juice with added calcium, functional foods and medical foods – thus, nutraceuticals are more correctly defined as an extracted part of a food (Atkins 1999) or a whole food that have a medical or health benefit, including the prevention and treatment of disease More clinically, according to the US guidelines of the Dietary Supplement Health and Education Act a nutraceutical is any non-toxic food extract supplement that has scientifically proven health benefits for both disease treatment and prevention. Then more generally, a nutraceutical may be seen as a functional food that has a positive impact on an individual's health, physical performance or state of mind, in addition to its nutritive value (University of Guelph). Nutraceutical foods include breakfast cereals that have been fortified with vitamins and minerals, milks containing added calcium, spreads containing omega-3 fatty acids, sports drinks containing amino acids, drinks containing guarana and ginseng and different types of fibre. These goods are regulated in Australia by the Therapeutic Goods Act, but in the US they would probably not come within the scope of the FDA.
Oligomeric	A polymer that consists of two, three, or four monomers (units)
Oxidants	Unstable, 'free radical' oxygen atoms or molecules that set off chain reactions with other molecules and a process of oxidation that may damage or disrupt the normal workings of membranes, proteins, DNA and other cell structures – hence the emergence of anti-oxidants which are heavily concentrated in certain fruits and vegetables – blueberries, cherries, kiwifruit, pink grapefruit, oranges, plums, raisins, raspberries, red grapes, strawberries … alfalfa sprouts, beets, broccoli flowers, brussel sprouts, corn, eggplant, kale, onions, red bell peppers, spinach
Parasympathomimetic	A drug or an agent that produces effects similar to those produced when a parasympathetic nerve is stimulated
Periodontal	Relating to tissue and structures surrounding and supporting the teeth
P-glycoprotein	Membrane proteins which can, under certain conditions, cause drug resistance by pumping drugs out of the cellular compatments
Photo-ageing	Deterioration of tissues accelerated by exposure to light
Phytochemicals or phytonutrients	A chemical obtained from or produced by plants
Plasminogen	The inactive precursor to plasmin (an enzyme that dissolves fibrin and other blood clotting factors) found in body fluids and blood plasma
Plasticiser	Substances added to plastics or other materials to make or keep them soft or pliable
PMS	Pre-menstrual syndrome
Polyphenols (bioflavenoids)	Anti-oxidant seen to reduce the risk of heart disease and stroke by inhibiting the formation of blood clots – main sources are green tea, red wine
Polyunsaturated fatty acids	A fatty acid whose carbon chain has more than one double or triple bond per molecule; found chiefly in fish, corn and soybean oil
Prebiotics	Foods or nutrients that are used by specific bacteria and that can be added to the diet to increase the chances of these particular bacteria growing and thriving in the intestine
Probiotics	Live microbial preparations, which beneficially affect the host by improving its microbial balance. e.g. yogurts, acidophilus
Protease	In HIV infection, the HIV protease enzyme is required to produce the final proteins needed for viral replication
Psoriasis	A non-contagious inflammatory skin disease characterized by recurring reddish patches covered with silvery scales
Reverse transcriptase	An enzyme that catalyses the formation of DNA on an RNA template, found in retroviruses such as HIV
Rheumatoid arthritis	A chronic disease marked by stiffness and inflammation of the joints, weakness, loss of mobility, and deformity
Rubefacient	A substance that irritates the skin, causing redness
Schistosoma	Parasitic blood flukes found in man and other mammals
Sedative	Having a soothing, calming, or tranquillising effect; reducing or relieving anxiety, stress, irritability, or excitement
Senile dementia	A progressive, abnormally accelerated deterioration of mental faculties and emotional stability in old age
Serotonergic	Activated by or capable of liberating serotonin, especially in transmitting nerve impulses
Spp.	Species
Sub-epidermal	Situated immediately below the epidermis (top layer of e.g. the skin)
Sympathomimetic	Producing physiological effects resembling those caused by the activity or stimulation of the sympathetic nervous system
Synergy	The interaction of two or more agents or forces so that their combined effect is greater than the sum of their individual effects
Ulcer	A lesion of the skin or a mucous membrane that is accompanied by formation of pus and necrosis of surrounding tissue
Vitiligo	Partial or total loss of skin pigmentation, often occurring in patches

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