RURAL INDUSTRIES RESEARCH
& DEVELOPMENT CORPORATION

New food and pharmaceutical products from agriculture

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A report for the Rural Industries Research and Development Corporation

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Foreword

There have been major changes in the food and pharmaceutical sectors that provide opportunities for Australian agriculture to produce innovative products. Central to these developments is an increasing emphasis on health and nutrition and a growing preference for natural products.

Within the global food industry the link between food and health has resulted in a rapid growth in the market for functional foods, sometimes also referred to as nutraceuticals. These are defined as foods that have ingredients that provide health benefits beyond the traditional nutrients they contain.

About 25 per cent of the active components of pharmaceutical drugs are derived from plants and this proportion is increasing as the global market for plant derived drugs grows.

In November 2000, RIRDC published a survey of new pharmaceutical, nutraceutical and industrial products and their potential for Australian agriculture by Wondu Holdings. This report identified good opportunities for Australia as a clean, green, internationally competitive supplier of many of the raw materials for these new products. It also pointed to some important constraints such as natural resource limitations, lack of domestic processing capacity and limited economies of scale.

These papers, presented at the 2002 ABARE Outlook Conference, represent a further contribution to the debate about innovative products from agriculture.

Dr. Wilkinson discusses current pharmaceutical and nutraceutical products available from agriculture. He predicts that the share of natural-based medicines will penetrate the largely synthetic global pharmaceutical market by as much as 30 per cent by 2005. The products with the most prospect include ginko, ginseng, garlic, echinacea and St John's wort. The key target areas are cardiovascular disease, central nervous system disorders, cancer anti-ageing and infectious diseases. Theraputic uses of plants can also manifest through food, and personal care products.

Professor Wahlqvist discusses Australia's capacity to produce a wide range of basic food commodities, but refers to the growing challenge of producing them sustainably. He argues that consumers will increasingly look to a range of best practice measures in the whole food chain and are also likely to choose products that have a regional identification. New opportunities are offered by phytochemicals with human biological significance and the development of products that take account of food-health relationships. International food security is a significant issue.

Dr Clark argues that emerging technologies and increasing emphasis on preventative healthcare will have a profound impact on pharmaceutical development. He acknowledges Australia's strengths in supplying these products, but he also identifies a number of weaknesses. In particular the domestic industry is fragmented, with very few vertically integrated companies and limited extract processing capacity. Other constraints include limited pharmaceutical development and lack of investment in development and strategic leadership. He identifies opportunities in the development of functional ingredients and foods from bioprospecting, standardised extracts and transgenic production. Strengths in

molecular plant breeding and antibody engineering also provide a potential for specific pharmaceutical development

These papers identify rapidly changing market developments centred on health objectives and a growing consumer preference for natural-based products. Australian agriculture has some natural advantages in responding to these developments. However the challenge will be to meet the demand of more segmented, quality conscious markets. This will require changes to current structures, with more emphasis on building supply chains based on strategic alliances and more vertical integration.

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This report, a new addition to RIRDC's diverse range of over 700 research publications, forms part of our Resilient Agricultural Systems R&D program, which aims to foster the development of agri-industry systems that have sufficient diversity, integration, flexibility and robustness to be resilient enough to respond opportunistically to continued change.

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Peter Core
Managing Director
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1.1 Key Summary Points

1. It is predicted that natural-based products will penetrate the synthetic pharmaceutical markets by up to as much as 30% over the next 3 years.

2. Current leading products include ginkgo, ginseng, garlic, echinacea and St John's wort. Key target areas include cardiovascular disease, CNS disorders, cancer, anti-ageing and infectious diseases.

3. Therapeutic uses of plants can also manifest through food, (nutraceuticals), and personal care products, (cosmeceuticals).

1.2 Current pharmaceutical and nutraceutical products available from agriculture

Pharmaceuticals

Categories of pharmaceutical products
The largest group, in terms of sales, are those that are used to treat cardiovascular disease. Other classes include the drugs that are used for disorders of the alimentary system and metabolism, the central nervous system (CNS), the respiratory system, and infections.

Cardiovascular drugs
In 1996, drugs used to treat myocardial infection had a global market value of $US8billion, whilst those for hypertension had a value of $US22billion. In 1997, the market shares for cardiovascular drugs were held by ACR inhibitors (27%), calcium antagonists (26%), lipid-lowering drugs (22%), beta-blockers (11%), diuretics (6%), antithrombolyitics (5%), and anticoagulants (3%).

CNS drugs
The global market value of CNS drugs was $US975million in 1996, however, this was predicted to fall by 1% per year to $US800million in 2001. Senile dementia and Alzheimer's disease are the main focus of CNS drug. Despite their high prevalence in society they account for relatively small shares in the global pharmaceutical market. Another key area is anxiolytic drugs, which have a global market value of between $2.5-4 billion, (Steiner, 1996).

Pharmaceuticals derived from plants

In 1997, the global sales for plant-derived medicines, both prescribed and non-prescribed, was approximately $US22.6billion, which was predicted to increase to $US30.7billion by 2002. The main categories of plant-derived drugs are terpenes, (34%), glycosides, (32%), and alkaloids, (16%), whilst other types account for 18% of the market. Examples of drugs obtained from higher plants are listed in Table 1.

Table 1. Classic plant-derived pharmaceuticals

Drug	Clinical action or use	Primary botanical origin
Atropine	Anticholinergic	*Atropa belladonna*
Digitoxin	Cardiotonic	*Digitalis purpurea*
Ephedrine	Sympathomimetic	*Ephedra sinica*
Galanthamine *	Cholinesterase inhibitor	*Lycoris squamigera*
Gossypol	Male contraceptive	*Gossipium* spp.
Levodopa *	Anti-Parkinsonian	*Mucuna deeringiana*
Morphine	Analgesic	*Papaver somniferum*
Physostigmine	Cholinesterase inhibitor	*Physostigma venenosum*
Quinidine *	Anti-arrhythmic	*Cinchona ledgeriana*
Quinine	Anti-malarial	*Cinchona ledgeriana*
Theophylline	Bronchodilator	*Camellia sinensis*
Vincristine *	Anticancer	*Catharanthus roseus*

** Clinical action not correlated to traditional use. Farnsworth et al., 1985*

Licensed herbal medicines

Claims concerning the properties of the botanical preparation can be made only when given marketing authorisation. The market value of licensed botanical medicines is over $US475million. Preparations of *Ginkgo biloba* comprise the three top selling preparations. Ginkgo is implicated in blood circulatory changes and increases microcirculation to the CNS, this is thought to underlie its reported memory enhancing function. Ginkgo is recommended in dementia and Alzheimer's disease. The plant St. John's wort, (*Hypericum perforatum*), which is used to treat depression, is rapidly becoming more popular, as reflected by the increase in sales from 2.6 to 8.5 million units from 1993 to 1997, (Mertens, 2000). The revenue of selected herbs in 1992 and 1998 is represented in Table 2.

Table 2. European sales of herbal medicines

Herb	Brand	Manufacturer	Sales ($US million)*	
			1992	1998
Gingko biloba	Tanakin	Beaufour	82.7	85.6
	Gingkor	Beaufour	51.3	57.1
	Tebonin	Schwabe	79.9	44.7
	Gingium	Hexal	5.7	19.0
	Roekan	Intersan	4.6	18.1
	Ginkgobil	Ratiopharm	13.3	19.0
St. John's wort	Jarsin	Lichtwer	2.9	24.7
Garlic	Kwai	Lichtwer	20.0	19.0
Horse chestnut	Venostasin	Klinge	20.9	15.2
Peppermint	Gelomyrtol	Pohl	18.1	16.2

(Mertens/Financial Times Healthcare, 2000).
**Converted from Euros at June 2000 rate.*

It is predicted that by 2005 more natural-based medicines will penetrate the largely synthetic global pharmaceutical market by as much as 30%, (Wilkinson, 2000a). This is in-line with increased awareness and appreciation of plant-derived drugs and therapy in both the general public and scientific community. This latter point is easily reflected by the recent history of research activity of the top 250 pharmaceutical companies; in 1980 none were involved in projects concerning plants, however, by the early 1990's more than half of the companies were, (anon., 1994). With this increasing interest in more natural-based alternatives large pharmaceutical companies are buying small companies specifically specialising in herbal remedies, (Wilkinson, 2000e), examples of which are shown in Table 3.

Pharmaceutical versions of herbal medicines are now being developed. This will lead to an emergence of a whole new type of pharmaceutical drug, (Wilkinson, 2000e). As a consequence, the market for supply of high quality herbal extracts and supply of raw materials will drastically increase. The herbal market is likely to grow from around $US5billion to at least $US30billion as these medicines enter the $US100billion market for pharmaceuticals, (Wilkinson, 2000a). Companies leading these developments include Pharmaprint, (California, USA), Ancile Pharmaceuticals, (California, USA), Oxford Natural Products PLC, (UK), and Phytopharm PLC, (UK), (Wilkinson, 2000b).

Table 3. Pharmaceutical multinational companies that have overtaken small phytomedicine companies.

Pharmaceutical Company	***Phytomedicine Company Acquired***
American Home products	Dr. Much
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

Unlicensed herbal medicines

Plant-derived preparations account for a large proportion of dietary supplements, in the U.S. in 1999 this sector had a 29% market share with an approximate value of $US4.3billion, (Sauer, 1999).

Although pain relievers and preparations for upper respiratory tract infections constitute the largest OTC market shares herbal vitamins and supplements demonstrated the strongest growth at a rate of 16% in 1998-1999, (Sauer, 1999). This indicates the expanding scope of interest in self-medication other than just pain relief and cold remedies, Table 4.

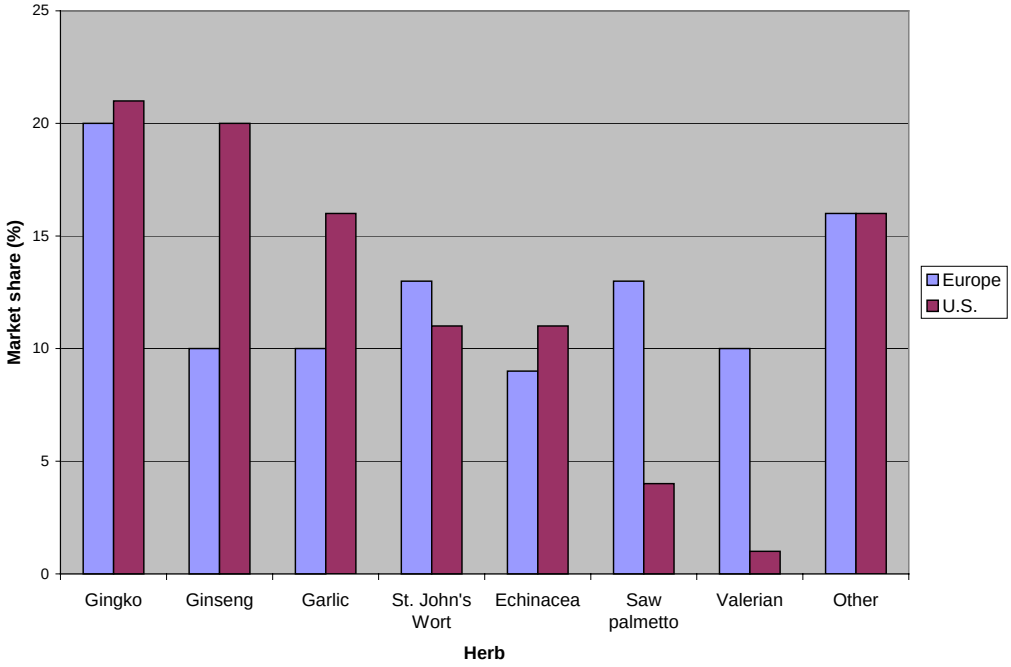
Table 4. Growth rates of self-medication markets, (1998).

(Sauer, 1999)

Category	**Annual growth rate (%)**
Vitamins, minerals and supplements	+16
Calming agents, sleep/mood enhancers	+8
Skin treatments	+6
Circulatory problems	+6
Pain relief	+4
Digestive/intestinal supplements	+4
Bladder/genital complaints	+4
Upper respiratory tract complaints	+2
Habit treatments	+2
Tonics/other stimulants	-2

Countries in which the prevalence of herbal remedies is small are predicted to have the greatest growth rates in the global phytopharmaceutical market. This is applicable to the U.S., where it was predicted there would be 50-100% and 20-25% growth rates in 1998-1999 and 2000-2001 respectively, (Scimone and Scimone, 1999). Popular herbal products in the U.S. have often already been successful in Europe, especially Germany where the market is well established, for example, ginkgo, ginseng, garlic, echinacea, St. John's wort and saw palmetto, Figure 2. Ginseng is a stimulant and adaptogen, (helps the body to deal with stress, fatigue and cold), furthermore, it is also taken as a tonic for general well being. Garlic is used to help fight infections and lower blood pressure, cholesterol, and sugar levels.

Figure 2. Leading phytomedicine market shares in Europe (1997) and the U.S.(1996-7)



(Nutrition Business Journal, 2000; Scimone and Scimone, 1999)

Global nutraceutical market

This term originates in the 1980's and refers to foods that possess properties that are beneficial to our health. The evolution of such functional foods began with refined foods, for example fibre and cod liver oil, green foods, which consisted of natural pesticide-free ingredients, and low or light foods in the sense of low fat/salt/sugar/calories/cholesterol. During the 1990s products emerged that contained dietary fibres, oligosaccharides, polyunsaturated fatty acids, cholines/phospholipids, glycosides, dietary vitamins/minerals, peptides and lactic acid bacteria. Research and development of current nutraceuticals are concerned with disease-prevention and the optimisation of health. Biotechnology will play a huge role, yielding genetically engineered plants with desired properties, for example, they may be altered to synthesise vaccines, contain elevated nicotine in tomatoes to aid smoking cessation, and possess higher levels of vitamins. Other examples are listed in Table 5.

Table 5. Current and emerging categories of nutraceuticals

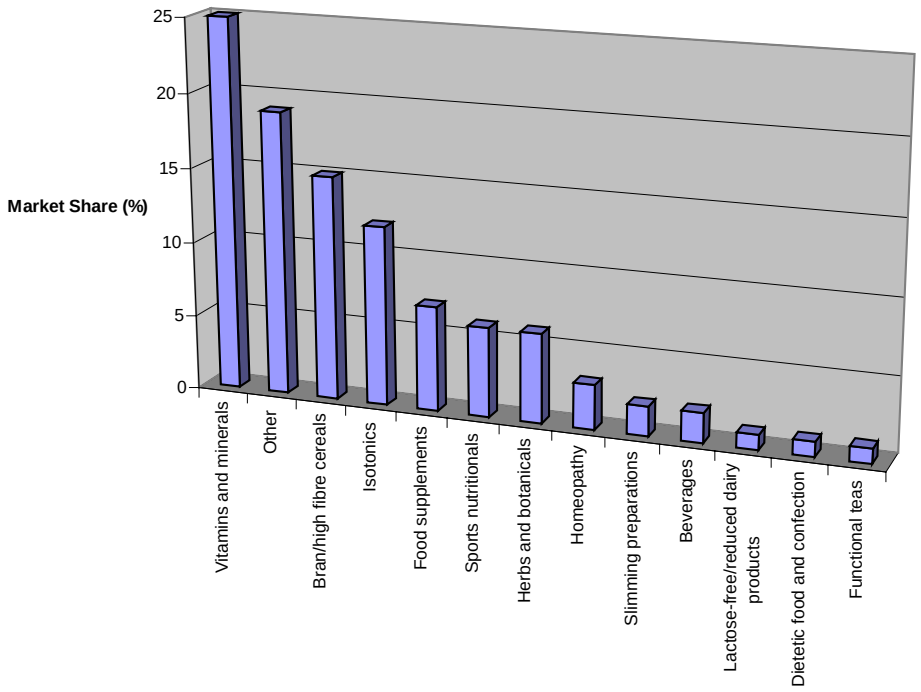
Category	Target Areas
Contain pre/pro-biotics	GI function, immune system, colon cancer, allergies.
Contain phytochemicals	Anti-oxidant, heart disease, cancer, high blood pressure.
Contain bioactive peptides/proteins	Immune system, bioavailability of minerals.
Contain n-3-polyunsaturated fatty acids	Heart disease, cancer, immune system.
Removal of allergens	Specific food allergy.

(Mertens, 2000)

The global market value for nutraceuticals doubled in the 1987-97 period, at the end of which it was valued at $US5.5billion. It has been predicted that by 2002, the value will stand at $US8.2billion, (Freedonia Group, 1998). Between 1987-97 the annual growth of plant-derived nutraceuticals was 12.9%, whilst during 1997-2002 this is estimated to be 11.3%. Although herbal functional foods do not comprise the largest market share, in both periods this category is the strongest performing sector over vitamins and minerals/nutrients.

The borderlines determining which foods qualify as a nutraceutical are not clear, and subsequently, there is large variation in global market values. An example of a breakdown of the market is shown in Figure 6, which represents the U.S. nutraceutical market share in 1997.

Figure 3. U.S. nutraceutical market share, (1997).



(Total market value: $US8.1 billion)

Nutraceutical beverages can be further sub-divided into categories including herbal teas, sports drinks and fortified juices. In 1997 isotonic sports drinks had market sales of $US1.2billion, whilst the annual turnover of fortified juices in this period was $US200million. Herbal teas account for a smaller share of the market with an annual turnover of $US75million, (Theodore, 1997). New contenders to this market include energy drinks such as Red Bull, and an even newer product that contains energy-enhancing, immune boosting Chinese Ants (Wilkinson 2002)

A selection of the leading nutraceutical companies is listed in Table 6.

Table 6. Market sales of the leading nutraceutical company, (1997-98)

Company	**Year**	**Turnover ($US billion)**	
		Total	**Functional Foods**
Novartis International (Switzerland)	1998	21.30	2.40
Yakult Honsha (Japan)	1998	1.27	1.27
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
Clapis Co. (Japan)	1997	0.80	0.48

(James, 1999)

The Australian food-manufacturing company Goodman Fielder had market sales of $US2.2billion in the period 1998-99, 10% of which may be classified as nutraceuticals. The top 60 Australian food companies had a total turnover of $33billion, this indicates great potential for herbal-based nutraceuticals, which are the strongest performing sector of functional foods.

Future trends in nutraceuticals

Disease conditions

Cardiovascular disease is recognised as having the greatest influence on the nutraceutical market, and, alongside obesity, it comprises the key disease area recognised by consumers in the U.S., Table 7.

Table 7. Consumer health issues: United States Opinions

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

(Peet, 1999)

Beneficial health claims

Surveys reveal that products which boost energy levels are within the top 5 desirable health claims in the UK, Germany and France. Other important properties include the promotion of healthy bones and healthy teeth, the lowering of blood cholesterol, and the boosting of the immune system, Table 8.

Table 8. Important beneficial health claims in the UK, Germany and France.

	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

(Sloan, 2000)

It was predicted that by 2002 products that enhanced energy or memory function would account for 47% of the $3.96billion functional products market, whilst cardiovascular disease would hold a 37.9% share, (Kroll, 1997).

Raw materials

In the U.S. botanical extract raw material accounts for 25% of the market, having a value of $US500million, whilst the rest is held by crude ground/crushed herbs. There is increasing demand for product consistency and quality, which is achievable with extracts rather than crude plant material. As a consequence, the market share for extracts is expected to increase as much as 75%, (Boswell, 1999). Two of the main categories of the $US1.89billion extractive market, as valued in 1998, are essential oils, ($US625million), and botanical extracts, ($US560million). The essential oils market is forecast to grow at 5.6% per year until 2003, whilst for the other category the predicted annual growth rate is 14.9%. It has

been estimated that in order to be successful, companies who supply raw botanical materials require annual sales of over $US20million, (Boswell, 1999). Examples of the leading suppliers are listed in Table 9.

Table 9. Major raw materials suppliers of botanicals

Company	US Sales ($US million)
Hauser/Botanical International	>100
Indena	>50
Hnekel	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

(Boswell, 1999)

The emergence of large pharmaceutical companies has placed huge pressure on the supply. The solution for this and the demand for more consistent, higher quality material has been in cultivated crops, (Wilkinson, 2000d), rather than wild-crafted raw materials, where prices and availability are subject to political, agricultural and environmental factors.

A few companies and institutes hold specialised libraries of plant extracts, for example, Herbal Sciences International Ltd based in the UK, has a database of over 55,000 plant species of which around 7000 have a previous recorded history of use in Man.

1.3 New pharmaceutical and nutraceutical products available from agriculture

Pharmaceuticals

With the increasing demand for herbal medicines, focus is placed on the quality and lack of toxicity of the cultivated crops. Any possible evidence of undesirable side effects or toxicity has the potential to reduce or even abolish the demand for the plant, (Wilkinson, 2000c).

Plant species that show potential

If a herb is already accepted for human administration, and thus would be easily marketed, has widespread use, or is likely to yield new discoveries then this would indicate that it has promising potential as a phytomedicine. The top ten herbs with the greatest potential are listed in Table 10.

Table 10. Herbs that demonstrate the potential to be successful as a herbal medicine

Herb	Currently accepted for human administration	Widespread use	New discoveries
Chamomile	✓		
Garlic	✓	✓	✓
Ginger	✓		
Echinacea		✓	
Feverfew		✓	
Ginkgo		✓	
Hawthorn		✓	
Saw Palmetto		✓	
Milk Thistle			✓
Valerian			✓

(Tyler, 1988)

Other herbs that show potential for future development include the African potato, (*Hypoxis hemerocallidea*), which demonstrates immunomodulation properties with implications in HIV, and sage, (Salvia spp.), which is implicated in Alzheimer's disease due reported cholinesterase inhibition and antioxidant activity (Wilkinson 2000e).

Key market areas

Key market areas for new phytopharmaceuticals focus on treatments of cardiovascular disease, CNS disorders and infections.

There is a large number of plants that possess antmicrobial activity, and it is therefore sensible to concentrate on those that can provide products that possess multiple actions. An example is chaparral, (*Larrea tridentata*), which, in addition to its implications against skin bacteria, has potential applications as an anticancer treatment. Another is rosemary, (*Rosemarinus officinalis*), which also has use in the perfume industry. Furthermore, this would be preferable, for rapid entry into the market place, to focus on antimicrobial plant species that are already widely available, for example in Australia a likely candidate would be eucalyptus, (*Eucalyptus spp*.).

Other areas of the antiinfective market include *Helicobacter pylori*, which underlies many intestinal complaints, and methicillin or multiple resistance *Staphylococcus aureus*, (MRSA). Tea tree oil, (Melaleuca alternifolia), has been shown to possess activity against MRSA, (Carson et al., 1995; Harkenthal et al., 1999).

Drugs to treat CNS disorders are mainly split between anxiolytics and those used to enhance memory function. Plants that possess tranquilising or sedative actions are forecast to remain popular as anxiolytics. Examples are St John's wort, *(Hypericum perforatum*), hops, (*humulus lupulus*), passionflower, (*Passiflora spp*.), and kava, (*Piper methysticum*). A licenced preparation of St John's wort called Jarsin demonstrated a huge increase in sales from $2.9million in 1992 to $24.7million in 1998. The global anxiolytic market has a value

of around $2.5-4billion, (Steiner, 1996), and if the future synthetic market penetration by herbal products is as much as 30%, (Wilkinson, 2000), then they could have a value of up to $1billion.

Collaboration between academia, research institutes and the government

Companies specialising in the research and development of plant-derived medicines often collaborate with larger pharmaceutical companies. This is important in the progress of the knowledge and discoveries made in this area. An example is with Xenova's product XR9576, (piperazinedione derivatives), for which it joined with Eli Lilly & Co., this preparation is indicated as a P-glycoprotein inhibitor and may help in multi-drug resistance.

Increased funding of research, alongside the integration of knowledge and discoveries, will enable a greater number of plant species and target areas to be tackled. The rate of progression and success of herbal medicines, as well as the use of herbs in functional foods and cosmetics, is likely to depend on the collaboration between academia, research institutes and the government. Specific examples of which include at Australia's University of Southern Cross. Located here is the Centre for Phytochemistry, set up in early 2000 and directed by Peter Waterman, and the Cellulose Valley Technology Park, which encourages the presence of companies involved in natural products. Their research topics include celcy oil, ginger extracts, Backhousia citriodora leaf oil, melaleuca alternifolia oil, and eucalyptus. At the University of Mississippi in the U.S. there is the National Centre for the Development of Natural Products, (NCNPR). Set up in mid 1995 it is the only research centre in the U.S. that is associated with academia. On the pharmaceutical level, it specialises in natural treatments for disorders including cancer and infectious diseases, and in the improvement of nutraceuticals. Whilst in the U.K., a Phytochemistry and Pharmacognosy group at the University of Middlesex, found and led by Dr John Wilkinson, specialises in herbal medicine research and commercial new product development of herbal extracts. Examples of their work include the African potato (immune modulation), sage (dementia), echinacea (colds and flu), locating source of plant materials, ectoparasitic treatments (head- and sheeplice, see International Patent Application No. PCT/GB00/01589), foot-and-mouth viral disease, anthrax, the development of phytopharmaceuticals, and in vitro assays of herbal extracts. Their work is achieved through the collaboration with companies on an international level (see http://www.phytochemistry.freeserve.co.uk)

Nutraceuticals

It is predicted that in the future the majority of foods will qualify as nutraceuticals. This is in keeping with the increasing number of people becoming interested in the role of nutrition in promoting a better quality of life and longer life expectancy. Key areas of interest are the prevention of diseases such as cancer, heart disease and dementia, and memory and energy enhancement.

Herbal teas

The market for functional foods and beverages was expected to grow at a rate of 12.4% per year, reaching $314million by 2002, (Kroll, 1997). In 1997, functional beverages accounted for 53% of this market, and it is forecast that they will demonstrate the largest growth. During 1997-98, "powder-to-mix" drinks held 40% of the market, whilst teas in bags held 37%. Less than 10% was accounted for by cultured drinks.

Future key research areas

- Phytochemicals especially in the prevention and treatment of diseases. Emphasis is placed on grains and fibres, fruit and vegetables, herbs and spices, and beverages such as tea, wine, and grape, cranberry and blueberry juices.

- Omega-3 oil, plus oils and fatty acids, available from nuts, seeds and plants. Alongside cancer and heart disease, they are believed to reduce the risk of allergies, arthritis, eczema, depression, fatigue, infections and PMS.

- Fructo-oligosaccharides are natural carbohydrates that cannot be digested or absorbed by humans but support the growth of gut flora, which are required for healthy functioning of the intestine.

- Stanol esters help to reduce the absorption of cholesterol from the intestine, and thus, reduce blood cholesterol and LDL cholesterol.

Key market areas

There are several sectors of the nutraceutical market but one major area is the treatment of upper respiratory tract infections, (URTI). Currently the dominant botanical used is derived from *Echinacea* spp., which is one of the leading herbal remedies in both Europe and the U.S., accounting for 9% and 12% of herbal sales respectively. In the U.S. herbal sales of echinacea were between $US71-109million in 1999, (Aarts, 2000; Brevoort, 2000). In this period self-medication treatments for URTIs had sales of $US9billion, which is forecast to increase by 2% per year, (Sauer, 1999). If as much as 30% of the synthetic nutraceutical market is penetrated by natural-based products, (Wilkinson, 2000a), they could have a market value approaching $3billion. Other plant species with potential in this sector include garlic, (*Allium sativum*), goldenseal, (*Hydrastic candensis*), and African potato, (*Hypoxis hemerocallidea*).

Antioxidants, a key product class

Due to their wide industrial applications the demand for antioxidants is likely to increase. There are concerns about the safety of synthetic ones, and thus, this indicates great scope for natural-based alternatives. Antioxidants reduce damage to cellular structures, DNA and the body's building blocks by neutralising free radicals. They have great potential in the prevention of cancer, atherosclerosis, (and thus, heart disease), and premature ageing.

Annual sales of the well-known antioxidant vitamin C increased 9% in 1998 to $314million. Largest growth was of the free radical scavenger vitamin E, which demonstrated an annual growth of 24.8% and market sales of $323.9million in the same period. The sector for carotenoid supplements increased 11.4%, ($96.8million), and that of vitamins A, D and K rose by 16.1%, ($11.5million).

Emerging antioxidants include lycopene, which is found in tomatoes and other red fruit and vegetables. Its antioxidant activity is believed to underlie possible anti-carcinogenic effects. Another is reseveratol, (3, 5, 4'-trihydroxystilbene), which is found in green vegetables, citrus fruits and red wine. An alcohol of the essential oil constituent limonene, perillyl alcohol, is currently being tested in phase I trials as an anticarcinogenic agent in Europe and the U.S., (Kane, 1999).

Liquorice extract is an example of a future plant-derived antioxidant that is currently undergoing investigation, it has been shown to inhibit oxidation of LDL. Research shows sunflower extracts to be comparable to the synthetic antioxidants BHT and BHA, (Yoshiaki and Koj, 1994). Other plants of particular interest are the herbs rosemary and oregano.

Cosmeceuticals

The addition of botanicals to cosmetics is consistent with the increased awareness of wanting better quality lives and the prevention of diseases but also in the demand for more natural-based products. The term cosmeceuticals refers to personal care products that contain substances that exert beneficial effects such as anti-wrinkle, antioxidant, skin conditioning, analgesia, sun protection, stimulation of hair growth. Furthermore, they may also impart a desirable physiological effect such as stimulation of microcirculation. Anti-ageing is a key target area, this includes antioxidants and sun protection, which also help to prevent diseases such as skin cancer. The cosmeceutical global market value is $10billion, (Ouellette, 1998). In the U.S., the 1998 market value of cosmeceuticals that had their origin in plants stood at $345million. This is predicted to increase 7.9% per year to $505million by 2003. Examples of botanical cosmeceutical ingredients are shown in Table 11.

Alpha hydroxy acids, (AHAs), and aloe vera are massively popular, which is reflected by their frequency in new products that were surveyed during 1995-97, (Brown, 1998). Other key botanical cosmeceuticals include chamomile, lavender, green tea and jojoba.

AHAs, such as lactic, tartaric, malic and citrus, remove the dead skin cells to give a smoother, softer and fresher appearance to the skin. In the U.S. they had sales of $500million, (1996), and it has been forecast that the market value will reach $600million by 2002. Controversial issues over AHAs concern its potential to cause skin irritation and UV damage. A safer alternative to AHAs may be beta hydroxy acids, which actually exert greater activity. Furthermore, papain, an enzyme derived from papaya, is currently being tested in the U.S., this may also be used instead of AHAs.

Enzymes constitute a major part of current research for cosmeceuticals. Future products may contain enzymes that affect collagen and elastin, lipid and oil production in the skin, and regulation of cellular turnover; however, enzymes can induce allergic reactions and are unstable, which affects their formulation.

Table 11. Examples of botanicals used in cosmeceuticals

Company	Botanical	Property
Indena	Marigold dry extract	Soothing
Indena	Soybean saponins	Anti-ageing
Indena	Peruvian bark fluid extract	Stimulation of scalp
Bioelements	Echinacea	Anti-wrinkle, enhances skin elasticity
Janet Sartin Inc.	Kalaya oil	Anti-wrinkle
Bio-Botanica	Olive leaf	Antifungal, antiviral

(Brown, 1999)

Suncare products are predicted to account for the greatest growth in the skincare and make-up sectors, their compound annual growth rate for the period 1998-2002 was forcast to be

2.8%. The addition of specific plants to suncreen products can offer two advantages, enhancement of the sun protection factor (SPF) of suncreen products, and their own therapeutic properties, (Raman et al., 1996; Wilkinson and Brown, 1999).

Plant oils including avocado (*Persea americana*), almond, (*Amygdalus communis*), and jojoba, (*Simmondsia chinensis*), are another potential key area for cosmeceuticals. A promising example is Meadowfoam seed oil, (*Limnathes alba*), which has the highest C_{20-22} fatty acid content than any other seed oil commercially available. Its high stability increases resistance to oxidation, which helps to prevent rancidity of fats. This oil could be used as an emollient in make-up, hand and body creams, and hair products, (Harvilicz, 2000).

Discussion

Therapeutic uses of plants was recorded as early as 7000 years ago and since then has continued to be part of our society. Their popularity declined with the introduction of synthetic pharmaceuticals. Recently, there has been a surge of interest in the use of plants, which is consistent with an increased awareness and interest in the quality of life and the prevention of diseases as well as unsatisfactory therapeutic needs. Furthermore, it reflects the demand for more natural-based products.

It is expected that by 2005 the world market value of all herbal medicines would have reached $US30.7billion. Currently, preparations of Ginkgo biloba comprise the top 3 selling herbs, with combined sales of $US182.4million in 1998. Evidence suggests that the increasing interest in and demand for more natural-based products will continue in both the general public and the scientific community. It has been predicted that by 2005, herbal preparations will have penetrated the largely synthetic $US100billion pharmaceutical market by up to 30%; as a consequence, their sector would be worth as much as $US30 billion, (Wilkinson, 2000a). The fastest growing sector of unlicensed botanicals was herbal, vitamins and supplements, demonstrating that the scope of interest in alternative medicines is expanding beyond just pain relief and treatments for coughs and colds. Key areas for new phytopharmaceuticals are cardiovascular disease, CNS disorders and infections. Similarly, the herbal products sector of the nutraceuticals market is not the largest category but it does show the most rapid growth. In the U.S. cardiovascular disease and obesity are the conditions that have created the most awareness. Other strong performing areas include the treatment of coughs, colds and other respiratory complaints. Whilst popular beneficial health claims included energy enhancement, boosting of the immune system and healthy bones and teeth. Such surveys reflect key areas for nutraceuticals. Functional teas are predicted to demonstrate an increase in demand, whilst antioxidants are likely to feature strongly.

Another application of herbal remedies is in cosmeceuticals, which are a cross between a cosmetic and a drug. Suncare and anti-ageing products are key areas. In 1998, the U.S. market value of plant-derived cosmeceuticals was $345million.

The number of target areas, plant species and compounds within each plant is vast indicating the great potential of agriculture in the pharmaceutical industry as well other aspects of health care, i.e. functional foods and personal care products.

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2. New Food Products from Agriculture

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Abstract

Australia has an exceptional capacity to produce a wide range of basic food commodities, but with increasing demands on its ability to do so in a sustainable way.

Increasingly, community and political interest and commitment to healthy longevity requires a healthful food supply which relates to best practice in food production, processing and transport.

Agricultural, horticultural and aquacultural and science have increased the capability to produce biologically-advantageous, food component dense food-stuffs.

Australia has a critical role in ensuring international food security.

There is a suite of newly understood food-health relationships which can be addressed by new food products, provided the governance is in order.

The stimulus to development of new food products from agriculture arises from both pressures for economic development and the quest for further advances in health through food, with opportunities provided by advances in the sciences and technologies, but limits imposed on account of environmental concerns.

2.1 Australian Food Production

All basic food commodities can be produced in Australia, both animal and plant-derived. This is because it has a wide range of climatic conditions, soil-types and ecological niches. *Australian food production has diversified* as well, because of the increasing cultural diversity of its population and the general expansion of taste horizons - most notable with fruits, vegetables and fermented dairy products.

This means that there is the potential to produce now an array of species, breeds, types or cultivars of birds, fin-fish and other seafood, monogastric and ruminant animals; eggs, milk and dairy products; grains, nuts, fruits, vegetables; and edible fungi. These food-stuffs could achieve relatively greater food-component dense (ie nutritious) characteristics. And, provided consumers subscribe to *food variety* as a fundamental guiding principle in food choice, *biodiversity* will be supported and a sustainable food supply more likely (1,2).

The major caveats about the sustainability of Australia's domestic food production are how waterways are used (notably the Murray-Darling River system) and how ecosystems are preserved around human settlements - these provide not only for safe and adequate suppliers, but also "buffer zones" to protect against pestilence, including at present unknown risks.

Questions must be asked about certain monocultures like wetland rice, and crops in marginal rainfall areas with risk of desertification.

The sensible progress of Australian food production will be to produce more niche foods with health relevance.

2.2 Best Practice in Food Production, Processing and Transport

One of the great opportunities for Australia is to represent its "whole of food chain approach" by measures of best practice. It ought to be able to do this to take account of *Food Integrity* in regard to:

- Sustainability
- Safety and Security
- Ethical Principles
- Community and Regional Development
- Culture
- Nutrition and Health

There is more and more prospect that individuals, communities and their leaders will look to these elements in food choice and be more confident if the foods they choose are identified with food-producing regions. A widening of the *appellation system* will be increasingly attractive at home and internationally. Here there is conjunction between regard for locality and internationalisation (if not globalization).

The development "best practice for food integrity" will be conducive to healthy environments, healthy human settlements and individual healthy longevity.

2.3 Biologically Advantageous Food Component Dense Foods (BAFCDF)

Humans have forever sought advantage by way of the foods available to them and how they might be prepared for consumption. There have been some impressive waves of this endeavour in human history - the advent of herds-people, of fishing communities, of subsistence agriculture, of intensive local agriculture in China, of propagation of plants in the Andes by the Incas, and of the adaptation of food plants on migration, as with European settlement in Australia.

We are now able to propagate and evaluate the nutritional value of plant food-stuffs over shorter and shorter time-frames, by both non-GM and GM (genetically modified) methods, with the former inspiring more public confidence at present. Much of the exciting prospect resides in so-called 'phytochemicals' where human biological significance has only recently been realised - the myriad of polyphenolics and carotenoids are the best examples.

The application of these superior plant propagation techniques, along with animal breeding, requires a new order of collaboration between agricultural, food and biomedical-nutrition scientists.

2.4 International Food Security

With poverty, more active trade, and environmental degradation, there are increasing threats to food security. Mindful of how crucial this issue is, ICSU (the International Council of Scientific Unions) has established a taskforce for scientific union cooperation in this area. At a meeting in Paris in January 2002, new impetus was given to the food security effort. A proposal has been developed to enhance governance of the food supply with the assistance of a risk science in relation to vulnerable groups and environments, and the use of appropriate information, food and biotechnologies.

Australia, its food system and food trade have a vital role to play in this work.

2.5 Food-Health Relationships

A more comprehensive approach to food-health relationships is now desirable (3) (Table 1).

Table 1. Categorising food-health relationships for the purposes of food product development

Health Category	Food Characteristics
1. Disease related to environmental Degradation and methods of food production	Eco-sensitive foods (eg. Produced in sustainable ways; biodegradable or edible packaging; identifiable biosecurity for animal-derived foods; nature of genetic material)
2. Food shortage and PEM (protein energy Malnutrition)	Technologies which minimise post-harvest loss, increase shelf life and maintain palatability
3. Disease related to protein quality, fat quality and micronutrient status	Nutrient dense foods; fish or its plant or microbial food surrogates
4. Physical inactivity and health (especially over fatness; also loss of lean mass, particularly muscle)	Food of low energy density and high nutrient density
5. Phytochemical deficiency disorders including menopause, macular degeneration, osteopenia	Greater emphases on plant-derived foods and their variety
6. *Diseases of changing demography* Ageing	Anti-ageing food, especially ones to delay body compositional change (bone, muscle and fat); loss of sensory function; decline in immune function; proneness to neoplastic disease; decline in cardio-respiratory function; and decline in cognitive function; and anti-inflammatory foods
Rapid loss of traditional food culture and acquisition of new food cultures	Maintenance of traditional foods in convenient, affordable and recognisable form
7. New psycho-social stressors and mood change	Food which favourably affects mood
8. Food borne illness and the microbiological safety of foods	Pre- and pro-biotic foods - Immune system enhancing foods
9. Illness related to the chemical safety of foods (eg. pesticide residues)	Regional origin and certification of foods

When food-health relationships are viewed in this way, there are considerable opportunities for the development of novel foods with agricultural inputs which are sustainable. Regulatory arrangements by government, international agencies and industry, with attention to monitoring and surveillance, as well as enforcement, will need to be well-developed for the public to be satisfied about the future food supply as it undergoes rapid change.

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3. Capacity to produce pharmaceutical products from agriculture

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3.1 Summary

1. Emerging technologies and increasing emphasis on preventative healthcare will have a profound impact on pharmaceutical development

2. Australia has significant capability and capacity weaknesses – especially in processing technology, pharmaceutical development, investment in development and strategic leadership

3. Opportunities exist in the development of functional ingredients and foods from bioprospecting, standardised extracts and transgenic production

4. Strengths in molecular plant breeding and antibody engineering provide a potential for specific pharmaceutical development

3.2 Background

Traditionally, the food and pharmaceutical sectors have been viewed as being completely separate. In recent years there has been a rapid convergence of these sectors to result in a "continuum" of development spanning food, functional foods, nutraceuticals, phytomedicines and pharmaceuticals. Major changes in the application of technologies and evolving approaches to product regulation have been driving this development, and value-added products from agriculture present new opportunities at all points along this continuum.

At first glance the case for attempting to produce pharmaceuticals from Australian agriculture appears attractive. The globally competitive production of morphine from Tasmanian poppies is a good example. This discussion will emphasise that a) it is unlikely that many new pharmaceuticals will actually get to market, b) the way in which pharmaceuticals are discovered and developed is undergoing major change, c) Australia has major gaps in resources and capabilities for pharmaceutical development and d) better returns from Australia's agricultural capabilities are likely to come from a strategy focusing on functional foods and ingredients. We must accept that success in pharmaceuticals will be opportunistic and possibly a "random" event. While this discussion will focus on products from plants and agriculture, the points are equally applicable to production from aquaculture.

3.3 Importance of plants as a source of pharmaceuticals

Plants are the basis for a major proportion of current pharmaceuticals. The fact that estimates range from 25 to 75% of drugs[1-4] reflects different criteria ranging from direct sourcing of chemicals from plants, to synthetic derivatives to the discovery of new

molecules that are subsequently manufactured synthetically. The search for and use of drugs and dietary supplements derived from plants have accelerated in recent years and contributions have been made to all major therapeutic areas except antimicrobial activity[4].

Drugs used to treat breast cancer give a clear example of the importance of plant-derived compounds for a specific therapeutic application and include paclitaxel/docetaxel (*Taxus baccata*), etoposide (*Pedophyllum peltatum*), camptothecin (*Camptotheca acuminata*) and vinblastine/vinorelbine (*Vinca rosea*)[3]. Other major plant-derived drugs include digitalis (*Digitalis purpurea*), atropine (*Atropa belladonna*), ephedrine (*Ephedra sinica*), novocaine (*Erythroxylum coca*), pilocarpine (*Pilocarpus microphyllus*) and morphine (*Papaver somniferum*).

3.4 The context

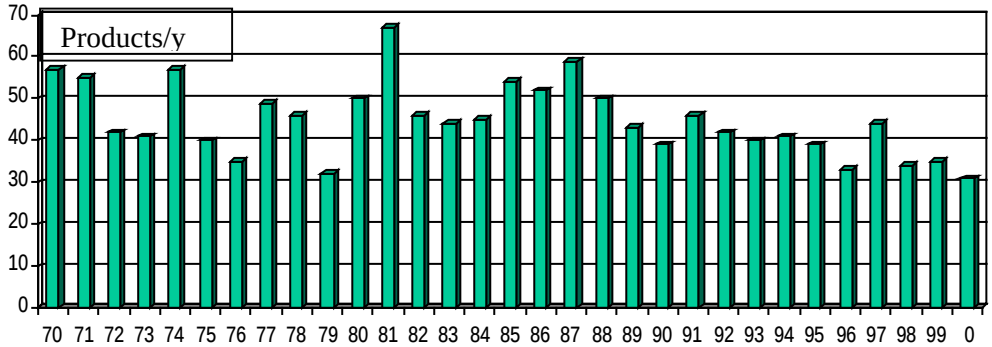
Any attempts to develop a strategy for developing pharmaceuticals from agriculture must take into account the drivers of this area of healthcare. The fact that successful drug development is a rare event, disruptive technologies are emerging and a move towards prevention is gaining momentum means that it is dangerous to assume that the current development model will remain unchanged, especially given the long lead times in agriculture and drug development.

The chance of successfully developing a drug is low

There is massive attrition of candidate molecules during drug development. Approximately 6,000 -10,000 compounds are required to result in a single approved drug[5]. Even if a compound survives the preclinical stage of development and enters Phase I clinical trials there is on average only a 5% chance of reaching market[6]. Current world sales of prescription pharmaceuticals are estimated to be more than US$350 billion[based on 6]. Global R&D investment is approximately 12% of sales and currently more than US$42 billion per annum[5]. In spite of the rapid increase in R&D expenditure the number of new drugs approved each year has remained relatively stable for 30 years and is possibly declining (figure 1).

Any strategy to develop pharmaceuticals from agriculture must take into account that success is a rare event and becoming increasingly expensive. Alliances with transnational pharmaceutical companies will be required and such alliances must be managed in the context of the continuing consolidation of the global pharmaceutical industry. This means that the agriculture industry will require access to skills and links in order to manage risk and the likely complex global relationships and supply chains.

Figure 1: Number of new pharmaceutical launches per year[6]



Technology span is escalating

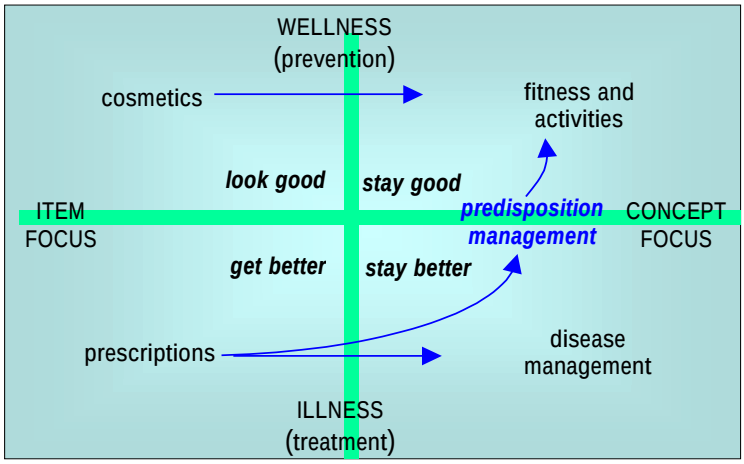
The emergence of genomic, proteomic, bioinformatic and high-throughput screening technologies will have a profound impact on drug discovery and development. An entirely new world with complexity and opportunities unlike the "traditional" pharmaceutical industry is emerging and the number of drug targets will increase from the "traditional 500" that have been the base of all pharmaceutical development to date, to an expected several thousand targets, many of which will be multicomponent[7].

These new technologies and targets will provide opportunities to revisit libraries of natural product extracts and to continue bioprospecting activities in search of new candidate molecules. Continued advances in digital processing have seen the entry of major IT companies such as IBM, Motorola, Compaq and Sun Microsystems into drug development technologies through major advances in bioinformatics, *in silico* modeling and structural analysis. Whether these advances will increase the rate of new product launches per year remains to be seen. Given the relatively static number of new products launched over the last 30 years in the face of major technological developments (e.g. combinatorial chemistry, X-ray crystallography, monoclonal antibodies, polymerase chain reaction, biopeptides, etc), it would be wise to assume that current trends in drug approval will continue for the foreseeable future.

Move towards prevention

Escalating healthcare costs and continued unmet consumer needs are resulting in growing emphasis on preventative healthcare rather than the current domination of reactively managing incidents. Traditional food and pharmaceutical companies were slow to respond to a major shift in approach to healthcare and wellness that was taking place in the 1990's (figure 2). The functional food, nutraceutical, and complementary medicines markets have grown rapidly and are likely to find support from developments in the new technologies to assist in identification of predisposition and longitudinal management of health at the level of the individual. This major shift in approaches to health will present new opportunities and result in the emergence of new players.

Figure 2: Perception map of the shift towards prevention and wellness



A major shift towards personal medicine will emerge

The combined impact of a market pull towards prevention and technology enabling greater understanding of health at the individual level will result in a shift towards personal medicine. Currently, drugs are developed largely on the basis of mass trials and "average responses". Recognition of polymorphisms influencing drug metabolism (140 have already been identified) and the sources of variation in individual response to drugs will lead to a change in approaches to drug design[8-9].

Knowledge of an individual's genotype compared with structural and molecular interaction databases will allow design and prescription of drugs suited to the individual's genotype and drug metabolism properties. This same bioinformatics approach, applied to the study of human metabolites, has the potential to identify and validate targets to improve personalised nutritional health and thus serves to define the added value for the next generation of foods and crops[10].

Longer term planning should anticipate the creation of integrated health databases containing "multiparallel" metabolite profiles over time for an individual, and combined with genomic and gene expression profiles. Such application of the knowledge of an individual's genotype and phenotype could revolutionise the ability to deliver health benefits through food and targeted pharmaceutical therapy[10]. Under such a scenario it would be prudent to assume that agriculture could play a major role in the production of "designer products". The ramification will be a move from single generic supply chains for crops to multiple lower volume high value adding supply chains.

3.5 Australian situation

Relatively weak domestic plant extract industry

The ability to produce value added plant extracts is a strong indicator when considering the potential to produce phytomedicines and pharmaceuticals from agriculture. Australia's sustainable management of natural resources, diversity of climate, good infrastructure, sound farm management, and clean green image are clear marketing benefits. However, such benefits have not yet been realised in the competitive manufacture of plant extracts. The domestic industry for plant extracts is very fragmented with a large number of small growers. There are very few vertically integrated companies and continued compartmentalisation into growers or importers, manufacturers and marketers. While there are rare exceptions, the Australian plant extract industry is largely generic and does not add enough value to be sufficiently attractive. As a consequence Australian mass marketers purchase more processed forms of plant extracts and more than 75% are imported (approx value $70 million)[11]. The dominating marketers and manufacturers (Blackmores, Cenovis, Bullivants, Roche, MediHerb, Scherer, Pan, Lipa etc) account for a major proportion of these imports citing consistent quality, batch size, specifications and reliability of supply as being key issues[11].

With the exception of morphine, Australia has little integrated experience in the development of highly value added phytomedicines. The key global industry players are still mainly European and include Indena, Finzelberg, Flachsmann, Linnea, Schwabe, and Bionorica. These suppliers set a benchmark with their focus on clinical evidence, leading separation technologies and analytical chemistry.

Need to expand domestic processing technologies

The growing demand for process development, pilot production, scale-up and providing data for registration has created new opportunities for contract research and development from agricultural biotechnology[11]. In general, Australia is relatively weak with respect to downstream biotechnology and extract processing facilities, particularly as they relate to GMP compliant manufacturing. The processing of plant extracts in Australia has been largely restricted to traditional methods of ethanolic or steam extraction.

The leading manufacturers of standardised plant extracts are largely European and they use supercritical fluid and multisolvent extraction processes extensively. Furthermore, these companies operate at a pharmaceutical manufacturing standard. If Australia is to have a significant position in plant extracts beyond basic cultivation and harvesting an investment in extraction capabilities will be required.

Weak track record in pharmaceutical development

While Australian science has contributed to the development of several major pharmaceuticals very few have been fully developed in Australia. For example Kapanol (Faulding) and Relenza (Biota) were the first Australian New Drug Applications in the US and both required a transnational partner for development and commercialisation.

Total Australian investment in R&D is only approx 7% of GDP (ranked 13 in OECD/EU) and less than the average for the EU and OECD (approx 8%). Business investment in R&D in Australia is less than 1% of GDP placing Australia in rank 21 (OECD/EU). This is of major significance in an R&D intensive area such as pharmaceutical development. This poor competitive position is compounded by a significant investment in basic research not being matched by investment in resources and capabilities downstream in development and technology transfer.

Total pharmaceutical sales in Australia are $5.8 billion with an R&D investment of approx $300 m (approx. 5% of sales), and well below the global industry average of approximately 12%. Most investment in Australia to date relates to product modifications, new presentations, new indications and later stage clinical trials rather than full development. Most pharmaceutical companies in Australia are steered by strategic priorities set by headquarters in the Northern hemisphere. It should however be noted that there is a growing number of domestic companies, mostly small and vulnerable, that have identified lead compounds and have continued further development (examples include Xenome, Cerylid, AMRAD, Starpharma, Peplin, Gropep, Bresagen, Novagen).

Specific weaknesses that need to be addressed if Australia is to have a genuine domestic pharmaceutical development industry include the lack of significant toxicology capabilities, clinical trial material manufacture, early stage clinical trial infrastructure, limited bioinformatics capabilities and shortage of clinical pharmacologists and medicinal chemists with experience in drug development. Findings and recommendations from the current Pharmaceuticals Industry Action Agenda will be particularly relevant in the context of evaluating opportunities for producing pharmaceuticals from Australian agriculture[13].

Stronger strategic approach required

Two significant characteristics of Australian strategies to date do not realise the full potential of market opportunities. Firstly, there is a tendency to focus on the production of high quality commodities using generic processes without sufficient concentration on establishing significant intellectual property positions and value add. Few resources are directed towards proprietary composition of matter or process intellectual property. With the benefit of hindsight the tea tree oil industry illustrates this situation.

Secondly, opportunities presented by the regulatory system and consumer pull are not sufficiently exploited. Product development in Australia tends to be compartmentalised into either pharmaceutical or consumer products with few companies capable of handling both. Parallel strategies for the codevelopment of Over-The-Counter and prescription products with differing levels of claims, clinical evidence and purity can assist cash flows and optimise returns (Novogen is an example of this strategy). Few companies have exploited the availability of European complementary medicine dossiers that are of pharmaceutical industry standard, including extensive clinical trial data. The opportunity for "evidence-based" phytomedicines is under-exploited in Australia, in spite of having a regulatory system capable of specifically handling different levels of claims.

3.6 Three parallel approaches to pharmaceuticals from agriculture

Different approaches need to be considered when developing a capacity to produce pharmaceuticals from agriculture and these include a) bioprospecting the broad biota as well as established foods and complementary medicines, b) developing standardised and evidence-based extracts, and c) using plants for alternative production of transgenic molecules.

Potential from bioprospecting

Natural products provide an important source of new molecular themes for subsequent modification and synthesis[14]. The difficulty of obtaining sufficient supply is often given as a reason for not becoming involved in natural-product drug development or discovery[1]. In certain cases bioprospecting can also include the option for wildcrafting and agriculture. A current example is the need to cultivate *Euphorbia peplus* since the lead molecules identified as having anticancer properties have a large number of asymmetric centres that make synthesis unattractive[2].

Bioprospecting can also be relevant to the development of consumer products as part of the ultimate goal of developing a pharmaceutical product. Importantly for agriculture, there is an emerging awareness that bioactive substances in food and currently consumed plant extracts are poorly understood and provide significant potential for potency adjustment and the development of functional ingredients or modified foods that deliver a specific, clinically proven health benefits. TARAC Technologies, Novogen, Mount Romance, Cerylid and Mayne Health are examples of Australian companies exploring the link between specific components and health benefits. TARAC Technologies is developing clinical evidence-based food ingredients (Vinlife™) using specific polyphenol fractions from grapeseed. Another example of this approach is Mayne Consumer's recent launch of Cenovis

Nutraplan™. This product is based on a unique combination of isolates from soybean and the metabolic management applications are supported by extensive intellectual property and clinical trials in collaboration with Nutri-Pharma (Norway).

Traditional bioprospecting approaches based on ethnobotanical knowledge involving healers and oral histories of indigenous peoples are now augmented by the emergence of high-throughput screening and related analytical and computational technologies[15]. The increasing emphasis on identifying biomarkers and new targets provides an important opportunity for renewed focus on bioprospecting. However, it is important to note that successful bioprospecting will require integration of efforts in conservation, regional economic development and drug/functional food development into one program[1].

Any strategy for the production of pharmaceuticals from plants must consider the risk of alternative methods being used due to concerns related to supply, conservation and cost. Chemical synthesis and protoplast culture provide alternative methods that will always be tested when products achieve significant sales and there is a highly probability of achieving bioequivalence. Paclitaxel was originally produced from the bark of yew trees and considered to be too difficult to synthesise. A major synthesis patent now provides Florida State University with significant revenues from sales of paclitaxel (US$67m from Bristol-Myers Squibb in 2000/01)[34]. Another example is the continued efforts to refine protoplast culture of ginseng due to labour intensive and slow field cultivation[35].

It should be recognised that Australia has strong units for bioprospecting and analysis of novel compounds from plants including Cerylid, AstraZeneca, Australian Institute of Marine Science, BioProspect, Australian Phytochemicals and CSIRO.

Standardised extracts

There are significant opportunities to move from high quality but generic bulk extracts of plants to add significant value through standardisation. Although there are different interpretations of "standardisation" it ultimately refers to the standardisation of an extract around molecular patterns (both markers and active compounds) to ensure a reproducible clinical response. The European industry leads in standardisation and is driven by the requirements of the pharmaceutical industry to ensure consistent potency and safety. There is a significant opportunity for the Australian plant extract industry to increase value through standardised extracts that can also lead to the production of specific phytomedicines and pharmaceutical compounds.

A clear example of value from standardisation is Schwabe's (Germany) extract from *Gingko biloba* (EGb 761) that has been well characterized, used in a large number of clinical trials and has a strong proprietary position. EGb 761 has been commercialised as Tanakan, Tebonin and Rokin[16]. EGb 761 is a standardized extract containing 24% ginkgo-flavonol glycosides, 6% terpene lactones such as ginkgolides A, B, C, J and bilobalide. The spectrum of pharmacological activities has proven clinical results in cardiovascular and central nervous system conditions[17-19]. Similar examples exist for standardised ginseng extract (G115) for improved cognition[20], and standardised St John's Wort extract (WS 5572) for depression[21-22].

Plants for alternative production

Molecular farming of pharmaceuticals in plants has the potential to provide large quantities of recombinant peptides and proteins for use in diagnosis and therapy. Stable transgenic

plants can be used for the cost-effective production of leaves or seeds rich in the recombinant protein for long-term storage or direct processing[23].

Products from transgenic plants are already being marketed and recent clinical trials of pharmaceuticals produced from transgenic plants are encouraging, with plant glycans showing reassuringly poor immunogenicity[24]. Further engineering has enabled the humanisation of plant glycosylation patterns, thus reducing further the risk of immunogenicity[25]. Vaccine antigens, antibodies, and peptides have been produced in a variety of systems and to date a variety of host plants have been used including cotton, rice, bananas, tobacco, maize, potatoes, tomatoes, cereal seeds, and lettuce[26-30].

Wilke has proposed that new plant-based production routes may also challenge established chemical and biochemical domains at the same time providing new opportunities for value added feedstocks, intermediates and end-products[31]. The strategic shift by major chemical companies into molecular plant genetics and agrobiotechnology reflects these opportunities.

In a recent breakthrough, transgenic chloroplasts offer unique advantages in plant biotechnology, including high-level foreign protein expression, absence of epigenetic effects, and gene containment due to the lack of transgene transmission through pollen. Ruf *et al* recently published the first report on the generation of fertile transplastomic plants in a food crop with an edible fruit[32]. Chromoplasts in the tomato fruit expressed the transgene to approximately 50% of the expression levels in leaf chloroplasts. Subject to further refinement such a system could form the basis for effective production and delivery of edible pharmaceuticals, antibodies and vaccines.

Another recent report on multiple gene transformation illustrates the potential of metabolic engineering of tobacco plants by introducing multiple genes[33]. The tobacco plastid was transformed with a polycistron consisting of three bacterial genes for the biosynthesis of a biodegradable polyester, polyhydroxybutyrate (PHB). The ester accumulated in the leaves of the transgenic tobacco and this metabolic conversion indicates a future for plant production of various diverse chemicals.

Rather than focus on diverse pharmaceuticals Australia has a potential opportunity through concentration on the production of antibodies from plants. The rapid rate of approval of antibodies by regulatory authorities has resulted in a global production capacity shortfall that is expected to deteriorate. Australia's strengths in antibody engineering and plant molecular biology (e.g. in CSIRO) could be combined to provide a unique capability.

3.7 Conclusion

Australia does not yet have the full spectrum of capabilities and capacity to support a major successful strategic investment in pharmaceutical development from plants. In the immediate future investment and success will be opportunistic, although a combination of strengths in molecular plant breeding and antibody engineering would provide a strong point of entry. Any concerted effort must take into account that Australia significantly under-invests in development, particularly pharmaceutical development.

Specific capabilities that must be addressed include separation and processing technologies, pharmaceutical development (several disciplines), and the ability to invest in proprietary

added value. Success will depend on changing from a focus on quality commodities to protected and branded products supported by strong clinical evidence, and the ability to develop retail and prescription products in parallel.

Significant opportunities exist in using emerging technologies for bioprospecting of the biota and foods. Such activities could result in significant evidence-based food ingredients, functional foods as well as potential pharmaceutical candidates.

A high degree of national coordination would be required given the rapidly evolving nature of the technologies, increasing emphasis on prevention and subsequent changes in pharmaceutical development. Any intentions to use agriculture for the production of pharmaceuticals must be supported by community discussion of the issues, especially if transgenic technologies are to be exploited.

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