MEDICINAL AND AROMATIC PLANTS - AUSTRALIA

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This volume is dedicated to my father, Ted Cock, who passed away during the preparation of this manuscript. He will be missed.

Keywords: Australian plants, medicinal plants, aromatic plants, ethnopharmacology, phytochemical, pharmacological screening.

Contents

Summary

Plants contain a myriad of natural compounds which exhibit important bioactive properties. These compounds may provide alternatives to current medications and

afford a significant avenue for new drug discovery. As a result of geographic isolation, Australia is home to a large variety of unique and distinct flora not found elsewhere in the world. Due to the harsh conditions seen in many parts of Australia, plants have developed unique survival methods and phytochemicals specific to the environmental conditions they inhabit and may hold the key to the treatment of many diseases and medical conditions. Herbal medicines have played an important role in the health, culture and traditions of Australian Aboriginal people prior to the arrival of Europeans. Much of our understanding of the medicinal potential of Australian native plants is from accounts of Aboriginal ethnopharmacology. However, traditional Aboriginal knowledge of plants as therapeutics is disappearing as the Aboriginal culture merges into main stream society and the passing of oral traditions between each generation diminishes. Given the diverse nature of the flora present and the diminishing traditional knowledge, Australian plants remain relatively unstudied and it is surprising more research has not been done.

Much of our understanding of Australian medicinal plants is fragmented. With the exception of Lassak and McCarthy's book "Australian Medicinal Plants" and various early colonial texts (such as the 1889 work "The Useful Plants of Australia" by Maiden) which describe Aboriginal and early colonial ethnopharmacologies, most information is scattered throughout various scientific journals and government reports. Whilst readily available to scientific researchers in this field, much of this information is difficult to obtain for interested lay persons. Furthermore, the Lassak and McCarthy and the Maiden texts deal almost exclusively with our understanding of Australian ethnopharmacology and little understanding of phytochemistry and bioactivity mechanisms is provided. This volume builds on these ethnopharmacological reports and summarizes the current knowledge of Australian medicinal and aromatic plants. The ethnopharmacologies of various groups, from Aborigines, to early colonial settlers, to later migrant ethnopharmacologies are explored and tabulated as quick reference sources. Knowledge of Australian medicinal plants phytochemistry and mechanisms of action are also summarized, particularly where relating to the aromatic Australian plants (e.g. Eucalypts, Melaleukas, Leptospermums etc). This volume also provides an introduction to current scientific studies into Australian medicinal plants (with specific examples) and some of the techniques used in the hopes of stimulating interest and further studies in this field.

1. Medicinal and Aromatic Plants - Australia

1.1. Natural Plant Medicines Worldwide - A Historical Perspective

Plants have a long history of being used for a wide variety of purposes including food, clothing, shelter, tools, weapons, and as therapeutic agents. Before the advances of modern medicine, civilizations confronted with illness and disease discovered a wealth of useful therapeutic agents from within the plant and fungi kingdoms. Knowledge of these medicinal preparations and of their toxic potential was passed down through generations by oral tradition and sometimes recorded in herbal literature. The earliest records outlining mans usage of plant medications are more than 6000 years old. Sumerian clay tablets (4000 BC) detail 1000 medicinal plants and plant remedies (Afzal and Armstrong, 2002; Levetin and McMahon, 2003). The Pun-tsao, a Chinese record of thousands of herbal cures dates to 2500 BC. The Hippocratic Corpus (a collection of medical texts of herbal remedies) by Greek physician Hippocrates was recorded in the late fifth century BC and the Roman writings De Materia Medica by Dioscorides, document more than 600 plant species with medicinal value (Levetin and McMahon, 2003). These records have more value than merely as an anthropologic or archaeological. They provide an understanding of ancient plant medicinal preparations, some of which are currently still in use.

Many developing cultures (particularly Asian and African) have assimilated herbal medicine into their primary modality of health care (Farnsworth et al., 1985) and herbal medications remain an important component of their medicinal systems. By documenting and practicing traditional medicine these cultures have accumulated comprehensive ethnobotanical data and improved their skills over time. Today, Ayurvedic medicine is still commonly practiced within India with an estimated 85% of Indians still using crude plant formulations for the treatment of various diseases and ailments (Kamboj, 2000).

Even allopathic/Western medicine practiced in developed countries owes much to our understanding of plant based remedies. Table 1 lists some commonly used allopathic drugs derived from plants. The listed drugs have widespread medicinal uses including as analgesics, central nervous system stimulants/depressants, anti-malarial drugs, antiseptics, anti-tumor and anti-cancer agents, cardiac drugs, cholesterol lowering agents, anti-diabetic agents, as well as psychoactives. This is merely a sampling of current plant derived pharmaceuticals and serves only to illustrate the importance of herbal derived medicines and semi-synthetic drugs derived from purified phytochemicals to allopathic medicine. Indeed, it has been estimated that approximately 25% of all prescription drugs currently in use are originally derived from plants (Hostettmann and Hamburger, 1993; Newman et al., 2000; Walsh, 2003). Furthermore, approximately 75% of new anticancer drugs marketed between 1981 and 2006 are derived from plant compounds (Newman et al., 2000).

Acetyldigoxin	Colchicine	Khellin	Rotenone
Adoniside	Convallotoxin	Lanatosides A, B, C	Rotundine
Aescin	Curcumin	Lobeline	Salicin
Aesculetin	Cynarin	Lovostatin	Santonin
Agrimophol	Danthron	Morphine	Scillarin A
Ajmalicine	Deserpidine	Neoandrographolide	Scopolamine
Allantoin	Deslanoside	Noscapine	Sennosides A & B
Allyl isothiocyanate	Digitalin	Ouabain	Silymarin
Andrographolide	Digitoxin	Papain	Stevioside
Anisodamine	Digoxin	Phyllodulcin	Strychnine
Anisodine	Emetine	Physostigmine	Teniposide

Arecoline	Ephedrine	Picrotoxin	Tetrahydropalmatine
Asiaticoside	Etoposide	Pilocarpine	Theobromine
Atropine	Gitalin	Podophyllotoxin	Theophylline
Berberine	Glaucaroubin	Protoveratrines A & B	Trichosanthin
Bergenin	Glycyrrhizin	Pseudoephedrine	Tubocurarine
Bromelain	Gossypol	Quinine	Valepotriates
Caffeine	Hemsleyadin	Quisqualic Acid	Vincamine
(+)-Catechin	Hydrastine	Rescinnamine	Xanthotoxin
Chymopapain	Hyoscamine	Reserpine	Yohimbine
Cocaine	Kainic Acid	Rhomitoxin	Yuanhuacine
Codeine	Kawain	Rorifone	Yuanhuadine

Table 1. Plant derived drugs commonly used in allopathic medicine.

As a result of geographic isolation, Australia is home to a large variety of unique and distinct flora not found elsewhere in the world. Due to the harsh conditions seen in many parts of Australia, plants have developed unique survival methods specific to the environmental conditions they inhabit. Australian Aborigines had developed a good understanding of the botany in their local areas and have used a variety of plant medicines to help maintain their health for approximately 40, 000 years (Barr et al., 1993; Lassak and McCarthy, 2006). However, traditional Australian Aboriginal knowledge of plants as therapeutics is disappearing as the Aboriginal culture merges into main stream society and the passing of oral traditions between each generation diminishes (Lassak and McCarthy, 2006). Given the diverse nature of the flora present and the diminishing traditional knowledge, Australian native plants remain relatively unstudied and it is surprising more research is not being undertaken. There is a very real need to document the traditional usage of Australian native and indigenous plants before this knowledge is permanently lost.

This volume aims to document and summarize the current understanding of Australian aromatic and medicinal plants and to stimulate further research in this field. Before undertaking a description of the usage of Australian native plants, it is necessary to understand the classes of phytochemicals present in plants and the divergent evolution that has resulted in Australia's high degree of endemic species. Many of these species live in extremely harsh environments, making them candidates for scientific examination.

1.2. Phytochemicals of Therapeutic Significance

Plants have evolved to synthesize an extremely diverse range of chemical compounds known as secondary metabolites. These secondary metabolites have no apparent role in primary plant growth or development processes, are often unique to plants from a single species and increase during times of high stress such as drought, fire and bacterial infection (Taiz and Zeiger, 2006). Many of these compounds exhibit anti-microbial, anti-oxidant, cytotoxic and other medicinally useful properties (Taiz and Zeiger, 2006). These activities can be attributed to the presence of a variety of phytochemical constituents, which can be divided into three main chemically distinct groups: terpenes, phenolics and nitrogen containing compounds (alkaloids).

The nomenclature and classification of secondary metabolites can be confusing. In many instances, properties common to the three major classes overlap (e.g. a phenolic compound may contain nitrogen, making it both a phenolic compound and an alkaloid). Proanthocyanidins are examples of tannins (phenolic compounds) which contain nitrogen and are found in Australian *Acacia* species. Similarly, terpenes present within the essential oils from a variety of Australian plant species (e.g. Eucalyptus and Melaleuca species) may be considered both terpenes and phenolics as they structure their five carbon atoms into phenolic rings.

1.2.1. Terpenes

Terpenes or terpenoids are formed by the union of five carbon elements (isoprene units) (Figure 1) to form more complex biomolecules.

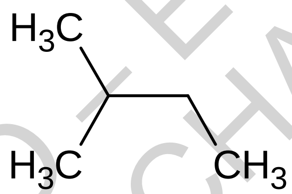

Figure 1. The structure of isoprene, the basic unit of terpenes and terpenoids.

The union of two isoprene units forms a monoterpene. Examples of well known monoterpenes include limonene (lemon oil) (Figure 2a) and menthol (peppermint oil) (Figure 2b) which provide defense against potential predators and are sometimes used as food flavoring agents (Taiz and Zeiger, 2006). Monoterpenes can undergo further modification to form sesquiterpenes (15 carbon units), diterpenes (20 carbon units) and polyterpenes (many carbon units).

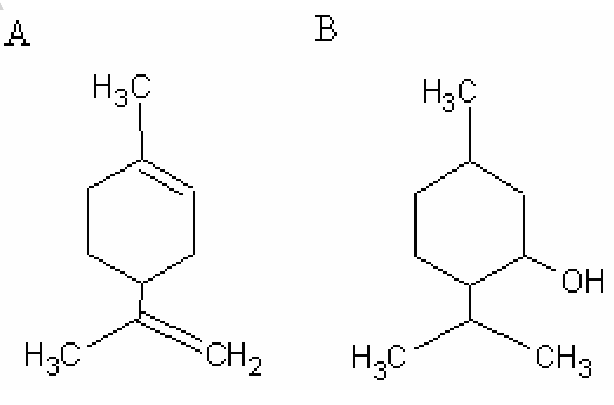

Figure 2. The chemical structure of (a) limonene and (b) menthol.

Terpenes are toxins which act as feeding deterrents to many plant feeding insects and mammals and are relatively insoluble in water (Taiz and Zeiger, 2006). Pyrethroids for example, are a class of terpenes which exhibit toxicity as well as insecticidal and anti-microbial activities. They occur in the leaves and flowers of Chrysanthemum species (Taiz and Zeiger, 2006). They are often used as a component of insecticides due to their low persistence in the environment and negligible toxicity to mammals (Taiz and Zeiger, 2006). Recent research has shown that some terpenes are only produced and emitted from the plant after insect feeding has begun (Taiz and Zeiger, 2006). These substances may have no effect on the insects that stimulated their production, but increase resistance to future attack, or they may attract predatory and parasitic insects which in turn kill the plant feeding insects (Taiz and Zeiger, 2006).

Many Australian plants contain mixtures of terpenes known as essential oils. In particular, the essential oils of members of the family Myrtaceae (Eucalypts, Melaleucas, Leptospermums and Callistemons) are known to be particularly rich in terpenes. These plants, their medicinal uses and their phytochemistry will be described separately in more detail in later sections of this volume. The terpene containing essential oils of these plants add a characteristic odor and flavor to plant foliage and some therefore may be used as food flavoring agents. Some essential oils possess a broad spectrum of anti-microbial activities and may be used to fight against pathogens (Deininger, 1984; Manohar et al., 2000).

1.2.2. Phenolic Compounds:

Phenolic compounds are secondary metabolites that contain a phenol group (Figure 3).

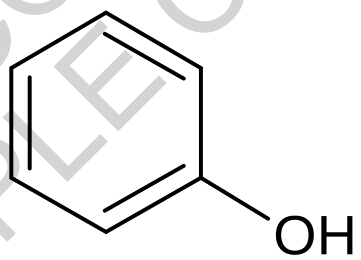

Figure 3. A phenolic ring, the primary building block of a phenolic compound.

Phenolic compounds include a variety of different sub-classes including tannins, flavones, isoflavones, flavonols, anthocyanins, coumarins, chalcones and phytoelaxins (Figure 4). In plants, phenolic compounds act as a defense mechanism against herbivores and pathogens, attract pollinators, absorb UV radiation, minimize oxidative stress and reduce the growth of nearby competing plants (allelopathy) (Taiz and Zeiger, 2006).

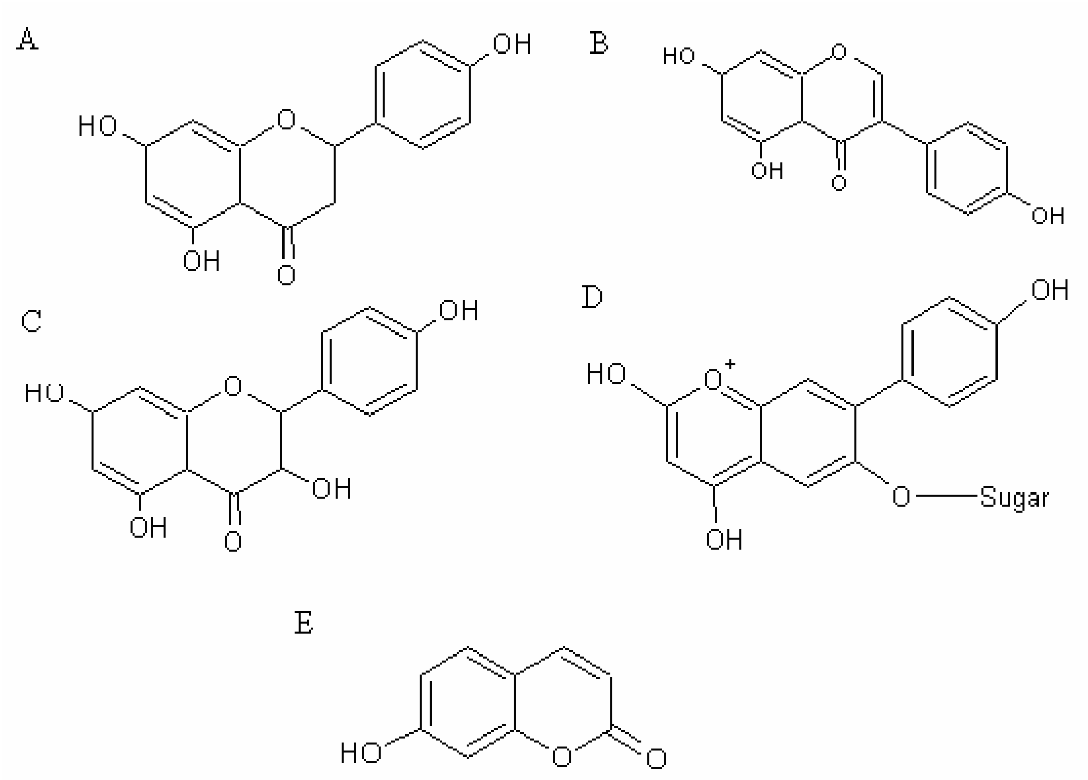

Figure 4. Structure of (a) Flavones, (b) Isoflavones/Isoflavonoids, (c) Flavonols, (d) Anthocyanins, and (e) Coumarins.

The function of phenolic compounds varies greatly. Flavones and flavonols (Figure 4a and 4c) are present in the leaves of all green plants and protect them from UV damage by absorbing light in the shorter wavelengths (Taiz and Zeiger, 2006). Anthocyanins (Figure 4d) are pH dependent colored flavonoids which attract pollinators (Taiz and Zeiger, 2006) whilst isoflavones/isoflavonoids (Figure 4b) exhibit strong antimicrobial activity (Taiz and Zeiger, 2006). Isoflavones and isoflavonoids have also been identified for use in the treatment of a wide range of health conditions such as menopause, cardiovascular disease, cancer and osteoporosis (Yen et al., 2008).

Tannins may act as general toxins that reduce growth and survival of many herbivores when added to their diet (Taiz and Zeiger, 2006). Tannins inhibit the growth of many fungi, yeast, bacteria and viruses and have also been suggested as anti-carcinogens (Scalbert, 1991). Tannic acid and propyl gallate inhibit food borne, aquatic and off-flavor-producing micro-organisms (Scalbert, 1991). In contrast, foods containing tannins (e.g. tea tannins) are regularly consumed by humans and have been shown to promote health rather than hinder it (de Mejia et al., 2009).

Phytoalexins are antibiotics produced by plants when under stress. They exhibit strong antimicrobial activity and are generally undetectable before initial infection. They are synthesized very rapidly after microbial attack and accumulate around the site of infection (Taiz and Zeiger, 2006). Phytoalexins from different plant families can be produced as different secondary metabolites e.g. Capsidiol (from pepper and tobacco; Figure 5a) is a sesquiterpene whilst resveratrol (from grape skin; Figure 5b) is an isoflavonoid. Because of its structural resemblance to estrogen, resveratrol exhibits agonistic and antagonistic activities towards the estrogen receptor and it has been suggested that resveratrol could reduce localized estrogen production in breast cancer cells (Wang et al., 2006). Resveratrol also displays chemo-preventive activity by inhibiting, delaying or reducing carcinogenesis (Signorelli and Ghidoni, 2005).

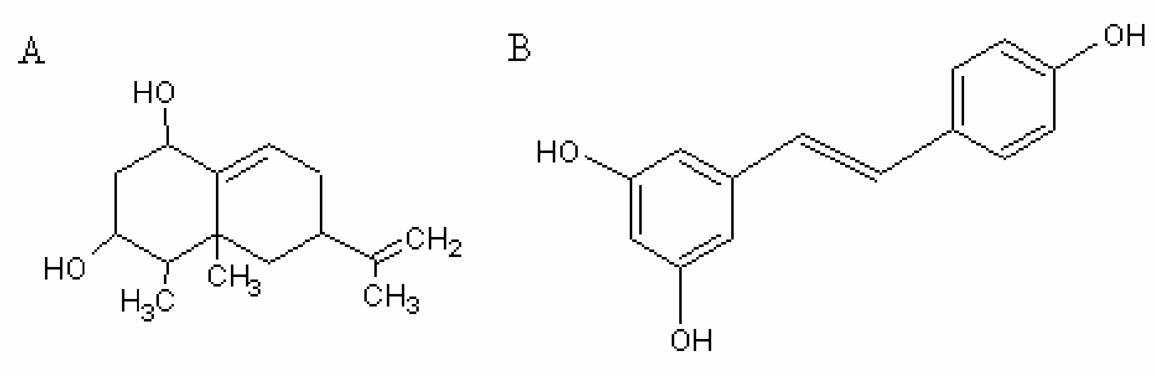

Figure 5. Chemical structures of (a) Capsidiol and (b) Resveratrol.

The interaction of several flavonoids with ATP-binding cassette (ABC) transporters such as P-glycoprotein (Di Pietro et al., 2002), multi drug resistance associated protein 1 (Leslie et al., 2001), and Breast Cancer Resistance Protein (BCRP) (Zhang et al., 2004) (which are believed to limit the intracellular accumulation of cytotoxic agents in cancer cells when over expressed) have been reported. These same flavonoids have been shown to modulate breast cancer resistance protein BCRP on a transcriptional level in Caco-2 and MCF-7 cells (Ebert et al., 2007). The flavonoid, acacetin-7-o-b-D-galactopyranoside from *Chrysanthemum morifolium* was found to be active towards HIV by inhibiting HIV replication (Hu et al., 1994).

Many Australian plants are known to contain high levels of phenolic compounds. These plants, their medicinal uses, and their phytochemistry will be described in more detail in later sections of this volume.

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Biographical Sketch

Ian Cock obtained his PhD for studies in reproductive biology/immunology into “Early Pregnancy Factor (EPF)” and very early pregnancy detection from Griffith University, Brisbane, Australia in 1994. Following his PhD studies, Dr Cock undertook postdoctoral studies into cytochrome’s P450 and multiple drug interactions in the Department of Biochemistry and in the Department of Physiology and Pharmacology, both at the University of Queensland. He returned to Griffith University as an academic staff member in 1998 and has taught and developed a number of courses across three campuses of Griffith University since this time. His teaching broadly encompasses biochemistry, biological chemistry, cell biology, immunology, plant biology and biotechnology. Specific areas of expertise and interest include metabolism and its regulation, phytochemistry and natural product discovery, redox biochemistry and redox control systems, protein structure/function, enzymology, biomolecular isolation and characterization techniques, and drug bioassays.

Dr Cock currently also leads a research team in the Department of Biomedical and Biophysical Sciences at Griffith University. The Griffith University research team is involved in bioactivity and phytochemical studies into a variety of plant species of both Australian and international origin. The current research interests of this team involve bioactivity, structural and mechanistic studies into the medicinal potential of *Aloe vera*, South Asian and South American tropical fruits, as well as Australia plants including *Scaevola spinescens*, *Pittosporum phylliraeoides*, *Terminalia ferdinandiana* (Kakadu plum), Australian Acacias, Syzygiums, Petalostigmas and *Xanthorrhoea johnsonii* (grass trees). This range of projects has resulted in numerous scientific publications in a variety of peer reviewed journals. Dr Cock is also a member of the editorial boards of four scientific journals, including being the chief and foundation editor of the journal Pharmacognosy Communications.