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Review Article

The phytochemistry and chemotherapeutic potential of *Tasmannia lanceolata* (Tasmanian pepper): A review

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ABSTRACT: 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. Despite this, little information is available in the literature regarding many native Australian plants and their potential for medicinal and industrial uses. *Tasmannia lanceolata* (Tasmanian pepper) has a long history of usage by Australian Aborigines and European settlers as a food flavouring agent. Aborigines also used it for the treatment and cure of skin disorders, venereal diseases, colic, stomach ache and as a quinine substitute. Apart from the reported ethnopharmacological uses of Tasmanian pepper, surprisingly few studies have rigorously examined this species for its medical properties. Recent studies have reported Tasmanian pepper to be an extremely good source of antioxidants. Indeed, Tasmanian pepper has been reported to have free radical scavenging activities more than 4 times higher than blueberries despite having ascorbic acid levels below the level of detection. Tasmanian pepper is particularly high in terpenes and phenolic compounds but also has high levels of a variety of other antioxidants, including anthrocyanins and anthrocyanins glycosides. Antioxidants have been associated with the prevention of cancer, cardiovascular disease and neurological degenerative disorders. They are also linked with anti-diabetic bioactivities and have been associated with the reduction of obesity. Antioxidants can directly scavenge free radicals, protecting cells against oxidative stress related damage to proteins, lipids and nucleic acids. Therefore, *T. lanceolata* has potential in the treatment of a variety of diseases and disorders and its potential bioactivities warrant further investigation.

KEYWORDS: Winteraceae, *Tasmannia lanceolata*, Tasmanian pepper, Australian medicinal plants, antioxidants, flavonoids, terpenoids

INTRODUCTION

Plants produce a wide variety of chemically diverse compounds which form the basis of their defense systems against animal foraging, microbial infections and competition.[1] These phytochemicals often have medicinally important bioactivities and may be harnessed for new drug discovery or used directly as therapeutic agents. Natural therapies not only form the basis of many traditional medicinal systems (particularly in developing countries), but are also gaining wide spread acceptance and increased usage in Western medicinal systems. Furthermore, medicinal plants serve as a starting point for natural products discovery and the development of semi-synthetic agents with enhanced medical properties. Indeed, approximately 25% of all prescription drugs currently in use were originally derived from plants or are semi-synthetic analogues of plant derived compounds.[2] The statistics are even more impressive when we consider the role of plants in the development of new anticancer agents: approximately 75% of new anticancer drugs marketed between 1981 and 2006 are derived from plant compounds.[1] Despite the impressive array of therapeutics derived from plants, only 10% of the estimated 250,000 species worldwide have been screened for any bioactivities. Most of these studies have utilized traditional knowledge and ethnopharmacology to target specific plants. The study of plant pharmacognosy could lead to the discovery of commercially and/or therapeutically useful phytochemicals possessing a diverse range of activities. As Asian, Middle Eastern and European traditional medicine systems have been the most extensively

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documented compared to those of other world regions, the majority of studies have concentrated on plants from these regions. Recently there has been an increase in interest in the therapeutic potential of plants from other regions internationally and the medicinal potential of plants from Africa, South America and Australia are increasingly being reported.

As a result of its 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 the continent, Australian plants have developed unique survival methods specific to the environmental conditions they inhabit and they may hold the key to the treatment of many diseases and medical conditions. Traditional Australian Aboriginal knowledge of plants as therapeutics is disappearing as the indigenous cultures merge 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 into their potential. A recent study into the antioxidant properties of several Australian plants has identified several species (including *Tasmannia lanceolata*) as being of particular interest due to their very high antioxidant activities and interesting phytochemistry.[3,4]

The family Winteraceae

Winteraceae is a family of flowering plants consisting of approximately 90 species of trees and shrubs divided into 5 genera (Drimys, Pseudowintera, Takhtajania, Tasmannia and Zygogynum).[5] The Winteraceae have developed as almost exclusively southern hemisphere plants, originating from precursor species on the Gondwanna super continent. Their current distribution ranges from the cool climate regions of the southern Australia (particularly Tasmania) and New Zealand through to the temperate and tropical regions of Borneo, Madagascar, Molucca, New Caledonia, Papua New Guinea, the Philippines and Southern and Central America, with the majority concentrated in Australasia and Malesia.[6]

The Winteraceae are characterized as woody evergreen plants with vessel-less xylem and plicate carpels.[5,6] They generally have leaves without stipules. The leaves, which are almost always glabrous, have entire margins and are spirally arranged. Flowers are terminal, generally condensed and can be either bisexual or unisexual, depending on the individual species. The fruit forms as a fleshy berry with a hard seed. Many Winteraceae species are fragrant and are often used to produce essential oils. Zygogynum is the largest Winteraceae genus with approximately 50 species.[5–7] Until recently, Belliolum, Bubbia and Exospermum were classified as distinct genera, although most botanists now classify these as subgroupings of the Zygogynum genus. Tasmannia is the next largest genus with approximately 30 species.[8] Drimys consists of 6 species, Pseudowintera has 2 species, and Takhtajania consists of a single species.[8]

Members of family Winteraceae have been used for a broad range of dietary and medicinal purposes by a wide variety of ethnic and cultural groupings. The best documented of these is the South American species *Drimys winteri*. The stem and bark of this species has been used as a stimulant and as a tonic in traditional Brazilian medicinal systems.[9] They are also used for the treatment of a wide variety of diseases and medicinal conditions including use as an analgesic, and to treat diarrhoea, inflammation, and ulcers.[9,10] This species also has widespread usage in the treatment of scurvy due to its high antioxidant content.[11] Of the other Winteraceae species, several have a history of ethnobotanical usage, usually for purposes related to their high antioxidant contents and as flavourants. Indeed, high levels of the compound polygoidal (which gives the Winteraceae a characteristic peppery flavour) and high antioxidant contents are characteristic of several Winteraceae species.

Tasmannia lanceolata (Tasmanian pepper)

Tasmannia lanceolata (commonly known as Tasmanian pepper or mountain pepper; Figure 1a) is shrub which is endemic to the woodlands and cool temperate rainforests of Tasmania and the south-eastern region of the Australian mainland (Figure 1b). The species was originally described by the French botanist Jean Louis Poiret. Until 1969 it was classified in the genus Drimys and was named *Drimys lanceolata*. It is a medium to large shrub that varies between 2–5 m in height. Individual plants are unisexual, having either male or female flowers. The stems, branches and twigs are red in colour. The aromatic leaves are lanceolate to narrowly elliptical in shape (4–12 cm long, 0.7–2 cm wide) with a distinctly pale undersurface. Small creamy-white unisexual flowers appear during the summer months. These develop into small fleshy black 2 lobed berries (5–8 mm wide) during autumn.

As with many of the other Winteraceae species, *T. lanceolata* berries, leaves and bark have historical uses as a food and as a medicinal plant.[12] When the berry is air dried it forms a small, hard peppercorn which is suitable for milling or crushing. The berry has a pleasant spicy flavor and sharp aroma. *T. lanceolata* was used as flavouring agent

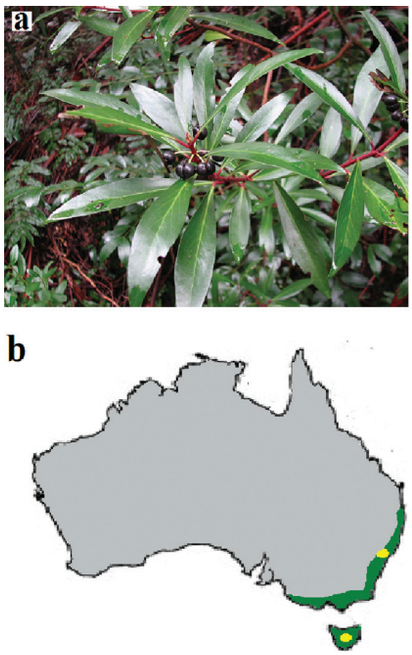

Figure 1. (a) *Tasmannia lanceolata* showing leaves and mature fruit. This photograph was obtained from Wikipedia commons (http://en.wikipedia.org/wiki/File:Tasmannia_lanceolata.jpg) and is reproduced here with the relevant permissions under the terms of the GNU Free Documentation Licence. (b) The distribution of *Tasmannia lanceolata* on the Australian continent (indicated by the green areas). The yellow areas indicate areas where the plant is particularly common.

by Australian Aborigines and more recently by European settlers. Historically, the leaves have been used as a herb and the berries have been used as a spice. Australian Aborigines also used *T. lanceolata* as a therapeutic agent to treat stomach disorders and as an emetic, as well as general usage as a tonic.[13,14] Reports also exist of the use of *T. lanceolata* by Australian Aborigines for the treatment and cure of skin disorders, venereal diseases, colic, stomach ache and as a quinine substitute.[13,15,16] Later, European colonists also recognized the therapeutic potential of *T. lanceolata* and the bark was used as a common substitute for other herbal remedies (including those derived from the related South American Winteraceae species, *Drimys wintera* (winter bark))[17] to treat scurvy due to its high antioxidant activity.[13,14]

ANTIOXIDANT CONTENT

Epidemiological studies have shown that a diet high in fruits/vegetables is associated with lower risk of developing chronic diseases.[18] High antioxidant levels have previously been demonstrated to act as preventative effects against the development of degenerative diseases such as cancer,[19] cardiovascular diseases,[20] neural degeneration,[21] diabeties and obesity.[22] The antioxidant activity of many plants has been associated with their phenolic contents. Many phenolic compounds have been shown to have strong antioxidant activities and may protect cells against oxidative damage by directly scavenging free radicals.[23] Phenolic compounds may also interact directly with receptors or with enzymes involved in cellular signal transduction.[24] Common classes of plant phenolic compounds include flavonoids, tannins and anthrocyanins.

Recent studies have documented the exceptionally high antioxidant content of *T. lanceolata*.[3,4] These studies have reported that *T. lanceolata* leaves have antioxidant contents more than 4 fold higher than those reported for blueberries (which themselves are considered to have high antioxidant contents). Interestingly, ascorbic acid (which itself makes a significant contribution to the antioxidant content of many fruits) was reported to be below the threshold of detection in this study and therefore would not contribute significantly to the high antioxidant content of *T. lanceolata*. Furthermore, the levels of *T. lanceolata* leaf phenolic antioxidants were reported in the same study to be over 3 fold higher than the levels in blueberries.[4] *T. lanceolata* leaves have also been reported to have phenolic antioxidant contents up to 4 times higher than in basil leaves (*Ocimum basilicum*),[25] higher levels than determined for peppermint leaves[26] and similar levels to the phenolic antioxidant contents of maple, silver birch and spruce leaves.[27] The antioxidant phenolic contents of *T. lanceolata* berries are also high, although these levels are significantly lower (less than 20%) than the leaf phenolic antioxidant levels. The contents are similar to those reported for those reported for *Piper nigrum* (black pepper) and *Lycium barbarum* (Chinese Barbary Wolfberry fruit),[26] but approximately half the level of black sesame and peach kernel.[27]

T. lanceolata leaves and berries also contains other compounds which contribute to their high antioxidant activities [3,4] While many of these compounds are yet to be identified, *T. lanceolata* fruit has been shown to contain benzoic acids, flavanols, or flavanones.[3] *T. lanceolata* is a good source of eugenol (Figure 2a), methyl eugenol (Figure 2b) and gallic acid (Figure 2c),[28,29] all of which demonstrate strong antioxidant activity *in vitro*.[30,31] *T. lanceolata* fruit extracts are also rich in lutein (Figure 2g—a carotenoid antioxidant compound associated with eye health) and with vitamin E (Figure 2g), vitamin A (Figure 2h) and folic acid (Figure 2i).[3] The glycosides quercetin (Figure 2e) and rutin (Figure 2f) are some of the other

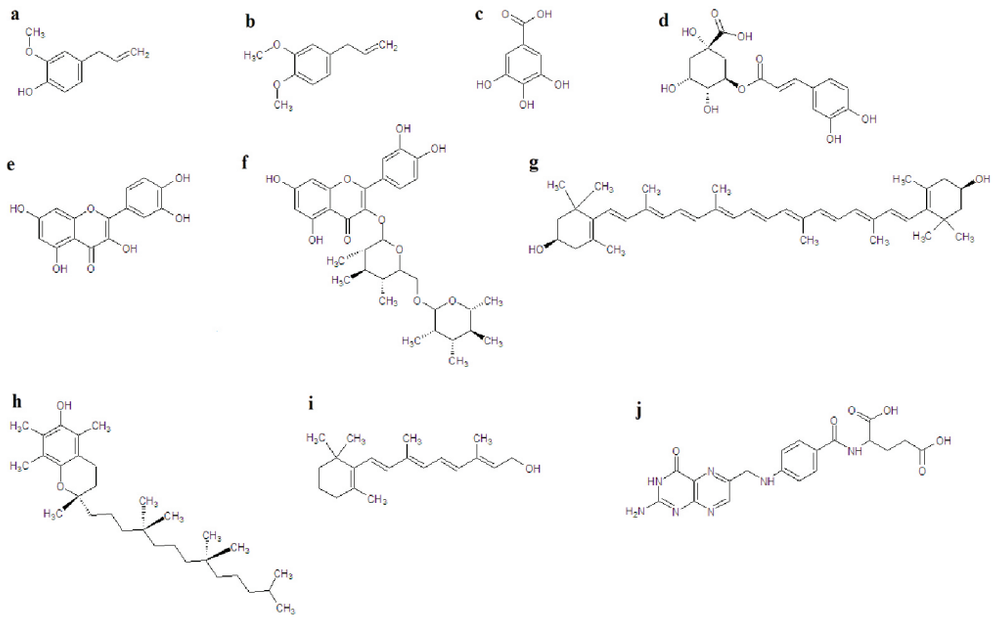

Figure 2. Chemical structures of selected antioxidant molecules identified in *T. lanceolata*: (a) eugenol, (b) methyl eugenol, (c) gallic acid, (d) chlorogenic acid, (e) quercetin, (f) rutin, (g) lutein, (h) α-tocopherol (vitamin E), (i) vitamin a, (j) folic acid.

antioxidants present in *T. lanceolata* fruit and leaves.[3] *T. lanceolata* fruit is also a good source of the minerals magnesium, zinc, calcium, potassium, sodium, iron, phosphorous, manganese, copper, and molybdenum.[3] It has previously been postulated that the exceptionally high antioxidant content of other plant species may be responsible for the therapeutic effects displayed by those plants.[32,33] Therefore, it is likely that the high antioxidant contents reported for *T. lanceolata* extracts and essential oils would convey similar therapeutic properties.

The medicinal potential of plants with high antioxidant contents has been receiving much recent attention[3,4] and reports have linked antioxidant levels and redox management with anticancer activity.[32] A recent study has demonstrated that a fruit extract from a different plant rich in polyphenolic compounds (*T. ferdinandiana*) displayed antiproliferative activity against a panel of cancer cell lines.[34] Studies into the antioxidant/prooxidant effects of extracts from other plant species have demonstrated that the ability of a plant extract to exert antioxidant activity depends on multiple factors. Aloe vera antioxidant components for example may function as either antioxidants or prooxidants, with their action being dependent upon their concentration.[33] The Aloe vera anthraquinone aloe emodin exerts antioxidant behaviour at lower concentrations, yet acts as a prooxidant at high concentrations. In contrast, a different Aloe vera anthraquinone (aloin) has an antioxidant effect at higher concentrations, yet a prooxidant effect at low concentrations. Thus, Aloe vera extracts and components may act as either antioxidants or as oxidants, dependent on differing levels of the various constituents, and on their ratios. Thus, although *T. lanceolata* has very high antioxidant contents, it is possible that the individual components may act as either antioxidants or as oxidants and thus may also be effective in the treatment of cancer, as well as in its prevention at different concentrations.

Similar concentration dependent prooxidant effects have been reported for other antioxidant phytochemicals including many of the flavonoids[35] which are present in high concentrations in *T. lanceolata* leaves and berries.[36] Previous studies have also shown that the presence of transition metal ions such as copper or iron in the extract can enhance the conversion of the antioxidant to the prooxidant state.[37,38] The prooxidant/antioxidant concentration dependent effects of plant extracts are due to a balance between the free radical scavenging activities and reducing power of their phytochemical components.[32,33]

Reactive oxygen species (ROS) based tumour therapy would cause tumour regression should the tumour cells not be apoptotic/oxidant resistant cells. Therefore, if *T. lanceolata* antioxidant components are present in concentrations and ratios consistent with prooxidant activity, the extract would be expected to induce apoptosis and therefore would have anticancer activity. If the levels of components are consistent with a reducing environment, antioxidant activity would result and the extract would not have anticancer activity. Conversely, should the protocol

be repeated on a tumour with apoptotic resistant/oxidant resistant cells, the converse would apply, where tumour progression would be observed.

High antioxidant plants such as *T. lanceolata* also have potential in the maintenance/control of diabetes. Glycosylation of blood proteins including haemoglobin, albumin and lipoproteins is characteristic of diabetes mellitus.[39] Under the hyperglycaemic conditions of diabetes mellitus, blood glucose interacts with specific amino acids on the surface of proteins, forming glycosylated protein products. These may undergo a series of further chemical modifications, resulting in the production of advanced glycation end products (AGE).[40] The binding of AGEs to their receptors results in altered cell signalling which in turn results in free radical production.[41] Indeed, diabetes mellitus has been shown experimentally to be associated with an increase in free radical formation and an associated decrease in antioxidant potential [42,43] Studies have directly linked oxidative stress with the impaired maintenance of glucose homeostasis and the enhanced lipid peroxidation seen in diabetes mellitus.[42] Furthermore, increased total antioxidant levels have been measured in the blood and saliva of diabetic patients, further supporting the proposed role of oxidative stress in diabetes mellitus.[44]

Oxidative stress induction has also been suggested to be the common link between the diverse medical complications (including cardiovascular disease, renal and neural degeneration, impaired vision and erectile dysfunction) seen in diabetes mellitus.[45,46] Therefore, treatment with antioxidants would be expected to counteract many of these complications. *T. lanceolata* leaves and berries have a number of compounds (both phenolics and nonphenolic compounds) that can act as antioxidants. Many phenolic compounds could potentially behave as either antioxidant or prooxidant dependant on their concentration, redox state and ratio between compounds.[33]

Eugenol (Figure 2a) has been shown to suppress the growth of B16 melanoma and human HL-60 leukemia cells.[81] A recent study has also reported that eugenol induces apoptosis in HCT-15 and HT-29 human colon cancer cell lines.[47] The same study also showed that eugonol blocks cell cycle progression. Another study reported that eugenol modulates cyclooxygenase 2 (COX-2) expression in HT-29 human colon cancer cells.[48] Furthermore, eugenol has additional therapeutic potential due to its other reported bioactivities.[49] Its ingestion reduces the levels of blood glucose, triglycerides and cholesterol, indicating its potential in the treatment and maintenance of diabetes mellitus and as a hypolipidemic agent. Eugenol relaxes arterial smooth muscle and has potential as a vasodilator. It also has membrane stabilizing properties on synaptosomes, erythrocytes and mast cells as well as providing it with therapeutic potential in the treatment of inflammation and allergic disorders as well as neurological conditions such as epilepsy. Eugenol also has potential in the treatment of rheumatoid arthritis due to its effect in lowering uric acid levels in rabbits.[50] It has also been reported to have have antimicrobial activity.

PHYTOCHEMISTRY

T. lanceolata has been used as a flavouring agent by both Aboriginal Australians as well as by later colonists and settlers. It is well noted for its peppery taste and aroma. Multiple studies have reported that the drimane sesquiterpene polygoidal (Figure 3a) is the major component responsible for the flavour and aroma characteristics of this species. Indeed, it has been reported that polygoidal may account for nearly 40% of commercial *T. lanceolata* essential oil components.[51] Many studies have reported the therapeutic properties of this compound, including its antibacterial,[52] antifungal,[53–55] antihyperalgesia,[56] anti-inflammatory, antiallergic and vasorelaxation activities.[57]

Studies examining the antibacterial activity of polygoidal have provided conflicting reports. Early studies have reported little or no antibacterial activity against limited panels of bacteria, although many of these studies tested polygoidal at relatively low concentrations (100 μg/ml).[55] In contrast, more recent studies have demonstrated good bactericidal activity against both Gram-positive and Gram-negative bacteria.[52] Antifungal efficacy and mechanistic studies have been more definitive, with several publications highlighting polygoidal's potent fungicidal activity.[53–55] Polygoidal appears to exert its antifungal activity by several mechanisms. It nonspecifically disrupts/denatures fungal integral membrane proteins by functioning as a nonionic surfactant.[52] It also readily reacts with amino acids (especially cysteine and aromatic amino acids), resulting in further denaturation. As an additional antifungal mechanism, polygoidal may permeate cells by diffusing across the cell membrane. Once inside the cell, polygoidal interacts with various intracellular components and affects metabolic processes.

T. lanceolata also produces phenylpropenes including safrole (Figure 3b) and myristicin (Figure 3c). Similar phenylpropenes occur naturally in several other aromatic spices including cinnamon, nutmeg, black pepper and basil.

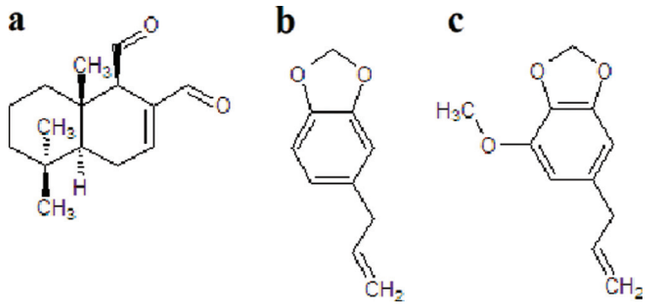

Figure 3. Chemical structures of (a) polygoidal; (b) safrole; (c) myristicin.

The presence of safrole in *T. lanceolata* is concerning as it has been reported to be mildly genotoxic and carcinogenic in rats.[58] Furthermore, safrole is also a weak hepatotoxin and has been shown to induce oxidative damage to liver cells.[59] The carcinogeneicity and toxicity of safrole has been shown to be due to the conversion by rat cytochrome P450 enzymes to electrophillic esters which form covalent adducts with DNA.[60] In the past, safrole was widely used as an additive to beverages such as root beer and sassafras tea although its use is now banned by the US Food and Drug Administration (FDA) as a food additive and monitoring of its levels is recommended in products in which it occurs naturally. However, it must be noted that these early carcinogenisis/toxicity studies were performed in rodent experimental systems. Parallel safrole metabolism studies in humans demonstrated that the carcinogenic metabolites present in rat urine were absent in humans[61] and thus the carcinogenic activity of safrole may be milder or even non-existent for humans. In contrast to safrole, the related compound myristicin (Figure 3c) has been reported to have tumorgenesis inhibitory activity via an induction of glutathione S-transferase activity.[62]

Phenolics/flavonoids

Phenolic compounds, and in particular the flavonoids, have been identified as the major class of antioxidant compounds in *T. lanceolata*. As such, the phenolics have potential in the prevention and treatment of cancer and cardiovascular disease. Some flavonoids have been linked to the induction of cellular mechanisms that affect cancer cell progression and proliferation, as well as inhibiting tumour invasion.[63] However, phenolics are also known to have further therapeutic properties in addition to their antioxidant activities (although some of these activities may be linked to the antioxidant activities). Flavonoids are considered to be particularly useful in maintaining good health and are often used as disease preventative agents. Preliminary reports suggest that flavonoids may modify our responses to allergens, viruses and carcinogens.[63] Indeed, studies have verified the antibacterial, antiviral, anti-inflammatory, anticancer and antidiarrhoeal activities of flavonoids.[63]

Recent studies have reported very high levels of antioxidant flavonoids and flavonoid glycoside compounds in *T. lanceolata* extracts compared to the levels in other plants. These flavonoids include quercetin (Figure 2e), rutin (Figure 2f), (c) cyanidin-3-glucoside (Figure 4c) and cyaniding-3-rutinoside (Figure 4d). There is evidence that similar bioflavonoids prevent oxidation of LDL cholesterol via their free radical scavenging activity,[64] inhibit endothelial activation[65]) and inhibit platelet aggregation.[66] They also possess cyclooxygenase inhibitory activity and can prevent thrombosis.[66] Evidence exists that the ingestion of high dietary levels of flavonoids is inversely proportional to the risk of coronary artery disease (CAD).[67–69] It is therefore likely that the high flavonoid contents reported in *T. lanceolata* (particularly in the leaves) may have beneficial effects in CAD.

Recent studies have reported that many phenolic compounds also have potent anti-inflammatory activities.[63] These anti-inflammatory effects are likely due to the inhibition of the enzymes cyclooxygenase and lipoxygenase, resulting in the inhibition of prostaglandin and leukotriene synthesis and the downstream release of cytokines.[70,71] Quercetin (Figure 2e) in particular has been shown to

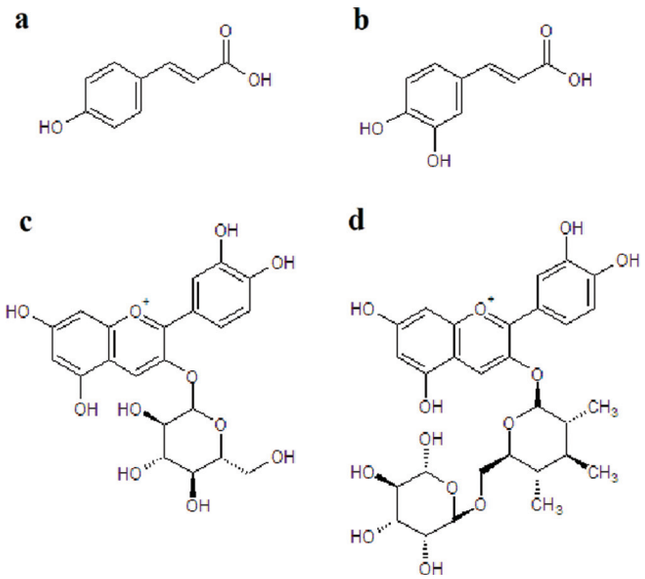

Figure 4. Chemical structures of known phenolic constituents of *T. lanceolata*: (a) coumaric acid, (b) caffeic acid, (c) cyanidin-3-glucoside, (d) cyanidin-3-rutinoside.

have potent inhibitory effects on both cyclooxygenase and lipoxygenase enzyme activities via its antioxidant activity, resulting in diminished eicosanoid biosynthesis.[72] These effects are exerted via a down regulation of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[63] This down regulation results in the inhibition of the inflammatory mediators such as nitric oxide (NO) and prostaglandin E_2 (PGE_2) production. As mitogen-activated protein kinases (MAPKs) which regulate inflammatory and immune responses may be activated by the production of reactive oxygen species (ROS), it is likely that the inhibition of ROS via quercetin is responsible for its anti-inflammatory activity.

Whilst studies of the antibacterial activities of flavonoids vary widely (possibly due to intra and inter assay variations), a number of flavonoids have been reported to have antibacterial activity against multiple bacterial species. One study examined the ability of quercetin and rutin and their corresponding glycosides to inhibit the growth of *Pseudomonas maltophilia* and *Enterobacter cloacae*.[73] This study showed that the quercetin glycosides showed the strongest inhibitory activity of the flavonoids glycosides tested. Many of the other glycosides also inhibited bacterial growth, albeit with lower efficacy. Another study tested the inhibitory activity of a panel of 38 flavonoids against methicillin resistant *Staphylococcus aureus* (MRSA) and reported moderate antibacterial activity for several flavonoids including quercetin and luteolin. Rutin was also shown to have a low MIC against multi-resistant β-lactamase producing *Klebsiella pneumoniae*.[74] Thus, flanonoids have potential in the treatment of infective diseases and much more study is required to examine the structure/activity relationships of the compounds as well as the mechanisms of their action.

Flavonoids also have antiviral bioactivities.[68] Some of the viral diseases that were reported to be inhibited by flavonoids were adenovirus, herpes viruses, HIV, parainfluenza virus and respiratory syncytial virus.[75,76] These studies have shown that flavonoids have affects of on multiple stages of viral replication and infectivity in vitro. For example, quercetin exhibits both antiinfective and antireplicative bioactivities.[75] Many of the current investigations into the antiviral activities of flavonoids have reported on their effects on the various stages of the HIV replicative cycle. Most have focused on the ability of flavonoids to inhibit HIV reverse transcriptase[77] as well as antiintegrase and antiprotease activities.[68] Furthermore, epidemiological studies have indicated that dietary flavonoids may have a protective role against coronary disease.[78]

Essential oil components

Volatile components account for the majority of the *T. lanceolata* phytochemical profile, accounting for as high as 6% of the dry weight of the plant material.[51] For this reason, until recently, research into *T. lanceolata* phytochemistry has largely concentrated on these components. A recent analysis of commercial essential oil components[51] reported these to be predominantly sesquiterpenic, with polygoidal (36.74%) (Figure 3a) being the major component. Other sesquiterpenoids occur at lower levels in *T. lanceolata* essential oils and are known to vary widely between individual plants. An analysis of commercial *T. lanceolata* essential oils[51] reported that guaiol (4.36%) (Figure 5f2), calamenene (3.42%) (Figure 5c2), spathulenol (1.94%) (Figure 5f3), drimenol (1.91%) (Figure 5c3), cadina-1,4-diene (1.58%) (Figure 5c1), 5-hydroxycalamenene (1.47%) (Figure 5d3), bicyclogermacrene (1.15%) (Figure 5e1), α-cubebene (0.88%) (Figure 5c5), caryophyllene (0.87%) (Figure 5e3), α-copaene (0.48%) (Figure 5c4), cadalene (0.44%) (Figure 5b7), δ-cadinol (0.4%) (Figure 5d4), elemol (0.39%) (Figure 5d2), T muurolol (0.39%) (Figure 5d5) and germacrene D (Figure 5e2) are particularly abundant. Other sesquiterpenoids present in *T. lanceolata* essential oils include camphene (0.02%) (Figure 5d1), α-gurjunene (0.04%) (Figure 5f1) and viridiflorol (Figure 5f4).[51]

Several sesquiterpenes detected in *T. lanceolata* essential oils have been reported to have cytotoxic activities against cancer cells. Polygoidal (the main component of *T. lanceolata* essential oils) has demonstrated moderate cytotoxicity towards V79 hamster lung fibroblasts, Ehrlich ascites tumour cells (ECA) and mouse L1210 leukemia cell lines.[79] That study also demonstrated strong cytotoxic activity for drimenol and several of its derivatives against a wide range of cancer cell lines. β-caryophyllene induces apoptosis in PC-3 (prostrate cancer) and MCF-7 (breast cancer) cell lines via ROS mediated pathways.[80] Similarly, β-caryophyllene and camphene both demonstrate suppressive growth activity towards B16 melanoma and human HL-60 leukemia cells.[81] Cadalene and its derivatives (such as δ-cadinol) inhibit lung tumourigenesis via the induction of apoptosis and by causing cell cycle arrest.[82] T muurolol sesquiterpenoids have been shown to have mild cytotoxicity towards several human tumour cell lines.[83] Spathulenol treatment blocks cell proliferation by inducing apoptosis via caspase-3 independent pathways.[84] *T. lanceolata* sesquiterpenoids have also been shown to block cell proliferation. Calamenene has been reported to exhibit potent anti-proliferative activity against human A2780 ovarian cancer cell lines.[85]

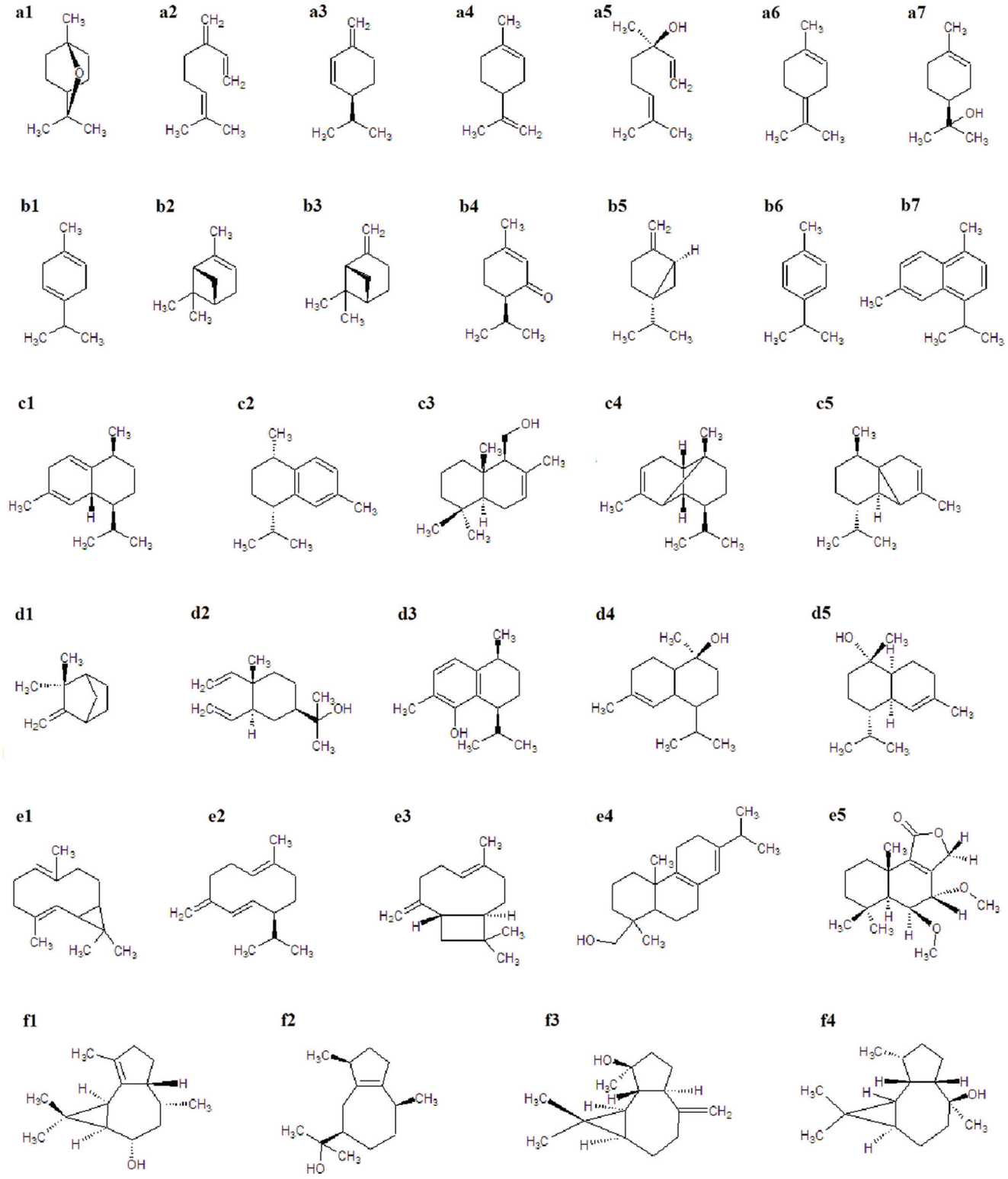

Figure 5. Chemical structures of terpenoid molecules identified in T. lanceolata: (a1) 1,8-cineole, (a2) myrcene, (a3) β-phellandrene, (a4) limonene, (a5) linalool, (a6) terpinolene, (a7) α-terpineol, (b1) γ-terpinene, (b2) α-pinene, (b3) β-pinene, (b4) piperitone, (b5) sabinene, (b6) cymene, (b7) cadalene, (c1) cadina-1,4-diene, (c2) calamenene, (c3) drimenol, (c4) α-copaene, (c5) α-cubebene, (d1) camphene, (d2) elemol, (d3) 5-hydroxycalamenene, (d4) δ-cadinol, (d5) T muurolol, (e1) bicyclogermacrene, (e2) germacrene D, (e3) caryophyllene, (e4) palustrol, (e5) drimenin, (f1) α-gurjunene, (f2) guaiol, (f3) spathulenol, (f4) viridiflorol.

Many monoterpenic compounds are also present in significant levels in *T. lanceolata* with 1,8-cineole (0.77%) (Figure 5a1), α-pinene (0.86%) (Figure 5b2), β-pinene (0.38%) (Figure 5b3) and linalool (1.81%) (Figure 5a5) predominating.[51] Other characteristic monoterpenes detected in the commercial *T. lanceolata* essential oils analysed in that study included sabinene (Figure 5b5), β-phellandrene (Figure 5a3), myrcene (Figure 5a2), terpinolene (Figure 5a6), α-terpineol (Figure 5a7), γ-terpinene (Figure 5b1), piperitone (Figure 5b4), limonene (Figure 5a4) and cymene (Figure 5b6), although all of these were generally present at levels below 0.1%.

Monoterpenes have been reported to exert a wide variety of biological effects including antibacterial, antifungal, anti-inflammatory and antitumour activities. Several monoterpenes detected in *T. lanceolata* essential oils have been reported to have cytotoxic activities, directly killing cancer cells. 1,8-cineol induces apoptosis in human leukemia cell lines.[86] Similarly, linalool induces apoptosis and potentiates doxorubicin induced cytotoxicity in MCF-7 adenocarcinoma cell lines.[87] Further studies have also demonstrated that cotreatment of linalool with anthracyclines improves the therapeutic index in the management of breast cancer cell lines.[87] Pinene has been reported to induce apoptosis in melanoma models.[88] Several other *T. lanceolata* essential oil monoterpene components also display cytostatic activities against cancer cell lines. Limonene is particularly promising as it blocks all phases of cancer progression. Limonene has been shown to block the induction of mammary cancer by 7, 12-dimethylbenzl anthracene (DMBA).[87] Furthermore, limonene also blocks the progression of cancer post-initiation and is effective in treating established breast cancers. In addition, a comprehensive study examined the ability of a wide range of terpenes to suppress the growth of B16 melanoma and human HL-60 leukemia cells.[81] Of the monoterpenes previously reported to be present in *T. lanceolata* essential oils, 1,8-cineol, α-pinene, limonene, linalool, cymene, α-terpineol and myrcene all were reported to have potent tumour suppression activity in that study.

Several terpenoids have been reported to suppress NF-κB signaling (the major regulator of inflammatory diseases and cancer).[89] The monoterpenes limonene[90,91] and α-pinene[92] have been reported to inhibit NF-κB signaling pathways. Limonene inhibition of mammary and parcreatic tumours has been reported and has been shown to be due to direct DNA binding.[93] α-Pinene also affects inflammatory diseases and cancer by inhibiting p65 translocation into the nucleus in LPS-induced NF-κB signaling.[92] Furthermore, many other sesquiterpenes and sesquiterpene lactones also have well established anticancer and anti-inflammatory activities.[89] Whilst much work is still needed to characterize the mechanisms of action of these compounds, it appears that NF-κB inhibitory activities may be responsible.

The antimicrobial activity of *Drimys winteri* (a species closely related to *T. lanceolata*) essential oils have been well documented against a variety of bacterial species and it has been established that terpenoids contribute to this activity.[94] *Drimys winteri* essential oils contain many of the same monoterpenoid constituents as *T. lanceolata* essential oils (including polygoidal, α-pinene, β-pinene, sabinene, mycrene, terpinene, limonene and β-phellandrene). That study demonstrated good antibacterial activities for all of these compounds. Further studies have also shown that the monoterpene piperitone reduces the resistance of several strains of Enterobacteriaceae to the antibacterial agent nitrofurantoin.[95] Other studies have reported similar antibacterial activities for the sesquiterpenoids α-cubebene, copaene and caryophyllene isolated from *Pilgerodendron uviferum*.[96]

Hydrocarbons

Unsaturated fatty acids and unsaturated hydrocarbons are components in many plant oils including safflower oil, soyabean oil and cotton seed oils and have also been shown to be abundant in *T. lanceolata* oils.[51,97] Amongst these, linolenic acid (Figure 6b) has received attention for its antioxidant activity and therapeutic potential. Increased dietary intakes of unsaturated fatty acids (including linolenic acid) has been associated with a decreased incidence of cardiovascular disease.[98] Linolenic acid has also been reported to have anti-inflammatory activity due to its antioxidant potential.[99] The same study determined that linolenic acid blocks nitric oxide synthase gene expression via NF-κB and mitogen activated protein kinase (MAPK) pathways, resulting in inhibition of nitric oxide production. Thus it is possible that linolenic acid may also have anticancer affects. Similarly, squalene (Figure 6c) has therapeutic potential and has been associated with the antioxidant activities of other plant species.[100] As squalene (Figure 6c) is known to inhibit the ras gene,[101] it is likely that it also affects cancer progression. Similarly, squalene inhibits inhibit HMG-CoA reductase[101] and thus it may lower endogenous sterol synthesis and decrease cardiovascular disorders.

Medium length (C16-18) straight chain fatty acids (MCFA) have been reported to have strong antimicrobial effects against a wide variety of bacteria, fungi, viruses and

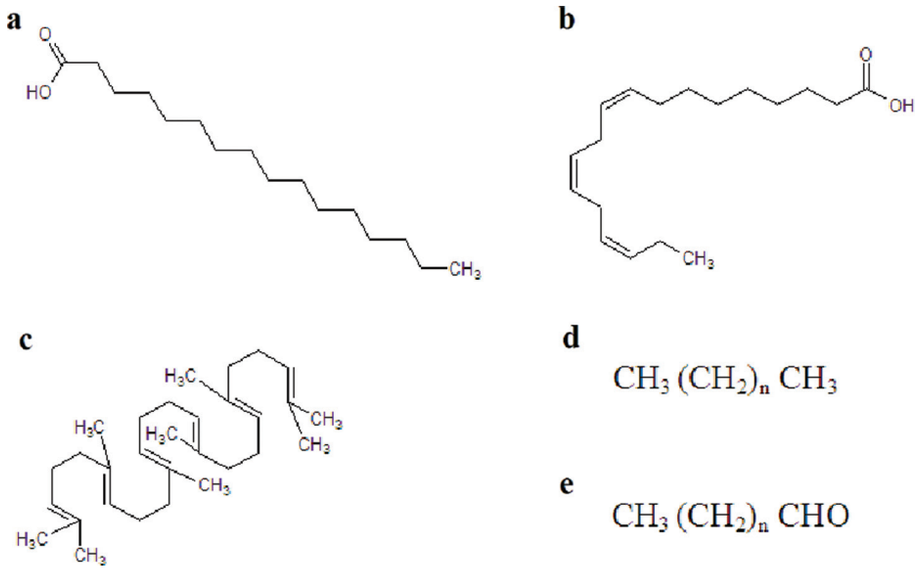

Figure 6. Chemical structures of selected hydrocarbon components identified in T. lanceolata: (a) palmitic acid, (b) linolenic acid, (c) squalene, (d) general alkane structure (common chain lengths detected in T. lanceolata extracts include C = 23, 25, 27), (e) general saturated primary fatty alcohols (common chain lengths detected in T. lanceolata extracts include C = 24, 26, 28).

protozoa. Multiple studies have reported the potential of MCFA in the control of such diverse pathogenic bacteria as *Bacillus anthracis*,[102] *Neisseria gonorrhoeae*,[103] *Heliobacter pylorus*,[104] *Vibrio cholera*[105] and various Streptococci species.[106] MCFA's can also inactivate a wide range of infective viral agents including cytomegalovirus (CMV),[107] Dengue virus,[108] influenza,[108] measles,[108] polio virus,[108] herpes viruses[108] and HIV.[110] Similarly, MCFA have been reported to have good fungicidal activity against the medicinally important fungi *Aspergillus niger*[111] and *Candida albicans*[112] and antiprotozoal activity against *Giardia duodenalis*.[113] Of the MCFA's, the C18 straight chain unsaturated fatty acid linolenic acid (with is abundant in *T. lanceolata* extracts and essential oils[51,97]) has been reported to have particularly potent antibacterial activity. Several reports have reported growth inhibition against *Bacillus cereus* and *Staphylococcus aureus* at concentrations as low as 10 µg/ml.[114] More recently, linolenic acid has been reported to have antibacterial activity on its own against a broader range of bacteria, as well as increasing the antibacterial effects of monoglycerides.[115] Of the other *T. lanceolata* fatty acids, the C16 straight chain saturated fatty acid palmitic acid has also been reported to have antibacterial activity against both Gram-negative and Gram-positive bacterial species.[116] The same study also showed the ability of this MCFA to inhibit the replication of the influenza A virus.

The fatty alcohols and unbranched paraffins detected in *T. lanceolata* essential oils also have therapeutic potential. Both classes of compounds have surfactant properties.[117] Therefore they may nonspecifically disrupt/denature fungal integral membrane proteins and have potential as antibiotic agents. An increased intake of long chain fatty alcohols (C24-34) similar to those present in *T. lanceolata* extracts and essential oils[51,97] has also been reported to lower LDL cholesterol levels by as much as 88%.[118] Thus, it is possible that *T. lanceolata* ingestion may also have beneficial cardiovascular affects and more investigation is needed in this area.

CONCLUSION

Despite the history of traditional *T. lanceolata* usage, until recently, there has been little rigorous scientific research into the medicinal potential of this species. Recent studies,[3,4] whilst initially focussed on the food properties of *T. lanceolata*, have also indicated the potential of this plant as a therapeutic agent. Indeed, several recent reports indicate a growing interest in examining medicinally important bioactivities induced by *T. lanceolata*. Recently, *T. lanceolata* has been reported to have good antioxidant,[3,4] anticancer,[119] antidiabetic[120] and antimicrobial effects.[121] In most cases the active phytochemicals have not been established although several of these studies have linked these activities to their antioxidant activities. Instead, often the partially purified compounds of a crude extract are itemised yet the active component(s) not identified. In other studies, the active compounds have not been characterised and instead only the classes of compounds in the crude mixture have been determined.

Given the impressive antioxidant activity of this species and the medicinal properties of many of its known phytochemicals, it is likely that bioactivity studies will detect further therapeutic properties for *T. lanceolata*. Much work is still required to fully understand the phytochemistry and pharmacognosy of *T. lanceolata*. Furthermore, few of these studies have provided substantial mechanistic detail to explain how the active principles achieve their medicinal effects.

Cancer is a major public health burden, both in developed and developing countries. Plant derived agents such as taxol, vinblastine, vincristine, and the camptothecin derivatives topotecan and irinotecan and etoposide (derived from epipodophyllotoxin) are in clinical use globally[122] for the treatment of cancer. With regard to the phytochemical studies summarised in this review, it is surprising that the chemotherapeutic potential of *T. lanceolata* remains largely unexamined. Although *T. lanceolata* extracts and essential oils are not yet fully characterised due to difficulties in separating some components, high levels of antioxidant molecules have been reported. Apart from the antioxidant compounds discussed in this report, *T. lanceolata* also contains high levels of other phenolic and terpenoid compounds which have therapeutic potential that is not just limited to cancer treatment. Polar *T. lanceolata* extracts contains over 4-fold higher levels of antioxidants than in blueberries.[3] Studies into the therapeutic potential of this species are still in their infancy and most of the studies regarding this plant are focussed on the total antioxidant capacity, with several recent studies beginning to examine the medicinally important bioactivities. The current review highlights the chemotherapeutic potential of the phytochemicals of *T. lanceolata*. In particular, this manuscript describes the potential of this plant in treatment for disorders related to cellular redox control (eg cellular proliferation, inflammation, cancer, diabetes, obesity, cardiovascular and neurodegenerative diseases).

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