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Review Article

A Review of the Ethnobotany, Phytochemistry and Medicinal Properties of Australian *Terminalia* Species

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ABSTRACT

The genus *Terminalia* contains some of the most widely used plants in traditional medicine. Many species possess antifungal, antibacterial, antiviral, antiprotozoal, analgesic, antidiarrheal, antioxidant, antimalarial, anticancer, and anti-inflammatory properties. Some species also have cardiovascular and wound-healing effects. Despite their myriad of traditional uses, relatively few studies have examined the medicinal properties and phytochemistry of most Australian *Terminalia* spp. The high tannin content of *Terminalia* spp. has been postulated to be a major contributor to the medicinal properties of this important genus. However, the complexities of tannins are generally believed to make them a poor choice for drug design. Therefore, much of the interest in *Terminalia* species has been for their nutraceutical and pharmacognostic value, and they remain under-explored in terms of drug discovery. Recent studies have identified many other important phytochemicals within *Terminalia* species apart from the tannins and have established that these compounds may contribute to their therapeutic bioactivities. Several Australian *Terminalia* species (particularly *Terminalia carpentariae* C.T.White, *Terminalia catappa* L., *Terminalia ferdinandiana* Exell and *Terminalia grandiflora* Benth) have received the most attention due to their reported high antioxidant contents. In contrast, other Australian *Terminalia* spp. have been relatively ignored. This review discusses recent studies into the phytochemistry, medicinal properties and the underlying therapeutic mechanisms of Australian *Terminalia* species to help direct future areas of research into this important genus.

Keywords: Australian *Terminalia*, Medicinal plant, Antioxidant, Anticancer, Antiinflammation, Antimicrobial.

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INTRODUCTION

Before the advancements of modern medicine over the last century, plants were the main source of medicine. In many developing countries, traditional medicines are still used as the main treatment modality for many diseases. Indeed, 85% of Indians still use crude plant preparations for the treatment of a wide variety of ailments and diseases.[1] Multiple African medicinal systems and Traditional Chinese Medicine (TCM) are also widely used by people in those populations. Even in countries where Western/allopathic medicine dominates, plant medicinal systems are also frequently used, often in conjunction with allopathic medicines. Traditional medicines are generally considered (often erroneously) to be a safer alternative than allopathic drugs and may be effective against complaints for which there is no effective current allopathic alternative.

Notably, many prescription drugs were originally derived from plants. It has been estimated that around 25% of all prescription drugs that are currently in use are derived from plant compounds.[2,3] Indeed, approximately 75% of new anticancer drugs developed between 1981 and 2006 are derived from plants, or are semi-synthetic analogues of plant compounds.[2,3] Traditionally, plant-based medicines are used as crude formulations such as essential oils, extracts and powders. The current trend is to isolate the individual phytochemical components and produce an analogue of increased bioavailability/bioactivity by semi-synthetic methods. Such research has given rise to many beneficial drugs including digoxin (from *Digitalis* spp.), quinine (from *Cinchona* spp.) and the anticancer drugs vinblastine and vincristine (from *Catharanthus roseus* (L.) G. Don). However, the bioactivities that are seen in crude extracts are often much greater than those seen in individual components.[4,5] Crude plant extracts may contain numerous different phytochemicals that interact in complex ways. Unfortunately, it is often difficult to determine

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how an extract works, even when its therapeutic benefits are well established.

The genus *Terminalia* consists of approximately 200-250 species, many of which have a history of usage to treat a variety of ailments.[6] *Terminalia* species are widely distributed throughout tropical and subtropical regions globally, with approximately 28 species of *Terminalia* occurring in the South Pacific and Australian region.[7] Of these, *Terminalia ferdinandiana* Exell. has attracted the most substantial recent attention due to its high antioxidant content and interesting phytochemistry. Indeed, *T. ferdinandiana* has been reported to have the highest antioxidant activity of any plant worldwide.[8] The levels of ascorbic acid (Figure 1A) alone are more than 900 times greater (g/g) than those of blueberry.[8]

Ethnopharpacology

Terminalia spp. have been used for a myriad of medicinal purposes (Table 1).[7] The best documented of these are for the species used in the Indian traditional medicinal systems, particularly Ayurveda. In Ayurvedic medicine, *Terminalia* spp. are used for a wide variety of medicinal purposes including diarrhoea, back and abdominal pain, cough and cold, ulcers, wounds and as a general tonic. They are also used to treat a broad-spectrum of infections.[7]

Similarly, in several African traditional medicinal systems, native *Terminalia* species are used for the treatment of multiple different ailments.[7] As different species can be found in different regions of the world, their usage is often associated with specific ethnic/cultural groupings. Thus, a species that is used by one cultural grouping for a specific treatment may have different therapeutic usage by other groups, or even no usage in other regions in which it grows. *Terminalia avicennioidies* Guill. and Perr., *Terminalia ivorensis* A.Chev., *Terminalia macroptera* Guill. and Perr. and *Terminalia glaucescens* Planch. Ex Benth. are amongst the most beneficial West African species that are used for a variety of disorders such as fungal, bacterial, infections and viral infections, cough treatments and bloody sputum.[7] Similarly, many *Terminalia* species are used by diverse cultural and ethnic groupings in

Table 1: The origin, medicinal properties, and phytochemical constituents (where known) for selected Australian and Oceanic *Terminalia* species worldwide.

Species	Common name	Geographical	Medicinal properties	Known constituents	References
Terminalia arenicola Byrnes	Brown Damson	Australia	None known	Unknown	7
Terminlia aridicola Domin	Arid peach, tropical almond, wild plum.	Australia	None known	Unknown	12
Terminalia arostrata Ewart and O.B. Davies	Crocodile tree, nutwood.	Australia	None known	Unknown	13
Terminalia bursarina F. Muell.	Yellow wood.	Australia, South Asia	None known, but toxicity has been reported.	Unknown	14
Terminalia canescens (DC.) Radlk.ex. T. Durand	Joolal, winged nut tree.	Australia	None Known	None known	13
Terminalia carpentariae C.T. White	Wild peach.	Australia	Anticancer, antimicrobial, antidiarrheal activities which have been linked to antioxidant content	High levels of Vitamin C and total phenolic content.	15
Terminalia catappa L.	Indian almond, tropical almond, umbrella tree.	Broad distribution from Australia and South East Asia, India to Africa and South America	Treatment of liver disease (Taiwan), dysentery and diarrhoea (Suriname), antioxidant and anticancer activity, inhibits chloroquine-resistant *Plasmodium falciparum.*	Flavonoids (including kaempferol, quercetin), tannins, saponins and phytosterols.	16
Terminalia complanata K. Schum.	Claudie Damson, yellow *Terminalia.*	Australia, New Guinea, Solomon Islands	Broad spectrum Antibacterial activity.	Arjunolic acid, asiatic acid.	17

Species	Common name	Geographical	Medicinal properties	Known constituents	References
Terminalia cunninghamii C.A. Gardner	Pindan quondong, pindan. walnut, kalumburu almond.	Australia	None known	Polyphenol, hydrophilic antioxidant.	18
Terminalia erythrocarpa F. Muell.	Pink plum.	Australia	None known	Unknown	12
Terminalia ferdinandiana Exell	Kakadu plum, gubinge.	Australia	High antioxidant contents used for the treatment of coughs and colds, as has antiseptic, antibacterial, antifungal, anticancer, anti-inflammatory activities.	High ascorbic and gallic acid contents, as well as triterpenes, flavonoids, tannins.	7,19-22
Terminalia fitzgeraldii C.A. Gardner	Unknown	Australia	None known	Unknown	13
Terminalia grandiflora Benth.	Nut tree	Australia	High antioxidant activity, treatment of coughs and colds, antiseptic, antibacterial, antifungal, anticancer, anti-inflammatory activities.	High ascorbic and gallic acid contents, triterpenes, flavonoids, tannins.	15
Terminalia kumpaja R.L. Barret	Pindan walnut	Australia	None known	Unknown	13
Terminalia latipes Benth.	Unknown	Australia	None known	Unknown	13
Terminalia melanocarpa F. Muell.	Black Damson	Australia	None known	Unknown	12
Terminalia microcarpa Decne.	Damson plum, bandicoot plum, sovereign wood.	Australia, Malaysia, Indonesia, Philippines	Anticancer, and anti-inflammatory activities.	Unknown	23
Terminalia muelleri Benth.	Ketapang kencana.	Australia	Antibacterial, antifungal, anticancer, and antioxidant activities.	Cyclic triterpenoids, flavonoids, tannins.	24
Terminalia oblongata F. Muell.	Rosewood, yellow wood.	Australia	The tannin terminalin (isolated from *T. oblongata*) has been reported to be toxic and has caused the death of several animals.	Ellagitannins, phenolic compounds.	25
Terminalia petiolaris Benth.	Blackberry tree, billygoat plum, maroll.	Australia	Antibacterial	Gallic acid, chebulic acid, flavonoid, monoterpenoids, terpinol.	26
Terminalia platyphylla F. Muell.	Wild plum	Australia	None known	Unknown	12

Species	Common name	Geographical	Medicinal properties	Known constituents	References
Terminalia platyptera F. Muell.	Unknown	Australia	None known	Unknown	13
Terminalia porphyrocarpa Benth.	Bandicoot plum, brown Damson.	Australia	None known	Unknown	12
Terminalia prostrata Pedley	Unknown	Australia	None known	Unknown	13
Terminalia pterocarya F. Muell.	Unknown	Australia	None known	Unknown	13
Terminalia subacroptera Domin	Unknown	Australia, New Guinea	None known	Unknown	12
Terminalia supranitifolia Byrnes	Unknown	Australia	None known	Unknown	13
Terminalia volucris R.Br. ex Benth.	Yellow-wood.	Australia	None known	Unknown	12

Central and Southern Africa.[7] *Terminalia bentzoe* (L.) L.f., *Terminalia brownii* Fresen., *Terminalia brachystemma* Welw. ex Hiern, *Terminalia sericea* Burch. ex DC., *Terminalia mollis* M.A. Lawson and *Terminalia stenostachya* Engl. and Diels all have well documented ethnopharmacological usage in Southern Africa to treat a variety of ailments including cancer, colds and cough, diarrhoea, hypertension, fever, diarrhoea, malaria, diabetes, and for the treatment of fungal, bacterial and viral diseases.[7]

There is also a range of *Terminalia* species in the Americas. However, few studies have examined the therapeutic benefits of those species. *Terminalia triflora* (Griseb.) Lillo and *Terminalia acuminata* (Fr. Allem.) Eichl. may be the most beneficial *Terminalia* species from that region, based on their documented ethnobotanical usage. These species have been used traditionally to treat fungal, bacterial, and viral infections.[7] Indeed, *T. triflora* leaf extracts possess anti-HIV activity, and this activity has been scientifically verified and confirmed.[9]

Less information is available about the ethnobotanical usage of Australian *Terminalia* species. The first Australians had a good understanding of the medicinal properties of Australian plants and had used them successfully for at least 50,000 years to treat a variety of ailments. However, little of this information has been recorded. Traditional Australian indigenous knowledge of plant-based therapies was generally passed orally from one generation to the next, with little written ethnopharmacological records. Therefore, much of this traditional knowledge has been lost overtime. However, several species, such as *Terminalia hadleyana* W.Fitzg., *Terminalia carpentariae* C.T.White, *Terminalia ferdinandiana* and *Terminalia lapties* Benth., are known to have been used as both medicinal and food plants.[10,11]

Phytochemistry and antioxidant content

The consumption of high levels of antioxidant helps to decrease the incidence of multiple chronic disease.[27] Antioxidants also protect against the development of degenerative diseases including cancer,[28] neural degeneration,[29] cardiovascular disease,[30] obesity and diabetes.[31] Phenolic compounds are strong antioxidants and protect the cell against oxidative damage through the scavenging of free radicals.[32] Phenolic compounds also interact directly with receptors or enzymes that are involved in signal transduction,[33] highlighting the diverse roles phenolic compounds play a role in human physiology. Typical phenolic compounds found in plants consist of flavonoids, tannins, and anthocyanins, all of which are prevalent within the *Terminalia* genus.[7]

Previous studies have reported particularly high levels of antioxidants in the Australian species *T. ferdinandiana,* with particularly high levels of ascorbic acid (Figure 1a).[21,34] *Terminalia ferdinandiana* fruit also contains many other compounds that may contribute to the therapeutic properties of this species.[21,34] Whilst many of *Terminalia* spp. compounds are yet to be identified, multiple flavanols, flavonoids and benzoic acids have been identified in *T. ferdinandiana* fruit.[21] The fruit of this species is a good source of ellagic (Figure 1B) and gallic acids (Figure 1C),[35,36] which have strong antioxidant activities *in vitro.*[37,38] *Terminalia ferdinandiana* fruit is also rich in chlorophyll a (Figure 1D) and chlorophyll b (Figure 1E), which can minimize oxidative stress. The fruit extracts are also rich in lutein (Figure 1K), vitamin E (Figure 1F) and vitamin E analogues.[35] Glycosides of kaempferol (Figure 1I), hesperitin (Figure 1J), quercetin (Figure 1G) and luteolin (Figure 1H) are also present in *T. ferdinandiana* fruit. Similarly, *T. ferdinandiana* fruit is also a good source of the mineral's calcium, zinc, sodium, potassium, phosphorus, iron, molybdenum, copper and manganese[35]. It has been hypothesized that the presence of high antioxidant contents may be responsible for the therapeutic effects of *T. ferdinandiana.*[19] Furthermore, it has been suggested that the high levels of tannins and flavonoids may contribute to the antioxidant activities of this genus.[39,40]

Terminalia catappa contains tannins, flavonoids, gallotannins, cyanidin and ellagitannins that contributes to its anti-HIV activity.[41] Recently, chemical analysis of *T. catappa* bark and leaf extracts identified multiple hydrolysable tannins including punicalagin, punicallin, and gallic acid, as well as several flavonoid C-glycosides.[42] The aqueous and methanol extracts obtained from *T. grandiflora*, including both the nut and fruit, exhibited substantial levels of tannins, low quantities of flavonoids and anthraquinone, and noteworthy concentrations of water-soluble phenolics.[22] Additionally, the *T. carpentariae* leaf extract contained high levels of water-soluble tannins and phenolics.[22] Isolation and identification of phytochemicals from *Terminalia* spp. may lead to the discovery of new drug targets for the control and management of several diseases.

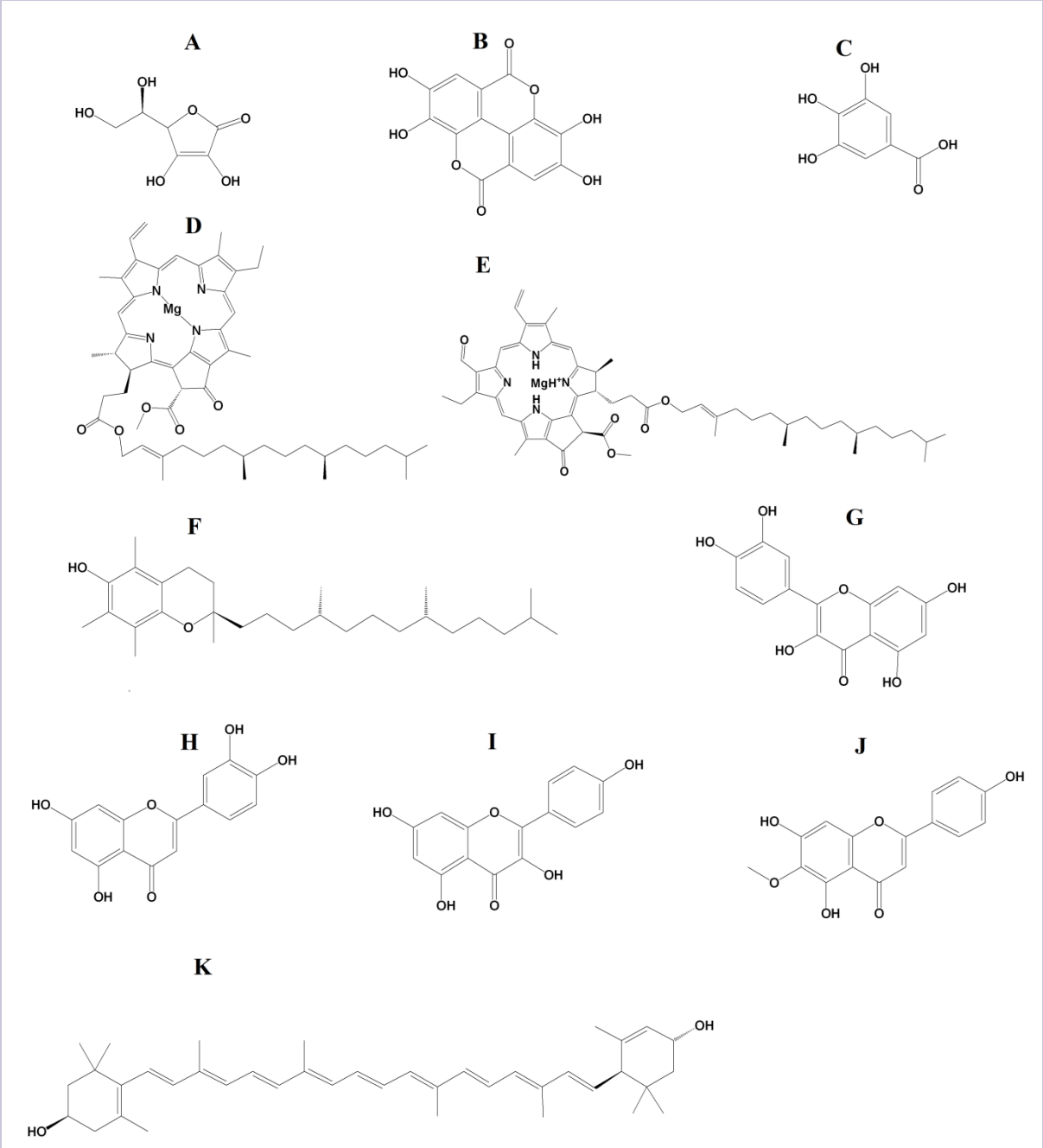

Figure 1: Chemical structures of the molecules that possess antioxidant properties that are identified in *T. ferdinandiana*; (A) ascorbic acid, (B) ellagic acid, (C) gallic acid, (D) chlorophyll a, (E) chlorophyll b, (F) α-tocopherol (Vitamin E), (G) quercetin, (H) luteolin, (I) kaempferol, (J) hesperitin, (K) lutei.

Therapeutic Properties

Anti-inflammatory activity

- Inflammation is a multifaceted reaction that is triggered in response to injury. It is characterized by a wide variety of symptoms[43] including:
- Swelling due to increased capillary permeability, which allows the migration of leukocyte to the site of injury, as well as the accumulation of fluid.
- Redness and heat due to vasodilation reduced blood pressure and increased circulation.
- Pain, that arises from the release of prostaglandins and short peptides.

Terminalia species contain numerous phytochemicals, many of which possess antioxidant activity. These compounds may likely contribute to the anti-inflammatory activity of these species. Inflammatory processes result in the release of several classes of molecules. Vasoactive compounds including prostaglandins, bradykinin and vasoactive amines are required for blood vessel dilation, as well as opening the junctions between the cells that allow leukocytes to pass through the capillaries. Any compound that can block these vasoactive substances may therefore possess anti-inflammatory activity. β-sitosterol is a phytosterol found in many *Terminalia* species.[44] It stimulates smooth muscle cells to release Prostacyclin (PGI_2) and blocks the release of PGI_2 and prostaglandin E_2 from macrophages.[45] Hence, β-sitosterol would affect vasodilation and may have therapeutic inflammatory activities.

The anti-inflammatory effect of *T. ferdinandiana* extracts on mammalian cell exposed to H_2O_2 suggests the potential use of this traditional medicinal plant in preventing inflammatory disease.[46] An aqueous *T. ferdinandiana* extract enriched with ellagic acid (EAE) significantly reduced the production of ROS when Caco-2 and KERTr cell lines were treated with 100 or 200 ug/mL of either EAE or pure Ellagic Acid (EA).[46] Treatment of cells with EA or EAE showed upregulation of mRNA expression of the antioxidative gene superoxide dismutase (SOD)-2 and downregulated the expression of inducible nitric oxide synthase (iNOS), soluble cell adhesion molecule (sICAM) and cyclooxygenase.

Terminalia catappa leaves have anti-inflammatory and analgesic activities, without inducing sedation.[47] In particular, ethanolic leaf extracts of *T. catappa* had anti-inflammatory properties in both chronic and acute animal models that were induced by 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear oedema. Additionally, a chloroform leaf extract was examined in the study and ursolic acid and 2-α, 3-β, 23-trihydroxyurs-12-en-28-oic acid were identified as the major anti-inflammatory component.[47] A novel foetal haemoglobin-inducing compound was also isolated from the leaves of *T. catappa*, which modulates erythropoiesis.[48]

Anticancer activity

The growth and development of healthy cells depends on the fine regulation of growth promoting and inhibiting pathways. Tumour suppressor genes and proto-oncogenes are responsible for encoding proteins of the cell cycle, as well as the proteins that induce apoptosis, and proteins that repair damaged DNA. Mutation in these genes can induce the onset of cancer.[49] When such mutations arise, they may no longer require external signals to proliferate. Additionally, those cells may also fail to recognise signals that restrict cell division, resulting in uncontrolled cell growth. In tumour genesis, multiple genes may undergo mutations, which can be transmitted to daughter cells. These mutated genes may subsequently escape normal growth restraints and form a tumour, which can be either malignant or benign. Oxidative stress induction has been linked to multiple forms of cancer.[50] Consequently, the substantial presence of antioxidants in numerous *Terminalia* species may impede the development and advancement of cancer, although this remains to be verified. Chromosome instability is a common feature of many of cancers that has been linked with oxidative stress. Thus, increased levels of oxidative stress may contribute to the development of genetic instability. Consumption of high level of antioxidants (as present in many *Terminalia* species) may therefore block tumour genesis.

The pro-oxidant/antioxidant effects of extracts from other plant species depend on multiple factors. For example, *Aloe vera* L. antioxidant components may function as either as oxidants or antioxidants, depending upon their concentration.[27] The anthraquinone compound aloe emodin (found in *A. vera*), exhibits pro-oxidant properties when present at high concentrations, but functions as an antioxidant at lower concentrations. Conversely, another *A. vera* anthraquinone (aloin) displays pro-oxidant effects at lower concentrations and antioxidant effects at higher concentrations. Therefore, components and extracts derived from *A. vera* have the potential to act as either oxidants or antioxidants, depending on their concentration levels and ratios of the individual components. While numerous *Terminalia* species have high levels of antioxidants, individual components within these species may have the capacity to function as either oxidants or antioxidants. These components may be effective in both the treatment and prevention of cancer, depending on their concentrations and ratios.

Pro-oxidant effects have also been reported for other antioxidant phytochemicals including tannins[51] and flavonoids,[52] both of which are present at a high concentration in many *Terminalia* species. Studies have also shown that the presence of transition metal ions such as iron or copper in the extract can enhance the conversion of antioxidant to a pro-oxidant state.[53] For example, ascorbic acid (which is present in a high level in multiple *Terminalia* species)

has well characterized antioxidant bioactivities, although it also acts as a pro-oxidant at high concentrations.[54] In the presence of transition metal ions, ascorbic acid function as a reducing agent, reducing metal ions, thereby converting them to pro-oxidant states. Therefore, high levels of ascorbic acid in individuals with high iron levels may result in unexpected health outcomes due to the induction of oxidative damage.[54]

Reactive oxygen species (ROS) based tumour therapy may induce the regression of tumours, should the tumour cells not be oxidant/apoptotic resistant. Therefore, if the antioxidant compounds in *Terminalia* spp. are present in concentration and ratios that are consistent with the pro-oxidant activity, the extract may induce anticancer activity. However, if there is a reducing environment, pro-oxidant activity would result, and the extract would not have anticancer activity and tumour progression may occur.

The Australian *Terminalia* species *T. ferdinandiana* has attracted much attention recently due to its high level of antioxidant activity.[36] A recent study reported that *T. ferdinandiana* fruit extracts, which are rich in polyphenolic compounds, display anti-proliferative activity against a range of cancer cell lines.[20] Similarly, the tannin casuarinin, which was isolated from the bark extracts of *T. arjuna*, induces apoptosis in human A549 lung cancer cell lines.[55] It was postulated that high ratio of Fas/APO-1 and increases in membrane-bound and soluble Fas ligands may be responsible for the apoptotic effects of casuarinin. In addition, casuarinin also arrests the progression of the cell cycle in the G_0/G_1 phase, which may be due to the p53 dependent induction of p21/WAF1.

Terminalia catappa has been reported to inhibit several vital steps of metastasis, including cell migration and invasion of cells, and regulates the actions and protein levels of urokinase-type plasminogen activator and its natural inhibitor.[56] In addition, *T. catappa* extracts inhibit the phosphorylation of ERK1/2 signalling pathway by down regulating the levels of transcription factors SP-1, as well as NF-κB DNA binding activities, leading to suppression of urokinase-type plasminogen activator and inhibition of metastasis.[56]

Oral administration of *T. catappa* significantly decreases the number of aberrant crypt foci and *β*-catenin crypts when compared to the control group.[57] The colonic proliferating cell nuclear antigen-labelling index is also significantly lower than the control group,[57] demonstrating that *T. catappa* has a potent short-term chemo-preventive effect on various biomarkers of colon carcinogenesis induced by carcinogen azoxymethane. This activity may relate to the inhibition of development of aberrant crypt foci and *β*-catenin crypts.[57]

In cultured CHO cells, pre-treatment with *T. catappa* water leaf extract or its major tannin component, punicalagin, prevents gene mutations and represses the generation of intracellular free radicals on bleomycin-induced genotoxicity.[58] Punicalagin and crude *T. catappa* extracts suppress the proliferation of H-ras-transformed NIH3T3 cells in a dose-dependent manner and have only moderate effects on non-transformed NIH3T3 cell proliferation, indicating that punicalagin and *T. catappa* extracts are selective inhibitors of cell proliferation. Treatment with either pure punicalagin or crude *T. catappa* extract reduces anchorage-independent growth, which may be due to cell cycle arrest at G0/G1 phase. Treatment with punicalagin also results in a reduction of intracellular oxide levels, along with decreases in the levels of phosphorylated c-Jun N-terminal kinase 1 (JNK1) and protein kinase.[58] These findings provide support for the chemo-preventive potential of punicalagin.

Terminalia catappa (500 mg/kg) significantly reduces plasma lipid levels to normal range in rats with high levels of very low-density lipoproteins and cholesterol, indicating that *T. catappa* extracts possess anti-lipidemic and anti-tumour activities.[59] *Terminalia catappa* also significantly elevates the level of superoxide dismutase (SOD) and catalase (CAT), while reducing the levels of lipid peroxidation (LPO) and of reduced glutathione (GSH). *Terminalia catappa* exhibits anti-tumour activity by changing the levels of LPO and this may to be due (at least in part) to the presence of flavonoid and phenolic components.[60]

An ethanolic *T. catappa* leaf extract of was reported to reduce the expression of MMP-9, MMP-2, urokinase-type plasminogen activator, and their endogenous inhibitors in a dose-dependent manner. Furthermore, *in vivo* studies also confirm the growth inhibitory effects of the extracts, as well as inhibiting metastasis of Lewis Lung Carcinoma (LLC) cells.[61] Hence, *T. catappa* may provide an effective therapy against cancer, as well as inhibiting its spread.

Similarly, *T. carpentariae* leaf and *T. grandiflora* fruit, leaf and nut extracts have significant anti-proliferative activity against HeLa and Caco-2 carcinoma cells.[15] *Terminalia grandiflora* methanolic leaf extract was particularly effective at blocking the proliferation of the colorectal carcinoma Caco-2. Methanolic *T. grandiflora* and *T. carpentariae* leaf extracts also possess antiproliferative activity against HeLa cervical cancer cells.[15] The level of inhibitory activity by the *T. carpentariae* was dose-dependent, decreasing at lower concentrations. *Terminalia grandiflora* leaf extracts were substantially more effective in inhibiting proliferation than the *T. carpentariae* leaf extract. Indeed, a decrease in cellular metabolic activity below the starting level was evident for the Caco-2 cells exposed to the methanolic *T. grandiflora* leaf extract. This may indicate that apoptotic mechanisms were responsible for the inhibition of proliferation induced by this extract.

Similarly, *T. ferdinandiana* fruit and leaf extracts have significant anti-proliferative activity against Caco2, HeLa, Jeg-3, JAR, MC3T3-E1, and MG63 proliferation. The leaf ethyl acetate extract of *T. ferdinandiana* was also a potent inhibitor of proliferation. The morphological characteristics observed through cell imaging

were in line with the occurrence of apoptosis in Caco2 cells when exposed to methanolic, aqueous, and ethyl acetate extracts.[20]

Antimicrobial activity

Antibacterial activity

Multiple *Terminalia* spp. also has a documented history of ethnobotanical usage against microbial infections. The Australian species *T. ferdinandiana* possesses strong antibacterial activity against a broad range of both Gram-positive and Gram-negative bacteria.[62] The polar *T. ferdinandiana* extracts tested in that study were more effective antibacterial agents than other solvent extracts, indicating that the antibacterial components are polar in nature. Indeed, the polar extracts inhibited the growth of nearly every bacterial species tested in that study. Although the individual antibacterial components were not identified, the authors postulated that the extremely high levels of antioxidants in *T. ferdinandiana* fruit (including ellagic acid and gallic acid) may be responsible for this antimicrobial activity.

Terminalia ferdinandiana has also been tested against the odour-forming bacteria *Staphylococcus epidermidis, Corynebacterium jeikeium, Cutibacterium acnes* and *Brevibacterium linens*.[63] Methanolic extracts prepared from *T. ferdinandiana* leaves produced Minimum inhibitory concentration (MIC) values against *S. epidermidis* (220 µg/mL), *C. jeikeium* (233 µg/mL), *P. acnes* (625 µg/mL) and *B. linens* (523 µg/mL). Bark, seed and fruit extracts of *T. ferdinandiana* inhibited *Bacillus cereus* and methicillin-resistant *S. aureus* (MRSA), with the zones of inhibition ranging from 7-18 mm.[64]

Studies have also highlighted the potential of Australian *Terminalia* spp. as growth inhibitors of bacterial species that trigger autoimmune disease. *Terminalia ferdinandiana* is a potent inhibitor of *Proteus mirabilis*,[65] *Acinetobacter baylyi* and *P. aeruginosa*,[66] and thus has potential in the prevention and treatment of rheumatoid arthritis and multiple sclerosis. *Terminalia ferdinandiana* leaf extracts are also good inhibitors of *K. pneumoniae* and thus may be used for the prevention of ankylosing spondylitis.[67] In those studies, tannin and stilbene components were identified as likely contributors to the inhibitory activity of the Australian species.

Methanolic and chloroform extracts of *T. catappa* have good antimicrobial activity against both Gram-negative and Gram-positive pathogens. The chloroform extract was particularly effective against *E. coli* and *S. aureus.* A methanolic extract of *T. catappa* exhibited an MIC value of 65 µg/mL against *E. coli,* whilst a chloroform extract exhibited an MIC of 400 µg/mL against *S. aureus*.[68] Additionally, the leaves of *T. catappa* are rich in tannins and can inhibit quorum sensing in some test strains.[69] Other studies have also reported that *T. catappa* leaf extracts inhibit the growth of *S. aureus* and *P. aeruginosa.*[70] Similarly, methanol extracts prepared from *T. grandiflora* and *T. carpentariae* leaves exhibit substantial antimicrobial activity against *Bacillus anthracis*, with MIC values of 155 and 74 µg/mL, respectively.[22]

Additionally, methanolic leaf extracts of *T. carpentariae* have strong inhibitory activity against *K. pneumoniae*. Similarly, *T. grandiflora* fruit and leaf methanol extracts also have good inhibitory activity against *K. pneumoniae.*[67] However, a notable difference was evident for the *T. grandiflora* leaf extracts compared to fruit extracts. An aqueous *T. grandiflora* leaf extract was a substantially stronger inhibiter of clinical and reference strains of *K. pneumoniae*. Another Australian *Terminalia* species, *T. petiolaris*, also possesses inhibitory activity against *K. pneumoniae*. Thus, these Australian *Terminalia* species may inhibit the onset of ankylosing spondylitis. In contrast, the antibacterial activity of many Australian *Terminalia* species remains unexplored.

Antiprotozoal activity

Several studies have also reported the antiprotozoal activities of the genus *Terminalia*. Indeed, *T. catappa* has inhibitory activity against *Trypanosomiasis brucei* (a parasite that causes sleeping sickness).[71] However, that study did not examine the antiprotozoal mechanisms of these species, nor did they identify the bioactive compounds. Additionally, the Australian species *T. ferdinandiana* was recently reported to be a potent inhibitor of the gastrointestinal protozoan parasites *Giardia duodenalis* and seventeen compounds were identified by mass spectrometry.[72] In contrast, there are few studies on the anti-Giardiasis activity of other Australian *Terminalia* spp. and further work is needed.

Wound healing activity

Wounds are classified as the loss or breaking of functional and cellular ability of the living tissues. Resistance and toxicity of drugs may hinder the advancement of synthetic antimicrobial agents to treat wounds. The application of *T. catappa* bark extract ointment on wounds reduced the wound area by 97% in a rat model compared to betadine ointment (81%), which was included as the standard drug. *Terminalia catappa* ointment induces rapid epithelization and thus promotes considerable wound-healing activity.[73]

Cardiovascular and circulatory effects

Various *Terminalia* spp. are used in traditional medicine to treat cardiovascular ailments. Studies have shown that the use of *T. catappa* leaf extracts at a dosage of 300 mg/kg significantly impacts the activity of enzymes associated with the Tricarboxylic Acid (TCA) cycle, lysosomes, and respirations. Rats treated with the plant extract exhibited a notable reduction in troponin levels compared to those induced by doxorubicin (DOX). Similarly, the elevated levels of creatinine kinase and lipids observed in DOX-treated animals were significantly mitigated following treatment with the plant extract.[74] This cardioprotective activity may be due to the presence of specific phytoconstituents and

secondary metabolites in *T. catappa*. *Terminalia catappa* and *T. grandiflora* also have potent protease inhibitory activities[68] that offer protection against cardiovascular disorder.[75]

Terminalia catappa extracts also have the potential to be used for the treatment of sickle cell anaemia (SCA). This disease is characterised by the haemolytic anaemia due to erythrocyte haemolysis under hypoxic conditions. The cells become sickle-shaped and rigid, with an increased tendency to adhere to the endothelium, resulting in vaso-occlusion. *Terminalia catappa* has long been used to treat SCA in Western African traditional medicine and has been shown to inhibit haemolysis[76] and stimulate the production of erythrocytes.[77] The active extract was shown to contain anthraquinones and alkaloids and the authors postulated that these may act synergistically to produce erythropoietic and haematopoietic effects. Thus, *T. catappa* extracts have potential for alleviating some of the symptoms of SCA. However, the erythropoietic and haematopoietic effects of other Australian *Terminalia* spp. are less rigorously studied, and more work is needed to study their effects.

CONCLUSION

This review of the therapeutic properties and bioactivity studies of Australian *Terminalia* has highlighted the medicinal importance of this important genus of plants. Despite the long history of traditional usage, comprehensive scientific research has been predominantly limited to a select few Australian species. Among these, *T. catappa* and *T. ferdinandiana* have garnered the most significant attention. In these species, multiple therapeutic bioactivities have been documented. These species exhibit a wide range of beneficial properties, including antimicrobial, anticancer, antioxidant, antidiabetic, and anti-inflammatory effects. Additionally, they aid in the process of wound healing. In some cases, the active phytochemicals responsible for the activity has been established, although for many medicinal properties the active compounds have only partially been characterized. In other studies, the active compounds have not been established and only the class of compounds in the crude extract have been determined. Much work is still required to understand the phytochemistry of Australian *Terminalia* spp. Even for the species that are most extensively studied, much work is still needed to fully evaluate the phytochemistry and medicinal properties. Additionally, few studies have established the mechanistic detail of the active compounds and how they exert their medicinal effects.

Australian *Terminalia* species have been poorly studied compared to species in other areas of the world, despite the oral history of their medicinal usage. *Terminalia ferdinandiana* has garnered particular attention due to its extremely high levels of antioxidants. However, those studies have generally focussed on phytochemical or bioactivity screening, without combining these disciplines to characterise the active components and mechanisms. While *T. ferdinandiana* has received recent attention, the other Australian species remain largely unstudied and significant work is required in this area.

Given the taxonomic similarities between the species of this genus, it is evident that further bioactivity studies are warranted, and where a therapeutic bioactivity is detected, mechanistic and phytochemical studies should also be undertaken. Such an approach may lead to the development of valuable nutraceuticals and may result in the development of novel pharmaceuticals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TCM: Traditional Chinese medicine; **ROS:** Reactive oxygen species; **PGI2:** Prostacyclin; **EAE:** Extract enriched with ellagic acid; **EA:** Ellagic acid; **SOD:** Superoxide dismutase-2; **iNOS:** Nitric oxide synthase; **sICAM:** Soluble cell adhesion molecule; **LPO:** Lipid peroxidation; **GSH:** Reduced Glutathione; **LLC:** Lewis lung carcinoma; **MIC:** Minimum inhibitory concentration; **MRSA:** Methicillin-resistant *S. aureus*; **TCA:** Tricarboxylic acid; **DOX:** Doxorubicin; **SCA:** Sickle cell anaemia.

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