

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/280601958>

The medicinal properties and phytochemistry of plants of the genus Terminalia (Combretaceae)

Article in *Inflammopharmacology* · July 2015

DOI: 10.1007/s10787-015-0246-z · Source: PubMed

CITATIONS

61

READS

5,077

1 author:



Ian Edwin Cock

Griffith University

375 PUBLICATIONS 2,965 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



Probing for Antibacterial Properties within Australian Native Plants [View project](#)



Antibacterial activity of native Australian plants [View project](#)



The medicinal properties and phytochemistry of plants of the genus *Terminalia* (Combretaceae)

I. E. Cock^{1,2}

Received: 19 July 2015 / Accepted: 20 July 2015
© Springer Basel 2015

Abstract Plants of the genus *Terminalia* are amongst the most widely used plants for traditional medicinal purposes worldwide. Many species are used for their antibacterial, antifungal, antiprotozoal, antiviral, antidiarrhoeal, analgesic, antimalarial, antioxidant, antiinflammatory and anticancer activities. Wound healing and cardiovascular effects have also been credited to some species. Many *Terminalia* species have multiple beneficial effects for multiple diseases and ailments. Indeed, the Indian species *Terminalia chebula* is known as the king of plants in Ayurveda due to its broad range of medicinal uses. However, apart from the reported ethnopharmacological uses of many *Terminalia* species, surprisingly few studies have rigorously examined this important genus for their medical properties/mechanisms and phytochemistry. This is likely due to the high tannin content common to many *Terminalia* species and the perception that these tannins may be responsible for much of their beneficial properties. As the complexities of tannins make them poor candidates for drug design, most interest in *Terminalia* species has been for their pharmacognostic and nutraceutical value and they have often been overlooked as potentials for drug discovery. However, recent reports have identified many other interesting phytochemicals and demonstrated that these may be responsible for several of the reported bioactivities

of the *Terminalia* species used in traditional medicinal systems. The last decade has seen a large increase in the number of studies into the use of *Terminalia* species as therapeutic agents. Several species used in Ayurvedic medicine (*Terminalia arjuna*, *Terminalia bellerica*, *Terminalia catappa*, *T. chebula*) in particular have received much recent attention. Similarly, recent reports have also highlighted the medicinal potential of species from Africa, Australia and the Americas. The aim of this report is to summarise the recent research into the medicinal properties, phytochemistry and therapeutic mechanisms of *Terminalia* species and thus to highlight and direct future areas of research into the medicinal activities of this important genus.

Keywords Antioxidant · Anticancer · Inflammation · Antimicrobial · Diabetes · Medicinal plants

Introduction

Plants have a long history of usage as therapeutic agents and were the main source of medicines prior to the advances of modern medicine. In many developing countries, herbal medicinal systems remain important in the treatment of many ailments. Ayurvedic medicine is still commonly practiced within India with an estimated 85 % of Indians still using crude plant preparations for the treatment of a wide variety of diseases and ailments (Kamboj 2000). Traditional Chinese medicine (TCM) and African medicinal systems also account for a major portion of health care in their populations. Even in countries where allopathic/Western medicine is dominant, much is also owed to plant medicinal systems. Furthermore, many users are returning to herbal medicinal systems due to the

✉ I. E. Cock
I.Cock@griffith.edu.au

¹ Biomolecular and Physical Sciences, Nathan Campus, Griffith University, 170 Kessels Rd, Nathan, Brisbane, QLD 4111, Australia

² Environmental Futures Centre, Nathan Campus, Griffith University, 170 Kessels Rd, Nathan, Brisbane, QLD 4111, Australia

perception that natural medicines are often a safer alternative than allopathic drugs, as well as seeking treatments for diseases which modern medicine does not yet have solutions.

Many of the prescription drugs currently marketed for a wide variety of ailments were originally isolated from plants and/or are semi-synthetic analogues of phytochemicals. It has been estimated that approximately 25 % of all prescription drugs currently in use are of plant origin (Walsh 2003; Newman and Cragg 2007). Furthermore, approximately 75 % of new anticancer drugs marketed between 1981 and 2006 were derived from plant compounds (Newman and Cragg 2007). Traditionally, plant-based medicines have been used as crude formulations, such as infusions, tinctures and extracts, essential oils, powders, poultices and other herbal preparations. The current trend is to isolate and characterise the individual phytochemical components with the aim of producing an analogue of increased bioactivity/bioavailability. Such studies have given rise to many useful drugs such as quinine (from *Cinchona* spp.) and digoxin (from *Digitalis* spp.) as well as the anticancer drugs vincristine and vinblastine (from *Vinca rosea*). However, the bioactivities seen for crude extracts are often much enhanced, or even totally different to those seen for the individual components (Karalliedde and Gawarammana 2008; Choi and Chung 2003). Crude plant extracts may contain hundreds, or even thousands of different chemical constituents that interact in complex ways. Often it is not known how an extract works, even when its therapeutic benefit is well established.

The genus *Terminalia* (Family Combretaceae) comprises approximately 200–250 species of medium to large flowering trees, many of which have a history of usage in traditional medicinal systems (McGaw et al. 2001). *Terminalia* species are widely distributed through the tropical and subtropical regions of Asia, Australia and Africa. With arguably the greatest number and diversity, the Asian *Terminalia*'s cover many of the most useful species with the most extensive documentation of their therapeutic effects. Asian *Terminalia* species are widespread, occurring from the Malaysian peninsula and the Indonesian archipelago in the east, across Southern Asia to Western Asia and into the Middle East. The biology of many of these species is especially well studied due to their usage in a variety of Asian medicinal systems. Of the species that are native to Asia, *Terminalia arjuna* and *Terminalia chebula* are particularly well documented due to their myriad of uses in Ayurvedic medicine. Approximately, 28 species are known to occur in Australia and the South Pacific region. Of these, *Terminalia ferdinandiana* has been receiving recent attention due to its interesting phytochemistry and its high antioxidant content/activity. A further 30 species approximately occur in Africa, with the

majority of these occurring in the southern part of the continent. A number of *Terminalia* species are also native to the North, Central and South America.

The bark of many *Terminalia* species is often fissured and the branches are arranged in tiers. The genus name is derived from the Latin word *terminus*, referring to the fact that the leaves are located at the very tips of the shoots. Leaves of the most species of *Terminalia* are usually large and have a leathery feel. The small (usually) greenish-white flowers appear on spikes or in clusters. Fruit may be yellow, dark red or black drupes which are usually angled or winged. The fruit from some plants is edible and may in fact be highly nutritious.

Many *Terminalia* species are renowned for their high antioxidant activities. Indeed, the Australian species *T. ferdinandiana* has been reported to have the highest antioxidant activity of any plant worldwide (Netzel et al. 2007). Its ascorbic acid levels alone are more than 900 times higher than those of blueberry (g/g). Similarly, studies have also shown the Asian species *T. chebula* (Chang and Lin 2012; Mety and Mathad 2011; Hazra et al. 2010), *Terminalia belerica* (Mety and Mathad 2011; Hazra et al. 2010), *Terminalia paniculata* (Agrawal et al. 2011), *T. arjuna*, *Terminalia catappa* (Mety and Mathad 2011), and the African species *Terminalia prunioides*, *Terminalia brachystemma*, *Terminalia gazensis*, *Terminalia mollis* and *Terminalia sambesiaca* (Masoka and Eloff 2007) to also have high antioxidant contents.

Ethnopharmacology

Members of genus *Terminalia* have been used for a broad range of medicinal purposes by traditional healers from a wide variety of ethnic and cultural groupings (Table 1). The best documented of these are the traditional Indian medicinal systems, particularly the Ayurveda. Ayurvedic practitioners employ various species of *Terminalia* for a wide variety of medicinal purposes, including abdominal and back pain, coughs and colds, conjunctivitis, diarrhoea and dysentery, fever, headache, heart disorders, inflammation, leprosy, pneumoniae, sexually transmitted diseases, worms, wounds, haemorrhages, ulcers, and as a general tonic. Of the Ayurvedic plants, *T. arjuna*, *Terminalia bellerica*, *T. chebula* and *T. catappa* are arguably the most useful, being utilised for multiple ailments as summarised in Table 1 and discussed for each medicinal bioactivity.

Similarly, African medicinal systems made use of native *Terminalia* species in the treatment of multiple different disorders. Different species occur in different parts of the continent and their usage, whilst often widespread, is also often associated with specific cultural/ethnic groupings. Thus, a species used by one cultural grouping for a specific

Table 1 A summary of the origin, medicinal properties, and phytochemical constituents (where known) for selected *Terminalia* species worldwide

Species	Common name	Origin	Medicinal properties	Known constituents
<i>Terminalia acuminata</i>	Abalo, Darot, Biiiris, Mbarao, Weiba	Brazil	Treatment of yellow fever, pink eye, hepatitis	High tannin content
<i>Terminalia altissima</i>	White afara	Tropical west Africa, Sierra Leone, Congo, Nigeria, Cameroon	None known. Mainly used for its quality wood	Unknown
<i>Terminalia amazonia</i>	White olive	South America	None known. Mainly used for its quality wood	Unknown
<i>Terminalia arbuscula</i>	White olive	Jamaica and the Caribbean region	None known. Mainly used for its quality wood	Unknown
<i>Terminalia arenicola</i>	Brown Damson	Australia	None known	Unknown
<i>Terminalia arjuna</i>	Arjuna, Koha, White Marudah	India, Sri Lanka and Southern Asia	Analgesic, antiinflammatory, antioxidant, cardiac stimulant, antihypertensive, astringent, increases cholesterol elimination	Triterpenoids, flavonoids, tannins, gallic and ellagic acid, sitosterol, proanthocyanidins
<i>Terminalia australis</i>	Palo amarillo, Tanimbu	South America	Antiseptic, antifungal	Triterpenes, flavonoids, tannins
<i>Terminalia avicennioides</i>	Kpace, kpayi, baushe	West Africa	Treatment of cough, bloody sputum, antimycobacterial activity	Ellagic acid, punicalagin, flavogallonic acid and terchebulin
<i>Terminalia bellirica</i>	Beleric	India and South East Asia	Expectorant, laxative, treatment of coughs and colds, anaemia, diuretic, anthelmintic, antipyretic, analgesic, aphrodisiac, alopecia	The glycoside bellericarin, gallic acid, Ellagic Acid, lignans, 7hydroxy-3,4-(methylene dioxy)-flavone, anolignan B, sitosterol
<i>Terminalia bentzoe</i>	Multiple in different cultures	Southern Africa, Reunion Island	Antimalarial activity	Citronellyl acetate, flavonoids, triterpenes, tannins
<i>Terminalia bialata</i>	Indian silver greywood	India, Southern Asia	None known. Mainly used for its quality wood	Triterpenes, flavonoids, tannins
<i>Terminalia brachystemma</i>	Kalahari cluster leaf	Southern Africa	Antibacterial, antifungal	Triterpenes, flavonoids, tannins
<i>Terminalia brownii</i>	Multiple names in different African cultures	Southern and Central Africa	Antibacterial, antifungal, antiviral	Sitosterol, stigmasterol, triterpenes, flavonoids, tannins
<i>Terminalia buceras</i>	Black olive	Central America, Caribbean	None reported	Triterpenes, flavonoids, tannins
<i>Terminalia bursarina</i>	Yellow wood	Australia, South Asia	None known but reported toxicity	Unknown
<i>Terminalia calamansanai</i>	Phillipine almond, Anarep	South East Asia, Philippines	Astringent, lithotriptic	Ellagitannins, phenolic compounds, gallic acid
<i>Terminalia catappa</i>	Indian almond, tropical almond, umbrella tree	Broad distribution from Australia and South East Asia, India to Africa	Treatment of liver disease (Taiwan), dysentery and diarrhoea (Suriname), antioxidant and anticancer activity, activity against chloroquine-resistant <i>Plasmodium falciparum</i>	Flavonoids (including kaempferol, quercetin), tannins, saponins and phytosterols

Table 1 continued

Species	Common name	Origin	Medicinal properties	Known constituents
<i>Terminalia chebula</i>	Black Mytrobalan, Chebulic Myrobalan, Inknut	Southern Asia, from India to Nepal, China, Sri Lanka, Malaysia, Vietnam	Anti-tumour activity, eye disorders, treatment of coughs and colds, digestive disorders, inflammation, anthelmintic, cardiotonic, aphrodisiac, tonic	Terflavin B and chebulinic acid
<i>Terminalia citrina</i>	Yellow myrobalan, Manahei	India, South Asia	Diuretic, Cardio-tonic	Triterpenes, flavonoids, tannins
<i>Terminalia coriacea</i>	Leathery Murdah	India	Cardiac stimulant, accelerates wound healing, diarrhoea, antioxidant activity	Alkaloids, flavonoids, glycosides, saponins, sterols, tannins, triterpenoids and phenolic compounds
<i>Terminalia elliptica</i>	Indian laurel	South East Asia, India, Nepal, Bangladesh, Myanmar, Thailand, Laos, Cambodia, Vietnam	Diarrhoea and dysentery	Oxalic acid, pyrogallol, catechol
<i>Terminalia eriostachya</i>	Black Mastic	Cuba, Cayman Islands	Antiseptic properties	Unknown
<i>Terminalia ferdinandiana</i>	Kakadu plim, gubinge	Australia	High antioxidant activity, treatment of coughs and colds, antiseptic, antibacterial, antifungal, anticancer, antiinflammatory activities	High ascorbic and gallic acid contents, triterpenes, flavonoids, tannins
<i>Terminalia glaucescens</i>	Multiple names in different African cultures	Tropical Africa	Treatment of diabetes, dysentery, diarrhoea, venereal diseases, analgesic	Triterpenes, flavonoids, tannins
<i>Terminalia grandiflora</i>	Nut tree	Australia	High antioxidant activity, treatment of coughs and colds, antiseptic, antibacterial, antifungal, anticancer, antiinflammatory activities	High ascorbic and gallic acid contents, triterpenes, flavonoids, tannins
<i>Terminalia ivorensis</i>	Idigbo, Black Afara, Blackbark, Brimstone Wood, Shingle Wood	Western Africa, Cameroon, Ivory Coast, Ghana, Liberia, Nigeria, Sierra Leone	Antimalarial activity, treatment of trypanosomiasis	Triterpene saponins (including ivorenosides A, B and C), flavonoids, tannins
<i>Terminalia kaernbachii</i>	Okari Nut	Papua New Guinea, Solomon Islands	None known. Mainly used for its quality wood	Unknown
<i>Terminalia macroptera</i>	Bayankada	Tropical West Africa	Antiseptic, treatment of sexually transmitted diseases	Ellagitannins, phenolic compounds
<i>Terminalia mauritana</i>	Indian almond	Broad distribution from Australia and South East Asia, India to Africa	Treatment of liver disease (Taiwan), dysentery and diarrhoea (Suriname), antioxidant and anticancer activity, activity against chloroquine-resistant <i>Plasmodium falciparum</i>	Flavonoids (including kaempferol, quercetin), tannins, saponins and phytosterols

Table 1 continued

Species	Common name	Origin	Medicinal properties	Known constituents
<i>Terminalia mollis</i>	Bush willow	Southern Africa	Antiseptic, antifungal, antimalarial, anti-HIV activity	Triterpenes, flavonoids, tannins
<i>Terminalia muelleri</i>	Ketapang kencana	Indonesia, South East and Southern Asia	Antibacterial, antifungal, anticancer, antioxidant activities	Cyclic triterpenoids, flavonoids, tannins
<i>Terminalia myriocarpa</i>	Tolhao, Mezok, Panisoj	South East Asia	Diuretic, Antioxidant, cardiac stimulant, treatment of chest pains	Methyl (<i>S</i>)-flavogallate, gallic acid, methyl gallate, ethyl gallate, 2,3-di- <i>O</i> -[(<i>S</i>)-4,5,6,4',5',6'-hexahydroxybiphenyl]-2,2'-diylidicarbonyl-(α/β)-D-glucopyranose, vitexin, isovitexin, orientin, iso-orientin, kaempferol 3- <i>O</i> - β -D-rutinoside, rutin, neosaponarin, ellagic acid, flavogallonic acid and (α/β)-punicalagin
<i>Terminalia oblongata</i>	Rosewood, yellow wood	Australia	None reported but there are reports of toxicity	Ellagitannins, phenolic compounds
<i>Terminalia paniculata</i>	Vellamaruth	India	Treatment of cholera, inflammation, menstrual disorders, cough, bronchitis, cardiac disorders, diabetes, wounds, skin diseases	Phenols, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides
<i>Terminalia parviflora</i>	Indian almond, tropical almond, umbrella tree	Sri Lanka	Treatment of liver disease (Taiwan), dysentery and diarrhoea (Suriname), antioxidant and anticancer activity, activity against chloroquine-resistant <i>Plasmodium falciparum</i>	Flavonoids (including kaempferol, quercetin), tannins, saponins and phyosterols
<i>Terminalia prunioides</i>	Purple pod Terminalia, Sterkbos, Hareni, Mwangati	Southern Africa from South Africa to Ethiopia	Relief of postnatal abdominal pain	Triterpenes, flavonoids, tannins
<i>Terminalia schimperiana</i>	Idi odan	Tropical Africa, Guinea, Sierra Leone, Uganda, Ethiopia	Antiseptic, oral hygiene, antibacterial and antifungal properties	Triterpenes, flavonoids, tannins
<i>Terminalia sericea</i>	Silver Terminalia, Mususu, Vaalboom	Southern Africa	Stomach ailments, treatment of bilharzia, diarrhoea, pneumonia, diabetes, antiseptic	Stilbene glycosides phenolic compounds
<i>Terminalia spinosa</i>	Kasansa, Spiny cluster leaf, Musosahwai	Southern Africa	Abdominal disorders, pain, bilharzia, cancer, coughs and colds, dysentery, diarrhoea, fever, venereal diseases, heart disorders, hypertension, jaundice, diabetes, antiseptic	Triterpenes, flavonoids, tannins

Table 1 continued

Species	Common name	Origin	Medicinal properties	Known constituents
<i>Terminalia stenostachya</i>	Rosette leaf Terminalia	Southern Africa	Abdominal disorders, pain, bilharzia, cancer, coughs and colds, dysentery, diarrhoea, fever, venereal diseases, heart disorders, hypertension, jaundice, diabetes, antiseptic	Triterpenes, flavonoids, tannins
<i>Terminalia subspatulata</i>	Talisei	Malaysia and Indonesia	None known. Mainly used for its quality wood	Triterpenes, flavonoids, tannins
<i>Terminalia superba</i>	Limba	Tropical Western Africa	None known. Mainly used for its quality wood	Unknown
<i>Terminalia triflora</i>	None found	Tropical South America, Argentina	Antibacterial and antifungal activity, reputed anti-HIV activity	Ellagitannins, phenolic compounds

Ethnopharmacological uses, constituents and common names are derived from searches of Google Scholar and PubMed databases

property may have had different therapeutic uses (or no uses) by other groups in different regions of the continent. *Tereminalia ivorensis*, *Terminalia avicennioides*, *Terminalia glaucescens* and *Terminalia macroptera*, are amongst the most useful West African species, with documented ethnopharmacological uses for such diverse disorders as bacterial, fungal and viral diseases and infections, malaria, trypanosomiasis the treatment of coughs, bloody sputum and antimycobacterial activity. Similarly, many *Terminalia* species were used by diverse ethnic and cultural groupings in Southern and Central Africa. *Terminalia bentzoe*, *T. brachystemma*, *Terminalia brownii*, *T. mollis*, *Terminalia sericea*, *Terminalia spinosa* and *Terminalia stenostachya* all have documented ethnopharmacological uses in Southern Africa for the treatment of abdominal disorders, pain, bilharzia, cancer, coughs and colds, dysentery, diarrhoea, fever, venereal diseases, heart disorders, hypertension, jaundice, malaria, diabetes and for the treatment of bacterial, fungal and viral diseases. Indeed, the Southern African species *T. mollis* has even been linked with anti-HIV activity.

Despite a diverse range of *Terminalia* species in the Americas, (especially in tropical South American) and a history of usage in traditional medicine, there have been few studies on species from these continents. *Terminalia acuminata* and *Terminalia triflora* are perhaps the most promising *Terminalia* species based on their ethnobotanical usage. These species have been traditionally used to treat bacterial, fungal and viral diseases and infections. Indeed, *T. triflora* also has reputed anti-HIV activity and this activity has been scientifically verified and demonstrated to be due to the inhibitory effect of leaf extract components on the polymerase and ribonuclease activities of the HIV reverse transcriptase enzyme (Martino et al. 2002).

Less information is available about the ethnobotanical usage of Australian *Terminalia* species. Traditional indigenous Australian knowledge of plant-based therapeutics was generally passed on orally, with little written ethnopharmacological record. Thus, as Australian Aboriginal culture merged into mainstream society, with a corresponding increased reliance on Western medicine, much of this knowledge has been lost. However, several species, including *Terminalia carpentariae*, *Terminalia hadleyana*, *Terminalia latipes* and *T. ferdinandiana*, are known to have been used both as food, and as medicinal plants (Cock 2011a, b; Lassak and McCarthy 2006).

Phytochemistry and antioxidant content

Epidemiological studies have shown that a diet rich in antioxidants is associated with a decreased incidence of chronic diseases (Potter 1997). High antioxidant levels have

also been shown to act as a preventative against the development of degenerative diseases such as cancer (Hertog et al. 1996), cardiovascular diseases (Vita 2005), neural degeneration (Youdim et al. 2002), diabetes and obesity (Tsuda et al. 2003). Phenolic compounds are generally strong antioxidants (Rice-Evans et al. 1997). Their primary action involves the protection of cell constituents against oxidative damage through the scavenging of free radicals, thereby averting their deleterious effects on nucleic acids, proteins, and lipids in cells (Rice-Evans et al. 1997). Phenolics interact directly with receptors or enzymes involved in signal transduction (Moskaug et al. 2005), clearly indicating that they play a specific role in human physiology. Common plant phenolic compounds include flavonoids, tannins, anthocyanins, and gallic acid, all of which are common phytochemical constituents of Terminalia species.

Recent studies have documented the exceptionally high antioxidant content of the Australian species *T. ferdinandiana* (Konczak et al. 2010; Netzel et al. 2007). These studies have reported that the fruit of this plant has the highest ascorbic acid levels of any plant in the world, with levels reported as high as 6 % of the recorded wet weight (Woods 1995; Miller et al. 1993). This is approximately 900 times higher (g/g) than the ascorbic acid content in blueberries (which were used as a standard). As a further comparison, oranges and grapefruit (which are considered good sources of ascorbic acid) only contain approximately 0.007 % wet weight (0.5 % dry weight) (Johnson 2003). Due to its high vitamin C levels, the primary use of *T. ferdinandiana* fruit is currently for the production of vitamin C in health food, cosmetic, and pharmaceutical industries. However, *T. ferdinandiana* fruit also contains many other compounds which also contribute to its high antioxidant activity (Konczak et al. 2010; Netzel et al. 2007). Whilst many of these compounds are yet to be identified, *T. ferdinandiana* fruit has been shown to contain benzoic acids, flavanols, or flavanones (Konczak et al. 2010). *T. ferdinandiana* fruit is a good source of gallic acid (Fig. 1b) and ellagic acid (Fig. 1c) (Cunningham et al. 2009; Chirikoff and Kowalski 2008), which also demonstrate strong antioxidant activity in vitro (Losso et al. 2004; Ohno et al. 1999). *T. ferdinandiana* fruit is also very rich in chlorophyll a (Fig. 1e) and chlorophyll b (Fig. 1f), which have previously been shown to be capable of quenching oxidative stress. Lipophilic *T. ferdinandiana* fruit extracts are also rich in lutein (Fig. 1g—a carotenoid antioxidant compound associated with eye health) and with vitamin E (Fig. 1d) and vitamin E analogues (Konczak et al. 2010). Hesperitin (Fig. 1h), as well as the glycosides kaempferol (Fig. 1i), luteolin (Fig. 1j), and quercetin (Fig. 1k) are some of the other antioxidants present in *T. ferdinandiana* fruit (Konczak et al. 2010). *T. ferdinandiana* fruit is also a good source of the minerals magnesium, zinc, calcium,

potassium, sodium, iron, phosphorous, manganese, copper, and molybdenum (Konczak et al. 2010). It has previously been postulated that the exceptionally high antioxidant content of *T. ferdinandiana* fruit may be responsible for the therapeutic effects of this plant (Mohanty and Cock 2012).

High antioxidant contents have also been reported for Asian Terminalia species (Hazra et al. 2010; Jaiwal et al. 2012; Mety and Mathad 2011). One study reported the Trolox equivalent antioxidant content (TEAC) of Asian Terminalia as approximately 12.4, 1.6, 44.3 and 1.4 mg/ml extract for *T. arjuna*, *T. belerica*, *T. catappa* and *T. chebula*, respectively (Jaiwal et al. 2012). Other studies have reported similarly high TEAC values for other Asian Terminalia species, including *T. paniculata* (Agarwal et al. 2011) and *T. alata* (Mety and Mathad 2011). Similarly, high antioxidant contents have also been reported for the African species *T. brachystemma*, *T. gazensis*, *T. mollis*, *T. prunioides*, *T. sambesiaca* and *T. sericea* (Masoko and Eloff 2007). The high antioxidant activities of plants of the genus Terminalia seem to correlate with their phenolic contents (Jaiwal et al. 2012). The high tannin and flavonoid contents, characteristic of this genus, have been suggested as being responsible for this activity (Chang and Lin 2012; Jain et al. 2009). Indeed, the tannin antioxidant content of the Asian species *T. chebula* has been reported to be as high as 32 % (Chattopadhyay and Battacharyya 2007). The bioactivities of the individual components will be considered for each individual medicinal property discussed.

Cardiovascular effects

Ayurvedic practitioners employ several Terminalia preparations for the treatment of cardiovascular disorders and for their lipid lowering activities. *T. arjuna* is considered particularly useful. The powdered tree bark is used to alleviate angina (Dwivedi and Udupa 1989), possibly via its antioxidant activity. The stem bark contains high levels of antioxidant compounds, including glycosides, flavonoids, tannins and inorganic minerals. Amongst the terpenoids reported in *T. arjuna* bark are β -sitosterol (Fig. 2a), terminic acid (Fig. 2b) (Anjaneyulu and Prasad 1983), terminoside A (Fig. 2c), (Ali et al. 2003a, b) and arjunaphthanolside. Terminoside A and arjunaphthanolside are particularly interesting due to their reported therapeutic activities. Terminoside A inhibits nitric oxide production and decreases nitric oxide synthase levels in lipopolysaccharide-stimulated macrophages, and arjunaphthanolside possesses strong antioxidant activity (Ali et al. 2003a, b). *T. arjuna* bark also contains very high levels of antioxidant flavonoid compounds compared to other plants. Indeed, one study estimated the total flavonoid levels in *T. arjuna* bark to be 5698 ± 531 mg/100 g compared to 1914 ± 106 ,

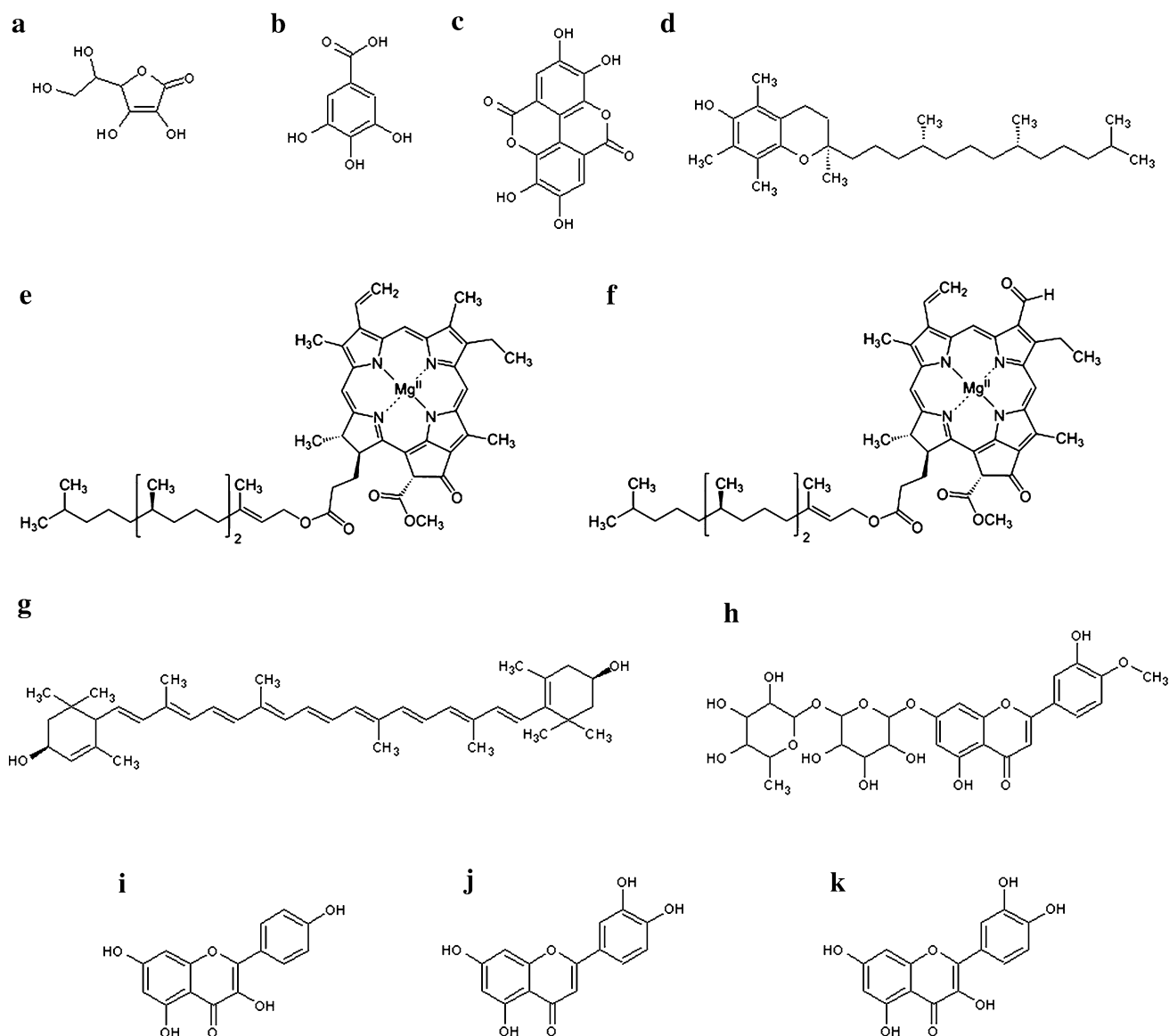


Fig. 1 Chemical structures of molecules with antioxidant potential identified in *T. ferdinandiana*: **a** ascorbic acid (vitamin C), **b** gallic acid, **c** ellagic acid, **d** α -tocopherol (vitamin E), **e** chlorophyll *a*, **f** chlorophyll *b*, **g** lutein, **h** hesperitin, **i** kaempferol, **j** luteolin, **k** quercetin

1255 \pm 119, 1302 \pm 55 and 487 \pm 23 mg/100 g for cinnamon, tea leaves capsicum and turmeric, respectively (Nair et al. 1996; Nair and Nagar 1997). These flavonoids include arjunolone (Fig. 2d), bicalein (Fig. 2e), flavones, kampferol (Fig. 1i), pelargonidin (Fig. 2f), quercetin (Fig. 1k) (Sharma et al. 1982) and luteolin (Fig. 1j) (Pettit et al. 1996). There is evidence that similar bioflavonoids prevent oxidation of LDL cholesterol via their free radical scavenging activity (Furman and Aviram 2001), inhibit endothelial activation (Carluccio et al. 2003) and inhibit platelet aggregation (Ruff 2003). They also possess cyclooxygenase inhibitory activity and can thus prevent thrombosis (Ruff 2003). Evidence exists that high dietary

levels of flavonoids are inversely proportional to the risk of coronary artery disease (CAD) (Martikainen et al. 2007; Middleton et al. 2000; Peluso 2006). It is, therefore, likely that high flavonoid contents in *Terminalia* species may be responsible for their beneficial effects in CAD.

In addition to the high flavonoids contents of plants of the genus *Terminalia*, another common phytochemical trait is the generally high tannin contents. Multiple hydrolysable tannins have been reported for *T. arjuna*, including pyrocatechols, punicallin (Fig. 2g), punicalagin (Fig. 3f), terchebulin (Fig. 2h), terflavin C (Fig. 2i), castalagin (Fig. 2j), casuariin and casuarinin (Fig. 3d) (Lin et al. 2001). Tannins can enhance nitric oxide synthesis and relax vascular tissue

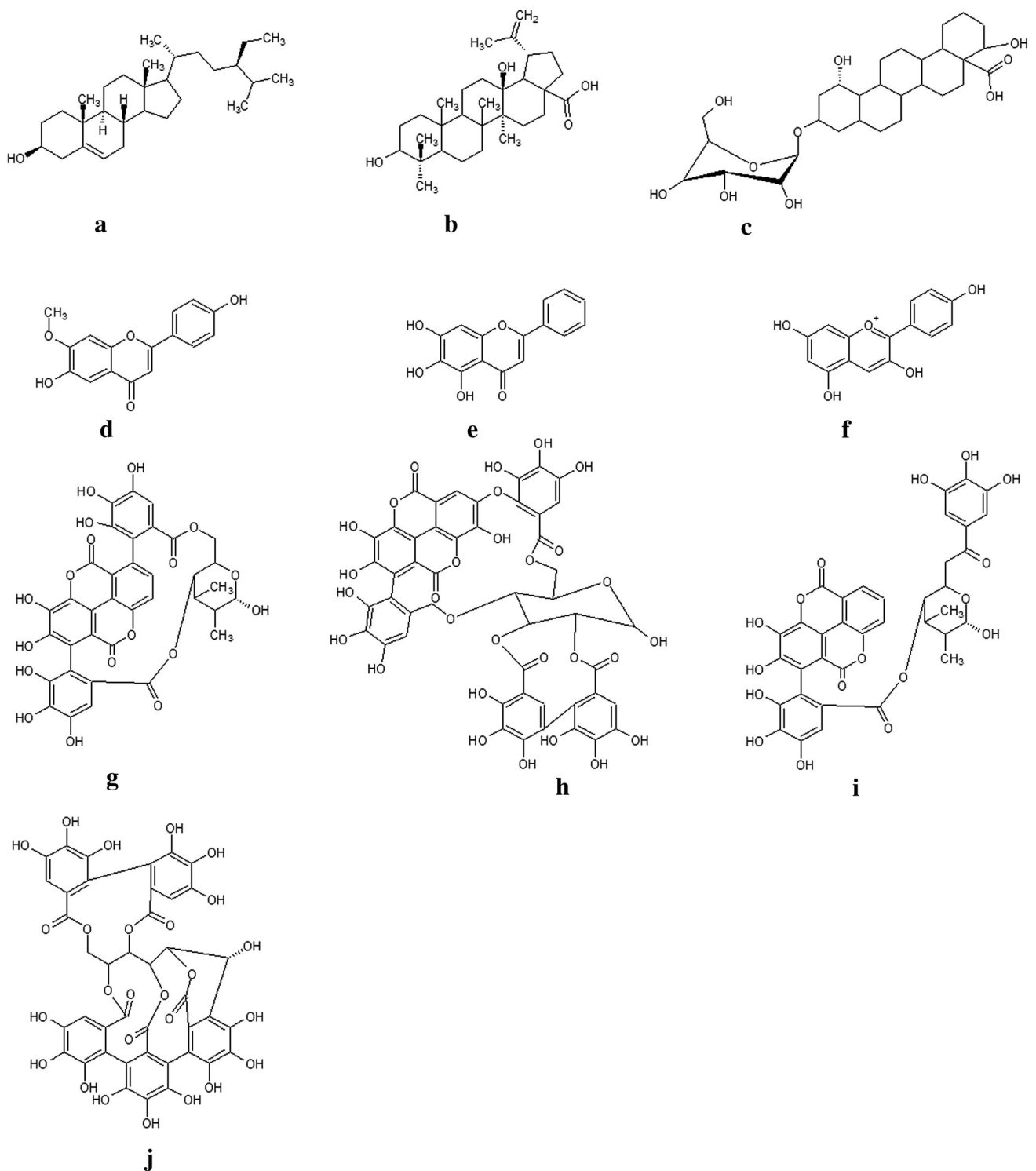


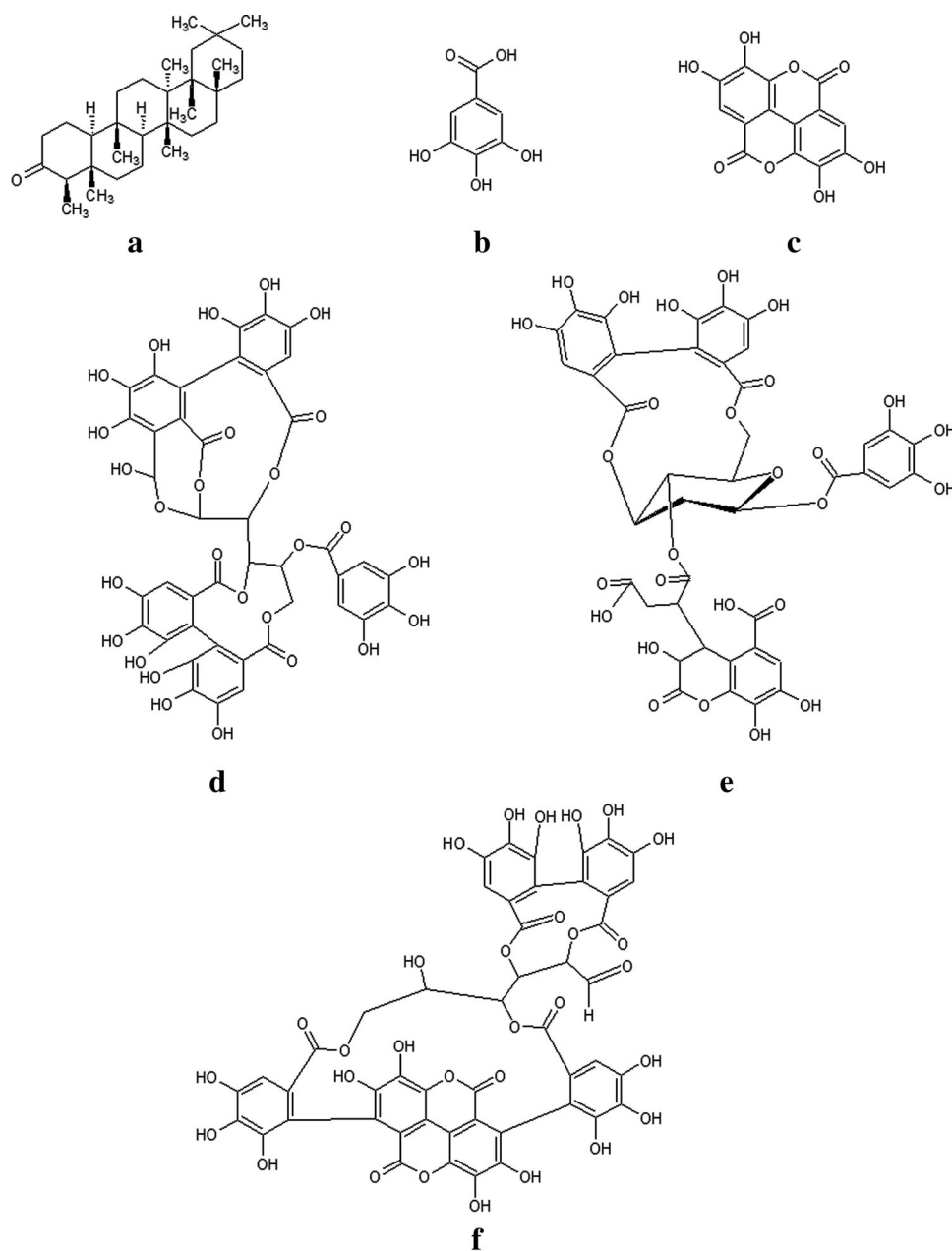
Fig. 2 Chemical structures of *T. arjuna* compounds with cardiovascular effects: **a** β-sitosterol, **b** terminic acid, **c** terminoside A, **d** arjunolone, **e** bicalcin, **f** pelargonidin, **g** punicallin, **h** terchebulin, **i** terflavin, **j** castalagin

stimulated to contract by norepinephrine and thus may be responsible at least in part for the hypotensive activity of *T. arjuna* bark (Nammi et al. 2003; Takahashi et al. 1997).

Terminalia arjuna is a particularly interesting plant for the treatment of cardiovascular disorders due to its multiple

modes of cardioprotection. Early studies have demonstrated that *T. arjuna* bark extracts increase the rate and force of cardiac contraction, as well as amplitude of contraction and the cardiac output (reviewed by Dwivedi 2007). Furthermore, *T. arjuna* bark extracts also produce substantial

Fig. 3 Chemical structures of Terminalia compounds with antimicrobial activity: **a** friedelin, **b** gallic acid, **c** ellagic acid, **d** casuarinin, **e** chebulagic acid, **f** punicalagin



ionotropic effects. Other effects noted for *T. arjuna* bark extracts include increases in coronary flow (Bhatia et al. 1998) and decreased blood pressure (Nammi et al. 2003; Takahashi et al. 1997). Furthermore, enhanced prostaglandin E₂ (PGE₂) activity has also been noted following *T. arjuna* treatment (Dwivedi et al. 1987). As PGE₂ is known to produce coronary vasodilation, this increase may be responsible for the increased coronary flow following *T. arjuna* treatment (Bhatia et al. 1998). Bark extracts of *T. arjuna* also reverse cardiac injury (Tandon et al. 1995), and have cardiovascular protective and tonic effects including improved cardiac cell mitochondrial uptake (Tandon et al. 1995), protection against oxidative stress (Gauthaman et al. 2001)

and decreased levels of lipid peroxidase activity (Sivalokanathan et al. 2006). Further cardio-protective effects of *T. arjuna* bark include decreases in total lipid levels, especially LDL lipids, with a coincident increase in HDL lipids (Shaila et al. 1998; Khanna et al. 1996).

Antimicrobial activity

Many *Terminalia* species have a history of usage to treat medical conditions related to microbial infections and numerous recent investigations have reported on their antibacterial properties. Multiple studies have reported on

the antibacterial properties of *Terminalia* species used in traditional Indian medicine. Leaf and bark extracts of arguably the best studied *Terminalia* species, *T. arjuna*, have been reported in numerous studies to have antibacterial activity against a wide panel of microbes (Aneja et al. 2012; Shinde et al. 2009), partially justifying its use in the treatment of a wide range of diseases and medical disorders (Jain et al. 2009; Udupa 1986; Tripathi and Singh 1996). *T. chebula* also has a tradition of use in Ayurveda for the treatment of numerous diseases and conditions (Chopra et al. 1956; Nadkarni 1976; Das 1991). It is not surprising that *T. chebula* has also been reported to display potent antibacterial activity against a microbial panel (Aneja and Joshi 2009). Similarly, *Terminalia alata*, *Terminalia bellirica* and *T. catappa* have also been reported to have broad spectrum antibacterial activity (Shinde et al. 2009). Whilst none of these studies identified the antibacterial components, one study demonstrated that they were relatively nonpolar and that this activity was not due to tannin components (Shinde et al. 2009). In contrast, other studies have demonstrated antibacterial activity being associated with the polar extracts (Aneja et al. 2012; Aneja and Joshi 2009).

The antibacterial activity of other Asian species has also been reported. *Terminalia muelleri* leaf components have been shown to inhibit the growth of several *Staphylococcus aureus* strains, including a methicillin-resistant strain (Anam et al. 2010). This study also examined the antibacterial mechanism of these compounds and reported that the *Terminalia muelleri* leaf components induced similar morphological changes in the bacterial cells as were seen with vancomycin treatment of bacteria (shrinkage and thinning of the cell wall). From these studies, the authors have reported the inhibition of the cell wall as a putative antibacterial mechanism for *Terminalia muelleri* leaf components.

Numerous African *Terminalia* species also have potent antibacterial activity. One study of the South East African species *T. stenostachya* and *T. spinosa* reported strong antibacterial activity against a broad spectrum of medically important bacteria, including several *Mycobacterium* species, *Streptococcus faecalis*, *S. aureus*, *Vibrio cholera*, *Bacillus anthracis*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa* and *Escherichia coli* (Mbwambo et al. 2011). *T. brownii* also has a history of usage in traditional eastern and central African medicinal systems, including usage for the treatment of diverse medicinal conditions including diarrhoea and gonorrhoea (Fyhrquist et al. 2002; Dhetchuvi and Lejoly 1990). A recent report has confirmed the antibacterial activity of *T. brownii* against *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhi* and *B. anthracis*. The West African species *T. avicennioides*, which is widely used in Nigerian

traditional medicine (Gill and Akinwunmi 1986), has been reported to have good antimicrobial activity towards a methicillin-resistant strain of *S. aureus* (Akinyemi et al. 2005). Further studies have identified a terpenoid, friedelin (Fig. 3a), as the probable antibacterial component of *T. avicennioides*. Similarly, recent studies have demonstrated the growth inhibitory activity of *T. sericea* and *Terminalia pruinoides* against pathogenic (Cock and van Vuuren 2015a) and food spoilage bacteria (Cock and van Vuuren 2015b).

Terminalia ferdinandiana from Australia also has strong antibacterial activity against an extensive panel of bacteria. In a recent study, solvent extracts of various polarities were tested against both Gram-positive and Gram-negative bacteria (Cock and Mohanty 2011). The polar extracts proved to be more effective antibacterial agents, indicating that the antibacterial components were polar compounds. Indeed, the polar extracts inhibited the growth of nearly every bacteria tested against. Both Gram-positive and Gram-negative bacteria were susceptible, indicating that the inhibitory compounds readily crossed the Gram-negative cell wall. The individual antibacterial components were not identified in this study although the authors indicate the extremely high levels of antioxidants in *T. ferdinandiana* fruit [including gallic (Fig. 3b) and ellagic acids (Fig. 3c)] may be responsible for this antibacterial activity.

Several bacterial species can initiate autoimmune inflammatory diseases (Cock 2014). Recent studies have highlighted the potential of *Terminalia* spp. as growth inhibitors of these bacteria and thus of the initial events of several autoimmune diseases. *T. ferdinandiana* fruit is a potent inhibitor of *Proteus mirabilis* (Sirdaarta et al. 2015a), *Acinetobacter baylyi* and *P. aeruginosa* growth (Sirdaarta et al. 2015b) and thus have potential in the prevention and treatment of rheumatoid arthritis and ankylosing spondylitis, respectively. *T. ferdinandiana* leaf extracts have also been shown to be good inhibitors of these same bacteria, as well as of *K. pneumoniae* and, therefore, may also be useful in the prevention of ankylosing spondylitis (Courtney et al. 2015). Further studies have reported similar growth inhibitory activity for the South African species *Terminalia sericea* and *Terminalia pruinoides* against these microbial triggers of rheumatoid arthritis (Cock and van Vuuren 2014) and ankylosing spondylitis (Cock and van Vuuren 2015a, b, c). In these studies, stilbene and tannin components have been identified as likely to contribute to this inhibitory activity.

In contrast, the antifungal, antiviral and antiprotozoal activities of *Terminalia* species have been less extensively studied. Antifungal activity has been reported for several species, although less quantitative data are available for the antifungal activity of *Terminalia* extracts compared to

antibacterial activity. One study into the antifungal activity of several South African Terminalia species reported good antifungal activity for *T. prunioides*, *T. brachystemma*, *T. sericea*, *T. gazensis*, *T. mollis* and *T. sambesciaca* against the fungal species *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigates*, *Microsporum canis* and *Sporothrix schenckii* (Masoko and Eloff 2005). Indeed, particularly low MIC values between 0.2 and 0.8 mg/ml were reported in this study, indicating the efficacy of Terminalia extracts. This was a particularly interesting study as the *Cryptococcus* and *Candida* strains used were multi-antibiotic-resistant strains. As fungal infections cause significant mortality and morbidity in Africa (especially in immune-compromised individuals), this finding could potentially result in the development of life saving treatments. Whilst this study did not identify the bioactive compounds, it did demonstrate that tannins were unlikely to be responsible due to the non-polar nature of the antifungal components. Interestingly, little data are available on the antifungal activities of Terminalia species from other world regions and much work is needed in this area. In my own laboratory, the Australian species *T. ferdinandiana* has been tested against a limited panel of fungi (including *C. albicans* and *Aspergillus niger*) and has shown no antifungal activity against any species tested (unpublished results). However, the fungal species tested were nystatin-resistant strains and only a very limited panel was screened. Therefore, it is possible that further studies may detect antifungal activity for this plant against other fungi.

Whilst limited studies have evaluated the antifungal activity of the Terminalia, several reports document their antiviral potential. Cheng et al. (2002) reported that a tannin compound isolated from the bark of *T. arjuna* displayed potent inhibitory activity against herpes simplex virus type 2 (HSV-2). This study identified this compound as the hydrolysable tannin casuarinin (Fig. 3d). The anti-herpes activity was also particularly long lasting, still evident 12 h after viral infection. Furthermore, the Cheng study also exhibited a multifaceted antiviral activity for this compound. Casuarinin exposure prevented the attachment of HSV-2 to cells and blocked viral penetration, as well as inhibiting the late events of infection. Furthermore, casuarinin displayed good viricidal activity, with concentrations as low as 25 μ M reducing viral titres up to 100,000 fold.

Recent studies have also demonstrated the relatively good antiviral activity of *T. chebula* towards measles and mumps viruses (Sumithira et al. 2012). Whilst this study did not examine the antiviral mechanism or identify the active components, it did demonstrate that the extracts contained high levels of phenolic antioxidant compounds. It was also demonstrated that the extract was not toxic to

Vero cells. Another recent study reported that the *T. chebula* leaf extracts also have potent inhibitory activity against herpes simplex virus type 1 (HSV-1) (Lin et al. 2011). The hydrolysable tannins chebulagic acid (Fig. 3e) and punicalagin (Fig. 3f) were identified as the extract components responsible for this antiviral activity. Chebulagic acid and punicalagin inhibit HSV-1 entry into A549 lung cells in a multifaceted manner: they prevent binding of the virus to cells, viral penetration, cell to cell spread, as well as secondary infection. These compounds were shown to target the interaction between cellular glycosaminoglycans and HSV-1 glycoproteins.

A South American species (*T. triflora*) has been shown to have viral anti-infective activity against HIV in HLT4LacZ-IIIB cell cultures (Martino et al. 2002). This activity was demonstrated to be due to the inhibitory effect of leaf extract components on the polymerase and ribonuclease activities of the HIV reverse transcriptase enzyme. Furthermore, this study isolated the antiviral activity to a hydrophilic tannin containing fraction, indicating that tannins may be responsible for the anti-infective activity. Earlier studies have also reported that leaf extracts from this plant have antiviral activity against several other RNA viruses including rabies, foot and mouth disease and influenza (Planes de Babchero and Souto 1969; Rivas and Distefano 1973; Rivas et al. 1971). The African species *T. mollis* (stem and root extracts) has also been reported to have anti-HIV activity against virus type 1 (HIV-1, III_B strain) (Maregesi et al. 2010). This study did not report on the anti-HIV mechanisms or the active components.

The best studied antiprotozoal activities of the genus Terminalia are the antimalarial and antitrypanosomiasis (sleeping sickness) bioactivities. Several species including *T. mollis* (Maregesi et al. 2010), *T. catappa* (Mudi and Muhammad 2009), *T. chebula* and *T. bellerica* (Pinmai et al. 2010) have been reported to have activity against *Plasmodium falciparum*. *Terminalia avicennoides* (Alayande et al. 2011) and *T. ivorensis* (Agbedahunsi et al. 2006) have been reported to have inhibitory activity towards *Trypanosomiasis brucei* (the parasite responsible for sleeping sickness). *T. bellerica* has also demonstrated trypanocidal activity against the related organism *Trypanosma evansi* (Shaba et al. 2009a, b) although no reports were found its activity against *T. brucei*. None of these studies examined the antiprotozoal mechanism, nor did any report identify the bioactive compounds. Recently, the Australian species *T. ferdinandiana* was reported to be a potent inhibitor of the gastrointestinal protozoan parasite *Giardia duodenalis* and a number of bioactive components were identified (Rayan et al. 2015). Studies into the anti-Giardiasis activity of other *Terminalia* spp. are lacking and much further work is required to screen other species for this activity.

Antiinflammatory activity and immunomodulation

Inflammation is a complex response by the body to injury. It typically follows a variety of insults including burns, wounds, bites, stings, etc. It is characterised by a wide variety of symptoms (Macpherson 1992) including:

- Swelling. Injury may result in increased capillary permeability which allows leucocyte migration and fluid accumulation in the damaged tissue. This accumulation results in the swelling characteristic of inflammation.
- Redness and heat are caused by vasodilation, reducing blood pressure and increasing circulation.
- Pain is a complex reaction resulting from the release of short peptides and prostaglandins.

As Terminalia species contain multiple active phytochemicals, many with antioxidant activity, it is likely that several of these may be required to address different aspects of the inflammatory process. The inflammatory processes require the cellular release of several classes of molecules. Vasoactive substances (e.g. bradykinin, prostaglandins, and vasoactive amines) are required to dilate blood vessels, opening junctions between cells to allow leucocytes to pass through capillaries. Any compound capable of blocking these vasoactive substances would potentially have a therapeutic effect as an anti-inflammatory agent. β -sitosterol (Fig. 2a) is an abundant phytosterol in several Terminalia species (Anjaneyulu and Prasad 1982a, b). β -sitosterol stimulates smooth muscle cells to release prostacyclin (PGI_2) (Awad et al. 2004). Conversely,

β -sitosterol treatment blocks the release of PGI_2 and prostaglandin E_2 (PGE_2) from macrophages (Awad et al. 2004). Thus, β -sitosterol treatment would be expected to affect vasodilation and, therefore, have a therapeutic effect on inflammation.

Recent studies have reported that *T. arjuna* leaf extracts have potent anti-inflammatory activity in vivo (Biswas et al. 2011). This anti-inflammatory effect is likely due to the inhibition of the enzyme cyclooxygenase, resulting in the inhibition of prostaglandin synthesis (Biswas et al. 2011). Chebulagic acid (Fig. 4a) isolated from *T. chebula* extracts also has potent anti-inflammatory effects in LPS-stimulated RAW 264.7 (mouse macrophage) cells via its antioxidant activity (Reddy and Reddanna 2009). These effects are exerted via a downregulation of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX), tumour necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) (Reddy and Reddanna 2009; Reddy et al. 2009). This downregulation results in the inhibition of the inflammatory mediators such as nitric oxide (NO) and prostaglandin E_2 (PGE_2) production. Thus, chebulagic acid exerts anti-inflammatory effects. 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 chebulagic acids anti-inflammatory activity is involved.

Potent anti-inflammatory activity has also been reported for the African species *T. sericea* (Moshi and Mbwambo 2005). The triterpenoidal saponin sericoside (Fig. 4b) has been isolated from *T. sericea* extracts and is believed to be

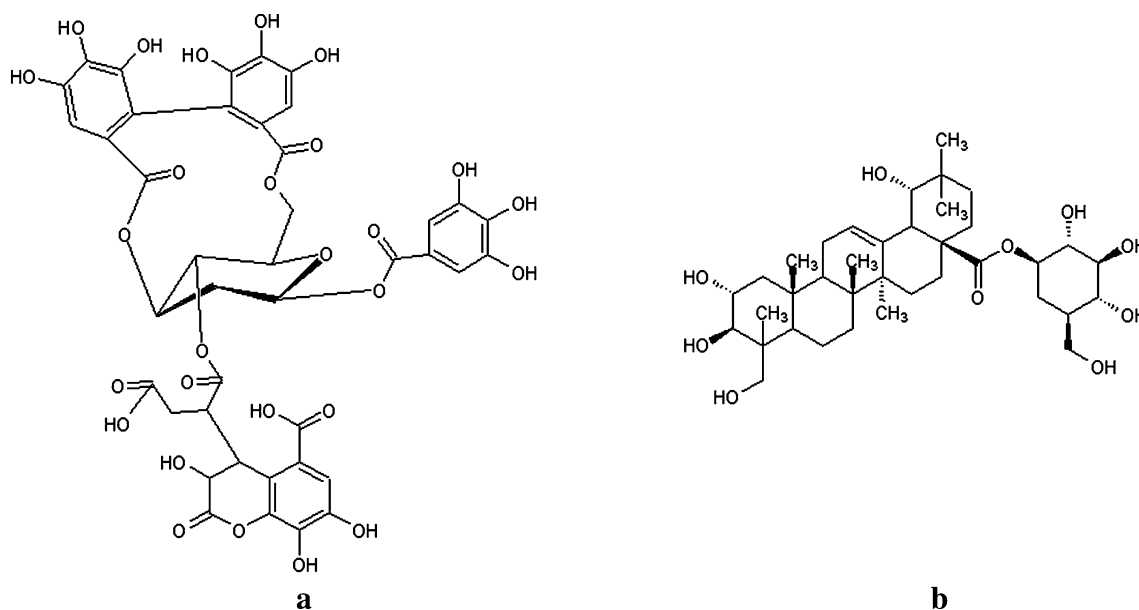


Fig. 4 Chemical structures of selected Terminalia compounds with antiinflammatory activity: **a** chebulagic acid, **b** sericoside

responsible for this activity (Mochizuki and Hasegawa 2007; Rode et al. 2003). Indeed, pure sericoside pretreatment *in vivo* has been shown to decrease the extent and severity of colon inflammation colitis in an induced inflammatory bowel disease (IBD) experimental model (Mochizuki and Hasegawa 2007). As superoxide radical (O_2^-) is generated in IBD model systems (Kankri et al. 2001) and sericoside has potent antioxidant activity (Mochizuki and Hasegawa 2007), it is likely that *T. sericea*'s anti-inflammatory activity is due at least in part to its free radical scavenging activity.

Chemotactic factors which include several proteins and peptides are also required to increase cell motility, especially the motility of leucocytes during inflammation. Blocking these chemotactic factors or blocking their effects prevents inflammatory swelling. Crude *T. sericea* extracts, as well as the purified component sericoside, have been shown to block chemotaxis. *In vivo* administration of sericoside to Sprague–Dawley rats prior to IBD induction results in a significant reduction in neutrophil activation and infiltration into the colon mucosa (Mochizuki and Hasegawa 2007). Furthermore, chebulagic acid isolated from *T. chebula* decreases cytokine production and IL-6 expression in human lymphoblastic T lymphocytes (Das et al. 2012), thereby decreasing chemotaxis. *T. chebula* extract treatment also results in decreased expression levels of TNF- α in Jurkat cells, which would subsequently downregulate other cytokines including IL-1 and IL-6 (Lin et al. 2010). The mechanistic details of the relationship between the antioxidant activity of the *T. chebula* extracts and these anti-inflammatory effects have not yet been extensively examined. Furthermore, these studies have not rigorously examined the dose-dependent effect of these phytochemicals.

Anticancer activity

The growth and development of healthy cells depend on fine regulation of growth promoting and inhibiting pathways. Proto-oncogenes and tumour suppressor genes are responsible for encoding proteins that regulate cell division/cell cycle, as well as for the repair of damaged DNA and programmed cell death by apoptosis. Mutations within these genes have been implicated in the onset of cancer (Hanahan and Weinberg 2000). Such mutations result in cells that no longer require external signals to proliferate. Furthermore, these cells fail to recognise signals that restrict cell division, resulting in uncontrolled cell growth. In tumour genesis, multiple genes may be altered and transmitted to daughter cells, which subsequently escape normal growth restraints and form a tumour that may be benign or malignant.

The induction of oxidative stress has been linked with several types of cancer (Brown and Bricknell 2001; Tome et al. 2001). Thus, it is possible that the high antioxidant contents of many *Terminalia* species may inhibit cancer formation and/or progression. Chromosome instability is also a common feature of many of the cancers that have been linked with oxidative stress, suggesting that increased oxidative stress may contribute to development of genetic instability. Oxidative stress leading to genetic instability would result in the emergence of new tumour phenotypes. In such populations, a decrease in apoptosis but an increase in tumour growth and subsequent tumour progression is observable. Consumption of high levels of antioxidants (as are characteristic of *Terminalia* species) may block this genetic instability and thus block tumourgenesis.

Currently used anti-cancer agents for the treatment of established tumours (e.g. doxorubicin, daunorubicin, mitomycin C, etoposide, cisplatin, arsenic trioxide, ionising radiation, photodynamic therapy) depend exclusively or in part on the production of ROS for cytotoxicity. Sensitivity of tumour cells to oxidative stress and/or apoptosis may affect treatment success (Davis et al. 2001; Ruefli et al. 2001). Studies indicate that WEHI7.2 mouse thymoma cells overexpressing catalase (CAT38) or thioredoxin (THX) are resistant to glucocorticoid-induced apoptosis *in vitro* (Freemerman and Powis 2000; Baker et al. 1997). This suggests that glucocorticoid-induced apoptosis occurs by an ROS-dependant mechanism. Average tumour weights increased in severe combined immune-deficient (SCID) mouse tumour xenografts from cells overexpressing catalase or thioredoxin (Baker et al. 1997). Tumours from both transfectants contained fewer apoptotic cells; however, mitotic cell numbers were similar. This suggests that cellular antioxidant overexpression results in increased tumour size due to a decrease in apoptosis.

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 an antioxidant or an oxidant with their action being dependent upon their concentration (Cock 2011a, b). The Aloe vera anthraquinone aloe emodin exerts antioxidant behaviour at lower concentrations, yet acts as a pro-oxidant at high concentrations. In contrast, a different Aloe vera anthraquinone (aloin) has an antioxidant effect at higher concentrations, yet a pro-oxidant 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 many *Terminalia* species have very high antioxidant contents reported, 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 pro-oxidant effects have been reported for other antioxidant phytochemicals including flavonoids (Rahman et al. 1990) and tannins (Singh et al. 2001a, b) which are present in high concentrations in many *Terminalia* species (Ahsan and Hadi 1998). 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 pro-oxidant state (Lastra and Villegas 2007; Wu et al. 2008). The pro-oxidant/antioxidant effect of plant extracts is due to a balance between the free radical scavenging activities and reducing power of their phytochemical components. This can be explained using the antioxidant vitamin ascorbic acid (which is present in high levels in several *Terminalia* species) as an example. Although ascorbic acid has well characterised antioxidant bioactivities, it is also known to act as a pro-oxidant at high concentrations (Joel 1995). This is due to the greater reducing power of ascorbic acid compared to its free radical scavenging activity. In the presence of transition metal ions, ascorbic acid will function as a reducing agent, reducing the metal ions. In this process, it is converted to a pro-oxidant. Therefore, high dietary intake of ascorbic acid in individuals with high iron levels (e.g. premature infants) may result in unexpected health effects due to the induction of oxidative damage to susceptible biomolecules (Halliwell 1996; Herbert et al. 1996; Samuni et al. 1983).

Reactive oxygen species (ROS)-based tumour therapy would cause tumour regression should the tumour cells not be apoptotic/oxidant-resistant cells. Therefore, if *Terminalia* antioxidant components are present in concentrations and ratios consistent with pro-oxidant 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.

The Australian species *T. ferdinandiana* has been receiving much recent attention due to its recently reported extremely high antioxidant content (Konczak et al. 2010; Netzel et al. 2007) and reports linking antioxidant levels and redox management with anticancer activity (Mohanty and Cock 2012). A recent study has demonstrated that a *T. ferdinandiana* fruit extract rich in polyphenolic compounds displayed antiproliferative activity against a panel of cancer cell lines (Tan et al. 2012). The proliferation of normal cell lines was also seen to be inhibited in this study, although several cancer cell lines (particularly gastric and colorectal cancer cell lines) showed a higher sensitivity to

the *T. ferdinandiana* fruit extract compared to the equivalent normal cell line. To understand the cancer cell viability suppression mechanisms of the *T. ferdinandiana* fruit extract, this study also examined the induction of apoptosis. The extract was shown to activate caspase-7 and caspase-9 as well as poly (ADP-ribose) polymerase (PARP), indicating that apoptosis induction is via an intrinsic pathway.

Similarly, the tannin casuarinin (Fig. 3d) isolated from bark extracts of the Indian medicinal plant *T. arjuna* has been reported to induce apoptosis in human A549 lung cancer cell lines (Kuo et al. 2005). It was postulated that an enhanced Fas/APO-1 ratio and increases in membrane bound and soluble Fas ligands may be responsible for casuarinin's apoptotic effect. Furthermore, casuarinin was also found to arrest cell cycle progression in the G₀/G₁ phase, possibly due to a p53-dependent induction of p21/WAF1.

The Ayurvedic medicine Triphala has cytotoxic effects against various cancer cell lines (Kaur et al. 2005), thymic lymphoma cells (Sandhya and Mishra 2006), human breast cancer cell lines (Kaur et al. 2005; Sandhya and Mishra 2006), human prostate cancer cell lines and human pancreatic cancer cell lines (Shi et al. 2008). Conversely, the cytotoxic effects of Triphala are negligible in various normal cell lines (Sandhya and Mishra 2006; Sandhya et al. 2006). Triphala comprises fruits of three plants including two *Terminalia* species (*T. chebula* and *T. belliricia*). Whilst the individual cytotoxic constituents were not identified in any of these Triphala studies, it is noteworthy that all three fruits used in this preparation have high antioxidant levels and high gallic acid contents (Baliga 2010). As pure gallic acid (Fig. 1b) has been shown to have similar cytotoxic effects as Triphala towards the same cancer cell lines (Kaur et al. 2005; Ishihara and Sakagami 2003; Sakaguchi et al. 1999), it is likely that gallic acid is at least in part responsible for the anticancer activity of Triphala.

T. belliricia extracts have also demonstrated growth inhibitory effects towards human A549 lung cancer cell lines and HepG2 hepatocarcinoma cell lines without the presence of the other plant components present in Triphala (Pinmai et al. 2008). Furthermore, the *T. belliricia* extract also showed a synergistic effect with conventional anticancer chemotherapeutics, enhancing the cytotoxic activity of cisplatin and doxorubicin towards the cancer cell lines, indicating its potential as a synergistic cancer chemotherapeutic agent.

Wound healing

Whilst antiinflammatory and antimicrobial bioactivities are complex processes requiring the synergistic action of several bioactivities, wound healing is more so. Wound

healing is the result of several complex bioactivities including:

- Inflammation
- Antiseptic bioactivity
- Cell growth and proliferation
- Matrix remodelling

The growth of endothelial, epithelial and fibroblast cells is critical in wound healing. As a first step, a fibrin clot is formed as a temporary repair. This step is vital as it helps avoid microbial infection which may retard the healing process. The wound is subsequently invaded by a variety of cell types, some which stimulate an inflammatory response, whilst others are directly involved in the repair mechanism (Davis et al. 1987). The effects of Terminalia extract components on inflammation processes and chemotaxis have already been discussed and will not be discussed further here. Wound repair itself occurs in three phases: the migration of epithelial cells and fibroblasts to the wound site, proliferation of cells and cellular maturation. It is likely that the wound healing effect of Terminalia extracts may involve the synergistic action of multiple components on several pathways.

Several Terminalia species have reported wound healing bioactivities. Of these, perhaps the best documented and the most extensively studied are the Asian Terminalia species used in Ayurvedic medicine. *T. arjuna* (Chaudhari and Mengi 2006), *T. chebula* (Li et al. 2011; Suguna et al. 2002) and *T. coriacea* (Ali Khan et al. 2012) have all demonstrated an ability to hasten the wound healing process. As wound healing is a complex process involving several bioactivities, no single experimental model is adequate to evaluate wound healing and various individual bioactivities need to be considered. These include antimicrobial, antiinflammatory and immunomodulatory activities which have already been considered, as well as cell proliferative activity, and tissue and matrix remodelling.

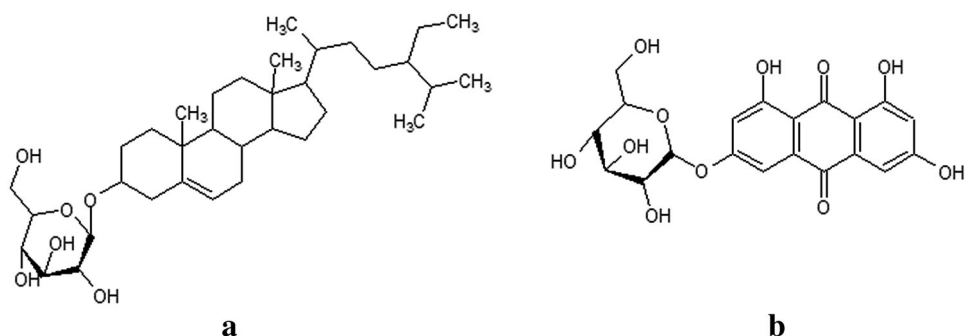
Terminalia arjuna demonstrates several bioactivities that are important for wound healing. Aside from its good broad spectrum antimicrobial activity (previously summarised in this review), it also has been shown to induce enhanced tensile strength in incision wounds as well as increasing the rate of epithelialisation of the wound (Rane and Mengi 2003). Further studies to characterise the bioactive components (Chaudhari and Mengi 2006) isolated the wound healing activities to 3 separate fractions. The fraction which induced the greatest rate of epithelialisation consisted almost exclusively of tannins, indicating that tannins are very important in wound healing processes. Incidentally, this fraction also had the greatest antimicrobial activity of the fractions tested. Treatment of excision wounds with this fraction resulted in the largest increase of

hexosamine levels (a component of the extracellular matrix) compared to the other fractions. Together with cellular growth and proliferation, wound healing also requires matrix remodelling. Thus, *T. arjuna* tannin components also appear to affect matrix formation. The remaining two fractions isolated from *T. arjuna* bark also increased the rate of wound healing compared to the control, but were significantly less effective than the high tannin containing fraction. Whilst these fractions also contained tannins, they additionally consisted of saponins and reducing sugars. As sugars are known to delay the wound healing process by decreasing tensile strength (Emanuel and Farber 1988), the slower rate of healing induced by these two fractions may be due to their higher sugar contents.

Similarly, *T. chebula* treatment also enhances extracellular matrix formation in wounds. In vivo wound healing studies have demonstrated that *T. chebula* treatment enhances protein synthesis and the deposition of matrix proteins in the granulation tissues (Suguna et al. 2002). The levels of collagen were particularly elevated during the early stages of healing. The deposition of collagen at the wound site enhances the tensile strength and thus the rate of healing (Balleisen et al. 1975). Furthermore, the same study also demonstrated an increase in the levels of the extracellular matrix components hexosamine and uronic acid following *T. chebula* treatment in the early stages of wound healing (when the extracellular matrix forms), followed by a return to normal levels in the later stages. In addition, *T. chebula* tannin extracts have been shown to have angiogenic potential, increasing the amount of newly formed capillaries during the inflammatory phase of wound healing, as well as increasing the degree of wound contraction in granulation tissue (Li et al. 2011).

Other Terminalia phenolic compounds have also been implicated in the wound healing effects of this genus. β -sitosterol (Fig. 2a) and β -sitosterol glucosides (Fig. 5a), which are common Terminalia phytochemicals, promote endothelial cell proliferation and angiogenesis (Moon et al. 1999) although their activity appears to be dependent on their redox states (Vivancos and Moreno 2005). Reduced sterols have antioxidant activity and stimulate wound healing processes, whilst oxidised sterols are prooxidants and induce cell death. Therefore, β -sitosterol and β -sitosterol glucosides have potential applications in wound management in their reduced state. Further phytochemicals with wound healing properties in *T. coriacea* extracts were identified as anthraquinone glycosides (Fig. 5b), flavonoids and tannins (Ali Khan et al., 2012). Similar anthraquinone glycosides have also been reported to stimulate cellular proliferation (Choi et al. 2001; Lee et al. 1997; Yagi et al. 2002). It has been postulated that the proliferative effect of anthraquinone glycosides may be due to their high

Fig. 5 Chemical structures of: **a** a β -sitosterol glucoside, **b** an anthraquinone glycoside



antioxidant activities (Araya-Maturana et al. 2008; Gomes et al. 2009).

The redox environment also affects cellular signal transduction, DNA and RNA synthesis, protein synthesis, enzyme activation, regulation of the cell cycle, ligand binding, DNA binding and nuclear translocation and, therefore, ultimately cell proliferation/death (Makino et al. 1999; Simons and Pratt 1995). Transcription factors are active in their reduced form and their translocation to the nucleus is also redox dependent (Okamoto et al. 1999). Studies have demonstrated that *T. chebula* treatment increases transcription and translation rates as well as DNA replication (Li et al. 2011; Suguna et al. 2002). These studies also linked these increases to the very high antioxidant activity of *T. chebula*. A reducing environment favours cellular proliferation whilst an oxidising environment results in an increase in reactive oxygen species, initiating cell death (Hamilos et al. 1989; Kim et al. 1996). Therefore, as discussed for anticancer activity, conditions favouring antioxidant activity would be expected to favour cellular proliferation whilst conditions favouring prooxidant activity would favour cell death. As high antioxidant contents are a common feature of plants of the genus Terminalia, it is not surprising that several Terminalia species have reported wound healing properties. It is likely that a synergistic action is required by several Terminalia extract components on multiple wound healing-associated bioactivities.

Antidiabetic activity

Diabetes mellitus refers to a group of metabolic disorders that result in increased blood glucose concentrations, either because the pancreas does not produce enough functional insulin (type 1 diabetes), or because cells do not respond to the insulin which is produced (type 2 diabetes). The causes of diabetes mellitus include the auto-immune destruction of pancreatic cells (Betterle et al. 1984), viral infections (Yoon et al. 1979), genetic and environmental factors (Pyke 1977), insulin or insulin receptor gene mutations

(Tager 1984), and altered pancreatic prostaglandin metabolism Robertson and Chen 1977). Diabetes has significant health effects, impacting on the quality of life and life expectancy of those suffering with it.

Glycosylation of blood proteins including haemoglobin, albumin and lipoproteins is characteristic of diabetes mellitus (Klein 1995). 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) (Singh et al. 2001b). The binding of AGEs to their receptors results in altered cell signalling which in turn results in free radical production (Penckofer et al. 2002). Indeed, diabetes mellitus has been shown experimentally to be associated with an increase in free radical formation and an associated decrease in antioxidant potential (Davi et al. 1999; Vessby et al. 2002). Studies have directly linked oxidative stress with the impaired maintenance of glucose homeostasis and the enhanced lipid peroxidation seen in diabetes mellitus (Davi et al. 1999). 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 (Astaneie et al. 2005).

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 (Rahimi et al. 2005; Shih et al. 2002). Therefore, treatment with antioxidants would be expected to counteract many of these complications. High antioxidant contents are a common feature for plants of the Terminalia genus. All Terminalia species 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 (Cock 2011a).

Several studies have indicated the beneficial effects of Terminalia species in diabetic patients. *T. glaucescens* is

used in traditional Cameroon medicinal systems in the treatment of diabetes. Administration of *T. glaucescens* leaf extracts to streptozotocin-treated mice has been shown to have a protective effect, inhibiting the hyperglycaemic effect of streptozotocin and blocking the induction of diabetes (Njomen et al. 2009). Phytochemical analysis of the *T. glaucescens* leaf extract revealed the presence of triterpenoids, flavonoids, tannins and alkaloid components, although the study did not determine the nature of the active components. Whilst the antidiabetic mechanism of the *T. glaucescens* leaf extract was also not determined, it has been suggested that the extract components may act either by directly competing with streptozotocin for

binding to cellular glucose receptors (Crouch et al. 1978), or alternatively by directly activating superoxide dismutase, thus blocking the toxic effects of streptozotocin on the β cells of the pancreas (Sandler and Andersson 1982; Robbins et al. 1980) and allowing for normal insulin production/secretion. Phytochemical evaluations of *T. glaucescens* bark extracts have identified glaucinoic acid, arjunic acid (Fig. 6a), arjungenin (Fig. 6b), sericoside (Fig. 4b) and friedelin (Fig. 3a) in the extract (Rahman et al. 2005). This study also reported the inhibition of β -glucuronidase activity by each of these compounds. As the enzyme β -glucuronidase is involved with carbohydrate breakdown, these compounds may also be capable of

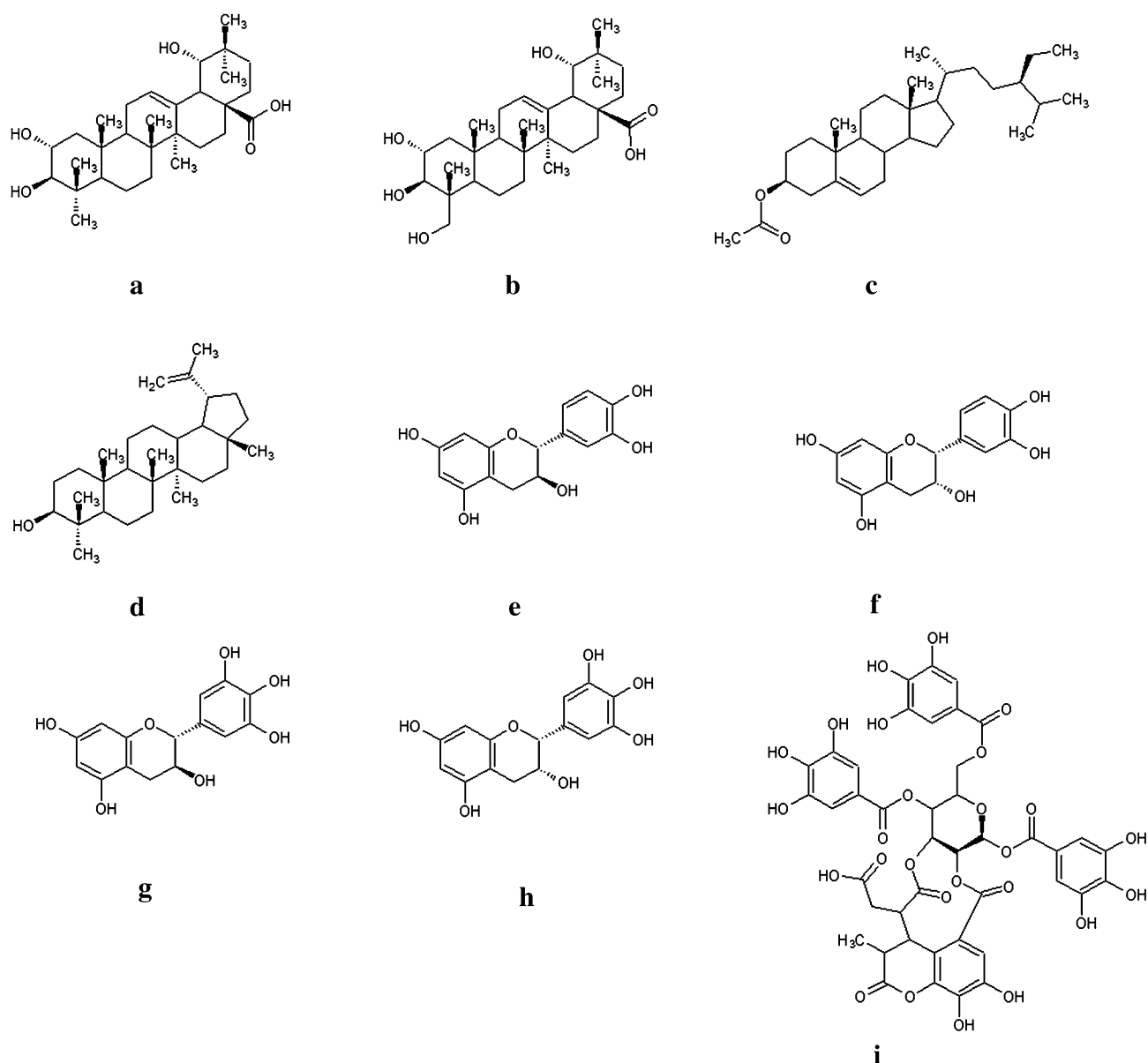


Fig. 6 Chemical structures of *Terminalia* compounds with antidiabetes activity: **a** arjunic acid, **b** arjungenin, **c** β -sitosterol-3-acetate, **d** lupeol, **e** catechin, **f** epicatechin, **g** galocatechin, **h** epigallocatechin, **i** chebulinic acid

altering the activity of other enzymes involved in carbohydrate metabolism, thus affecting the maintenance of glucose homeostasis in diabetes mellitus.

A further study into the medicinal properties of another West African species, *T. superba*, reported that a hydroethanolic root extract displayed potent α -amylase inhibitory activity (Momo et al. 2009). As α -amylase is involved in the breakdown of carbohydrate α (1 \rightarrow 4) glycosidic bonds, it functions to increase glucose bioavailability in the blood. As *T. superba* root extract blocks this enzyme, it would reduce the bioavailability of glucose and thus be useful in the treatment of diabetes. Furthermore, this α -amylase inhibitory activity was correlated to the antioxidant activity of the tannin, flavonoid and phenolic acid components of the extract. Similarly, anti- α -amylase and anti- α -glucosidase activities have been reported for the Southern African species, *T. sericea* (Nkobole 2009). This study identified β -sitosterol (Fig. 2a), β -sitosterol-3-acetate (Fig. 6c), lupeol (Fig. 6d), stigma-4-ene-3-one, catechin (Fig. 6e), epicatechin (Fig. 6f), gallicocatechin (Fig. 6g) and epigallocatechin (Fig. 6h) as the extract components with the anti- α -amylase and anti- α -glucosidase activities, and showed β -sitosterol and lupeol as having the strongest activity.

Antidiabetic activities have also been reported for several Asian *Terminalia* species including *T. arjuna* (Ragavan and Kumari 2006), *T. bellerica* (Kannan et al. 2012; Kasabri et al. 2010), *T. catappa* (Ahmed et al. 2005; Nagappa et al. 2003), *T. chebula* (Kumar et al. 2006; Rao et al. 2006), *T. pallida* (Rao et al. 2003) and *T. paniculata* (Ramachandran et al. 2012). *T. chebula* ethanolic extracts were found to decrease the levels of blood glucose and glycosylated haemoglobin in a streptozocin-induced diabetic rat model (Kumar et al. 2006). The extract also demonstrated inhibitory activity against the gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase, and stimulated hexokinase activity. Further studies have also shown inhibitory activity of α -glucosidase activity by *T. chebula* extracts and linked this inhibition to the antioxidant activity of chebulagic acid (Fig. 3e), chebulinic acid (Fig. 6i) and corilagin (Fig. 7d) (Sasidharan et al. 2012). Studies into the antidiabetic activity of *T. arjuna* bark extract in diabetic rats demonstrated that the extract reduced lipid peroxidation and significantly increased the activities in the enzymatic antioxidants superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and glutathione reductase, as well as increasing the non-enzymatic antioxidants reduced glutathione, vitamin A, vitamin E, ascorbic acid, total sulfhydryl groups (TSH) and nonprotein sulfhydryl groups (NPSH) in hepatic and renal tissue (Ragavan and Kumari 2006).

Terminalia bellerica methanolic extract treatment also blocks hyperglycaemia in diabetic rats via its antioxidant activity (Sabu and Kuttan 2009). Significant decreases in

ROS, as well as increased glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase activities, were reported in diabetic rats following *T. bellerica* extract administration. An aqueous extract of *T. bellerica* fruits was shown to stimulate insulin secretion from a pancreatic β -cell line to a similar extent to glibenclamide (Kasabri et al. 2009). Furthermore, the aqueous extract also displayed insulin mimetic activity, enhancing glucose uptake into 3T3-L1 adipocytes and decreasing starch digestion and protein glycation.

Protection against toxic compounds

Acetaminophen (paracetamol) is an effective analgesic and antipyretic drug. However, accidental or deliberate overdose may cause hepatotoxicity, resulting in liver damage and death. Whilst the mechanism of hepatic injury is not fully understood, it is thought that acetaminophen is converted to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) which is usually conjugated with glutathione in the liver to form the nontoxic compound mercapturic acid. When the concentration of acetaminophen is elevated during an overdose, the glutathione is rapidly depleted and thus is no longer available to conjugate further NAPQI. Instead, the excess NAPQI binds to hepatic proteins and DNA, resulting in elevated levels of lipid peroxidation and ultimately cellular necrosis (Jueschke and Knight 2003). *T. paniculata* extracts have recently been reported to alter the levels of biomarkers of hepatotoxicity in vivo, indicating a hepatoprotective activity (Eesha et al. 2011). The *T. paniculata* extract was shown to protect the liver by blocking lipid peroxidation which leads to tissue damage when the cellular antioxidant defences are overwhelmed, indicating that the protective mechanism may be due to the high antioxidant content of *T. paniculata* extracts. Furthermore, the extract was also shown to induce significant increases in blood and hepatic thiol contents, providing the hepatic cells with increased protection against the NAPQI-induced oxidative stress. Phytochemical screening in this study revealed the presence of high levels of flavonoids in the extract. As flavonoids are hepatoprotective via their antioxidant activities (Wilma et al. 2011), it is likely that the high flavonoids content of *T. paniculata* extract may contribute to its hepatoprotective activity.

Terminalia arjuna has also demonstrated hepatoprotective and renal-protective activity towards oxidative stress induced by exogenous drugs (Manna et al. 2006). Pretreatment of mice with aqueous *T. arjuna* extract prior to exposure to the hepatotoxin carbon tetrachloride (CCl₄) blocked the decrease in the levels of the cellular antioxidants glutathione, superoxide dismutase, catalase and

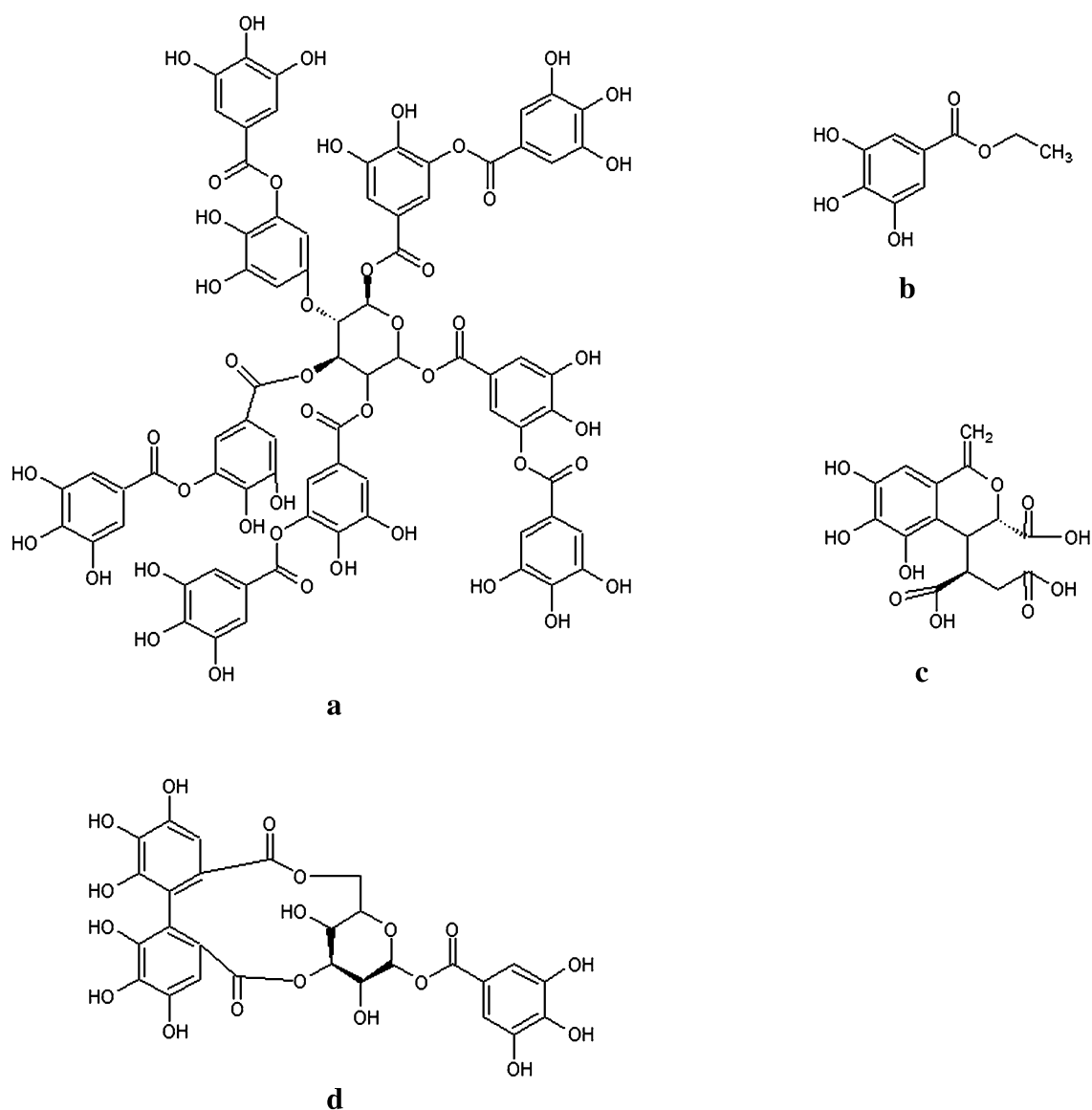


Fig. 7 Chemical structures of selected *Terminalia* compounds with neuroprotective activity: **a** tannic acid, **b** ethyl gallate, **c** chebulic acid, **d** corilagin

glutathione-*S*-transferase normally seen with CCl_4 exposure. Thus, *T. arjuna* treatment blocked oxidative stress-related free radical hepatocyte damage. This study did not identify the phytochemical(s) responsible for this protective effect. However, as the mechanism appears to at least in part involve protection against ROS, it is likely that the high antioxidant levels characteristic to this and other *Terminalia* species are involved.

Other therapeutic activities

A variety of other therapeutic properties have also been reported for *Terminalia* species. Indian and African *Terminalia* species have documented analgesic effects. Recent

studies have reported analgesic activity in *T. arjuna* (Biswas et al. 2011) and *T. superba* (Dongmo et al. 2006) in mice using hot plate and formalin bioassays. In both studies, the reported analgesic effect was approximately the same efficacy as recorded for acetylsalicylic acid. The *T. arjuna* study also examined the anti-inflammatory activity of the analgesic extract, reporting significant activity in an assay designed to evaluate the enzyme cyclooxygenase which is responsible for prostaglandin synthesis (Biswas et al. 2011). Whilst this study examined *T. arjuna* leaf extracts, other studies have reported the presence of β -sitosterol (Fig. 2a), terminic acid (Fig. 2b), (Anjaneyulu and Prasad 1983), terminoside A (Fig. 2c), arjunaphthanolside (Ali et al. 2003a, b), arjunolone (Fig. 2d), bicalein (Fig. 2e), flavones, kampferol (Fig. 1i),

pelargonidin (Fig. 2f), quercetin (Fig. 1k) (Sharma et al. 1982), luteolin (Fig. 1j) (Pettit et al. 1996), punicallin (Fig. 2g), punicalagin (Fig. 3f), terchebulin (Fig. 2h), terflavin (Fig. 2i), castalagin (Fig. 2j), casuariin and casuarinin (Fig. 3d) (Lin et al. 2001) in *T. arjuna* bark extracts. Many of these compounds have well established antiinflammatory potential. Similarly, the *T. superba* study also noted the presence of terpenoids, flavonoids and tannins in the analgesic fraction (Dongmo et al. 2006). It is thus likely that the reported analgesic effects of these two species in this experimental system may be due to their antiinflammatory activity and that these classes of compounds may be responsible.

Terminalia chebula extracts have also been reported to have neuroprotective potential (Chang and Lin 2012). Polar *T. chebula* extracts blocked H₂O₂-induced cell death in PC12 cells in a dose-dependant manner. Indeed, the extracts not only blocked cell death, but also demonstrated cell proliferative activity. This study demonstrated that the cell protective and proliferative activities were highest in the extracts with high antioxidant contents, indicating that redox control is likely involved (Chang and Lin 2012). Phytochemical analysis of *T. chebula* showed the presence of multiple phytochemicals with antioxidant activity including gallic acid (Fig. 1b), ellagic acid (Fig. 1c), tannic acid (Fig. 7a), ethyl gallate (Fig. 7b), chebulic acid (Fig. 7c), chebulagic acid (Fig. 3e), corilagin (Fig. 7d), mannitol and ascorbic acid (Fig. 1a) (Grover and Bala 1992). As gallic acid has demonstrated the ability to induce phosphorylation of c-Jun N-terminal protein kinase and the downregulation of Bcl-2 in PC12 cells, it was initially believed that gallic acid may be responsible for these activities (Chang and Lin 2012). However, the same study demonstrated that pure gallic acid alone does not protect PC12 cells against H₂O₂-induced cell death. Instead, it has been postulated that the neuroprotective and cell proliferative activities of *T. chebula* extracts may be due to the \bullet OH and H₂O₂ scavenging activities of the tannin and phenolic mixture in the extract. Thus, the synergistic action of multiple components may be responsible for the observed activities.

Schistosomiasis (bilharziosis) is a disease caused by parasitic trematodes. Whilst schistosomiasis has a low mortality rate, it is often a chronic illness that may result in damage to internal organs and may retard physical and mental development in children. Unfortunately, it appears that the schistosome parasite is developing a resistance to praziquantel (the current gold standard drug), so further treatments and controls are required (Chitrsulo et al. 2000). A recent study has examined the molluscicidal action of *T. catappa* against the snail hosts of schistosomiasis and reported good molluscicidal activity (Adentunji and Salawu 2010). As an earlier ethnobotanical study has also reported

T. catappa extracts to have antihelminthic activity (Corner 1997), there is the possibility of a multifaceted approach to schistosomiasis control using *T. catappa* extracts, although this has yet to be verified.

Terminalia catappa extracts also have potential in the treatment of sickle cell disease (SCD). This disease is characterised by haemolytic anaemia due to erythrocyte polymerisation and haemolysis under hypoxic conditions. The cells become rigid and sickle shaped with an increased tendency to adhere to the endothelium, resulting in vaso-occlusion. As erythrocytes are more prone to haemolysis in SCD, sufferers are also often anaemic (Aliyu et al. 2008). *T. catappa* has long been used to treat SCD in Western African traditional medicine and has been shown to inhibit haemolysis (Mgbemene et al. 1999) and to stimulate erythrocyte production (Aimola et al. 2011), validating their usage as a traditional medicine. The active extract was shown to contain alkaloids and anthraquinones and the authors postulated that these may be acting synergistically to elicit their haematopoietic and erythropoietic effects. Thus, *T. catappa* extracts have potential in alleviating some of the symptoms of SCD.

Conclusions

This survey of the traditional medicinal and pharmacognosy literature has highlighted the therapeutic importance of this useful genus of plants. Various *Terminalia* species have been widely used in such diverse traditional medicine systems as Ayurveda, Siddha, Traditional Chinese Medicine (TCM), Western, Southern and Central African medicinal systems, multiple traditional systems from the tropical regions of the Americas, as well as various Australian Aboriginal medicinal systems.

Despite this history of traditional usage, until recently, rigorous scientific research has been confined to the study of only a few species. Of these, the Ayurvedic medicinal plants (especially *T. arjuna*, *T. bellerica*, *T. chebula* and *T. catappa*) have received the most attention. In these species, multiple therapeutic bioactivities have been documented. These species have been reported to have good antioxidant, anticancer, antidiabetic, antiseptic, cardiogenic and anti-inflammatory effects as well as assisting in wound healing. In some cases, the active phytochemicals have been established, although for many medicinal properties the active principles have been only partially characterised. 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. Much work is still required to fully understand the phytochemistry of the

genus *Terminalia*. Even for the more extensively studied species, much work is needed to fully determine the extent of the medicinal properties and the phytochemistry. Furthermore, few of these studies have provided substantial mechanistic detail to explain how the active principles achieve their medicinal effects.

The scope for future pharmacognostic studies is perhaps broader for many of the *Terminalia* species not traditionally used in Ayurveda due to the lack of even the most basic studies into their therapeutic potential and phytochemistry. Some interesting bioactivity studies have begun to be reported, examining African and South American *Terminalia* species in recent years. However, most of the tested species have still only been tested for 1 or 2 medicinal properties and these studies are usually driven purely by an ethnobotanical history of use. Given the taxonomic similarities between species of this genus, it is evident that more bioactivity studies are needed, and where a therapeutic bioactivity is detected, phytochemical and mechanistic studies are also required. Similarly, Australian *Terminalia* species have been poorly studied despite an oral history of medicinal usage. Since several recent studies have reported on the extremely high antioxidant content of *T. ferdinandiana*, there has been recent interest in this species. However, these studies have generally only focussed on bioactivity screening or phytochemical screening, without combining these disciplines for a bioactivity driven approach to characterising the active components and mechanisms. Whilst *T. ferdinandiana* is receiving recent attention, the other Australian species remain largely unstudied and substantial work is needed in this area.

At present, the *Terminalia* species tested are generally only those with a history of use in traditional medicinal systems. Yet, the similarity between many species indicates that testing all species for bioactivities evident in the more established species is warranted. Much investigation is required for a more complete understanding, not only of the potential of plants from this genus, but also to understand their phytochemistry. Such an approach will definitely lead to the establishment of useful nutraceuticals, but may also result in the development of further pharmaceuticals.

References

- Adentunji VO, Salawu OT (2010) Efficacy of ethanolic leaf extracts of *Carica papaya* and *Terminalia catappa* as molluscicides against the snail intermediate hosts of schistosomiasis. *J Med Plants Res* 4(22):2348–2352
- Agarwal S, Kulkarni GT, Sharma VN (2011) A comparative study on the antioxidant activity of methanolic extracts of *Terminalia paniculata* and *Madhuca longifolia*. *Free Radic Antioxid* 1(4):62–68
- Agbedahunsi JM, Anao I, Adewunmi CO, Croft SL (2006) Trypanocidal properties of *Terminalia ivorensis* A. Chev (Combretaceae). *Afr J Complement Altern Med* 3(2):51–56
- Ahmed SM, Swamy BM, Gopkumar V, Dhanapal R, Chandrashekara VM (2005) Anti-diabetic activity of *Terminalia catappa* Linn. Leaf extracts in Alloxan-induced diabetic rats. *Iran J Pharmacol Therapeutics* 4(1):36–39
- Ahsan H, Hadi SM (1998) Strand scission in DNA induced by curcumin in the presence of Cu(II). *Cancer Lett* 124:23–30
- Aimola A, Inuwa HM, Mamman AI, Habila N, Agbaji AS, Omoniwa D (2011) *Terminalia catappa* extract enhances erythropoiesis in adult Balb C mice. *J Mol Biol Res* 1(1):40–46
- Akinyemi KO, Oladapo O, Okwara CE, Ibe CC, Fasure KA (2005) Screening of crude extracts of six medicinal plants used in South-West Nigerian unorthodox medicine for anti-methicillin resistant *Staphylococcus aureus* activity. *BMC Complement Altern Med* 5:6
- Alayande LB, Alayande MO, Mohammed AA, Adamu T, Abubakar U, Daneji A, Ajagbonna OP (2011) Efficacy of *Terminalia avicennoides* and its combination with diminazene aceturate (Berenil®) in rats experimentally infected with *Trypanosoma brucei brucei*. *Sokoto J Vet Sci* 9(2):11–15
- Ali A, Kaur G, Hayat K, Ali M, Ather M (2003a) A novel naphthanolglycoside from *Terminalia arjuna* with antioxidant and nitric oxide inhibitory activities. *Pharmacazie* 58:932–934
- Ali A, Kaur G, Hamid H, Abdulla T, Ali M, Niwa M, Alam MS (2003b) Terminoside A, a new triterpene glycoside from the bark of *Terminalia arjuna* inhibits nitric oxide production in murine macrophages. *J Asian Nat Prod Res* 5:137–142
- Aliyu ZY, Gordeuk V, Sachdev V, Babadoko A, Mamman AI, Akpanpe P, Attah E, Suleiman Y, Aliyu N, Yusuf J et al (2008) Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol* 83:485–490
- Anam K, Suganda AG, Sukandar EY, Broto L, Kardono S (2010) Antibacterial effect of component of *Terminalia muelleri* Benth against *Staphylococcus aureus*. *Int J Pharmacol* 6(4):369–374
- Aneja KR, Joshi R (2009) Evaluation of antimicrobial properties of fruit extracts of *Terminalia chebula* against dental caries pathogens. *Jundishapur J Microbiol* 2(3):105–111
- Aneja KR, Sharma C, Joshi R (2012) Antimicrobial activity of *Terminalia arjuna* Wight & Arn: an ethnomedicinal plant against pathogens causing ear infection. *Braz J Otorhinolaryngol* 78(1):68–74
- Anjaneyulu ASR, Prasad AVR (1982a) Chemical examination of roots of *Terminalia arjuna* (Roxb.) Wight & Arnot. Part I. Characterisation of two new triterpenoid glycosides. *Indian J Chem* 21B:530–533
- Anjaneyulu ASR, Prasad AVR (1982b) Chemical examination of roots of *Terminalia arjuna*—the structure of arjunoside III and arjunoside IV, two new triterpenoid glycosides. *Phytochemistry* 21:2057–2060
- Anjaneyulu ASR, Prasad AVR (1983) Structure of terminic acid, a dihydroxy triterpene carboxylic acid from *Terminalia arjuna*. *Phytochemistry* 22:993–998
- Araya-Maturana R, Heredia-Moya J, Donoso-Taouda O, Vera M, Toledo Hernández J, Pavani M, Pessoa-Mahana H, Weiss-López B, Ferreira J (2008) Effects of simple and angular chromones on tumor cell respiration. *Nat Prod Commun* 3(4):519–525
- Astaneie F, Afshari M, Mojtahedi A, Mostafalou S, Zamani MJ, Larjani B, Abdollah M (2005) Total antioxidant capacity and levels of epidermal growth factor and nitric oxide in blood and saliva of insulin-dependent diabetic patients. *Arch Med Res* 36(4):376–381

- Awad AB, Toczek J, Carol CS, Fink S (2004) Phytosterols decrease prostaglandin release in cultured P388D₁/MAB macrophages. *Prostaglandins Leukot Essent Fatty Acids* 70(6):511–520
- Baker A, Payne CM, Briehl MM, Powis G (1997) Thioredoxin, a gene found overexpressed in human cancer, inhibits apoptosis in vitro and in vivo. *Cancer Res* 57:5162–5167
- Baliga MS (2010) Triphala, Ayurvedic formulation for treating and preventing cancer: a review. *J Altern Complement Med* 16(12):1301–1308
- Balleisen L, Gay S, Marx R, Kuhn K (1975) Comparative investigation of the influence of human and bovine collagen types I, II and III on the aggregation of human platelets. *Wein Klin Wochenschr* 53:903–905
- Betterle C, Zanette F, Pedini B, Presotto F, Rapp LB, Monciotti CM, Rigon F (1984) Clinical and subclinical organ-specific autoimmune manifestations in type I (insulin-dependent) diabetic patients and their first-degree relatives. *Diabetologia* 26:431–436
- Bhatia J, Bhattacharya SK, Mahajan P, Dwivedi S (1998) Effect of *Terminalia arjuna* on coronary flow—an experimental study (Abstract). *Indian J Pharmacol* 30:118
- Biswas M, Biswas K, Karan TK, Bhattacharya S, Ghosh AK, Haldar PK (2011) Evaluation of analgesic and anti-inflammatory activities of *Terminalia arjuna* leaf. *J Phytol* 3(1):33–38
- Brown NS, Bicknell R (2001) Hypoxia and oxidative stress in breast cancer. Oxidative stress: its effects on the growth, metastatic potential and response to therapy of breast cancer. *Breast Cancer Res* 3:323–327
- Carluccio MA, Sicuella L, Ancora MA, Massaro M, Scoditti E, Storelli C, Visioli F, De Caterina DAR (2003) Olive oil and red wine antioxidant polyphenols inhibit endothelial activation: antiatherogenic properties of Mediterranean diet phytochemicals. *Arterioscler Thrombos Vasc Biol* 23:622–629
- Chang CL, Lin CS (2012) Phytochemical composition, antioxidant activity, and neuroprotective effect of *Terminalia chebula* Retzius extracts. *Evid Based Complement Altern Med* article ID 125247
- Chattopadhyay RR, Battacharyya SK (2007) Plant review: terminalia chebula: an update. *Pharmacogn Rev* 1(1):151–156
- Chaudhari M, Mengi S (2006) Evaluation of phytoconstituents of *Terminalia arjuna* for wound healing activity in rats. *Phytother Res* 20:799–805
- Cheng HY, Lin CC, Lin TC (2002) Antiherpes simplex virus type 2 activity of casuarinin from the bark of *Terminalia arjuna* Linn. *Antivir Res* 55:447–455
- Cherikoff V, Kowalski G (2008) Superfoods for Superhealth. Discover the Wonders of Australian Native Fruits. [Last cited on 2010 Oct 07]. Available from: <http://www.kakadujuice.com/clientinc/upload/Promotional.Tools/SuperFoods%20Excerpt.pdf>
- Chitsulo L, Engels D, Montresor A, Savioli L (2000) The global status of schistosomiasis and its control. *Acta Trop* 77:41–51
- Choi S, Chung MH (2003) A review on the relationship between Aloe vera components and their biological effects. *Semin Integr Med* 1(1):53–62
- Choi SW, Son BW, Son YI, Park YI, Lee SK, Chung MH (2001) The wound-healing effect of a glycoprotein fraction isolated from aloe vera. *Br J Dermatol* 145(4):535–554
- Chopra RN, Nayar SL, Chopra IC (1956) Glossary of Indian medicinal plants. CSIR, New Delhi
- Cock IE (2011a) Problems of reproducibility and efficacy of bioassays using crude extracts, with reference to Aloe vera. *Pharmacogn Commun* 1(1):52–62
- Cock IE (2011) Medicinal and aromatic plants—Australia, In: *Ethnopharmacology section, Biological, Physiological and Health Sciences, Encyclopedia of Life Support Systems (EOLSS)*; Developed under the Auspices of the UNESCO, EOLSS Publishers, Oxford, UK. (<http://www.eolss.net>)
- Cock IE (2014) The early stages of rheumatoid arthritis: new targets for the development of combinational therapies. *OA Arthritis* 2(1):5
- Cock IE, Mohanty S (2011) Evaluation of the antibacterial activity and toxicity of *Terminalia ferdinandia* fruit extracts. *Pharmacogn J* 3(20):72–79
- Cock IE, van Vuuren SF (2014) Anti-Proteus activity of some South African medicinal plants: their potential for the prevention of rheumatoid arthritis. *Inflammopharmacology* 22:23–36. doi:10.1007/s10787-013-0179-3
- Cock IE, van Vuuren SF (2015a) A comparison of the antimicrobial activity and toxicity of six Combretum and two Terminalia species from Southern Africa. *Pharmacogn Mag* 11(41):208–218. doi:10.4103/0973-1296.149740
- Cock IE, van Vuuren SF (2015b) South African food and medicinal plant extracts as potential antimicrobial food agents. *J Food Sci Technol*. doi:10.1007/s13197-015-1806-3
- Cock IE, van Vuuren SF (2015c) The potential of selected South African plants with anti-Klebsiella activity for the treatment and prevention of ankylosing spondylitis. *Inflammopharmacology* 23:21–35. doi:10.1007/s10787-014-0222-z
- Comer EJH (1997) *Wayside Trees of Malaya*, 4th edn. Malayan Nature Society 1: 217
- Courtney R, Sirdaarta J, Matthews B, Cock IE (2015) Tannin components and inhibitory activity of Kakadu plum leaf extracts against microbial triggers of autoimmune inflammatory diseases. *Pharmacogn J* 7(1):18–31. doi:10.5530/pj.2015.7.2
- Crouch R, Kimsey G, Priest DG, Sarda A, Buse MG (1978) Effect of streptozotocin on erythrocyte and retinal superoxide dismutase. *Diabetologia* 15:53–57
- Cunningham AB, Garnett S, Gorman J, Courtenay K, Boehme D (2009) Eco-enterprises and *Terminalia ferdinandiana*: “Best Laid Plans” and Australian Policy Lessons. *Econ Bot* 63:16–28
- Das B (1991) *Materia medica of ayurveda*. Jain Publishers, New Delhi, p 8
- Das ND, Jung KH, Park JH, Choi MR, Lee HT, Kim MS, Lee SR, Chai YG (2012) Proteomic analysis of *Terminalia chebula* extract-dependent changes in human lymphoblastic T cell protein expression. *J Med Food* 15(7):651–657
- Davi G, Ciabattoni G, Consoli A, Mezzetti A, Falco A, Santarone S, Pennese E, Vitacolonna E, Bucciarelli T, Constantini F, Capani F, Patrono C (1999) In vivo formation of 8-iso-prostaglandin F_{2a} and platelet activation in diabetes mellitus: effects of improved metabolic control and vitamin E supplementation. *Circulation* 99:224–229
- Davis RH, Kabbani JM, Maro NP (1987) Aloe vera and wound healing. *J Am Podiatr Med Assoc* 77:165–169
- Davis W, Ze'ev Ronai JR, Tew KD (2001) Cellular thiols and reactive oxygen species in drug-induced apoptosis. *J Pharmacol Exp Ther* 296(1):1–5
- Dhetchuvi M, Lejoly J (1990) Contribution a' la connaissance ds plantes me'dicinales du Nord- Est du Zaire. *Mitt Inst Allg Bot Hamburg* 23b:991–1006
- Dongmo AB, Beppe, JG, Nole T, Kamanyi A (2006) Analgesic activities of the stem bark extract of *Terminalia superba* Engl. Et Diels (Combreaeaceae). *Pharmacologyonline* 2:171–177
- Dwivedi S (2007) *Terminalia arjuna* Wright & Arn.—a useful drug for cardiovascular disorders. *J Ethnopharmacol* 114:114–129
- Dwivedi S, Udupa N (1989) *Terminalia arjuna*: pharmacognosy, phytochemistry, pharmacology and clinical use. A review. *Fitoterapia* 60:413–420
- Dwivedi S, Chansouria JPN, Somani PN, Udupa KN (1987) Influence of certain indigenous drugs on the PGE like activity in the ischaemic rabbit aorta. *Indian Drugs* 2:378–382
- Eesha BR, Mohanbabu AV, Meena KK, Sarath B, Vijay M, Lalit M, Rajput R (2011) Hepatoprotective activity of Terminalia

- paniculata against paracetamol induced hepatocellular damage in Wistar albino rats. *Asian Pac J Trop Med* 4:446–469
- Emanuel R, Farber JC (1988) Repair, regeneration and fibrosis. In: Pathology. JB Lippincott Company, Philadelphia pp 77–89
- Freemerman AJ, Powis G (2000) A redox-inactive thioredoxin reduces growth and enhances apoptosis in WEHI7.2 cells. *Biochem Biophys Res Commun* 274:136–141
- Fuhrman B, Aviram M (2001) Antiatherogenicity of nutritional compounds. *Investig Drug J* 4:82–92
- Fyhrquist P, Mwasumbi L, Haeggstrom CA, Vuorela H, Hiltunen R, Vuorela P (2002) Ethnobotanical and antimicrobial investigation on some species of *Terminalia* and *Combretum* (Combretaceae) growing in Tanzania. *J Ethnopharmacol* 79:169–177
- Gauthaman K, Maulik M, Kumari R, Manchanda SC, Dinda AK, Maulik SK (2001) Effect of chronic treatment with bark of *Terminalia arjuna*: a study on the isolated ischemic-reperfused rat heart. *J Ethnopharmacol* 75:197–201
- Gill LS, Akinwunmi C (1986) Nigerian medicine practice and beliefs of the Ondo people. *J Ethnopharmacol* 18:257–266
- Gomes A, Neuwirth O, Freitas M, Couto D, Ribeiro D, Figueiredo AGPR, Silva AMS, Seixas RSGR, Pinto DCGA, Tomé AC, Cavaleiro JAS, Fernandes E, Lima JLFC (2009) Synthesis and antioxidant properties of new chromone derivatives. *Bioorganic Med Chem* 17(20):7218–7226
- Grover IS, Bala S (1992) Antimutagenic activity of *T. chebula* (myroblan) in *Salmonella typhimurium*. *Indian J Exp Biol* 30(4):339–341
- Halliwell B (1996) Vitamin C: antioxidant or pro-oxidant in vivo? *Free Radical Res* 25:439–454
- Hamilos DL, Zelarney P, Mascali JJ (1989) Lymphocyte proliferation in glutathione-depleted lymphocytes: direct relationship between glutathione availability and the proliferative response. *Immunopharmacology* 18:223–235
- Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* 100(1):57–70
- Hazra B, Sarkar R, Biswas S, Mandal N (2010) Comparative study of the antioxidant and reactive oxygen species scavenging properties in the extracts of the fruits of *Terminalia chebula*, *Terminalia bellerica* and *Emblca officinalis*. *BMC Complement Altern Med* 10:20
- Herbert V, Shaw S, Jayatileke E (1996) Vitamin C driven free radicals generation from iron. *J Nutr* 126:1213–1220
- Hertog MG, Bueno-de-Mesquita HB, Fehily AM, Sweetnam PM, Elwood PC, Kromhout D (1996) Fruit and vegetable consumption and cancer mortality in the caerphilly study. *Cancer Epidemiol Biomark Prev* 5:673–677
- Ishihara M, Sakagami H (2003) Application of semiempirical method to estimate the cytotoxic activity of gallic acid and its related compounds. *Anticancer Res* 23:2549–2552
- Jain S, Yadav PP, Gill V, Vasudeva N, Singla N (2009) *Terminalia arjuna* a sacred medicinal plant; phytochemical and pharmacological profile. *Phytochem Rev* 8(2):491–502
- Jaiwal BV, Shaikh FK, Waghire HB, Sarwade BP (2012) Comparative anti-oxidative potential of barks phenolics of genus *Terminalia*. *Int J Sci Pharma Educ Res* 1(4):6–10
- Joel LS (1995) The dual roles of nutrients as antioxidants and pro-oxidants: Their effects of tumor cell growth. In: Proceeding of the “Prooxidant Effects of Antioxidant Vitamins” experimental biology meeting, Atlanta, GA, Edited by Herbert V, American Society of Nutrition; Bethesda, MD pp 1221–1226
- Johnson PD (2003) Acerola (*Malpighia glabra* L., *M. punicifolia* L., *M. emarginata* D.C.): agriculture, production and nutrition. *World Rev Nutr Diet* 91:67–75
- Jueschke H, Knight TR (2003) The role of oxidant stress and species in acetaminophen hepatotoxicity. *Toxicol Lett* 144:279–288
- Kamboj VP (2000) Herbal medicine. *Curr Sci* 78:35–39
- Kankri E, Vaali K, Knowles RG, Lahde M, Korppela R, Vapaatalo H, Moilanen E (2001) Suppression of acute experimental colitis by a highly selective inducible nitric-oxide synthase inhibitor, *N*-[3-(aminomethyl)benzyl] acetamidine. *J Pharmacol Exp Ther* 298:1128–1132
- Kannan M, Dasari A, Karthikeyan M, Ashokkumar J, Rajasekar S (2012) Effect of *Terminalia bellerica* fruit Roxb on Alloxan induced diabetic related atherosclerosis on Wistar albino rats. *Int J Phytopharmacol* 3(1):5–9
- Karalliedde L, Gawarammana I (2008) Traditional Herbal Medicines. A Guide To Their Safe Use In: Shaw D (ed) Hammersmith Press Ltd London
- Kasabri V, Flatt PR, Abdel-Wahab YHA (2010) *Terminalia bellerica* stimulates the secretion and action of insulin and inhibits starch digestion and protein glycation in vitro. *Br J Nutr* 103:212–217
- Kaur S, Michael H, Arora S, Härkönen PL, Kumar S (2005) The in vitro cytotoxic and apoptotic activity of Triphala: an Indian herbal drug. *J Ethnopharmacol* 97:15–20
- Khanna AK, Chander C, Kapoor NK (1996) *Terminalia arjuna*: an Ayurvedic cardiotoxic regulates lipid metabolism in hyperlipidemic rats. *Phytother Res* 10:663–665
- Kim HS, Lee JH, Kim IK (1996) Intracellular glutathione level modulates the induction of apoptosis by delta 12-prostaglandin J2. *Prostaglandins* 51:413–425
- Klein R (1995) Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258–268
- Konczak I, Zabaras D, Dunstan M, Aguas (2010) Antioxidant capacity and hydrophilic phytochemicals in commercially grown Australian fruits. *Food Chem* 123:1048–1054
- Kumar GPS, Arulselvan P, Kumar DS, Subramanian SP (2006) Anti-diabetic activity of fruits of *Terminalia chebula* streptozotocin induced diabetic rats. *J Health Sci* 52(3):283–291
- Kuo PL, Hsu YL, Lin TC, Chang JK, Lin CC (2005) Induction of cell cycle arrest and apoptosis in human non-small cell lung cancer A549 cells by casuarinin from the bark of *Terminalia arjuna* Linn. *Anticancer Drugs* 16(4):409–415
- Lassak EV, McCarthy T (2006) Australian medicinal plants. New Holland Publishers, Australia
- Lastra CA, Villegas I (2007) Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. *Biochem Soc Trans* 35:1156–1160
- Lee KY, Park JH, Chung MH, Park YI, Kim KW, Lee YJ, Lee SK (1997) Aloesin up-regulates cyclin E/CDK2 kinase activity via inducing the protein levels of cyclin E, CDK2, and CDC25A in SK-HEP-1 cells. *IUBMB Life* 41(2):285–292
- Li K, Diao Y, Zhang H, Wang S, Zhang Z, Yu B, Huang S, Yang H (2011) Tannin extracts from immature fruits of *Terminalia chebula* Fructus Retz. Promote cutaneous wound healing in rats. *BMN Compliment Altern Med* 11:86
- Lin TC, Chien SC, Chen HF, Hsu FL (2001) Tannins and related compounds from Combretaceae plants. *Chin Pharm J* 52:1–26
- Lin SZ, Tong HF, Chen KG, Jing H, Yang X, Zheng SS (2010) Effect of emodin in suppressing acute rejection following liver allograft transplantation in rats. *Chin J Integr Med* 16(2):151–156
- Lin LT, Chen TY, Chung CY, Noyce RS, Grindley TB, McCormick C, Lin TC, Wang GH, Lin CC, Richardson CD (2011) Hydrolyzable tannins (chebulagic acid and punicalagin) target viral glycoprotein-glycosaminoglycan interactions to inhibit herpes simplex virus 1 entry and cell-to-cell spread. *J Virol* 85(9):4386–4398
- Losso JN, Bansode RR, Trappey A, Bawadi HA, Truax R (2004) In vitro anti-proliferative activities of ellagic acid. *J Nutr Biochem* 15:672–678
- Macpherson G (1992) Inflammation. Black's Medical Dictionary; A and C Black, London, UK
- Makino Y, Yoshikawa N, Okamoto K, Hirota K, Yodoi J, Makino I, Tanaka H (1999) Direct association with thioredoxin allows

- redox regulation of glucocorticoid receptor function. *J Biol Chem* 274:3182–3188
- Manna P, Sinha M, Sil PC (2006) Aqueous extract of *Terminalia arjuna* prevents carbon tetrachloride induced hepatic and renal disorders. *BMC Complement Altern Med* 6:33
- Maregesi S, Van Miert S, Pannecouque C, Feiz Haddad MH, Hermans N, Wright CW, Vlietinck AJ, Apers S, Pieters L (2010) Screening of Tanzanian medicinal plants against *Plasmodium falciparum* and human immunodeficiency virus. *Planta Med* 76:195–201
- Martikainen JA, Ottelin AM, Kiviniemi V, Gylling H (2007) Plant stanol esters are potentially cost-effective in the prevention of coronary heart disease in men: bayesian modelling approach. *Eur J Cardiovasc Prev Rehabil* 14:265–272
- Martino VS, López P, Martínez Irujo JJ, Sanromán M, Cuevas MT, Santiago E, Lasarte JJ, Font M, Coussio JD, Mongue A (2002) Inhibitory effect against polymerase and ribonuclease activities of HIV-reverse transcriptase of the aqueous leaf extract of *Terminalia triflora*. *Phytother Res* 16:778–780
- Masoka P, Eloff JN (2005) The diversity of antifungal compounds of six South African *Terminalia* species (Combretaceae) determined by bioautography. *Afr J Biotechnol* 4(12):1425–1431
- Masoka P, Eloff JN (2007) Screening of twenty-four South African *Combretum* and six *Terminalia* species (Combretaceae) for antioxidant activities. *Afr J Tradit Complement Alter Med* 4(2):231–239
- Mbwambo ZH, Erasto P, Nondo RO, Innocent E, Kidukuli AW (2011) Antibacterial and cytotoxic activities of *Terminalia stenostachya* and *Terminalia spinosa*. *Tanzania J Health Res* 13(2):1–8
- McGaw LJ, Rabe T, Sparg SG, Jäger AK, Eloff JN, van Staden J (2001) An investigation on the biological activity of *Combretum* species. *J Ethnopharmacol* 75:45–50
- Mety SS, Mathad P (2011) Antioxidative and free radical scavenging activities of *Terminalia* species. *Int J Biotechnol* 2(5):119–127
- Mgbemene CN, Ohiri FC (1999) Anti-sickling potential of *Terminalia catappa* leaf extract. *Pharm Biol* 37(2):152–154
- Middleton E, Kandaswami C, Theorharides TC (2000) The effect of plant flavonoids on mammalian cells: inflammation, heart disease and cancer. *Pharmacol Rev* 52:673–751
- Miller JB, James KW, Maggiore PM (1993) Tables of composition of Australian Aboriginal foods. Aboriginal Studies Press, p 256
- Mochizuki M, Hasegawa N (2007) Anti-inflammatory effect of extract of *Terminalia sericea* roots in an experimental model of colitis. *J Health Sci* 53(3):329–331
- Mohanty S, Cock IE (2012) The chemotherapeutic potential of *Terminalia ferdinandiana*: phytochemistry and bioactivity. *Pharmacogn Rev* 6(11):29–36
- Momo CEN, Ngwa AF, Dongmo IF, Oben JE (2009) Antioxidant properties and α -amylase inhibition of *Terminalia superba*, *Albizia* sp., *Cola nitida*, *Cola odorata* and *Harungana madagascarensis* used in the management of diabetes in Cameroon. *J Health Sci* 55(5):732–738
- Moon EJ, Lee YM, Lee OH, Lee MJ, Lee SK, Chung MH, Park YI, Sung CK, Choi JS, Kim KW (1999) A novel angiogenic factor derived from Aloe vera gel: b-sitosterol, a plant sterol. *Angiogenesis* 3:117–123
- Moshi MJ, Mbwambo ZH (2005) Some pharmacological properties of extracts of *Terminalia sericea* roots. *J Ethnopharmacol* 97:43–47
- Moskaug JO, Carlsen H, Myhrstad MC, Blomhoff R (2005) Polyphenols and glutathione synthesis regulation. *Am J Clin Nutr* 81:277–835
- Mudi SY, Muhammad A (2009) Antimalaria activity of ethanolic extracts of leaves of *Terminalia catappa* L. Combretaceae (Indian almond). *Bayero. J Pure Appl Sci* 2(1):14–18
- Nadkarni AK (1976) *Terminalia chebula*. In: Nadkarni Dr. KM Indian Materia Medica, 3rd edn, Bombay, Popular Prakashan Pvt. Ltd.; 1202-11
- Nagappa AN, Thakurdesai PA, Rao NV, Singh J (2003) Antidiabetic activity of *Terminalia catappa* Linn. fruits. *J Ethnopharmacol* 88:45–50
- Nair S, Nagar R (1997) Antioxidant flavonoids in common Indian foods. *South Asian J Prev Cardiol* 1:33–35
- Nair S, Nair R, Gupta R (1996) Dietary antioxidant, phenolics and flavonoids in coronary heart disease (Abstract). *Indian Heart J* 48:545
- Nammi S, Gudavalli R, Ravindra Babu BS, Lodagala DS, Boini KM (2003) Possible mechanisms of hypotension produced 70 % alcoholic extract of *Terminalia arjuna* (L.) in anaesthetized dogs. *BMC Complement Altern Med* 3:5
- Netzel M, Netzel G, Tian Q, Schwartz S, Konczak I (2007) Native Australian fruits—a novel source of antioxidants for food. *Innov Food Sci Emerg Technol* 8:339–346
- Newman DJ, Cragg GM (2007) Natural products as sources of new drugs over the last 25 years. *J Nat Prod* 70(3):461–477
- Njomem GBSN, Kamgang R, Soua PRN, Oyono JLE, Njikam N (2009) Protective effect of methanol-methylene chloride extract of *Terminalia glaucescens* leaves on streptozotocin-induced diabetes in mice. *Trop J Pharm Res* 8(1):19–26
- Nkoble NK (2009) Antidiabetic activity of pentacyclic triterpenes and flavonoids isolated from stem bark of *Terminalia sericea* Burch. Ex DC. Masters thesis; dept Plant Science: University of Pretoria
- Ohno Y, Fukuda K, Takemura G, Toyota M, Watanabe M, Yasuda N et al (1999) Induction of apoptosis by gallic acid in lung cancer cells. *Anticancer Drugs* 10:845–851
- Okamoto K, Tanaka H, Ogawa H, Makino Y, Eguchi H, Hayashi S, Yoshikawa N, Poellinger L, Umesono K, Makino I (1999) Redox-dependent regulation of nuclear import of the glucocorticoid receptor. *J Biol Chem* 274:10363–10371
- Peluso MR (2006) Flavonoids attenuate cardiovascular disease, inhibit phosphodiesterase and modulate lipid homeostasis in adipose tissue and liver. *Exp Biol Med* (Maywood) 231:1287–1299
- Penckofer S, Schwertz D, Florczak K (2002) Oxidative stress and cardiovascular disease in type 2 diabetes: the role of antioxidants and prooxidants. *J Cardiovasc Nurs* 16(2):68–85
- Pettit GR, Hoard MS, Doubek DL, Schmidt JM, Pettit RK, Tackett LP, Chapuis JC (1996) Antineoplastic agents 338. The cancer cell growth inhibitory constituents of *Terminalia arjuna* (Combretaceae). *J Ethnopharmacol* 53:57–63
- Pinmai K, Chunlaratthanabhorn S, Ngamkitdechakul C, Soonthornchareon N, Hahnvajanawong C (2008) Synergistic growth inhibitory effects of *Phyllanthus emblica* and *Terminalia bellerica* extracts with conventional cytotoxic agents: doxorubicin and cisplatin against human hepatocellular carcinoma and lung cancer cells. *World J Gastroenterol* 14(10):1491–1497
- Pinmai K, Hiriote W, Soonthornchareonnon N, Jongsakul K, Sireeratawong S, Tor-Udom S (2010) In vitro and in vivo antiplasmodial activity and cytotoxicity of water extracts of *Phyllanthus emblica*, *Terminalia chebula* and *Terminalia bellerica*. *J Med Assoc Thai* 93(Suppl 7):S120–S126
- Planes de Bancharo E, Souto J (1969) Actividad antivirica de algunas plantas indigenas. *Rev Invest Agropec (INTA Buenos Aires)* 6:155–171
- Potter JD (1997) Cancer prevention: epidemiology and experiment. *Cancer Lett* 114:7–9
- Pyke DA (1977) Genetics of diabetes. *J Clin Endocrinol Metab* 6:285–303
- Ragavan B, Kumari K (2006) Effect of *Terminalia arjuna* stem bark extract on antioxidant status in liver and kidney of Alloxan diabetic rats. *Indian J Physiol Pharmacol* 50(2):133–142

- Rahimi R, Nikfar S, Larijani B, Abdollahi M (2005) A review on the role of antioxidants in the management of diabetes and its complications. *Biomed Pharmacother* 59:365–373
- Rahman A, Shahabuddin M, Hadi SM, Parish J (1990) Complexes involving quercetin, DNA and Cu(II). *Carcinogenesis* 11: 2001–2003
- Rahman AU, Zareen S, Choudhary MI, Akhtar MN, Shujaat S, Ngounou FN (2005) Some chemical constituents of *Terminalia glaucescens* and their enzyme inhibition activity. *Zeitschrift für Naturforschung B, Chem Sci* 60(2):347–350
- Ramachandran S, Rajasekaran A, Manisenthikumar KT (2012) Investigation of hypoglycaemic, hydrolipidemic and antioxidant activities of aqueous extract of *Terminalia paniculata* bark in diabetic rats. *Asian Pac J Trop Biomed* 2:262–268
- Rane MM, Mengi SA (2003) Comparative effect of oral administration and topical application of alcoholic extract of *Terminalia arjuna* on experimental wounds in rats. *Fitoterapia* 74:553–558
- Rao NK, Nammi S (2006) Antidiabetic and renoprotective effects of the chloroform extract of *Terminalia chebula* Retz. Seeds in streptozotocin-induced diabetic rats. *BMC Complement Altern Med* 6:17
- Rao BK, Sudarshan PR, Rajasekhar MD, Nagaraju N, Rao CA (2003) Antidiabetic activity of *Terminalia pallida* fruit in Alloxan induced diabetic rats. *J Ethnopharmacol* 85:169–172
- Rayan P, Matthews B, McDonnell PA, Cock IE (2015) *Terminalia ferdinandiana* extracts as inhibitors of *Giardia duodenalis* proliferation: a new treatment for giardiasis. *Parasitol Res* 114:2611–2620. doi:10.1007/s00436-015-4465-4
- Reddy DB, Reddanna P (2009) Chebulagic acid (CA) attenuates LPS-induced inflammation by suppressing NK- κ B and MAPK activation in RAW 264.7 macrophages. *Biochem Biophys Res Commun* 381:112–117
- Reddy DB, Reddy TC, Jyotsna G et al (2009) Chebulagic acid, a COX-LOX dual inhibitor isolated from the fruits of *Terminalia chebula* Retz., induces apoptosis in COLO-205 cell line. *J Ethnopharmacol* 124:506–512
- Rice-Evans C, Miller N (1997) Paganga. Antioxidant properties of phenolic compound. *Trends Plant Sci* 2:152–159
- Rivas M, Distefano A (1973) Estudio de la acción antiviral de *Terminalia triflora*. *Rev Asoc Argent Microbiol* 5:55–56
- Rivas M, Distefano A, Graziano MN (1971) Congreso Latinoamericano de Microbiología. Punta del Este (Abstract 21)
- Robbins MJ, Sharp RA, Slonim AE, Burr IM (1980) Protection against streptozotocin-induced diabetes by superoxide dismutase. *Diabetologia* 18:55–58
- Robertson RP, Chen M (1977) A role for prostaglandin E in defective insulin secretion and carbohydrate intolerance in diabetes mellitus. *J Clin Invest* 60:747–753
- Rode T, Frauen M, Muller BW, Dusing HJ, Schonrock U, Mundt C, Wenck H (2003) Complex formation of sericoside with hydrophilic cyclodextrins: improvement of solubility and skin penetration in topical emulsion based formulations. *Eur J Pharm Biopharm* 55:191–198
- Ruefli AA, Davis JE, Sutton VR, Trapani JA, Smyth MJ, Johnstone RW (2001) Dissecting the apoptotic mechanisms of chemotherapeutic drugs and lymphocytes to design effective anticancer therapies. *Drug Dev Res* 52:549–557
- Ruff JC (2003) Wine and polyphenols related to platelet aggregation and atherothrombosis. *Drugs Exp Clin Res* 25:125–131
- Sabu MC, Kuttan R (2009) Antidiabetic and antioxidant activity of *Terminalia belerica* Roxb. *Indian J Exp Biol* 47(4): 270–275
- Saguna L, Singh S, Sivakumar P, Sampath P, Chandrakasan G (2002) Influence of *Terminalia chebula* on dermal wound healing in rats. *Phytother Res* 16:227–231
- Sakaguchi N, Inoue M, Isuzugawa K, Ogihara Y, Hosaka K (1999) Cell death-inducing activity by gallic acid derivatives. *Biol Pharm Bull* 22:471–475
- Samuni A, Aronovitch J, Godinger D, Chevion M, Czapski G (1983) On the cytotoxicity of vitamin C and metal ions. A site-specific Fenton mechanism. *Eur J Biochem* 137:119–124
- Sandhya T, Mishra KP (2006) Cytotoxic response of breast cancer cell lines, MCF-7 and T 47 D to triphala and its modification by antioxidants. *Cancer Lett* 238:304–313
- Sandhya T, Lathika KM, Pandey BN, Mishra KP (2006) Potential of traditional Ayurvedic formulation, triphala, as a novel anticancer drug. *Cancer Lett* 231:206–214
- Sandler S, Andersson A (1982) The partial protective effect of the hydroxyl radical scavenger dimethyl urea on streptozotocin-induced diabetes in the mouse in vivo and in vitro. *Diabetologia* 23:374–378
- Sasidharan I, Sundaresan A, Nisha VM, Kirishna MS, Raghu KG, Jayamurthy P (2012) Inhibitory effect of *Terminalia chebula* Retz. Fruit extracts on digestive enzyme related to diabetes and oxidative stress. *J Enzyme Inhib Chem; Early online*: 1–9
- Shaba P, Pandey NN, Sharma OP, Rao RJ, Singh RK (2009a) *In vitro* trypanocidal activity of comparative extraction of *Terminalia bellirica* (Combretaceae) dried fruits with solvents of different polarities against *Trypanosoma evansi*. *Int J Vet Med* 6(1)
- Shaba P, Pandey NN, Sharma OP, Rao RJ, Singh RK (2009b) Therapeutic evaluation of *Terminalia bellirica* (Combretaceae) dried fruits against *Trypanosoma evansi*. *Int J Vet Med* 7(1)
- Shaila HP, Udupa SL, Udupa AL (1998) Hypolipidemic activity of three indigenous drugs in experimentally induced atherosclerosis. *Int J Cardiol* 67:119–124
- Sharma PN, Shoeb PN, Kapil RS, Popli SP (1982) Arjunolone—a new flavone from stem bark of *Terminalia arjuna*. *Indian J Chem* 21B:263–264
- Shi Y, Sahu RP, Srivastava SK (2008) Triphala inhibits both in vitro and in vivo xenograft growth of pancreatic tumor cells by inducing apoptosis. *BMC Cancer* 8:294
- Shih CC, Wu YW, Lin WC (2002) Antihyperglycemic and antioxidant properties of *Anoectochilus Formosanus* in diabetic rats. *Clin Exp Pharmacol Physiol* 29:684–688
- Shinde SL, Junne SB, Wadje SS, Baig MMV (2009) The diversity of antibacterial compounds of *Terminalia* species (Combretaceae). *Pak J Biol Sci* 12(22):1483–1486
- Simons SS, Pratt WB (1995) Glucocorticoid receptor thiols and steroid-binding activity. *Methods Enzymol* 251:406–422
- Singh S, Farhan AS, Ahmad A, Khan NU, Hadi SM (2001a) Oxidative DNA damage by capsaicin and dihydrocapsaicin in the presence of Cu(II). *Cancer Lett* 169:139–146
- Singh R, Barden A, Mori T, Beilin L (2001b) Advanced glycation end-products: a review. *Diabetologia* 44:129–146
- Sirdaarta J, Matthews B, Cock IE (2015a) Kakadu plum fruit extracts inhibit growth of the bacterial triggers of rheumatoid arthritis: identification of stilbene and tannin components. *J Funct Foods* 17:610–620. doi:10.1016/j.jff.2015.06.019
- Sirdaarta J, Matthews B, White A, Cock IE (2015b) GC-MS and LC-MS analysis of Kakadu plum fruit extracts displaying inhibitory activity against microbial triggers of multiple sclerosis. *Pharmacogn Commun* 5(2):100–115. doi:10.5530/pc.2015.2.2
- Sivalokanathan S, Ilyaraja M, Balasubramanian MP (2006) Antioxidant activity of *Terminalia arjuna* bark extract on *N*-nitrosodiethylamine induced hepatocellular carcinoma in rats. *Mol Cell Biochem* 281:87–93
- Sumithira P, Dhivya Mangala S, Sophie AM, Padma Latha C (2012) Antiviral and antioxidant activities of two medicinal plants. *Int J Curr Sci* 256–261
- Tager H (1984) Abnormal products of human insulin gene. *Diabetes* 33:693–699

- Takahashi S, Tanaka H, Hano Y, Ito K, Nomura T, Shigenobu K (1997) Hypotensive effects in rats of hydrophyllic extract from *Terminalia arjuna* containing tannin-related compounds. *Phytother Res* 1:424–427
- Tandon S, Rastogi R, Kapoor NK (1995) Protection by abana, a herbomineral preparation, against myocardial necrosis in rats induced by isoproterenol. *Phytother Res* 9:263–266
- Tome ME, Baker AF, Powis G, Payne CM, Briehl MM (2001) Catalase-overexpressing thymocytes are resistant to glucocorticoid-induced apoptosis and exhibit increased net tumor growth. *Cancer Res* 61:2766–2773
- Tripathi VK, Singh B (1996) *Terminalia arjuna*- its present status (a review). *Orient J Chem* 12(1):1–16
- Tsuda T, Horio F, Uchida K, Aoki H, Osawa T (2003) Dietary cyaniding 3-O-b- D-glucoside-rich purple corn colour prevents obesity and ameliorates hyperglycemia in mice. *J Nutr* 133:2125–2130
- Udupa KN (1986) Scope of use of *Terminalia arjuna* in ischaemic heart disease. *Ann Natl Acad Indian Med* 1:54
- Vessby J, Basu S, Mohsen R, Berne C, Vessby B (2002) Oxidative stress and antioxidant status in type 1 diabetes mellitus. *J Intern Med* 251:69–76
- Vita JA (2005) Polyphenols and cardiovascular disease: effects on endothelial and platelet function. *Am J Clin Nutr* 81:292S–297S
- Vivancos M, Moreno JJ (2005) β -Sitosterol modulates antioxidant enzyme response in RAW 264.7 macrophages. *Free Radic Biol Med* 39(1):91–97
- Walsh G (2003) *Biopharmaceuticals: Biochemistry and Biotechnology*, 3rd edn. Wiley, Chichester
- Wilma DSC, Kavya N, Kulkarni S (2011) Evaluation of insulin sensitivity status in polycystic ovarian syndrome. *Asian Pac J Trop Disease* 1(1):67–70
- Woods B (1995) A study of the intra-specific variations and commercial potential of *Terminalia fredinandiana* (the kakadu Plum). M.Sc. thesis, Northern Territory University, Australia
- Wu CC, Lu YH, Wei BL, Yang SC, Won SJ, Lin CN (2008) Phloroglucinols with prooxidant activity from *Garcinia subelliptica*. *J Nat Prod* 71:246–250
- Yagi A, Kabash A, Okamura N, Haraguchi H, Moustafa SM, Khalifa TI (2002) 2002, Antioxidant, free radical scavenging and anti-inflammatory effects of aloesin derivatives in Aloe vera. *Planta Med* 68(11):957–960
- Yoon JW, Austin M, Onodera T, Notkins AC (1979) Virus induced diabetes mellitus: isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *N Engl J Med* 300:1173–1179
- Youdim KA, Spencer JP, Schroeter H, Rice-Evans CA (2002) Dietary flavonoids as potential neuroprotectants. *Biol Chem* 383:503–519