Journal of Medicinal Plants Research Vol. 5(9), pp. 1497-1507, 4 May, 2011
Available online at http://www.academicjournals.org/JMPR
ISSN 1996-0875 ©2011 Academic Journals

Review

Aegle marmelos (Linn.) Correa: A potential source of Phytomedicine

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Accepted 7 December, 2010

***Aegle marmelos* (linn) Correa commonly known as Bael (or Bel) belonging to the family rutaceae, is a moderate – sized, slender and aromatic tree. A number of chemical constituents and various therapeutic effects of *A. marmelos* have been reported by different workers. Extensive investigations have been carried out on different parts of *A. marmelos* and as a consequence, varied classes of compounds Coumarins (Marmelosin, marmesin, imperatorin), alkaloids (Aeglin, aegelenine), Tannins (skimmianine), Carotenoids and seed oils and other miscellaneous compounds have been isolated from this plant. Various phytochemical and biological evaluations have been reported in the literature for the importance of the *A. marmelos*. So, it has been used in ethnomedicine to exploit its medicinal properties including antidiabetic, antiulcer, antioxidant, antimalarial, anti-inflammatory, anticancer, radioprotective, antihyperlipidaemic, antifungal, antibacterial and antiviral activities. The presented review summarizes the information concerning the botany, ethnopharmacology query, phytochemistry, biological activity and toxicity of *A. marmelos* plant.**

Key words: *Aegle marmelos*, phytochemical, biological and ethnopharmacology evaluations, phytochemistry, coumarin, tannins.

INTRODUCTION

Occurrence, botanical description and ethnopharmacology

Man cannot survive on the earth for long life without plant kingdom because the plant products and their active constituents play an important role (Sudharaneshwari and Radhika, 2007). There is a widespread belief that the green medicines are healthier and more harmless or safer than synthetic ones (Parvath and Brindha, 2003). A number of traditional herbal medicines are used for the management of various diseases. Though the recovery is slow, the therapeutic use of medicinal plant is becoming popular because of its inability to cause side effects and combat antibiotic resistant micro-organisms (Rawat and Uniyal, 2003). The indigenous communities have played a vital role in understanding the multiple uses of natural resources and their long term conservation strategies. However, for long time such a valuable ethnobotanical and ethnoconservation knowledge has been ignored.

The present study therefore aims to document various indigenous uses of *Aegle marmelos* (L.) Correa, and to explore the ethnoconservation strategies for its long term sustainability. *A. marmelos* is one of the most important medicinal plants of India, Burma and Ceylon (Srivastva et al, 1996). It is found as a wild plant in central and south India and cultivated in north India. *Aegle* is a small genus

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Abbreviations: HPBLs, Human peripheral blood lymphocytes; **GST,** Glutathione; **LD50,** Lethal dose; **IC50,** Inhibitory concentration.

of three species distributed in tropical Asia and Africa. The *A. marmelos* belongs to the family Rutaceae and is known as (Opesheet, Ohshit) in Burmese; (Bail fruit, Indian Bail, Holy fruit, Golden apple, Elephant apple, Bangal quince, Indian quince, Stone apple) in English; (Oranger du Malabar, Cognassier du Bengale, Belindian) in French; (Belbaum , Schleimapfelbaum, Baelbaum) in German; (Bili) in Gujarati; (Baelputri, Bela, Sirphal, Siri-phal, Kuralam) in Hindi; (Maja batuh, Maja) in Indonesian; (modjo) in Javanese; (Bnau) in Khmer; (Toum, Sino-Tibetan) in lao; (Bilak, Bel, Bila, Mija pahit) in Malay; (marmelos) in Portuguese; (Matum , Mapin, Tum) in thai; (Trae mam, Mbau nau) in Vietnamese (Orwa et al., 2009).

A. marmelos is a subtropical species. In the Punjab, it grows up to an altitude of 1,200 m where the temperature rises to 48.89°C in the shade in summer and descends to -6.67°C in the winter, and prolonged droughts occur (Orwa et al., 2009). *A. marmelos* is said to do best on rich, well-drained soil, but it has grown well and fruited on the oolitic limestone of southern Florida. It also grows well in swampy, alkaline or stony soils having pH range from 5 to 8 (Orwa et al, 2009). In India flowering occurs in April and May soon after the new leaves appear and the fruit ripens in 10 to 11 months from bloom (March to June) of the following year (Orwa et al., 2009).

A. marmelos is a slow-growing, medium sized tree, up to 12 to 15 m tall with short trunk, thick, soft, flaking bark, and spreading, sometimes spiny branches, the lower ones drooping. Young suckers bear many stiff, straight spines. A clear, gummy sap, resembling gum Arabic, exudes from wounded branches and hangs down in long strands, becoming gradually solid. It is sweet at first taste and then irritating to the throat.

The deciduous, alternate leaves, borne singly or in 2's or 3's, are composed of 3 to 5 oval, pointed, shallowly toothed leaflets, 4 to 10 cm long, 2 to 5 cm wide, the terminal one with a long petiole. New foliage is glossy and pinkish-maroon. Mature leaves emit a disagreeable odor when bruised. Fragrant flowers, in clusters of 4 to 7 along the young branch-lets, have 4 recurved, fleshy petals, green outside, yellowish inside, and 50 or more greenish-yellow stamens.

The fruit, round, pyriform, oval, or oblong, 5 to 20 cm in diameter, may have a thin, hard, woody shell or a more or less soft rind, gray-green until the fruit is fully ripe, when it turns yellowish. It is dotted with aromatic, minute oil glands. Inside, there is a hard central core and 8 to 20 faintly defined triangular segments, with thin, dark-orange walls, filled with aromatic, pale orange, pasty, sweet, resinous, more or less astringent, pulp. Embedded in the pulp are 10 to 15 seeds, flattened-oblong, about 1 cm long, bearing woolly hairs and each enclosed in a sac of adhesive, transparent mucilage that solidifies on drying. Bael has enormous traditional uses against various diseases and many bioactive compounds have been isolated from this plant also (Maity et al., 2009). This plant is used in traditional medicine treatments, such as intermittent fever, intestinal ailments, fertility control and treatment after childbirth and fish poison (Bsu and Sen, 1974). The effectiveness of *A. marmelos* fruit in diarrhea and dysentery has resulted in its entry into the British pharmacopoeia (Chopra, 1982). Moreover, Chopra has appropriately stated that “No drug has been longer end better known nor more appreciated by the inhabitants of India than the Bael fruit”. A survey showed that in 2001 to 2002 in a Himalayan region (State of Uttaranchal, Indian Republic), Vaidas (Practitioners of Ayurveda) used Indian Bael as an ingredient in respective herbal formulation for boil, dysentery, earaches, discharge from the ears and fever/ cold.

The ripe fruit and unripe fruit, as well as the roots, leaves and branches have all been used in traditional medicine. In Ayurveda, the ripe fruit has been used for chronic diarrhea and dysentery, as a tonic for the heart and brain, and as adjuvant treatment of dysentery. A decoction of the root has been used to treat melancholia, intermittent fevers and palpitation; the roots have mainly been used as an ingredient of the Ayurvedic medicine, dashmool. The leaves have been given as febrifuge and as a poultice for the treatment of eye disorders and ulcer and administration of fresh leaves has been used for weakness of the heart ,dropsy and beriberi.

A detailed view of the ethno medicinal uses of different part of this plant is given in Table 1.

Phytochemical constituents isolated from *A. marmelos*

Various chemical constituents like alkaloids, coumarins and steroids have been isolated and identified from different parts of tree.

Coumarins

Marmelosin, marmesin, imperatorin, marmin, alloimperatorin, methyl ether, xanthotoxol, scopoletin, scoparone, umbelliferone, psoralen and marmelide (Farooq, 2005). Marmenol, a 7-geranyloxycoumarin [7-(2, 6-dihydroxy-7-methoxy-7-methyl-3-0ctaenyloxy)
Coumarins] has also been reported (Kokate et al., 2002).

Alkaloids

Aeglin, aegelenine, dictamine, fragrine ($C_{13}H_{11}O_3N$), O-methylhalfordinine, isopentenylhalfordinol (Farooq, 2005), N-2-[4-(3’, 3’-dimethylallyloxy) phenyl] ethyl cinnamide, N-2-hydroxy-2-[4-(3’, 3’-dimethylallyloxy) phenyl] ethyl cinnamide, N-2-hydroxy-(4-hydroxyphenyl) ethyl cinnamide (Tuticorin and Manakkal, 1983). O-(3, 3-dimethylallyl) halofordinol, N-2-ethoxy-2-(4-methoxy

Table 1. Ethnomedicinal importance of *A. marmelos*

S/N	Plant part used	Ethnomedicinal uses of plant
1	Leaves	Leaves are applied to inflamed parts and are very efficacious in the form of poultice to unhealthy ulcers. Young leaves are eaten and said to cause sterility or even abortion. Juice of fresh leaves has a laxative action and also employed in asthmatic complaints, opthalmia and other eye affections. Decoction of leaves is used as a febrifuge and expectorant. Medicated oil prepared from leaves gives relief from recurrent cold and respiratory infections. The juice extracted from leaves is mixed with equal quantity of sesame oil and heated thoroughly, a few seeds of black pepper and half a teaspoonful of black cumin are added to the hot oil, and then it is removed from the fire and stored for use when necessary. A teaspoonful of this oil should be massaged onto the scalp before a head bath. Its regular use builds up resistance against cold and cough. Leaves are also use in Abscess, backache, abdominal disorders, vomiting, cut and wounds, dropsy, beriberi, weakness of heart, cholera, diarrhea, cardio tonic, blood sugar, injuries caused by animals, nervous disorders, hair tonic, acute bronchitis, child birth (George et al., 2003). Veterinary medicine for wound, killing worms, fodder for sheep, goat and cattle, stimulation of respiration contraction of denervosed nictitating membrane in anaesthetized cats (Gaur, 1999).
2	Root (bark)	Root bark is used in intermittent fever and as fish poison, as a remedy for palpitation of heat and melancholia. Juice of the bark with a little cumin in milk is valued as remedy for poverty of seminal fluid. The alcoholic extract of roots having hypoglycemic activity (Ohashi et al., 1995). It is also used in dog bite, gastric troubles, heart disorders, intermittent fevers, antiamoebic, hypoglycemic, rheumatism (Veerappan et al., 2000).
3	Flower	Distillation of flowers yielded a drug used as tonic for stomach and intestine, anti-dysenteric, antidiabetic, diaphorectic and as local anaesthetic (Rahman and Ahmad, 1986). It is also used in epilepsy and as expectorant.
4	Fruit	Fruit is eaten during convalescence after diarrhea. It is valid for its mild astringency and as remedy for dysentery. The traditional healers of southern Chhattisgarh use dry powder of fruit with mustard oil for the treatment of burn cases. One part of powder and two part of mustard oil are mixed and is applied externally (Parmar and Kaushal, 1982). Fruits are also used in diarrhea, gastric troubles, constipation, laxative, tonic, digestive, stomachic, dysentery, brain and heart tonic, ulcer, antiviral, intestinal parasites, gonorrhea, epilepsy (Veerappan et al,2000), toys, edible, jam, preserve (Kaushik and dhiman, 1999).
	(A) Ripe fruit	The ripe fruit promotes digestion and is helpful in treating inflammation of rectum. The ripe fruit extract showed antiviral activity against ranikhet disease virus (Mazumdar, 1995). Pulp of ripe fruit is sweet, cooling, aromatic and nutritive when taken fresh. Fruit pulp marmalade is used as prevention during cholera epidemics, also given to prevent the growth of piles, useful in patients suffering from chronic dysenteric condition characterized by alternate diarrhea and constipation relieves flatulent colic from a condition of chronic gastrointestinal eatarrh. Fress juice is bitter and pungent fruit extract lower the blood sugar (Vyas et al., 1979).
	(B) Unripe fruit	Fine powder of unripe fruit showed significant effect on intestinal parasites and also effective against *Entamoeba histolytica* and *Ascaris lumbricoides* (Trivedi et al, 1978). Unripe fruit is used as an astringent in dysentery, stomachache in diarrhea, tonic, digeetive, demulcent, described as cardiacal, restorative, given in piles, Decoction of unripe fruit is astringent, useful in diarrhea and chronic dysentery.
5	Seed	Seed oil exhibits antibacterial activity against different strains of vibrios and inhibits the growth of *Vibrio cholerae*, *Staphylococcus aureus* and *Escherichia coli* (Banerji and Kumar, 1949). Essential oil exhibits antifungal activity against fungi *Physalospora tucumanesis*, *Eeratocystis paradoxa*, *Selerotium ralfsii*, *Curvularia lunata*, *Helminthosporium sacchari*, *Fusarium monthforme* and *cephalosporium sacchari (*Jain, 1977).

phenyl) ethyl cinnamide, N-2-methoxy-2-[4-(3', 3'-dimethylallyloxy) phenyl] ethylcinnamide, N-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamide (Manandhar et al., 1978).

Polysaccharides

Galactose, arabinose, uronic acid and L-rhamanose are obtained on hydrolysis (Basak et al., 1982).

Table 2. Different types of phytochemical compounds isolated from different plant parts of A. marmelos.

S/N	Plant part	Chemical compounds isolated from plant
1	Leaf	Skimmianine, Aeglin, Rutin, Y-sitosterol, β-sitosterol, Flavone, Lupeol, Cineol, Citral, Glycoside, O-isopentenyl , Halfordiol, Marmeline, Citronellal, Cuminaldehyde phenylethyl cinnamamides, Eugenol, Marmesinin.
2	Fruit	Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin
3	Bark	Fagarine, Marmin.
4	Seed	Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrnene, Cumin aldehyde.

Seed oil

Composed of palmitic, stearic, oleic, linoleic and linolenic acid (Farooq, 2005).

Tannins

The maximum tannin content in bael fruit was recorded in the month of January. There is as much as 9% tannin in the pulp of wild fruits, less in cultivated type. Tannin is also present in leaves as skimmianine, it is also named as 4, 7, 8-trimethoxyfuro, quinoline.

Carotenoids

Carotenoids are responsible for imparting pale colour to fruit. Marmelosin, skimmianine and umbelliferone are the therapeutically active principles of bael plant. Minor constituents like ascorbic acid, sitosterol, crude fibres, tannins, α-amyrin, carotenoids, and crude proteins are also present. Roots of the tree have also been found to contain psoralen, xanthotoxin scopoletin (Farooq, 2005). Compounds such as praealtin D, trans-cinnamic acid, 4-methoxy benzoic acid, betulunic acid and montanin have also been reported (Ali and Pervez, 2004).

A large number of bioactive compounds have been isolated from various part of the Bael trees, a few of them have been presented in Table 2. The structures of some of these bioactive compounds are presented in Figure 1.

Bioactivity

Bael *(A. marmelos)* is an important medicinal plant of India. Leaves, fruits, stem and roots of *A. marmelos* have been used in ethno medicine to exploit its medicinal properties including astringent, antidiarrheal, antidysenteric, demulcent, antipyretic and anti-inflammatory activities (Maity et al., 2009).

Antidiabetic activity

The antidiabetic mode of action is of multidirectional as the extract can significantly lower the levels of blood glucose and glycosylated hemoglobin and increased the plasma insulin as well as liver glycogen in diabetic rats (Kamalakkanan et al., 2003). Diabetes and its related complications are closely related with oxidative stress of the body (Ceriello, 2006). Diabetes is closely inter-linked with cardiovascular as well as renal disorder at advanced stage and creates fatal disease syndromes. Oral, as well as intraperitoneal administrations of the aqueous extract of Bael fruit exhibited hypoglycemic effect against streptozotocin induced diabetic rats (Kamalakkanan and Prince, 2005).

The fruit extract at a dose of 250 mg/kg exhibited to be more effective than glibenclamide, a well-known hypoglycemic drug (Kamalakkanan and Prince, 2007). This antidiabetic effect is probably due to the presence of Coumarins in the fruit extract, which potentiate the insulin secretion from existing beta cells of the isles of langerhans (Kamalakkanan and Prince, 2005). In an uncontrolled clinical trial the administration of leaf extract for 15 days significantly reduced blood cholesterol levels with slight lowering of blood glucose in some patients with diabetes mellitus (Chakrabarti et al., 1960).

Antiulcer activity

Ulcer develops when there is imbalance between the defensive and aggressive factors on the mucosa resulting from either potentiation of aggressive factors and/or lowering of mucosal protection (Wallace and Granger, 1996). Stress, non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* are the most common causes of ulceration (Bandyopadhyay et al., 2002). Cigarette smoking and alcohol ingestion are other inducers of this disease (Liu and Cho, 2000). Current medicinal therapy with proton pump inhibitors and selective H_2 receptor blockers can efficiently cure ulcers. But none of these are devoid of side effects and execute their action within a limit.

Moreover, the recurrence of ulcer after stopping the medication is very high. About 70% of ulcers could recur after stopping medication (Sachs et al., 2002). These drawbacks of the currently available antiulcer medicines

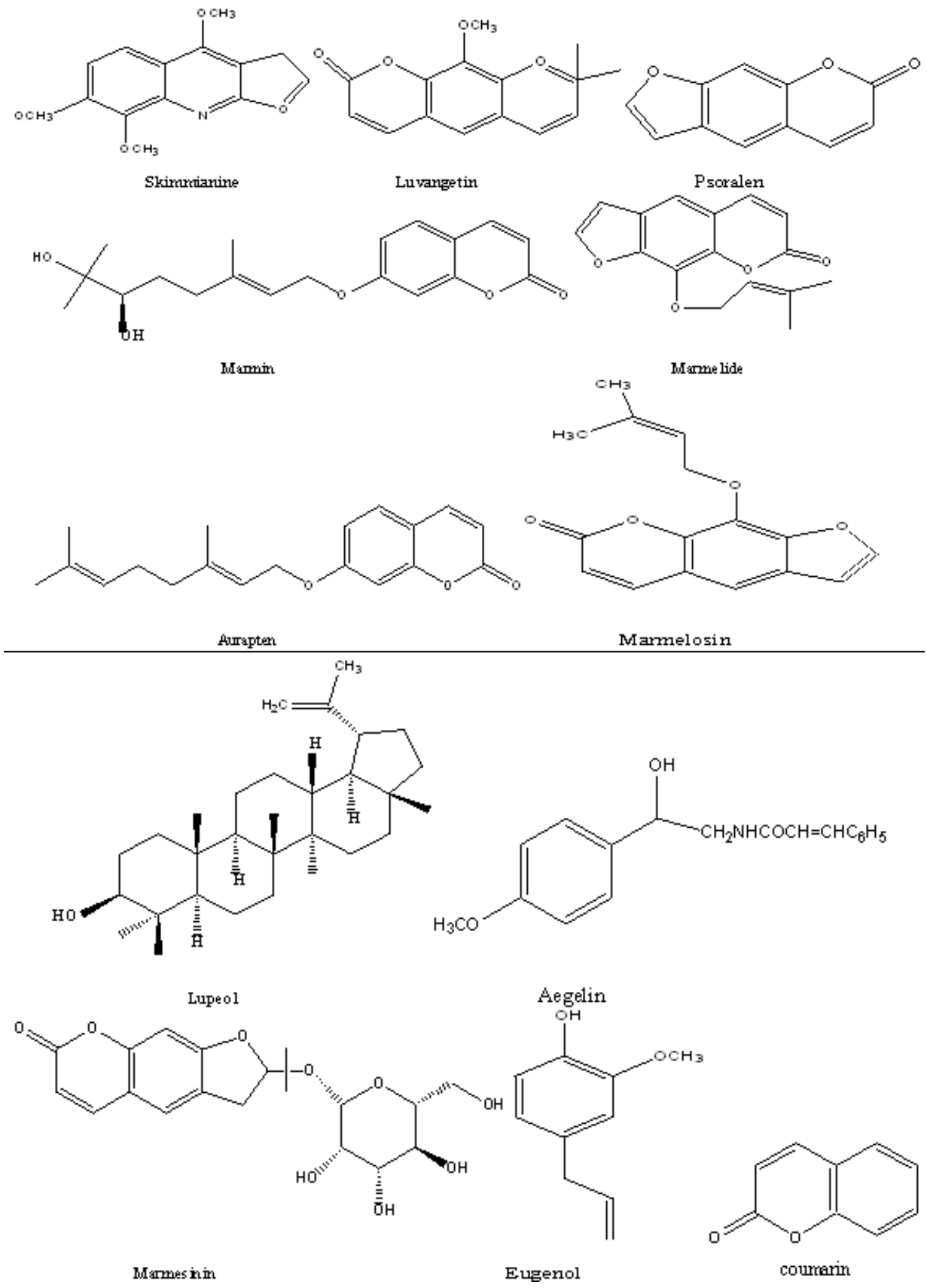

Figure 1. Structures of purified bioactive compounds from *A. marmelos* *(Maity et al, 2009).

necessitate the development of newer generation phytogenic drugs. Bael is an Indian indigenous plant which also has prominent gastroprotective effect. Pre-treatment of rats with unripe bael fruit extract produced a significant inhibition of absolute ethanol induced gastric mucosal damage (Dhuley, 2004).This activity may be due to the compound Luvangetin present in the fruit. Gastric ulcer is basically mediated by the development of oxidative stress and the compounds preventing ulcer formation may act through inhibition of oxidative stress in the gastro duodenal mucosa. The phenolic compounds are potent antioxidants (Karakaya, 2004) and have powerful antiulcer activities (Bandyopadhyay et al., 2002).

Antioxidant activity

Antioxidative parameters like reduced glutathione, glutathione peroxidase, glutathione reductase, super oxide dismutase (SOD) and catalase have shown a dose–related increase in their level /activity and a decrease in lipid peroxidation following the treatment with Bael leaf extracted (Sabu and Kuttan, 2004). The fruit extract at a dose of 250 mg/kg body weight is more effective than glitenclamide (300 µg/kg) (Kamalakkannan et al, 2003). Leaf extract (200 mg/kg) is as effective as alpha tocopherol (60mg/kg) in isoproterenal (ISO)-treated rats (Chakrabarti et al., 1960). The antioxidant phytochemical such as flavonoids, alkaloids, sterols, tannins, phlobotannins and flavonoid glycosides present in the leaf extract possess this free radical scavenging activity (Rajadurai and Prince, 2005).

Glutathione (GSH) is redused in erythrocyte whereas plasma glutathione-S-transferase (GST) and malodialdehyde (MDA) are increased in male albino rats with diabetes. However, these alterations returned to normal level with Bael leaf extract administration, suggesting antioxidental potential of Bael leaves (Upadhya et al, 2004). Eugenol and Marmesinin may be responsible for such activity because these compounds have independently shown their activity against oxidative stress (Vidhya and Devaraj, 1999).

Antimalarial activity

Protozoal disease like malaria is of the most troublesome problems in tropical countries. Malaria caused by *Plasmodium falciparum* causes about 2 million deaths annually (Guha et al., 2006). Development of resistance to existing antimalarial drugs has led to complications in treating this dreadful disease (White et al, 2004). Thus, identification of novel molecules to treat this multidrug resistant malaria is vital (Choubey et al., 2006). The alcoholic extracts of the Bael seeds and leaves have been tested *in vivo* and *in vitro* for antimalarial activity against the NK65 strain of *Plasmodium berghei*. The seeds have shown schizontocidal activity in both the system, whereas, the leaves have shown activity only in the in-vitro system (Mishra et al., 1991).

Anti-inflammatory activity

Different organic extracts of the Bael leaves possess highly significant acute and subacute anti-inflammatory analgesic and antipyretic activities (Arul et al., 2005). These activities may be due to the presence of Lupeol and Skimmianine in the leaves because both the compounds have shown the same potentialities in pure form (Getha and Varalakshmi, 2001). Activation of histamine receptor is essential for allergic and asthmatic manifestation (Macglashan, 2003). The alcoholic extract of Bael leaves antagonized the histamine –induced contractions and demonstrated positive relaxant effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H_1-receptor activity this extract may underlie these effects (Arul et al., 2004).

This activity may be due to the presence of some anti-inflammatory and anti-allergenic constituents, such as Lupeol and Citral present in the alcoholic extract, as most of the anti-inflammatory and anti-allergenic compounds act through inhibition of histamine mediated signaling (Getha and Varalakshmi, 2001).

Anticancer activity

The hydroalcoholic extract of Bael leaves has shown anticancer effect in the animal model of Ehrlich ascites carcinoma (Jagetia et al., 2005). Administration of the extract (400 mg/kg) has shown the greatest antitumor effect. The exact mechanism of this extract is yet to be established. The plant extract exhibits cytotoxicity against tumor cell lines in brine shrimp lethality assay and methyl thiazolyl tetrazolium (MTT) based assay (Costa-Lotulo et al, 2005). Bael inhibited *in vitro* proliferation of human tumour cell lines including the lecukenic K562, T-lymphoid jurhat, Beta lymphoid Raji, Erythro leukemic HEL (Lampronti et al., 2003).

The extract also possesses anti-proliferative activity on MCF7 and MDA-MB-231 breast cancer cell lines (Lambertini et al., 2004). Induction of apoptosis may be due to the presence of Skimmianine in the leaf extract which may have killed the tumor cells (Jagetia et al, 2005).

Taxol is an important anticancer drug widely used in the clinic. An endophyte fungus *Bartalinia robillardoides* (strain AMB-9) was isolated from Bael, a medicinal plant. This endophytic fungus produced 187.6 µg/l of taxol which suggests that the fungus can serve as a potential material for genetic engineering to improve the production of taxol (Gangadevi and Muthumary, 2008).

Radioprotective activity

The radio protective effect of hydro alcoholic extract of Bael leaves has been evaluated in cultured human peripheral blood lymphocytes (HPBLs). The irradiation of HPBLs with different doses of gamma-radiation caused a dose-dependent increase in the frequency of lymphocytes bearing one, two and multiple micronuclei. Treatment of HPBLs with 5 µg/ml leaf extract significantly reduced the frequency of lymphocyte bearing one, two and multiple micronuclei when compared with the irradiated control. The mechanism of this type of radio protective activity of the leaf extract may be due to the scavenging of radiation –induced free radicals (Jagetia et al., 2003). Radio protective activity of Bael leaf extract has also been studies in Swiss albino male mice. The mice were administered with various intraperitoneal single dose of the extract. The optimum radio protective dose of the extract has been found to be five consecutive doses of 15 mg/kg body weight (Jagetia et al., 2004).

Irradiation caused a dose dependent decline in the level of glutathione accompanied by an elevation in the lipid peroxidation. Bael leaf extract arrested glutathione decline and lipid per oxidation significantly (Korkina and Afanasev, 1997). Hydro alcoholic extract of Bael fruit has also been studied for its radio protective effect in mice expose to various doses of gamma-radiation. The extract (20 mg/kg) administered intraperitoneally for 5 consecutive days before irradiation of gamma ray has been found to afford maximum protection as evidenced by the highest number of survivors after 30 days post-radiation (Jagetia et al., 2004). Symptoms of sickness and mortality of the animals are due to irradiation resulting in a dose-dependent elevation in lipid per oxidation in liver, kidney, stomach and intestine as well as depletion in GSH concentration.

Treatment of the Bael fruit extract before irradiation caused a significant decrease in the lipid per oxidation accompanied by a significant elevation in the GSH concentration in liver, kidney, stomach and intestine of mice (Jagetia et al., 2004).

Antihyperlipidaemic activity

Pretreatment with Bael leaf extract at 100 mg/kg and 200 mg/kg doses for 35 days have shown significant improvement on the activities of marker enzymes, decrement of lipid peroxides, plasma lipids and lipoproteins in isoproterenol-treated rats, suggesting its antihyperlipidaemic effect (Rajadurai and Prince, 2005). Oral administration of the aqueous extract of Bael fruits and seeds separately at dose of 250 mg/kg to streptozotocin-induced diabetic rats significantly lowered the serum and tissue lipid profile (Kesari et al, 2006).

Ethanolic extract of Bael leaves also inhibited the elevation of serum cholesterol and triglycerides level in triton WR 1339 treated hyperlipidaemic rat (Vijaya et al, 2009). This extract also potentiates glucose utilization. The higher level of fatty acid and their metabolites such as acyl carnitine and long chain acyl CoA usually interfere with NA^+/K^+ ATPase activity level (Kamalakkanan and Prince, 2005).

Antifungal activity

The essential oil isolated from the leaves of Bael tree has proved to antifungal activity against animal and human fungi like *Trichophyton mentagrophytes*, *T. rubrum, Microsporum gypseum*, *M. audounii*, *M. cookie*, *Epidermophyton floccosum*, *Aspergillus niger*, *A. flavus* and *Histoplasma capsulatum* (Jain, 1977). The unsaponifiable matter of the seed has exhibited considerable *in vitro* activity against various fungi namely: *Trichophyton rubrum*, *T. terrestre*, *E. floccosum*, *Aspergillus fumigatus*, *A. niger* and *A. flavus* (Singh et al, 1983). The ethanolic extract of the root has shown activity against *A. fumigatus* and *T. mentagrophytes* (Pitre and Srivastava, 1987).

The germination of any spore (that is bacterial or fungal) is related to Ca^{+2} –dipicolonate and /or free Ca^{+2} ions availability in the medium as well as within cytoplasm of microbes. This Ca^{+2} ion uptake and utilization by spore is one of the prime factors that determine whether the spore will germinate or remain dormant (Pelzar et al, 1998). The essential oil from the Bael leaves may interfere with the Ca^{+2} –dipicolonic acid metabolism pathway and possibly inhibit spore germination. Thus it exhibits the antifungal activity by lowering the vegetative fungal body inside the host or in solid medium. This is the possible mechanism of the protective role of Bael leaf oil against fungal infection (Rana et al., 1997).

Antibacterial activity

Various extracts of Bael leaves, roots and fruits have been reported to be active against many bacterial strains. Leaf extract have shown activity against *Escherichia coli* (Joshi and Magar, 1952). The essential oil obtained from the leaves exhibited activity against *Aeromonas sp.*, *E. coli*, *Pseudomonas salanacearum* and *Xanthomonas vesicatoria* (Pandey et al, 1981). The ethanolic extract of the root has shown activity against *Vibrio cholerae, Salmonella typhimurium*, *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus* (Pitre and Srivastava, 1987). The ethyl acetate extract of the plant has exhibited activity against *Vibrio cholerae*, *S. typhi*, *S. aureus*, *Pseudomonas putida* and *Bacillus anthracis* (Rusia and Srivastva, 1988).

Methanol and aqueous extract of Bael fruit have shown strong activity against multidrug resistant *S. typhimurium*.

Methanolic extract is more potent than the aqueous extract. The minimum inhibitory concentration (MIC) value of the methanolic extract is around 256 µg/ml. The unsaponifiable matter of the seed has shown considerable in vitro activity against *E. coli*, *S. typhi, Salmonella paratyphi*, *Proteus vulgaris*, *Streptococcos faecalis, V. cholerae*, *Klebsiella pneumoniae*, *P. aeruginosa* and *Neisseria gonorrhoeae* (Singh et al, 1983). Both the oil and unsaponifiable matter of the seed have also been found to be active against *B. subtilis, E. coli*, *Klebsiella aerogenes*, *S. typhi*, *S. paratyphi*, *S. aureus*, *Erwinia carotovora, Pseudomonas solanacearum, Xanthomonas citri* and *Xantha malvacearum* (Singh et al., 1983). Thus it is evident that Bael has antibacterial activity and the mechanism of action may be the blockage of protein synthesis either at transcription or translation level and /or peptide-glycan synthesis at membrane level.

The antibacterial activity of leaf extract may be due to the presence of Cuminaldehyde and Eugenol because these compounds have already shown their activities against various bacterial strains (Duke, 1992).

Antiviral activity

The *in vitro* viral activity of various parts of Bael tree has been evaluated for their efficacy against human Coxsackie viruses B1-B6. The IC_{50} of leaves, stem and stem bark, fruit, root and root bark and pure compound Marmelide are 1000, 500 to 1000, 250 to 500, and 62.5 µg/ml, respectively, whereas, the IC_{50} of Ribavirin, a standard antiviral agent, is 2000 µg/ml for the same viruses and at the same time period (Badam et al., 2002). Marmelide is the most effective virucidal agent interfering with early events of its replicative cycle (Badam et al., 2002). It seems that Bael has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents (that is ribavirin), which usually act in the later stages of viral replication and have potent side effect (Fenner et al., 1993).

The effect of Bael extracts also on the late protein synthesis need to be studied to evaluate its degree of potentiality as an antiviral agent. The 50% ethanolic extract of the fruits has shown antiviral activity against ranikhet disease virus (Dhar et al., 1968). The fruit extract has exhibited interferon –like activity against the same virus but not against vaccinia virus (Babbar et al., 1982). Thus Bael has better virucidal potential and may be exploited as a potent antiviral agent in the nearest future.

Other activities

Leaf extract (1 gm/kg) of *A. marmelos* was investigated in the regulation of thyroid hormone in male mice. While serum level of both $T_{(3)}$ and $T_{(4)}$ were inhibited by extract of *A. marmelos* could decrease only $T_{(3)}$ concentration about 62% indicating its possible use in the regulation of hyperthyroidism (Kar et al., 2003). Effects of methanolic extract of root bark of Bael, an Ayurvedic crude drug used for heart disease and constituents isolated from the extract on the spontaneous beating of cultured mouse myocardial cells were examined. The extact at a concentration of 100 µg /ml inhibited the beating rate by approximately 50%. Among the isolated constituents, Aurapten was the most potent inhibitor; the IC_{50} of Aurapten is 0.6 µg/ml, which is comparable with that of Verapamil, a calcium antagonist.

Addition of Aurapten at concentration higher than 1 µg/ml significantly reduced the ratio of morphologically changed myocardial cells which originated from calcium overload caused by successive treatment with calcium – free and calcium – containing solutions (Kakiuchi et al., 2003). Bioassay- directed fractionation of the ethyl acetate extract of the stem bark of *A. marmelos* afforded a new compound, named Skimmiarepin C, along with Skimmiarepin A. These compounds exhibit moderate insecticidal activity against *Phaedon chleariae* and *Musa domestica* in comparison with natural pyrethrum extract (Samarasekera et al., 2003). A compound Ayurvedic preparation (with *A. marmelos* Correa plus *Bacopa monniere* linn) along with Placebo was found to be effective against Irritable Bowel Syndrome (IBS).

Bael plant acts as a 'Sink' for chemical pollutants as it absorbs poisonous gases from atmosphere and make them inert or neutral. It is a member of plant species group known as 'Climate Purifiers', which emit greater percentage of oxygen in sunlight as compared to other plants. The tree is also consider under the category of 'Fragrant' species, whose flowers and volatile vapours neutralize bad smell of petrified organic matter or decaying refuge and thus save human life from bacterial attack by making them inert and deodorizing the bad odour of air (Agarwal, 1997).

Toxicological studies

A. marmelos has been used for centuries in India not only for its dietary purposes but also for its various medicinal properties (Chopra, 1982). Hence, it is generally considered safe and few studies have been carried out with respect to its toxicity. Nevertheless aqueous extract of *A. marmelos* fruit has been reported to be non mutagenic to *S. typhimurium* strain TA 100 in the Ames assay (Kruawan and Kangsadalampai, 2006). In addition, acute toxicity studies have reported that a hydroalcoholic extract of *A. marmelos* fruit is non toxic up to a dose of 6 g/kg body weight in mice (Jagetia et al, 2004). Pharmacological studies on animal models involving repeated doses of *A. marmelos* fruit extract over

a period of up to 30 days have not reported any adverse effect up to a maximum dose of 250 mg/kg body weight (Jagetia et al., 2004).

There were no remarkable changes noticed in histopathological studies after 50 mg/kg body wt. of the extracts of *A. marmelos* when administered intraperitoneally for 14 days successively. Pathologically, neither gross abnormalities nor histopathological changes were observed. After calculation of $LD_{(50)}$ values using graphical methods, we found a broad therapeutic window and a high therapeutic index value for *A. marmelos* extracts. Intraperitoneal administration of the extract of the leaves of *A. marmelos* at doses of 50 to 90 and 100 mg/kg body wt. for 14 consecutive days to male and female wistar rats did not index any short-term toxicity. Collectively these data demonstrate that the extracts of the leaves of *A. marmelos* have a high margin of drug safety (Veerappan et al., 2007).

CONCLUSIONS

It is strongly believed that detailed information as presented in this review on the phytochemicals and various biological properties of the plant extracts might provide detailed evidence for the use of this plant in different medicines. Historically, bael has been used for the number of ethnobotanical purposes. At present, bael has become an important source of medicine for curing various human and animal diseases. Apart from exploring possibilities to prepare standardized drugs by using different plant parts of bael, production of jam by using its fruits should be promoted as a health tonic at commercial scale.

Unfortunately, most of the compounds have not properly been evaluated for the exploration of new lead molecule or pharmacophore. Moreover mechanisms of action of a few bioactive compounds have been identified so far. Hence, extensive research is required to find out the mechanisms of action as well as bioactivity of the various phytochemicals and efficacy of the medicinal values of *A. marmelos*. Thus in the near future *Bael* extracts could be further exploited as a source of useful phytochemical compounds and may play a very important role in modern system of medicine.

ACKNOWLEDGEMENT

This work has been supported by council of scientific and industrial research (CSIR).

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