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AN UPDATED REVIEW ON THE PHYTOPHARMACOLOGICAL SIGNIFICANCE OF *AEGLE MARMELOS* (L.)

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ABSTRACT

Aegle marmelos L. a slow-growing, medium sized tree belonging to the family Rutaceae is distributed throughout dry forests, hilly and plain areas. Different parts of this tree have been used in folklore medicine and traditional systems of medicine. Research studies also exhibited several pharmacological properties of this plant. This review work focused on phyto pharmacological significance of *Aegle marmelos* provides scientific evidences for the traditional uses and folklore claims of this tree.

KEYWORDS: *Aegle marmelos*, Ethnobotanical use, Folklore claims, Pharmacological activites.

INTRODUCTION

The Rutaceae family has about 150 genus and 900 species distributed throughout temperate and tropical regions, particularly in southern Africa and in Australia.[1] In India, it is represented by 23 genera and over 80 species occurring mostly in the tropical and subtropical Himalayas and the western peninsular India.[2] The bael tree is the only species in the genus *Aegle*.

Aegle marmelos(AM) is a slow-growing, medium sized tree, up to 12-15 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 in taste at first and then irritating to the throat. All the parts of the plant have been reported to have medicinal properties and more than 100 bioactive principles

have been isolated from the plant. These include aegeline, imperatorin, skimmianine, psoralen, auraptene, lupeol, eugenol, marmin etc.[3]

It is commonly called Bael. Vernacular names of this species include Bilva, Shivapala(Sanskrit), Opesheet, Ohshit(Burmese), Bael Fruit, Indian Bael, Holy Fruit, Golden Apple(English), Belbaum, Schleimapfelbaum, Baelbaum(German) Bili(Gujarati), Baelputri, Bela, Sirphal, Siri-phal, Kooralam(Hindi), Majabatuh, Maja(Indonesian), Modjo(Javanese), Bel, Gudu(Nepali), Bnau(Khmer), Sino Tibetan, Toum(Lao), Bilak, bel, bila, majapahit(Malay), Marmelos(Portuguese), Matum, Mapin, Tum(Thai), Traimam, mbaunau(Vietnamese), Vilvamaram(Tamil), Kuvala(Malayalam), Bel(Marathi) Bilabu(Telugu), Bilwapatre(Kannada), OrangerduMalabar(French), Bel, Shreefal(Bengali), Belo(Orissa).[1]

Distribution

A. marmelos is a subtropical plant and grows up to 1, 200 m altitude from sea level. It grows well in the dry forests on hilly and plain areas. It is a widely distributed in India, Ceylon, China, Nepal, Sri Lanka, Myanmar, Pakistan, Bangladesh, Nepal, Vietnam, Laos, Cambodia, Thailand, Indonesia, Malaysia, Tibet, Sri Lanka, Java, Philippines and Fiji. In India it is found in Sub-Himalayan tracts from Jhelum eastwards to West Bengal, in central and south India. It is found almost in all the states of India.[4]It is also grown in Egyptian gardens in surinam and Trinidad.[5]

Habitat

The tree grows wild in dry forests on hills and plains, also in mixed deciduous and dry dipterocarp forests. It grows up to an altitude of 1, 200 m where the temperature rises to 48.89º C in the shade in summer and descends to -6.67º C in the winter, and prolonged droughts occur. It will not fruit where there is no long, dry season as in southern Malaysia.[4]

Biophysical limits

Altitude	: 0-1200 m.
Mean annual temperature	: -6- 48 º C.
Mean annual rainfall	: 570-2000 mm.
Soil type	: Well – drained soil, Oolitic limestone, Swampy, Alkaline or stony soils.
pH range	: 5 to 8.[6]

This tree requires pronounced dry season to give fruit. In india it has a reputation of thriving where other fruit trees cannot survive.[7]

Aegle marmelos in Indian mythology

Aegle marmelos is one such plant described in the ancient medicinal treatise in sanskrit, Charak Samhita. It is popular medicinal plant in Ayurvedic and siddha systems of medicine and folk medicines used to treat wide variety of ailments. In Ayurveda Bael is termed tridosh har- remedy for three disturbances – bile, wind, phlegm.[8]

Bilva tree is said to have manifested from goddess Sri Maha Lakshmi and Sri Sooktham eulogize Goddess Lakshmi as…

" Aadithya varnae tapassodhi jaatho
Vanaspathi stava vrukshotha *bilvaha*
Tasya phalani tapasaanudantu
Mayaantha raayaashcha baahya alakshmeehi"

The translation of this stotra is given below.

"Oh Lakshmi, your complexion is like that of a morning Sun, a vanaspathi(trees bearing fruits without blossoming) called by name *Bilva* was brought forth by your devout austerity. Through your favour may the fruits of the tree drive away my misfortunes and poverty both internal (ignorance) and external. It is believed and said that one who does penance under the *Bilva* tree and meditate on Goddess Sri Maha Lakshmi will be bestowed with fulfilment of all desires".[9]

Botanical description

Leaves

Leaves commonly alternate and trifoliate rarely penta foliate arrangements. Petiole is 2.5-6.3 cm long, terete. Dimension of the leaflets 5-10 by 2.5-6.3cm. In T.S., Petiole is broad ‘C’ shaped in outline with a single layer of schizogenous cavity and a conspicuous broad ‘C’ shaped vascular bundle in the centre. Epidermis is single layered occasionally interrupted with sunken stomata on both surfaces and over- lined by a thick layer of cuticle. Interior to the epidermis is a many layered palisade tissue, which consists of closely, packed oval cell without much intercellular space. The chloroplasts are more abundant in the palisade cells and less in the spongy tissue. Both upper and lower epidermal layers bear stomata. Each stoma has two guard cells and two subsidiary cells and they correspond to rubiaceous type.

The numerical values like vein- islet number, palisade ratio and stomata index are significant diagnostic features of this species.[10]

Flower

Flower is generally greenish white; sweet scented, about 2.5cm across, bisexual, in short axillary panicles. Calyx flat, pubescent, four lobed; lobes 36 rounded, sometimes obscure. Petals 4, spreading, oblong, thick, glanddotted, much exceeding the sepals, imbricate. In India flowering occurs in April and May soon after the new leaves appear and fruits ripen in 10 to 11 months from bloom March to June of the following year.[6]

Spine

Spine is present in the axils of leaves. They are either single, double or absent in some variants. If a pair of spine is present the arms are either equal or unequal. length of the spine is 2-3cm.

Stem bark

Grey in color more warty and less number of cracks and fissures. Thickness 4-8mm; cork zone showing 5-8 stratification. Stone cells present in more number of groups in the phelloderm in the phloem, fibers present in groups are arranged in concentric rings.[11]

Stem

The stem is short, thick, soft, flanking bark and spreading, sometimes spiny branches, the lower ones drooping. There are sharp, axial one inch long spikes on this tree.[6] T.S of the stem reveals the presence of well developed periderm consisting of cork, phellogen and phelloderm, distinct patches of stone cells above the phloem region, several layers of cambium, conspicuous xylem with large vessels and uniseriate medullary rays and parenchymatous pith.

Root

T.S. of root shows the presence of outer zone of cork which gets peeled off consequent on secondary growth. This is followed by phellogen and secondary cortex whose cells contain abundance of starch grains. Interior to the cortex is the characteristic concentric patches of sclerenchyma. Phloem is concentrically arranged; phloem cells alternating with narrow strip of sclerenchyma. Medullary rays, distinct ring of cambium, wood consisting of large vessels,

tracheids and fibers, uniseriate and biseriate medullary rays filled with starch grains, and pentarch primary xylem are other features.[10]

Fruits

Fruit, sub-globous, 5-18cm in diameter, externally greenish when young, yellowish brown when ripe, rind about 1.5mm-3mm thick hard and woody, surface smooth or slightly granular bearing circular scars at the point of attachment with peduncle. Inner side of the pulp shows a longitudinal central axis and eight to fifteen or more locules and each locule contains ten or more seeds. The pulp is yellow, soft, pasty, sweet, resinous and fragrant. The seeds are small (nearly 1 cm in length) embedded in the pulp. hard, flattened-oblong, bearing woolly hairs and each enclosed in a sac of adhesive.[12]Seed commonly is yellowish brown, oblong, slightly compressed and with a hard white hair or absent in some of variants. Seeds non-endosperm and surrounded by a mucilaginous mass. Embryo with thick fleshy cotyledons.[11]

Calyx lobe

Each lobe is supplied by a single vascular strand, which gets divided into three branches, from the base itself. These branches in-turn go on branching and re-branching irregularly and form a net work.

Petal

Each petal is supplied with five vascular strands of these, the middle one gets branched into two, near about the centre of the petal. The two laterals on either sides of the median, branch into three from the base itself. Each branch again gets abruptly branched. The two peripheral ones get simply branched into four from base itself giving rise to laterals.

Stamen

Each stamen is supplied with a single vascular strand, which traverse through the connective and reaches up to the rip without any branching.

Gynoecium

Eleven bundles enter into the ovary. Each one branches into two. Peripheral traverse through the ovary wall and the central one forms the ventral bundle and supplies the ovules. So eleven peripheral bundles and eleven central bundles which supply the ovules are seen in cross section of the ovary. The two branches of each bundle again join at the top of the ovary and enter into the stigma. Further each bundle gets feebly branched.

Gums and Resins

One of the sources of gum in Asia is Asiatic tropic gum from *Aegle marmelos* (Bengal quince). These are distinct plant products insoluble in water but dissolve in alcohol, ether, carbondi-sulfide and certain other solvents with heat they first soften and then melt to a more or less clear, sticky fluid. They burn with a smoky flame and are resistant to most reagents and to decay. Resin is generally secreted in plant tissue in special layer of secretary cells which secret the resin into the cavity through a thin cuticular skin.[13]

Nutritional value of Aegle marmelos

The fruit of *Aegle marmelos* possess high nutritional value. The fruit is used to make juice, jam, sirup, jelly, toffee and other products. The pulp is reported to contain water, sugars, protein, fiber, fat, calcium, phosphorus, potassium, Iron, minerals and vitamins (Vitamin A, Vitamin B1, Vitamin C and Riboflavin). The leaves and the shoot of the plant are used as green vegetable in Indonesia.[14][15]

Table 1: Nutritional value of bael fruit[16]

Components	Value (%)
Water	64.2
Protein	1.8
Fat	0.2
Carbohydrate	30.6
Mineral	1.5
Calcium	0.09
Potassium	0.6
Iron	0.3
Vitamin C	0.01
Vitamin B_1	0.01
Phosphorus	0.05
Riboflavin	1.2
Fiber	2.2
Nicotinic acid	0.9

Phytoconstituents reported in various part of the *Aegle marmelos*

Several researchers had reported the presence of various phytochemicals in different parts of *Aegle marmelos*.

Table 2: Phytoconstituents reported in various parts of *Aegle marmelos.*

Plant Part	Phytoconstituents	Reference
Leaf	Tannins, Limonene, Aegelin, p- Cymene Phellandrene, Cineole, Skimmianine	Maity *et al.*, 2009[17]
	O-(3, 3-dimethylallyl)- halfordinol	Manandhar *et al.*, 1978[18]
	Marmelosin	Nandkarni, 1976[19]
	Marmesinin, Rutin, β- Sitosterol-D- glucoside, Marmeline	Sharma *et al.*, 1980[20]
	Umbelliferone	Arul *et al.*, 2004[21]
	Y-Sitsterol, flavones, lupeol, eugenol, citral, Glycoside, O-isopentenyl, Citronellal, Cuminaldehyde phenylethyl cinnamamides	Farooq, 2005[22]
Fruit	Alloimperatorin, Imperatorin Scoparone, Scopoletin,	Sharma *et al.*, 1980[20]
	Auraptene	Kakiuchi *et al.*, 1991[23]
	Calcium compounds, Linoleic acid	Maity *et al.*, 2009[17]
	Glutamic acid, Glycine, Lysine, Magnesium compounds, Phenylalanine, Proline, Skimmin, Umbelliferone, Xanthotoxol	Barthakur and Arnold, 1989[24]
	Marmelosine	Badam *et al.*, 2002[25]
	Psoralen	Chakthong *et al.*, 2012[26]
	Luvangetin, Marmelide, Tannin	Farooq, 2005[22]
Stem Bark	Fagarine, Marmin	Chatterjee and Mitra, 1949[27]
	Skimmianine	Maity *et al.*, 2009[17]
Seed	Anthraquinones	Mishra *et al.*, 2010 [28]
	Linoleic acid, Linolenic acid, Palmitic acid, Stearic acid	Singh and Malik, 2000[29]
	Essential oil: D-limonene, A-D-phellandrene, Cineol, Citronellal, Citral, P-cyrnene, Cumin aldehyde	Farooq, 2005[22]
Root	A- Methyl scopoletin, Skimmin, Scopoletin, Timbamine	Shoeb *et al.*, 1973[30]
	Psoralen, Umbelliferone, Xanthotoxin	Basu and Sen, 1974[31]

Folklore claims of *Aegle marmelos*

In india, tribes of various states use the parts of this plant to treat several ailments.

Table 3: Folklore claims of *Aegle marmelos*

TRIBAL GROUPS	USES	REFERENCE
Santhal	They use the plant as medicine for abdominal pain, cholera, night fever, stomach disorder and snake bite. They use specially fruits and roots for treating gastric troubles.	Ritu Gupta, 2016[32]
Bhottada tribe of Orissa	They utilize the roots of Bael for curing bite of mad dog.	Ritu Gupta, 2016[32]
Tribals of Ranchi district of Bihar	They use the leaves of Bael for treatment of heat in abdomen and jaundice.	Ritu Gupta, 2016[32]
Gujarat	They use the leaves for treating abscess	Ritu Gupta, 2016[32]
Tribals of Southern Rajasthan	They use root bark as fish Poison and use the leaf paste as an antivenom against venom of poisonous insects and animals. The powder of fruit and bark is used for the treatment of stomachache and dysentery in eastern Rajasthan.	Joshi P., 1986[33]
Uttar Pradesh	They use the fruit as an astringent and tonic. Tribals of Eastern U.P. utilize the leaves for the treatment of cuts and wounds of human beings as well as animals. The leaves are used as antidiabetic agent in Terai region of U.P.	Ritu Gupta, 2016[32]
Assam	They use the leaves for backache and vomiting.	Bhattacharjee *et al*., 1980[34]
Andhra Pradesh	The bark is used for curing of diarrhoea and root for bone fracture.	Ritu Gupta, 2016[32]
Maharashtra	They use the leaves to cure diabetes	Ritu Gupta, 2016
Madhya Pradesh	The roots are used for treating palpitation of heart. People believe that an appeal to the Bilva tree and to Dhanvantari, the physician of Gods, cures snake bite.	Bhalla *et al*., 1982[35]
Jammu and Kashmir	The fruit is used as a laxative.	Ritu Gupta, 2016[32]

Medicinal uses of *Aegle marmelos*

Researchers have reported the pharmacological potentials of different part of *Aegle marmelos*.

Table 4: Medicinal uses of *Aegle marmelos.*

Plant parts	Medicinal uses	Reference
Leaf	Abscess, backache, eye complaints, abdominal disorders, vomiting, cut & wounds, ulcer, dropsy, beriberi, weakness of heart, cholera, diarrhoea, cardio tonic, blood sugar, injuries caused by animals, nervous disorders, hair tonic, acute bronchitis, child birth. Veterinary medicine for wounds, killing worms, fodder for sheep, goat and cattle, stimulation of respiration and contraction of denervosed nictitating membrane in anaesthetised cats.	Anonymous, 1989[11] Kritikar and Basu, 1984[36] Jain, 1991[37] Gaur, 1999[38] Veerappan *et al*., 2000[39] George *et al*., 2003[40]
Fruit	Astringent, diarrhoea, gastric troubles, constipation, laxative, tonic, digestive, stomachic, dysentery, brain & heart tonic, ulcer, antiviral, intestinal parasites, gonorrhoea, epilepsy. Toys, edible, jam, preserve.	Parmar and Kaushal, 1989[41] Kaushik and Dhiman, 1999[42]
Root	Dog bite, gastric troubles, heart disorders, intermittent fevers, antiamoebic, hypoglycaemic, rheumatism.	Kritikar and Basu, 1984[36]
Bark	Stomach disorder, intermittent fevers, heart disorder.	Veerappan *et al*., 2000[39] George *et al*., 2003[40]
Seed	Febrifuge.	Anonymous, 1989[11]
Flower	Expectorant, epilepsy.	Grieve and Leyel, 1992[43] Jain, 1991[37]
Seed oil	Laxative.	Grieve and Leyel, 1992[43]
Wood	Beads worn by low caste, special couches for rheumatic patients.	Parmar and Kaushal, 1982[41]

PHARMACOLOGICAL ACTIVITES

Antimicrobial activity

The bael plant has a long history of use in ethnomedicine for its antibacterial property.[44] Several studies have revealed the antibacterial activity of AM.[45][46] Petroleum ether extract obtained from callus culture of AM has been documented to have an inhibitory effect on the growth of *Salmonella typhi* in *in vitro* studies.[47] Shahidine, a highly labile oxazoline obtained from AM, has been reported to have antibacterial activity against Gram positive bacteria.[48] Aqueous and ethanol extracts of AM have been postulated to have strong inhibitory effect on the growth of some bacteria such as *Staphylococcus aureus*, *Pseudomnas*

aerugenosa and *Escherichia coli*.[49] Maity *et al.* (2009) have suggested AM to have therapeutic potential for developing novel antimicrobials.[17]

Hot aqueous decoction of unripe fruits of AM has been demonstrated to have cidal activity against *Giardia* and rota virus in comparison to limited activity against E. *coli*.[50] Studies have hypothesized AM to have a broad spectrum antibacterial activity against both the Gram positive and Gram negative bacteria, while certain bacterial strains such as *Bacillus subtilis* are resistant to the action of the plant extracts.[51] Plant extracts of AM and *Andrographis paniculata* have been reported to have synergistic antibacterial action.[52] The chloroform extract of the leaves of AM has been reported to have a higher activity against *Proteus mirabilis* and *Klebsiella pneumoniae* whereas the methanol extract has been studied to have a better action against *Salmonella typhi*.[53]

In 2009, Venkatesan *et al*. showed that aqueous and ethanolic extract has activity against E. coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis. The ethanolic extract showed considerably more activity than the aqueous extract. Maximum antibacterial activity was shown against Bacillus subtilis followed by Staphylococcus aureus, E. coli and Pseudomonas aeruginosa.[54]

In 2010, Jyothi and Rao showed that hexane, cold methanol and hot methanol extracts have inhibited Klebsiella pneumoniae, Micrococcus luteus, Entercococcus faecalis and Streptococcus faecalis groth in vitro. They also found that these three extracts have no effect on E. coli and Proteus vulgaris.[51]

The alcoholic extracts of the A. marmelos 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.[55]

Aqueous and ethanol extracts of the leaves of AM have shown significant activity against multi drug resistant strains of uropathogenic bacteria including *Acinetobactor baumannii, Citrobactor freundii, Klebsiella oxytoca, Proteus mirabilis, Proteus vulgaris* and *Pseudomonas aeruginosa*.[56] Chakthong *et al*(2012) have isolated alkaloids and coumarins from the acetone extract of green fruits of AM and investigated the antibacterial activity of these compounds.[26] The aqueous and ethanol extracts of AM have been shown to have

significant antimicrobial activity against ten species of multi drug resistant strains of enteropathogenic bacteria.[57] Volatile oil obtained from the leaves of plant has been documented to have potent antifungal activity against various strains of fungi.[58]

Worked on antimicrobial activity of ethanolic leaf extracts of *Aegle marmelos* (L) Corr. on selected microbial strains. Phytochemicals present in the ethanolic leaf extracts of *A. marmelos* exhibit considerable antibacterial activity. Further, at concentration of 300µl and above, ethanolic leaf extracts of *A. marmelos* exhibited significant activity towards all the selected bacterial strains. However, *B. subtilis* and *E. coli were* more sensitive towards the treatment when compared to *S. aureus, P. aeruginosa* and *K. pneumonia*.[59]

Worked on methanolic extract of fruit pulp of Aegle marmelos having antimicrobial effect against multi drug resistant clinical pathogens isolated from stool samples, by the bio-autography technique. Hence the method has potential in determining the efficacy of medicinal plants against other clinical pathogens as well.[60]

Determined the antibacterial activity of three extracts of leave of *Aegle marmelos* which was screened for its potential against five bacterial strains: *Lactobacillus, Pseudomonas aeruginosa, Staphylococcus aureus, Salmonella typhi, Escherichia coli* and three fungal strains *Pestolotia foedans, Paecilomyces variotii, Fusarium oxysporum.* Chloroform extract showed good antibacterial and antifungal against *E. coli* and *Fusarium oxysporum*.[61]

All plant extracts were found to show antibacterial activity against test bacterial stains and variability in activity were also found in fruit, leaf and stem extracts in different solvents. The study is done on *Escherichia coli* MTCC1652, *Pseudomonas aeruginosa* MTCC 647, *Bacillus subtilis* MTCC 441, *Salmonella typhii* MTCC733.[62]

Dahiya *et al*., 2015, evaluated the antimicrobial properties of *Aegle Marmelos*. In this study, antimicrobial activities of different extract of *AegleMarmelos* fruit were evaluated against different microbial strains like *Escherichia coli (MTCC-443), Bacillussubtilis* (MTCC-441), *Pseudomonas aeruginosa (MTCC 4673), Staphylococcus aureus (MTCC- 3160), Aspergillus brasiliensis* (MTCC-1344) *and Candida albicans* (MTCC-227) by agar well diffusion method & MIC determination by broth dilution method.[63]

Anti-microfilarial activity

Methanolic extract of roots of *vitex negundo* L. and extracts of leaves of *vitex negundo* L. *Ricinus communis* L. and *Aegle marmelos* corr. were explored for possible antifilarial effect against Brugia malayi microfilariae. It was observed that among the herbal extract, root extract of *vitex negundo* L and leaves extract of *Aegle marmelos* Corr. At 100 ng/ml concentration showed complete loss of motility of microfilariae after 48 hrs of incubation. Thin layer chromatography of the extracts revealed the presence of alkaloids, saponins and flavonoids in the roots of *vitex negundo* L and coumarin in the leaves of *Aegle marmelos* Corr.[64]

Anticancer and antiproliferative activity

Studies have revealed extracts of AM to have significant antiproliferative activity.[12] Intraperitoneal administration of ethanol extract of AM leaves has been found to have a strong inhibitory effect on Dalton's lymphoma ascites bearing mice.[65] Administration of AM extract has been found to inhibit micronuclei frequencies in the bone marrow cells of cyclophosphamide treated mice in a dose dependent manner.[66] Extracts from AM have been documented to have antiproliferative activity against MCF-7 and MDA-MB-231 breast cancer cell lines at higher doses.[67] Studies have revealed the plant extract to inhibit the proliferation of Ehrlich Ascites carcinoma transplanted into mice.[68]

The plant is documented to be used in Bangladeshi folk medicine for the treatment of cancer.[69] Bark extract of AM has been postulated to have an inhibitory effect on proliferation of various human tumour cell lines including leukemia, lymphoma, colon and breast cancer cell lines *in vitro* and phytochemicals such as butyl-p-tolyl sulfide, 6-methyl-4-chromanon and butylated hydroxyl anisole have been identified in these extracts.[70] Imperatorin, a linear furanocoumarin isolated from the fruit of AM has been documented to inhibit the proliferation of human leukemia cell lines.[71]

Antihyperglycimic activity

Extract of green leaves of the plant has been shown to have hypoglycaemic activity in diabetic animals.[72][73] Studies have revealed that a 75% methanol extract of AM decreases the blood glucose levels in alloxan induced diabetic rats when administered at a dose of 100 mg Kg^{-1}.[74] AM extract has also been found to increase the levels of reduced glutathione in the erythrocytes and decreases the levels of malondialdehyde in alloxan induced diabetic rats.[75] Studies have revealed significant improvement in the glucose tolerance in rats

administered the aqueous decoctions of the plant.[76] Administration of ethanol extract of the plant for a period of two weeks has been reported to have a hypoglycemic effect in diabetic rats.[77] Sachdewa *et al.* (2001) have reported glucose lowering effect of AM on one week administration of extract in diabetic rats.[78] The AM extract has been documented to have maximal antihyperglycemic effect at the end of second week of administration in a four week study.[75] AM leaves have been investigated to have hypoglycemic effect in normoglycemic rats as well.[79]

Treatment with AM extract is postulated to reverse the muscarinic M1 receptor gene expression which is decreased in diabetic rats and subsequently increase the vagal nerve stimulation and insulin secretion thereby having a regulatory effect on glucose homeostasis in diabetes.[80] Studies have revealed AM to have stimulatory action on PPAR-γ *in vitro*[81] and *in vivo*.[82]

The effect of the aqueous, alcoholic and petroleum ether extracts of *Aegle marmelos* for the hypoglycaemic and other pharmacological actions was studied and it was observed that the aqueous and alcoholic extracts at 500 mg/kg dose produce hypo glycaemia in normal fasted rabbits, but the petroleum ether extract did not.[83]

The effect *Aegle marmelos* leaves on histological and ultra structural changes in tissues of streptozotocin induced diabetic rats was studied. The treatment of leaf extract on diabetic pancreas showed improved functional state of pancreatic beta cells. This study indicates the hypoglycaemic nature of the leaf extract, helping in regeneration of damaged pancreas.[84]

Mohammad Y and Mohammad I (2009)worked on Clinical evaluation of antidiabetic activity of *Trigonella* seeds and *Aegle marmelos* leaves. The study was performed in four different groups for a period of 16 weeks. Each group was having 20NIDDM patients, whereas five patients were kept as control subjects. Inclusion and exclusion criteria were formed for the study. Written consent was taken from the patients. Initial postprandial blood glucose level (PPBGL) was estimated at the time of enrolment in the study and then after each week during the entire period of the study. At the end of the study, the initial and final readings were Compared.[85]

In 2012, Ram Prakash Prajapat studied the extraction and isolation of Marmelosin from *Aegle marmelos*, synthesis and evaluation of their derivative as antidiabetic agent. It was found that

the Marmelosin possesed highest significant reduction in blood glucose level as compared to synthesized compounds against alloxan induced diabetic rats, after daily administration of extract for 14 days.[86]

In 2014, R. Bhavani studied the anti-hyperglycemic activity of alcoholic leaf extract of *Aegle marmelos* (Linn.) on Alloxan induced diabetic rats. Due to the continuous administration of the extract, reduction in blood sugar level could be seen.[87]

Cardioprotective activity

The aqueous and alcohol extracts of the leaves of AM have been shown to reduce the pulse rate and increase the amplitude and tone of contractions in isolated frog heart.[88] The plant extract has also been found to attenuate the deleterious effects of calcium overload in frogs.[88] The methanol extract of the root bark of the plant is reported to contain auraptene which decreases the calcium paradox induced ischemic injury and spontaneous beating in isolated myocardial cells.[23]

Oral administration of the aqueous leaf extract of AM has been studied to prevent isoprenaline induced myocardial infarction in rats.[89] AM extract treatment for a period of 35 days has been postulated to reduce the levels of creatine kinase, lactate dehydrogenase, Na^+/K^+ ATPase in isoprenaline treated rats and hence confer cardioprotective effect.[89] Kamalakkannan and Prince (2003) have proposed AM extract to have a marked hypolipidemic effect in diabetic rats.[90] Ethanol extract of AM leaves is documented to inhibit the increase in serum cholesterol and triglycerides and increase high density lipoproteins in triton and diet induced hyperlipidemic rats.[91] A polyherbal preparation containing AM and five other plant extracts has been documented to decrease the rise in serum lipids, cholesterol and triglycerides significantly in experimental model of hyperlipidemia in rats.[92]

Periplogenin, a cardenolide obtained from the leaves of AM has been reported to have a protective effect against doxorubicin induced cardiotoxicity and lipid peroxidation in rats.[93] Oral administration of methanol extract of the leaves of AM has been proposed to have significant hypolipidemic effect in streptozotocin induced diabetic rats.[94]

Lupeol obtained from the leaves of AM has been studied to have antidyslipidemic activity in streptozotocin diabetic rats.[95] Unripe fruit extract has been documented to be used in cardiac

ailments.[55] AM has been proposed to have therapeutic potential in cardiovascular disorders due to inhibition of apoptosis induced by ischemia-reperfusion induced myocardial injury.[96]

Padma-28, a polyherbal Tibetian preparation containing AM has been reported to have beneficial effect on patients suffering from peripheral arterial disease in a meta- analysis study.[97] Aegeline, an alkaloidal- amide isolated from the leaves of AM has been found to have antidyslipidemic effect in streptozocin induced diabetic rats (Narendra *et al.*, 2007). Pharmacophoric and 3D QSAR studies have suggested that aegline may have a β_3 adrenergic agonistic activity.[98]

Studies have suggested fresh juice of AM to be better tolerated and less toxic, cardiotonic in isolated frog hearts as compared to digoxin.[99] The high dose of Aegle marmelos leaves extract (AMLE 500mg/kg) possess good cardioprotective activity against Isoproterenol (ISO) induced myocardial necrosis in rats but the low dose of AMLE (100mg/kg) failed to show significant cardio-protection.[100]

Hepatoprotective activity

The chloroform, alcohol and aqueous extracts of AM leaf have been documented to decrease the blood levels of serum glutamate pyruvate, serum glutamate oxaloacetate transaminase, alkaline phosphatase and bilirubin in ethanol induced hepatotoxicity in rats.[101] The aqueous fruit extract of the plant has also been documented to have a protective action in paracetamol induced hepatotoxicity in rats.[102]

Administration of the dried leaf powder of AM for a period of 14 days has been reported to have a hepatoprotective effect in carbon tetrachloride induced hepatotoxicity in rats.[103] Furthermore, the hepatoprotective effect of the dried leaf powder of the plant was comparable to that of the standard drug Liv 52.[103]

Activity in ulcerative colitis

AM has been reported to be used for gastroprotective effect in ethnomedicine.[104] Oral administration of the extract of unripe fruit of AM at different concentrations, once daily, has been reported to have a significant protective effect on acetic acid and indomethacin induced ulcerative colitis in rats.[105] The extract was found to decrease mast cell degranulation, disease activity index, macroscopic and microscopic scores of disease severity in both the

models significantly.[105] AM treatment has also been postulated to have protective effect on 2, 4-dinitrobenzene sulfonic acid induced colitis in rats.[106]

Antifertility effect

AM has been used in ethno medicine for antifertlity effect.[107]Studies have revealed that the various parts of AM including the stems, fruits, seeds and leave have antifertility effect in male animals.[108]The bark extract of AM contains marmin and fagarine, which are postulated to reduce male fertility in rats.[108]

Treatment of male rats with methanol extract of AM caused dose dependent decrease in sperm density, motility, viability and acrosomal integrity by decreasing the serum testosterone levels and the weight of the reproductive organs in male animals. These observations suggest that it may be used as a male contraceptive.[108]

Administration of the aqueous leaf extract of AM has been associated with reversible loss of fertility without affecting the vital parameters in rats.[109] Alkaloids, phenolics and triterpenoids present in the aqueous extract of the leaves of AM have been reported to decrease the vitality of human sperms in *in vitro* studies.[110]A dose of 300 $mgKg^{-1}$ of 50% ethanol extract of AM is documented to produce a complete inhibition of fertility in rats.[111][112]

Antidiarrheal activity

AM is used by the tribal populations in West Bengal and Assam for its antidiarrheal action.[45][113] Methanol extract of the unripe fruit of AM is documented to have protective effect on castor oil induced diarrhea.[17][114]

AM is documented to have a protective action against gastric mucosal damage and diarrhea induced by various agents including hypothermia restraint, absolute ethanol, indomethacin and castor oil and study reported AM to decrease the intestinal fluid accumulation and gastric mucosal damage significantly.[114] Mebarid, an Ayurvedic polyherbal formulation containing AM as one of the components, has been documented to have potent antidiarrheal, antimotility and antiulcer activities in rats.[115]

Studies have revealed that intracaecal administration of methanol extract of AM is more effective than oral dose in protection against experimentally induced diarrhea.[114] It has been postulated that free radical scavenging activity of AM plays a significant role in protection

against experimentally induced ulcers and diarrhea in rats.[116] The chloroform extract of the root of AM has also been suggested to have *in vitro* and *in vivo* antidiarrheal activity.[117] Hot water decoction of the dried unripe fruit of AM is documented to prevent infective diarrhea caused by micro-organisms such as *Giardia* and rota virus both of which are highly virulent.[118]

Harijagannatha rao and Lakshmi(2012)investigated the antidiarrhoeal activity of the aqueous extract from the leaves of *Aegle marmelos*. Preliminary phytochemical screening, acute toxicity study and antidiarrhoeal activity were studied on castor induced diarrhea, Magnesium sulphate induced diarrhea, and gastric transit time at 50, 100and 200mg/kg body weight. The preliminary phytochemical screening of the extract results with the presence of anthraquinoneglycosides, catechins, fixed oils and saponins etc.[119]

Antiviral activity

Studies have revealed the bark, fruit and root of AM to have activity against human coxsackie viruses and marmelide has been isolated as the antiviral phytoconstituent.[25] Marmelide is reported to interfere with the early stages of viral replication. The fruit extract of AM has been postulated to have an action similar to interferons.[120] The ethanol extract of bael fruit has been documented to inhibit the Ranikhet disease virus.[121]

Anti-inflammatory activity

Sharma *et al* (2011) Worked on anti-inflammatory effect of aqueous and methanol extracts of *Aegle marmelos* seeds was using carrageenan induced paw edema and cotton pellets induced granuloma in rats. To prove the dependency of pharmacological activity on certain phytoconstituent, total flavonoid contents were estimated, using a spectrophotometric technique.[82]

Different organic extracts of the AM leaves possess highly significant acute and subacute anti-inflammatory activity. In acute and chronic inflammatory animal models, AM showed significant anti-inflammatory activity and it can be a promising anti-inflammatory agent. 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. Activation of histamine receptor is essential for allergic and asthmatic manifestation. The alcoholic extract of AM leaves antagonized the histamine induced contractions and demonstrated positive relaxant

effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H1 receptor activity this extract may underlie these effects.[55]

George *et al*., (2016) evaluated anti-inflammatory activity and to determine phytochemical constituent of ethanolic leaf extract of *Aegle marmelos* (L.) Corr. Serr. Ethanolic extract was screened for different phytochemical constituents. Ethanolic extracts were screened for anti-inflammatory activity (induced by Carrageenan) in Wistar Albino rats.[122]

Antioxidant activity

Antioxidant and free radical scavenging activity of the ripe and unripe fruit of AM was compared. Results indicate that the enzymatic antioxidants increased in ripe fruit when compared to unripe fruit extract (except glutathione peroxidase). The percentage of free radical inhibition was also high in unripe fruit than that of the ripe fruit.

Methanol and aqueous extract of AM fruit pulp was screened for antioxidant activity by DPPH radical scavenging method, reducing power assay, nitric oxide scavenging assay, superoxide radical scavenging assay, ABTS radical scavenging assay and H_2O_2 radical scavenging assay. Both aqueous and alcoholic extract exhibited good antioxidant activity.

The antioxidant activity of the fruit of AM was reported. The aqueous extract of AM fruit was screened for antioxidant activity by the DPPH radical scavenging. The extract showed efficient antioxidant activity.[4]

Eugenol and marmesinin may be responsible for such an activity because these compounds have independently shown their activity against oxidative stress. Eugenol (C10H12O2), present in AM leaf extract, has potent antioxidant property.[123]

In vitro antioxidant activity of the methanolic extract of *Aegle Marmelos* leaf was studied using standard methods like DPPH scavenging activity, H2O2 scavenging activity and ferrous reducing power. In vitro activity of Methanolic extract of *Aegle marmelos* showed that it has good antioxidant activity with the IC50 value 23±0.08. It thus can be used as potential inhibitor of free radicals.[124]

Aegle marmelos leaves were screened for phytochemicals, antioxidant (DPPH) and polyphenol content (Folin-ciocalteu assay) using a series of solvents. The methanol and water extract of *Aegle marmelos* was found to be rich in ascorbic acid, glutathione, flavonoids,

saponins, reducing sugars, turpenoids and polyphenols (2.4g of Gallic acid per 100g of (dry wt.) of extract. Antioxidant activity of water extract was higher (92%) than BHT (81% standard antioxidant), It also exhibited significant radical scavenging activity due to higher content of tocopherol, glutathione and ascorbic acid in it.[125]

A study carried out an efficient record of the comparative antioxidant activity and phenol content in methanolic extract of the selected parts (leaves, root and stem bark) of *Aegle marmelos*. The total phenolic contents varied from 9.8367 ± 0.0235 to 1.7281 ± 0.049 mg g-1. Total flavonoid contents were between 8.248 ± 0.029 to 1.087 ± 0.002 mg g-1.The highest free radical scavenging effect (using DPPH) was observed in leaves with IC50 = 2.096µg/ ml which was about 10 times greater than reference antioxidant butylated hydroxy toluene (BHT). The greater amount of phenolic compounds leads to more powerful radical scavenging effect as shown by methanolic extract of *Aegle marmelos* leaves.[126]

In a study it was found that the ethanol extract of *Aegle marmelos* has higher antioxidant activity values of 46.08%, 50.56% and 54.32% at different concentration of 5, 10 and 15mg/ml respectively. The total phenolic compounds are major compounds responsible for antioxidant activity. Among the three solvents derivation of phenolic compounds was observed maximum by the ethanol solvent (1.921mg/g) and lowest by distilled water extract (1.510mg/g).[127]

Radioprotective activity

Radioprotective effect of AM extact was studied by Jagetia and Venkatesh (2005)., by exposing to different doses of gamma radiation in mice and found that oral administration of extract resulted in an increase in radiation tolerance by 1.6 Gy.Again, Jagetia and coworkers (2006), [128][129] studied effects of plant extract on the peripheral blood and small intestine of Swiss albino mice. They exposed the animals to gamma radiation and data were collected against radiation-induced changes in the peripheral blood, spleen colony forming units, and intestinal mucosa, reported that AM extract significantly reduces the deleterious effect of radiation in intestine and bone marrow of mouse.[82]

Nephro protective activity

The nephro- protective effect of Aegle marmelos in alloxan –induced diabetic rats was investigated. Alloxan caused increase in glucose, glycosylated haemoglobin,

microalbuminuria, urine albumin and decrease in protein, albumin and globulin considerably. Oral administration brought back the altered biochemical parameters to near normal.[130]

Immunomodulatory activity

The immunomodulatory action of methanolic extract of *Aegle marmelos* fruit (FEAM) in experimental model of immunity was investigated: Cellular immunity was carried out by neutrophil adhesion test and carbon clearance assay, whereas, humoral immunity was analyzed by mice lethality test and indirect haemagglutination assay. FEAM dose was selected by Stair case method (up and down) and administered at 100 and 500 mg/kg orally. The Ocimum sanctum (OSE, 100 mg/kg, p.o) was used as standard. FEAM at 100 and 500 mg/kg produced significant increases in adhesion of neutrophils and an increase in phagocytic index in carbon clearance assay. Both high and low doses of FEAM significantly prevented the mortality induced by bovine *Pasteurella multocida* in mice. Treatment of animals with FEAM and OSE significantly increased the circulating antibody in indirect haemagglunation test. Among the different doses, low one was more effective in cellular immunity models than the high. However, all the doses exhibited similar protection in humoral immunity procedures. From the above findings, it is concluded that FEAM possesses potential for augmenting immune activity by cellular and humoral mediated mechanisms more at low dose (100 mg/kg) than high dose (500 mg/kg).[131]

Wound healing activity

Effect of topical and intraperitoneal administration of methanolic extract of *Aegle marmelos* ointment and injection was studied respectively on two types of wound models in rats, the excision and the incision wound model. Both the injection and the ointment of the methanolic extract of *Aegle marmelos* produced a significant response in both of the wound type tested.

In the excision model the extract treated wounds were found to epithelialize faster and the rate of wound contration was higher, as compared to control wounds. The extract facilitated the healing process as evidenced by increase in the tensile strength in the incision model. The results were also comparable to those of a standard drug nitrofurazone.[132]

Analgesic effect

The methanol extract of leaves of *Aegle marmelos* at a dose level of 200 and 300 mg/kg showed significant analgesic activity on acetic acid-induced writhing and tail flick test in mice.[133]

Anti-spasmodic effect

Aegle marmelos extract possesses the maximum amount of antispasmodic activity. The study is done on smooth muscle contraction, especially in tubular organs of gastrointestinal tract of chicken of both sex.[134]

Anti asthmatic effect

Activation of histamine receptor is essential for allergic and asthmatic manifestation. The alcoholic extract of Bael leaves antagonized the histamine-induced contraction and demonstrated positive relaxant effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H1-receptor activity by this extract may underline these effect.[21]

Antianxiety and antidepressant effect

Methanol extract of *Aegle marmelos* shows significant anxiolytic and antidepressant activities possibly by increasing monoamine levels at post synaptic sites. Albino mice were taken for the experiment.[135]

George *et al* (2016)evaluated of antidepressant and antianxiety activity of ethanolic leaf extract of *Aegle marmelos.* The result suggests that the ethanolic extract of *Aegle marmelos* contains some active principles which may be responsible for these activities.[136]

CONCLUSION

The present literature review signifies the phytopharmacological value of *Aegle marmelos*. This ancient tree is economically, medicinally and environmentally important. Broad spectrum of biological activites is reported from several parts of the tree. This review will be useful to research community to contribute in developing scientifically validated herbal products from this tree.

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