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Phytochemistry and Pharmacological Properties of *Aegle marmelos* L (Rutaceae)*:* A Review

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Abstract

Aegle marmelos (L.) is perhaps one of the most esteemed medicinal plants in the Indian subcontinent with several beneficial pharmacological properties. From the past decades, regardless of the study of the chemistry of the compounds, considerable progress has also been made to study the biological activities and medicinal applications of Bael plant. In the present review, an attempt has been made to congregate all the pharmacological and phytochemical studies done on this important medicinal plant, *Aegle marmelos* (L.). Extensive studies show that this plant possesses various significant activities such as antifungal, antioxidant, antibacterial, antiprotozoal, antispermatogenic, anti-inflammatory, anthelmintic, antidiabetic, laxative, febrifuge, and expectorant, chemopreventive, antipyretic, ulcer healing, antigenotoxic, and diuretic. Thus it was worthwhile to review on this plant's studies to give a bird's eye view mainly on the activities and constituents of the plant to the scientists.

Keywords: *Aegle marmelos*, biological activity, chemical constituents

Introduction

Aegle marmelos, commonly known as Bael has drawn the attention of worldwide prominence owing to its upholding diversified medicinal properties [1]. Every single part of the plants such as roots, stems, leaves, seeds, and fruit can be used as ethnic medicines against countless diseases and thus it becomes commercially exploitable (ibid). The widely used part of the plant is the fruit (ibid). This plant holds different values at its different ripening period. *Aegle marmelos (L.)* is native to Indian subcontinent and south-east Asia, more precisely in Northern India, but extensively found throughout the Indian Peninsula, in Ceylon, Burma, Bangladesh, Thailand and Indo-China [2]. The plant is mid-sized. It is shaped like slender [3]. It is aromatic and armed gum-bearing tree (ibid). The adult branches are neither straight sharp single and not even paired. Moreover, these older branches get higher in an average of 2.5cm long (ibid). On the other hand, young or tender branches are green with zigzag and compressed appearance (ibid). Leaves are alternate, attenuate trifoliate, occasionally digitately 5-foliate, petiole and approximately gets 2.5 to 6.3 cm long (ibid). The parts of the plant such as stem, bark, root, leaves and fruit organic product at all phases of development have therapeutic ethics and have been utilized as the conventional solution for quite a while (ibid). *Aegle marmelos (L)* elaborates a vast number of biologically active compounds which are chemically very active and even are in a complex structure [3]. All the constituents have been demonstrated to unveil many pharmacological activities such as antifungal, antioxidant, antibacterial, antiprotozoal, antispermatogenic, anti-inflammatory, anthelmintic, antidiabetic, laxative, febrifuge and expectorant (ibid). In Ayurveda, this plant is being used for the treatment of several inflammatory disorders [4].

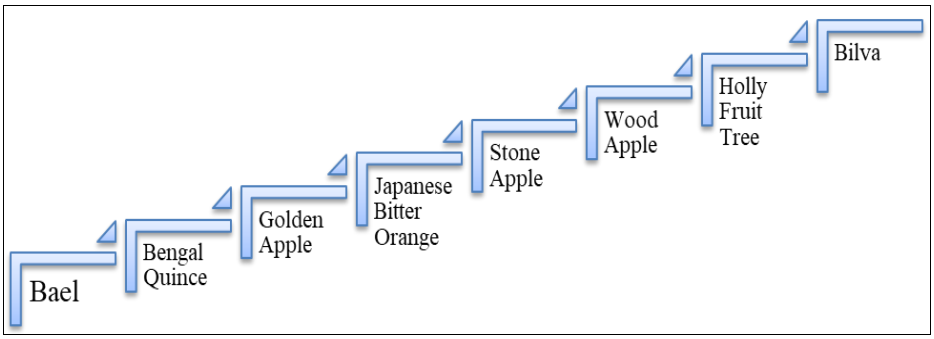


Fig 1: Common Names of *Aegle marmelos (L)* [5]

Botanical Description

Aegle marmelos (L.) is mid-sized and formed like slender [3]. The plant spreads fragrance. Further, the plant is an armed gum-bearing tree (ibid). Adult branches are neither straight

sharp single and not even paired and get higher in an average of 2.5cm long (ibid). On the contrary, young or tender branches are green with zigzag and compressed appearance (ibid). Leaves are alternate, attenuate trifoliate, occasionally digitately 5-foliate, petiole and approximately gets 2.5 to 6.3 cm long (ibid).

Fig 2: Fruit of *Aegle marmelos (L.)*

Fig 3: Plant of *Aegle marmelos (L.)*

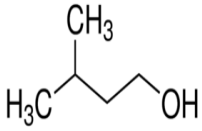
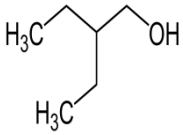
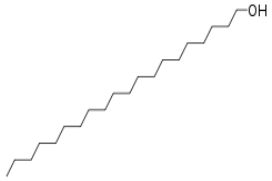
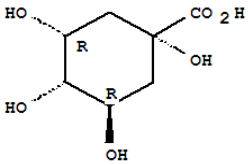
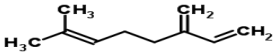
Scientific classification

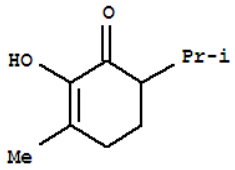
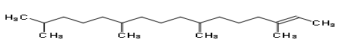
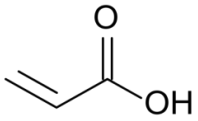
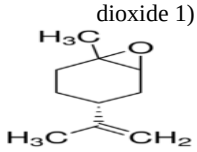
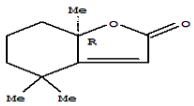
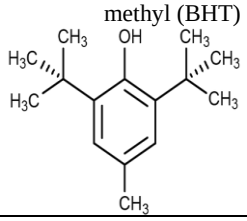
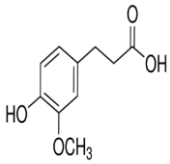
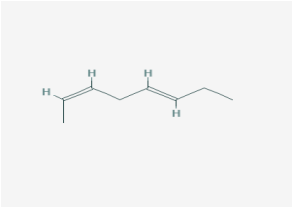
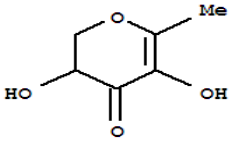
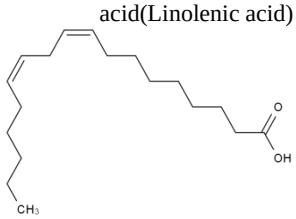
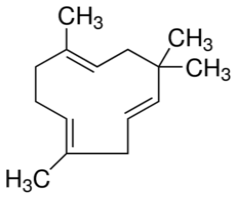
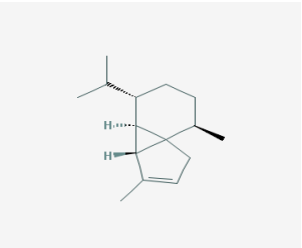
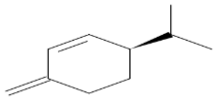
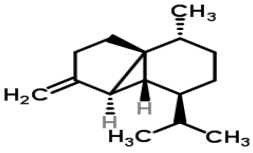
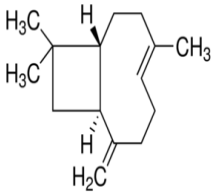
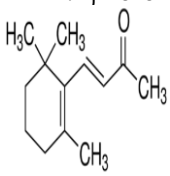
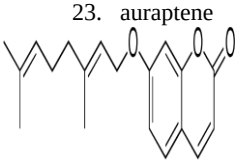
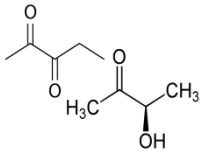
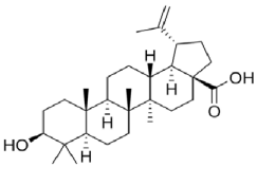
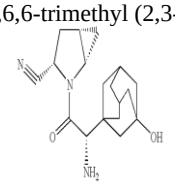
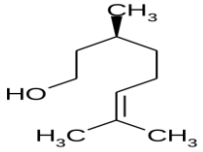
Kingdom- Plantae
Division- Magnoliophyta
Class- Magnoliopsida
Order- Sapindales
Family- Rutaceae
Subfamily- Aurantioideae
Genus- Aegle
Species- Aegle *marmelos*

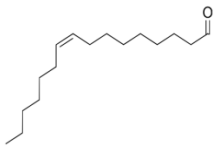
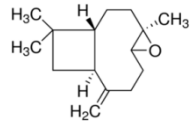
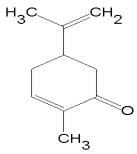
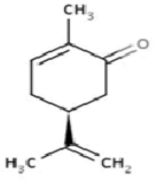
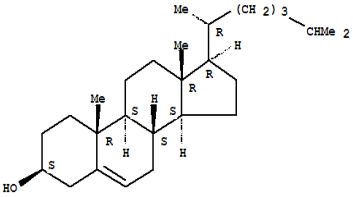
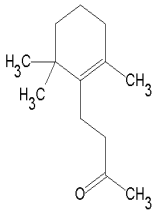
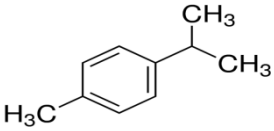
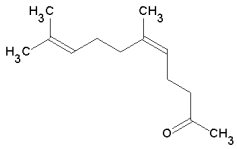
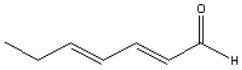
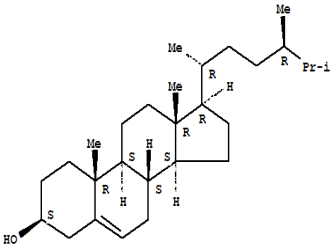
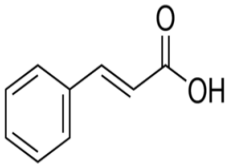
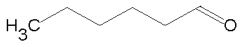
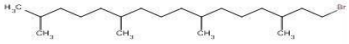
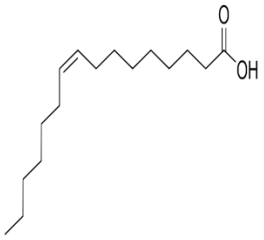
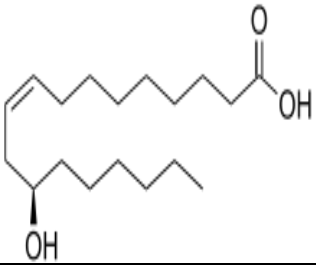
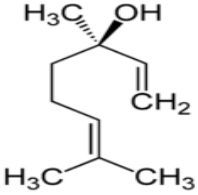
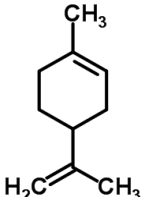
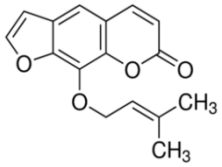
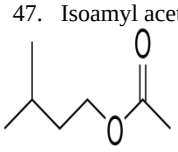
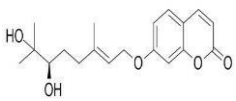
Phytochemical Constituents

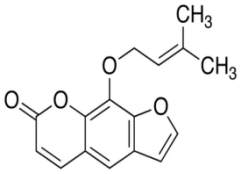
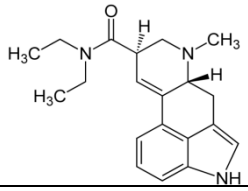
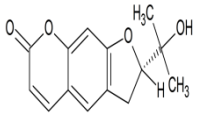
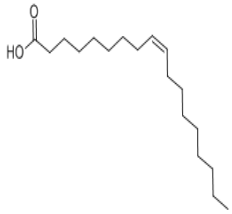
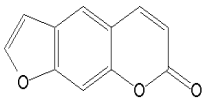
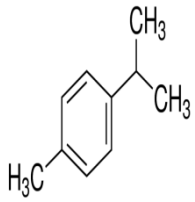
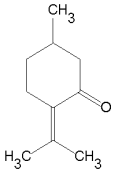
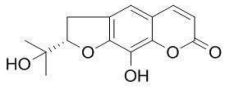
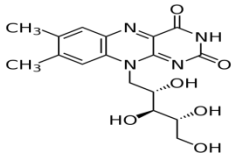
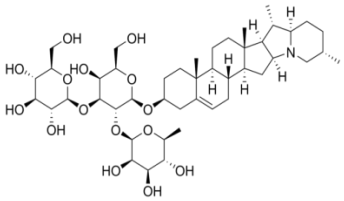
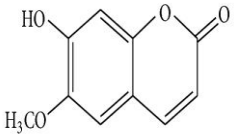
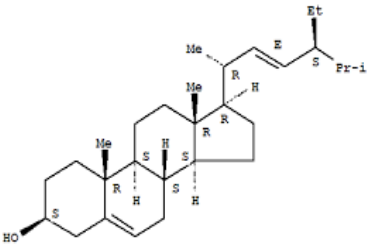
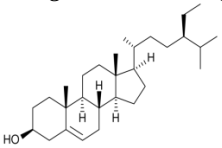
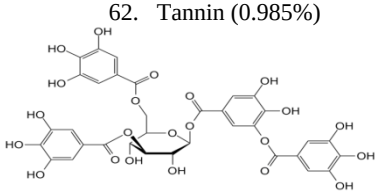
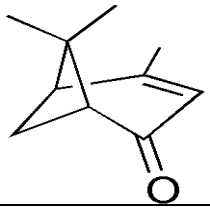
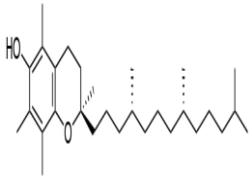
After several attempts to extricate and differentiate the constituents present in the concoction from different concentrates of *Aegle marmelos (L.)*, a large number of biologically active compounds are found in the plant such as various organic acids including oxalic, tartaric, malic and ascorbic acid, various phenolics in the fruit as chlorogenic acid (136.8 µg/g), ellagic acid (248.5 µg/g), ferulic acid (98.3 µg/g), gallic acid (873.6 µg/g), protocatechuic acid (47.9 µg/g) and quercetin (56.9 µg/g). Apart from all these, compounds like 1-Butanol, 3-methyl-, acetate, 1-Dodecanol, 1-Heptadecanol(1-Eicosanol), 1-Tetradecanol, acrylate; 1,3,4,5-Tetrahydroxy cyclohexane carboxylic acid (Quinic acid); 1,3-Cyclohexadiene,2-methyl-5-(1-methylethyl)-(1-Phellandrene); α-Cubebene; α–Tocopherol; allo imperatorin, Verbenone, vitamin E are found in the plant.

Table 1: Structures of several phytoconstituents collected from *Aegle marmelos* [6, 7, 8]

1. 1-Butanol, 3-methyl-, acetate 	2. 1-Dodecanol 	3. 1-Heptadecanol(1-Eicosanol) 
4. 1-Tetradecanol, acrylate	5. 1,3,4,5-Tetrahydroxy cyclohexane carboxylic acid (Quinic acid) 	6. 1,6-Octadiene, 7-methyl-3-methylene (beta.-myrcene) 

7. 2-Cyclohexen-1-one, 4-hydroxy-3-methyl-6-(1-methylethyl) 	8. 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl (Phytol isomer) 	9. 2-Propenoic acid 
10. 2,3 Dioxabicyclo[2.2.2]oct-5-ene, 1-methyl-4-(1-methylethyl)-(Limonene dioxide 1) 	11. 2(4H)-Benzofuranone 5,6,7,7atetrahydro-6-hydroxy-4,4,7a-trimethyl 	12. 2,6-bis(1,1-dimethylethyl)-4-methyl (BHT) 
13. 3-(4-hydroxy-3-methoxyphenyl) 	14. 3,5-octadiene-2-one 	15. 4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl 
16. 9,12,15-Octadecatrienoic acid(Linolenic acid) 	17. α-Humulene 	18. α-Cubebene 
19. β-phellandrene 	20. β-cubebene 	21. β-caryophyllene 
22. β-Ionone 	23. auraptene 	24. acetoin 
25. betulinic acid 	26. Bicyclo[3.1.1]heptane-2,3-diol, 2,6,6-trimethyl (2,3-Pinanediol) 	27. Citronellal 

28. Cis-9-Hexadecenal 	29. caryophyllene oxide 	30. Carvone 
31. Carvyl acetate 	32. Cholest-5-en-3-ol (3.beta.) 	33. Dihydro-β-Ionone 
34. Dehydro-p-cymene 	35. (E)-6,10-dimethyl-5,9-undecadien-2-one 	36. (E)-2-octenal 
37. (E,E)-2,4-heptadienal 	38. Ergost-5-en-3-ol, (3.beta.) 	39. Methyl ester (Cinnamic acid, 4-hydroxy-3-methoxy-,methyl ester) 
40. Hexanal 	41. Hexadecane 	42. Hexadecanoic acid 
43. Heptadecanoic acid 	44. Linalool oxide 	45. Limonene 
46. Imperatorin 	47. Isoamyl acetate 	48. Marmin 

49. Marmelosin 	50. Marmelide 	51. Marmesin 
52. Octadecanoic acid 	53. Psoralen 	54. P-cymene 
55. Pulegone 	56. Rutaretin 	57. Riboflavin (0.005%) 
58. Saponins 	59. Scopoletin 	60. Stigmasta-5,22-dien-3-ol 
61. Stigmast-5-en-3-ol, (3.beta.) 	62. Tannin (0.985%) 	63. Tetradecanoic acid (Myristic acid) 
64. Verbenone 	65. Vitamin E 	

Pharmacological Properties

Antidiabetic property

It has been reported that *Aegle marmelos* shows antidiabetic properties. In a study conducted by [9], it is seen that lectin extract of this plant gives antidiabetic effect in glucose-induced hyperglycemia and alloxan-induced diabetes [10, 11]. In alloxan-induced diabetes, methanolic extract (120 mg/kg body weight, ip) of the leaves of *Aegle marmelos* decreases sugar level in blood. This reduction was seen on day 6 and on day 12, sugar level got reduced to 54% [12]. Again, [13] have also reported that root extract gives hypoglycemic impact in alloxan-induced diabetic rats. Moreover, extracts from fruits and seeds have also witnessed hypoglycemic effects in streptozotocin-induced diabetic rats [14]. Besides, it is also seen that by changing pancreatic beta cell activity, *Aegle marmelos* inhibits the accumulation of advanced glycation end-products and collagen-iv.

Antidiarrhoeal activity

In *in vitro* and *in vivo* study by [15] it is found that chloroform

present in root extract gives antidiarrhoeal activity. *In vitro* study it was revealed that this extract was similar to that of ciprofloxacin. In most cases, it is active against the strains of *Vibrio cholerae*, followed by *Escherichia coli* (*E. coli*) and *Shigella* sp [15]. Furthermore, the ethanol extract of the fruits diminished the intestinal propulsion in rats [16, 17].

Diuretic activity

Bael plant demonstrates diuretic activity [18]. According to an article (ibid), it is seen that urine volume gets increased if we administer ethanolic fruit extracts to rats at a dose-dependent model. At a higher dose, it increases the frequent excretion of sodium (ibid). Apart from these, petroleum of the plant extract also shows diuretic impact but to a little extent [19].

Anti-inflammatory

To illustrate the anti-inflammatory activity of Bael plant, ethyl acetate and ethanol extracts were collected from the plant. In an animal paw edema models, inflammation was promoted and it decreased inflammation sign. Again, ethanolic extracts from Bael plant worked as a healing agent in colitis in rats which was 2, 4, 6-trinitrobenzene sulfonic acid (TNBS) induced [1]. As Bael has antimicrobial property as well, it helps in treating inflammation. Again, profoundly acute and sub acute anti-inflammatory activity is shown due to distinctive natural concentrates of the *A. marmelos* leaves [20]. This is because two constituents of similar activity are present in the plant extract namely lupeol and skimmianine. Initiation of histamine receptor is fundamental for unfavorably susceptible and asthmatic appearance. The alcoholic concentrate of *A. marmelos* leaves suppressed the histamine actuated constrictions. Thus it exhibited positive relaxant impact (ibid). In Ayurveda extensive and very frequent use of *A. marmelo s*is seen in prevention and curative purpose of many inflammatory diseases especially usage tender roots in different parts of India [21].

Antiamoebic and antihistaminic

The palatable fruit has been used for use as an antiamoebic and antihistaminic [22]. Seeds of unripe bael fruits are gum wrapped. A. marmelos gum is exceptionally expanded in nature with terminal units of galactose, galacturonic corrosive, rhamnose and arabinose [23].

Antimicrobial and antiviral activity

Antimicrobial activity of the plant ingredient was tested. To test this agar wall diffusion method was followed. Constituents such as aqueous, petroleum ether and ethanol extract of the leaves presented efficient antimicrobial activity. It showed activity against *Escherichia coli*, *Streptococcus pneumonia.* Ethanolic extract showed an effect against *Penicillium chrysogenum* [24, 25].

Antifungal

Essential oil of plant extract is proved antifungal against various fungi. They are *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, *Microsporum audouinii, Microsporum cookie*, *Epidermophyton floccosum*, *Aspergillus niger*, *Aspergillus flavus* and *Histoplasma capsulatum* [20]. It has worked against various dermatophytic fungi and showed high MIC and MFC. Actually, the extract interferes with Ca^{2+} dipicolinic acid metabolism pathway and thus prevents spore germination [20, 26].

Antibacterial

Antibacterial activity of the plant parts such as leaves, fruits and barks of *Aegle marmelos*is claimed and tested by disc diffusion method against *Bacillus subtilis*, *Staphylococcus aureus*,
Klebsiella pneumoniae, *Proteus mirabilis*, *Escherichia coli*, *Salmonella paratyphi* A and
Salmonella paratyphi B. Among chloroform, methanol extract and water-methanol extract showed significantly high activity against the bacteria [27]. Leaf extracts such as hexane, cold methanol, hot methanol and ciprofloxacin also showed antibacterial activity [28].

Antiviral

This plant extract showed impact against human coxsackieviruses B1-B6. It has even shown an effect against white spot syndrome in shrimp at IC150 concentration [29].

Antimalarial

In vivo and *in vitro* study reveals that alcoholic extract from seeds and leaves exhibit antimalarial activity against *Plasmodium berghei*. Seed showed impact both *in vivo* and *in vitro* however leaves showed impact *in vitro* only [20].

Anticancer activity

Cancer is the most concerned deadly disease in the whole universe. It will increase to 3 fold and scientists have predicted that. In such crisis situation, anything that can heal or soothe this disease will the boon for us. *A. marmelos* can be an effective weapon to boost our healing process in fighting cancer disease. Studies showed that plant extract can inhibit the increase of leukemic K562, T-lymphoid Jurkat, B-lymphoid Raji, erythroleukemia HEL, melanoma Colo38, and breast cancer cell lines MCF 7 and MDA-MB-231. It can even prevent cell proliferation [30]. Constituents such as 1-hydroxy-5, 7-dimethoxy-2-naphthalene-carboxaldehyde (Marmelin) present in the plant can prevent the growth of epithelial cancer cell. Furthermore, phytochemicals present in the plant such as lupeol, eugenol, citral, cineole and d-limonene present can show antineoplastic effects [31- 34].

Chemopreventive action

Chemoprevention provides a significant means of cancer treatment. According to a study, it is seen that fruit extract such as methanolic acid works against DMBA-induced skin carcinogenesis in mice. It has worked against hepatocarcinogenesis in Wistar rats. Constituents such as lupeol, eugenol, limonene, citral, rutin, and anthocyanins are responsible for this action [35, 36, 37].

Antioxidant activity

The role of antioxidants is preventing free radicals from cells by scavenging them and thus they also prevent cell damage which may lead to a major health concern. Due to the presence of some chemical compounds in Bael plant, it gives antioxidant impact. These compounds are flavones,

isoflavones, flavonoids, anthocyanin, coumarinlignans, catechins and iso catechins [38, 25]. In a compare- contrast study, it is seen that unripe fruits have more capability to diminish free radicals that ripe fruits. By using DPPH radical scavenging method, methanol and aqueous extracts were tested and both showed standard antioxidant activity [39].

Radioprotective effects

In radiotherapy is essential for cancer treatment and palliative care. However, it caused radio sensitivity of normal tissues. Invariable expose to cytotoxic effects of ionization radiation, tissue got damage. Here, antioxidant property containing constituent can give a soothing effect [22]. Further, bone marrow is the most vulnerable part to get affected by ionizing radiation as DNA gets ionized and some studies have revealed that leaf extract may diminish the impact. Similarly, leaf extract of Bael plant can even prevent gastrointestinal damage and liver damage as well (ibid). Diminishing lipid per oxidation is required in disease process by inducing free radicals. Due to antioxidant activity this reduces the damage (ibid). Lastly, radiation triggers inflammatory impact which in turn activates the physiologic and immunologic system. Immunity is weakened due to the opportunistic microbes. Bael leaf extract increase macrophage amount and thus gives immunomodulatory impact (ibid).

Antipyretic potential

In a study it is seen that Bael shows antipyretic effect. In a rat model (albino rats) where yeast induced pyrexia attacked rats were treated with Bael extracts and ethanolic extract elevated body temperature. This antipyretic impact was similar to the impact of 100 mg/kg body weight of paracetamol [40, 41].

Ulcer healing potential

Bael plant also demonstrates anti-ulcer activity. In a study, the ulcer was artificially induced by using indomethacin, stress, and pylorus. Methanolic showed potential anti-ulceration impact with a significant p-value of 0.05. It even reduces gastric juice amount, free acidity and increased pH. In another study, fruit pulp reduced mucosal thickness, superoxide dismutase, catalase activity and glutathione level [42].

Antigenotoxic activity

Antigenotoxic agents are those agents which prevent toxic elements to damage genetic information by cell mutation and finally cancer. Bael can work as an antigenotoxic agent. In a study conducted by [43], it is seen that methanol inhibits genotoxicity by diminishing SOS response (*E. coli* PQ37) in hydrogen peroxide and aflatoxin-induced toxicity. Methanol reduced the toxicity by 70.48% in hydrogen peroxide-induced toxicity [43]. In some studies, it is seen that Bael extract polyphenolic can reduce aflatoxin B1 induced toxicity by inhibiting the activity of cytochrome P450 [44].

Anti-arthritis activity

In collagen-induced arthritis in a rat model, leaves of this plant showed anti arthritis activity. Radiologic and histopathologic changes were prominent in the study [45].

Hepatoprotective Effect

The hepatoprotective effect is found in a study it is seen that hepatoprotective impact wherein alcohol-induced liver injury 30% ethyl alcohol was given [46].

Insect controlling properties

Essential oil present in Bael leaf were used against stored grain insect pests included *Callosobruchus chinensis* (L.), *Rhyzopertha dominica* (F.), *Sitophilus oryzae* (L.) and *Tribolium castaneum*. It significantly decreased and controlled crop damage [47]. It worked as an insect repellent against *Sitophilous oryzae* and *Tribolium castaneum*. However, it did not show complete repellent activity [48].

Cytoprotective Effect

In heavy exposure to heavy metal, Bael leaves work as cyto-protector by stabilizing plasma membrane and activates antioxidant activity. For instance, in *Cyprinus carpio* (Freshwater fish) it showed similar impact [49].

Antiproliferative activity

Ethanolic extract of stem bark is claimed to show an antiproliferative effect against the human tumor. In *in vitro* study. It inhibits proliferation in tumor cell lines, leukemia K562, melanoma Colo 38, breast cancer [50].

Antifertility activity

It is depicted that leaf, seed and fruit of Bael plant may interfere with male fertility in a reversible manner. In *A. marmelos* bark, two chemical compounds such as marmin and fagarineare present which is claimed to be responsible for the reduction of male fertility [51, 52]. According to [51] methanolic extract of *A. marmelos* reduces reproductive organ weight and serum testosterone levels (ibid). It can even reduce sperm density, motility, viability and sperm acrosomal integrity (ibid). Changes of elongated spermatids, nuclear chromatin condensation and degeneration were seen and significance histopathological changes such as necrosis are seen along with testicular cytotoxicity (ibid). But interestingly, on withdrawal it restores the morphological changes (ibid) [53].

Anti-obesity

A. marmelos has shown anti-obesity action in some studies. It was seen that plant leaf extracts such as dichloromethane (DCM), ethyl acetate (EtOAc), n-butanol, umbelliferone, and esculetin have the anti-obesity impact. In a rat model and dose-dependent study, it is seen that it counteracts obesity by lipolysis in adipocyte cells. Extracts like umbelliferone lower total cholesterol and total triglycerides in the body and reduces weight [54].

Toxicological and other studies

Bael plant is considered a a safe plant. But still Veerappan *et al* conducted a histopathological study to see the impact. It revealed no significant changes in cell structure and appearances in heart, liver, kidney, spleen, testis and brain. This study was conducted in a Wistar rats model for a consecutive study for 14 days with a dose of 50mg/kg. It did

not even cause any short-term toxicity. In another study for 30 days with a dose of 250mg/kg, it did not show any changes [55, 8, 56]. Moreover, in Bael plant. Riboflavin or vitamin B2 is present and they are the very essential nutrient in human nutrition [57]. They play a crucial role in producing energy (ibid). The nature and convergence of natural acids are vital variables impacting the organoleptic properties of a natural product. The ripe *A.marmelos* fruit is a potential source of energy mostly due to the presence of carbohydrates (ibid).

Conclusion

Nature has given us a whole warehouse of natural ailments remedies. From the warehouse, *Aegle marmelos* (L.) is one of the greatest essential medicinal plants. Constituents found in the plant are the key factors in this regard to provide very vital pharmacological activities such as antifungal, antioxidant, antibacterial, antiprotozoal, antispermatogenic, anti-inflammatory, anthelmintic, antidiabetic, laxative, febrifuge and expectorant, chemopreventive, antipyretic, ulcer healing, antigenotoxic and diuretic. Moreover, mostly all the parts of the plant are useful. From bark to root, everything is usable for disease curative purpose! Thus this study reveals that still there are scopes to investigate more on its potentiality to get used as a commercial drug. A fundamental innovative work ought to be embraced for the advancement of medicine for their better monetary and remedial usage.

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