Review Article

A Systematic Review on Biochemical and Pharmacological Properties of the Active Phytochemicals Present in *Aegle marmelos* (L).

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ABSTRACT

Aim: Medicinal plant research is becoming increasingly prevalent since it is devoid of pollution, toxins and adverse effects. In recent years, it has come to light that a variety of ailments can be treated with plant-derived compounds from fruits, seeds, leaves, bark, etc. *Aegle marmelos* (Bael tree) is an important medicinal as well as a sacred tree with diverse therapeutic values. This review is to present current knowledge on the ethnomedicinal applications, nutritional composition, bioactive constituents and pharmacological activity of *A. marmelos* to validate its therapeutic potential. **Materials and Methods:** Out of 120 articles identified, 62 met the inclusion criteria, forming the basis for synthesizing data on ethnomedicinal uses, bioactive constituents and pharmacological activities of *A. marmelos*, contributing to a holistic understanding of its therapeutic potential. The study employed a robust methodology, including a comprehensive literature search across prominent databases using keywords related to *Aegle marmelos* and also its medicinal properties. **Results:** These research and review articles provided about the pharmacological properties of *A. Marmelos*. It has been utilized to treat several health issues in ancient medicinal system, including diarrhea, diabetes, fever, ulcers, inflammations and bacterial infections. The bioactive metabolites including alkaloids, terpenoids, saponins, pectins, steroids, flavonoids, tannins, carotenoids and phenolics. **Conclusion:** Based on our studies, *in vitro* as well as *in vivo* investigations revealed that *A. marmelos* has therapeutic benefits such as antioxidant, analgesic, anti-inflammatory, antidiarrheal, cardioprotective, anticancer and antimicrobial properties that proved its historical uses.

Keywords: *Aegle marmelos*, Bael, Phytochemicals, Medicinal plant.

INTRODUCTION

Aegle marmelos (Linn.), belongs to the family Rutaceae, which is one of the prominent and underutilized aromatic medicinal trees of Indian heritage.[1] It is popularly known as the Bael fruit tree and the other common names include Indian quince, Bengal quince, golden apple and holy fruit. It is a moderate-sized, slender, slow-growing, tough tropical tree. It grows to an elevation of 1200 m in the western Himalayas and is found on Andaman Island and it is dispersed across deciduous woods of India.[2] *A. marmelos* is endemic to Northern India, although it can also be found in Bangladesh, Ceylon, Burma, Indo-China and Thailand.[3] Hindus often regard this tree as sacred because they offer its leaves when they worship Lord Shiva. Different parts of this tree at various stages of maturation are utilized as ethnomedicine to treat a variety of human as well as animal diseases. As far back as 800 B.C., this tree is recorded in prehistoric literature. It is planted all over India because of its mythological significance and is primarily grown close

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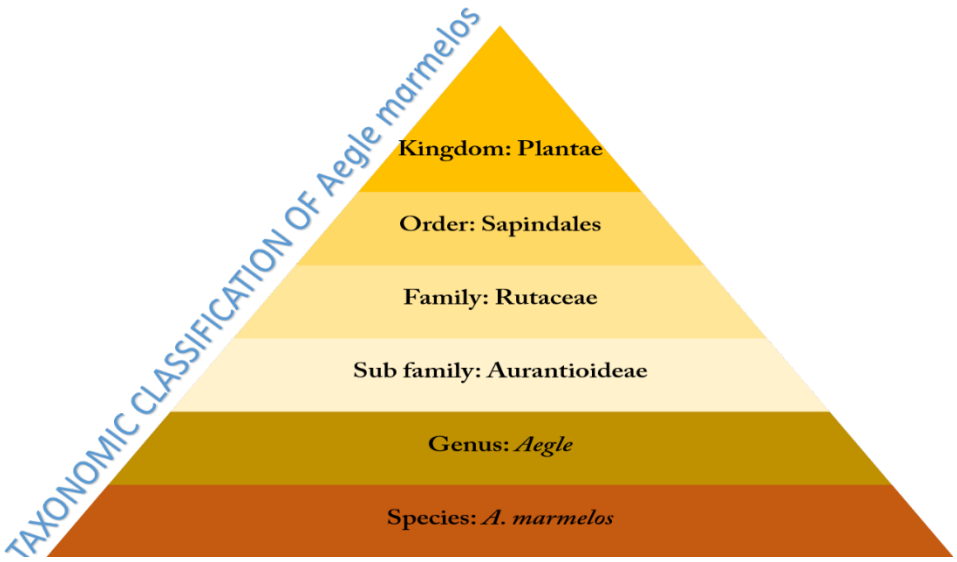

Figure 1: Taxonomic classification of *A. marmelos*.

to temples.[4] In this review, we have summarized the botanical description, therapeutic uses, non-therapeutic uses, phytochemistry and pharmacological activities of *A. marmelos*. Figure 1 represents the taxonomic classification of *A. marmelos*.

MATERIALS AND METHODS

Literature Search Strategy

A broad search was executed across multiple online databases, comprising Scopus, Web of Science, PubMed and Google Scholar. The search strategy involved keywords related to *Aegle marmelos*, ethnomedicinal applications, nutritional composition, bioactive constituents and pharmacological activity.

Eligibility criteria

Eligibility of articles was determined based on predefined criteria for inclusion and exclusion. Inclusion criteria encompassed studies focusing on ethnomedicinal uses, phytochemical composition and pharmacological properties of *A. marmelos*. Only peer-reviewed articles written in English were taken into consideration.

Data Extraction

Data relevant to ethnomedicinal applications, bioactive constituents and pharmacological activities of *A. marmelos* were extracted from selected articles. Information on methodologies, results and conclusions was systematically recorded to ensure accuracy and completeness. The compiled data were synthesized to offer a holistic perspective into the ethnomedicinal applications and pharmacological prospects of *A. marmelos*. Data synthesis involved categorization based on the types of bioactive compounds identified and the observed pharmacological activities. The findings were critically analyzed to validate the therapeutic potential of *A. marmelos* and identify areas for further research.

RESULTS

The exploration of Google Scholar, Web of Science, PubMed and Scopus resulted in the identification of 120 articles. Following the assessment of eligibility, 62 articles were identified as meeting the inclusion criteria and were thus included in the review. These articles collectively provided comprehensive insights into the ethnomedicinal applications, nutritional composition, bioactive constituents and pharmacological activities of *A. marmelos*.

Nutritional Properties

The nutrients of *A. marmelos* are particularly advantageous to human health, as evidenced by numerous research investigations. Recent studies have examined the nutritional advantages of *A. marmelos* as well as its low-cost manufacturing and marketing to promote environmental health. The major part of *A. marmelos* is water, ranges from 60% to 65%, followed by carbohydrate, sugars, fibers and other compositions includes vitamins, minerals, amino acids and various fatty acids.[5] Bael helps prevent rancidity and colour loss since as it holds a significant quantity of vitamin A, B and C all and these can serve as antioxidants.[6]

A. marmelos, like other fruits, provides varying nutritional contents based on the maturation stages. Bael seed contains a greater percentage of fat (14.94%).[7]

PHYTOCHEMISTRY

The GCMS profiling of alcoholic extract of *A. marmelos* leaves showed the existence of the bioactive compounds such as p-cymene, 1-dodecanol, Cyclooctasiloxane, Dotriacontane, Phthalic acid, Hexadecanoic acid, Cyclodecasiloxane, Oleic acid, Octadecanoic acid, Alpha-Neodene, Phenol, Nonahexacontanoic acid, Nonacosane, Benzoic acid, 13-docosenoic acid, Retinoic acid and Farnesyl acetone.[8] The fatty acid- derivatives like decanoic acid, methyl ester, octanoic acid ester, Pentadecanoic acid, methyl ester, 9-Hexadecanoic acid, methyl ester, Octadecatrienoic acid, ethyl ester, Eicosanoic acid, methyl ester were reported in *A. marmelos* seed oil.[9] The hydro-alcoholic extract of *A. marmelos* unripe fruit contains gallic acid and quercetin.[10] The study done by Shakya war *et al*.[11] concluded that the phytochemicals such as tannins, alkaloids, proteins, carbohydrates, starch, resin, coumarins, tannins, phlobatannins, polyphenols, vitamin C, steroids and glycosides have existed in the different parts of *A. marmelos* fruits such as pericarp and pulp.

PHARMACOLOGICAL ACTIVITIES

The pharmacological potential of *A. marmelos*, encompassing antioxidant, inflammation-suppressing, hypoglycemic, anti-cancer, insecticidal, anti-diarrheal properties, offers a multifaceted approach to therapeutic interventions (Figure 2).

ANTIOXIDANT EFFECTS

The methanol extracts of leaves, seeds, ripe fruit and half-ripe fruit of *A. marmelos* were found to scavenge DPPH and Nitric oxide radicals in a dose-dependent manner. Maximum DPPH radical scavenging activity (IC_{50}=251.2 µg/mL) was shown by a methanol extract from a half-ripe fruit.[12] From the earlier research, it was able to draw the conclusion that *A. marmelos* enhances the antioxidant state in the tissues of diabetic rats. It may be suggested that the mechanism of action of *A. marmelos* seems to be similar to glibenclamide action.[13] Furthermore, in an effort to discover an alternate form of treatment for different ailments, the therapeutic value of this plant is being investigated extensively.[14] A previous work revealed that *A. marmelos* showed a neuroprotective effect against STZ-induced oxidative imbalance and cognitive deficits in male rats, which has proven its anti-oxidant activity.[15] According to Surolia

Figure 2: Pharmacological activities.

et al.[16] *A. marmelos* pulp pectin has the highest percentage of DPPH radical inhibition when compared to *A. marmelos* shell and seed pectin at all concentrations.

ANTICANCER EFFECTS

The anticancer activity against gastric cancer cells was studied previously by Sampath *et al.*[17] showed an IC_{50} value of 40.33 µg/mL that concluded the synthesized AgNPs from *A. marmelos* can act as a novel anticancer agent. The anti-cancer potency of the *A. marmelos* fruit pulp (aqueous extract) was evaluated using an MTT assay, which shed light on the inhibitory activity (IC_{50}=47.92 µg/mL) against the Breast cancer cells (MCF-7). The study provided promising guidelines regarding the potential uses of *A. marmelos* as an anticancer agent.[18] The substantial anti-cancer benefits of methanol and acetone extracts from *A. marmelos* on HEp-2 and MDA-MB-231, while protecting normal Vero cells.[19] The ethanol extract of fruit pulp of *A. marmelos* exhibited remarkable anti-oncogenic effects against the DMBA-induced breast cancer mice model. This study also demonstrated that the pulp had considerably reduced the size of the mammary tumour along with a significant decrease in biomarkers in serum like malondialdehyde, glucose and TNF-α level.[20]

Topical application of *A. marmelos* bark extract resulted in a considerable increase in the average latent period of tumour development, a significant decrease in tumor volume, tumour frequency and the overall number of papillomas and also a substantial reduction in the concentration of glutathione, were observed in 7,12-dimethylbenz[a]anthracene-induced skin papilloma mice model.[21] The results of the study carried out by Kumar *et al.*,[22] demonstrated the anti-ocnogenic property of the leaves of *A. marmelos* extracted using methanol against MCF-7 cells. The therapeutic effectiveness of an anticancer drug depends on its capacity to prevent the growth of tumours both in their early and later stages of formation.

ANTI-BACTERIAL EFFECTS

A. marmelos plays a vital in herbal medicine and is far more beneficial and secure than synthetic compounds. The *A. marmelos* fruits extracted using various solvents inhibited the growth of *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*.[23] The methanol as well as chloroform derived leaves extracts showed excellent bactericidal effects against the gram-positive as gram-negative bacteria. The study suggested concentration-dependent anti-bacterial activity.[24] The *A. marmelos* leaves methanolic and acetone extract revealed substantial anti-bacterial action against tested microorganisms. *Serratia marcescens* exhibited the highest sensitivity among the tested organisms, as indicated by significant zones of inhibition across all four *A. marmelos* leaf extracts.[19] Interestingly, the bactericidal property of the synthesized nanoparticles was effective against the microorganisms like *Staphylococcus aureus*, *Escherichia coli*, *Aeromonas hydrophila*, *Pseudomonas aeruginosa* and *Streptococcus pyogenes*.[25] The extraction of *A. marmelos* leaves and fruit was carried out using ethanol, hexane and distilled water respectively. This study elicited that the ethanol extract had effectively inhibited the multi-drug resistant *Escherichia coli* than the aqueous and hexane extracts.[26]

ANTI-FUNGAL EFFECTS

The acetone, aqueous, methanol and chloroform extract of *A. marmelos* fruits exhibited fungicidal activity against *Candida albicans* (MTCC-227) and *Aspergillus brasiliensis* (MTCC-1344).[23] The essential oil extracted from the *A. marmelos* leaves possess anti-fungal activity, which was proven by the zone of inhibition with a diameter of 30 mm formed against the test organisms such as *Candida albicans* and *Aspergillus niger* respectively.[22] Significant fungicidal activity was exhibited against the *Fusarium oxysporum*, followed by *Pestalotia foe dans* and *Paecilomyces variotii* by the various concentrations (25, 50 and 75 µg/mL) of *A. marmelos* leaves extract.[28] *A. marmelos* extract completely inhibited the mycelial formation of *Pythium debaryanum* at the concentration of 1 mL concentration and so the methanol extract of *A. marmelos* leaves and fruits were recorded with a maximum inhibition of fungal growth.[29] The previous reports of Sriramulu and Sumathi[30] demonstrated the fungicidal effects of Iron oxide nanoparticles synthesized from *A. marmelos* against the phytopathogen *Fusarium solani* (12±0.53 mm), isolated from soil.

ANTI-VIRAL EFFECTS

The Seselin isolated from *A. marmelos* showed promising antiviral activity against (BmNPV) *Bombyx mori nucleopolyhedrovirus*.[31] *In silico* studies by Andleeb *et al.*,[32] revealed the good binding affinity of Quercetin, catechin and marmenol found in *A. marmelos* towards the HN Protein of NDV (Newcastle Disease Virus). The compound seselin of *A. marmelos* demonstrated the strongest receptor interaction with spike protein, main protease and its free enzymes of SARS CoV-2.[33]

ANTI-ULCER EFFECTS

A. marmelos have been shown to possess antiulcer activity against experimentally induced ulcer models. The anti-ulcer activity of an aqueous extract of *A. marmelos* leaves was examined in Wistar rats with ulcers induced using indomethacin. The effects of 175 mg/kg and 350 mg/kg of *A. marmelos* extract on gastrointestinal volume, acidity as well as ulcer index were noted, which was statistically significant ($p<0.01$) than the control group.[34] The ulcer protection percentage of ethanolic extract of *A. marmelos* leaves was found to be 56.33% in the ethanol-induced gastric ulcer model, which was higher than the standard drug Omeprazole (50.44%).[35] *A. marmelos* fruit extract has protective effects against the Aspirin-Induced Gastro-Duodenal ulcer in Albino mice Model.[36] The findings of Sharma *et al*.[37] showed the anti-ulcer action of aqueous and methanol extract of *A. marmelos* seed against the Indomethacin Induced and Stress-induced Ulceration models respectively.

ANTI-GLYCEMIC EFFECTS

Patients with Non-Insulin Dependent Diabetes Mellitus who were taking sulfonylurea at a dose of 5 or 10 mg/day had a decrease in their blood and urine glucose levels after taking *A. marmelos* extract for eight weeks.[38] Furthermore, the previous study of Arumugam *et al*.,[38] also evidenced the potent anti-diabetic activity of *A. marmelos* extract. Significant reductions the glycemic index were achieved in streptozotocin-induced diabetes in rabbits treated with extracts of *A. marmelos* leaves and calluses. Moreover, the bark extract of *A. marmelos* also showed anti-diabetic activity in the diabetic rats.[40] Likewise, the fruit extract of *A. marmelos* exhibited hypoglycemic activity in alloxan-induced diabetes in Male Sprague Dawley rats.[41] An aqueous extract of *A. marmelos* fruit administered orally two times a day for four weeks at a dosage of 250 mg/kg body weight effectively lowered the blood glucose levels of streptozotocin-induced diabetic rats. Comparing this dosage to the usual medication glibenclamide, the findings were effective.[42]

ANTI-DIARRHEAL EFFECTS

Many medications are prepared using fruit, roots, bark, leaves, ripe fruit rind and flowers. *A. marmelos* has been employed historically for a variety of ethnobotanical uses. Based on the data gathered, it appears that *A. marmelos* has anti-diarrheal properties.[43] *A. marmelos* decoction proved beneficial in treating a range of infectious diarrheal diseases brought on by *Vibrio cholerae, Shigella flexneri*, Enteropathogenic *Escherichia coli*, *Enter invasive Escherichia coli*, Heat-labile toxin producing enterotoxigenic *Escherichia coli* and, to a lesser degree, rotaviral infections and giardiasis.[44]

ANTI-INFLAMMATORY EFFECTS

A. marmelos root bark aqueous extract significantly decreased inflammation in paw edema induced by carrageenan and granuloma induced by cotton pellets, with the percentage of inhibition of 46% and 9.2%, respectively.[45] Young (2 and 3-year-old) roots from Gujarat and young (1-year-old) roots from Odisha displayed the maximum anti-inflammatory effects by inhibiting pro-inflammatory cytokines and enhanced the anti-inflammatory cytokines like IL-2. *A. marmelos* extracts' anti-inflammatory properties were found to be similar to those of mature stem and root barks when tested *in vivo* on roots, stems and leaves.[46] The phytocompound Marmelosin, from the *A. marmelos* elicited anti-inflammatory effects.[47] The study by Kumari *et al*.[48] demonstrated that the dried flowers extract of *A. marmelos* displayed a notable increase in the infiltrating of peritoneal cells in rats, reduction of Nitric oxide generation by rat peritoneal cells and suppression of urticaria on the rat's skin following histamine injection.

INSECTICIDAL EFFECTS

The essential oil extracted from the *A. marmelos* showed insecticidal effects against the stored grain pests.[49] Interestingly, the ovicidal, larvicidal, adulticidal and repellant effects of the essential oil from the *A. marmelos* leaves were examined against the insects *Aedes aegypti* and *Culex quinquefasciatus*.[50] Various concentrations of the petroleum ether, aqueous, methanol and ethanol extract of *A. marmelos* leaves dramatically decreased the oviposition and adult emergence of *Callosobruchus chinensis*.[51]

ANALGESIC EFFECTS

The study done by Shankarananth *et al*.[52] demonstrated the analgesic activity of *A. marmelos*. The acetic acid-induced writhing was greatly diminished by the methanolic leaves extract of *A. marmelos* whereas, the analgesic efficacy was significantly increased at doses of 200 and 300 mg/kg of methanolic extract of *A. marmelos* leaves in the tail flick test. The analgesic efficacy of the aqueous extract of *A. marmelos* stem bark was found to be dose-dependent in acetic acid-induced writhing and tail flick test in mice models.[53] The ethanol extract of *A.*

marmelos leaves (200 mg/kg) and fruit pulp (200 mg/kg) demonstrated their analgesic property by the reduced number of writhing and the period was increased in Eddy's hot plate method.[54]

CARDIOPROTECTIVE EFFECTS

Methanol extract of *A. marmelos* leaves pre-treated mice model showed a substantial reduction in serum indicators like creatinine phosphokinase MB, serum glutamate oxaloacetate transaminase and serum glutamate pyruvate transaminase in a dosage-related manner, indicating cardiac protection. Histopathological findings also further confirmed the cardioprotective effects and benefits of *A. marmelos*.[55] Likewise, the aqueous extract of *A. marmelos* leaves exhibited excellent cardioprotective action against the Isoproterenol induced Myocardial injury in adult male Albino Wistar rats.[56] The research of Jagetia and Venkatesh,[57] also confirmed the cardioprotective activities of the hydroalcoholic extract of *A. marmelos* against the Doxorubicin hydrochloride-induced cardiotoxicity in mice.

HEPATOPROTECTIVE EFFECTS

Methanolic extract of *A. marmelos* leaves also confirmed its hepatoprotective benefits against Carbon tetrachloride-treated albino Wistar rats.[58] *A. marmelos* treatment significantly reduced the impacts of paracetamol in a dose-related manner. The maximum hepatoprotective action of *A. marmelos* was observed at 100 mg/kg.[59] Interestingly, another work by Rathee *et al*.[60] demonstrated that the hepatotoxicity was dramatically reversed in the carbon tetrachloride-treated Wistar rat models by the oral administration of the substantially low dose of *A. marmelos* (25 mg/kg) combined with piperine.

WOUND HEALING EFFECTS

The methanolic extract of *A. marmelos* was applied topically twice daily for 12 days in a row, the excision wound area in mice was dramatically decreased (0.03 ± 0.02 mm^2) and healed.[61] The report of Gautam *et al*.[62] evidenced the remarkable wound-healing potency of the 50% ethanolic extract of *A. marmelos* fruit pulp in the excision, incision and dead wound models. *A. marmelos* treated groups showed complete constriction and epithelization of wounds on the 20th day, which was observed on the 24th day for the control group.

CONCLUSION

The above evidence shed a light on the folklore uses and various therapeutic potential of *A. marmelos*. It has been enriched with immense phytochemicals like alkaloids, tannins, coumarins, saponins, terpenoids, etc., The whole tree or any of its parts like stem, leaves, flowers, fruits, etc. can be used for several health ailments like diabetes, microbial infection, inflammation and as painkillers. Based on its relevance in folk medicine and the promise it has shown in preliminary studies, the *A. marmelos* fruit can also be consumed as a functional food, which merits a wide range of health advantages. *A. marmelos* continues to be a crucial natural medicine for a variety of health ailments since many of its traditional uses have been supported by research over time. However, a significant amount of work is still necessary to comprehend the role of *A. marmelos* in various therapeutic mechanisms and also to isolate the specific lead compounds effective against a variety of serious and chronic disorders.

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AUTHORS CONTRIBUTIONS

All the authors were contributed equally for concept making, data acquiring, investigating and writing the manuscript.

CONFLICT OF INTEREST

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

ABBREVIATIONS

DPPH: 2,2-diphenyl-1-picrylhydrazyl; **STZ:** Streptozotocin; **IL-1β:** Interleukin-1β; **MIP1:** α-Macrophage inflammatory protein-1 alpha; **IL-6:** Interleukin-6; **TNF α:** Tumour Necrosis Factor

alpha; **MTT:** 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide.

SUMMARY

A. marmelos (Bael tree) holds significant therapeutic value in traditional medicine, addressing ailments like diarrhea, diabetes, fever and bacterial infections. This review aims to consolidate current knowledge on its ethnomedicinal applications, nutritional content, bioactive constituents and pharmacological activities. The work utilized an extensive search in major databases using *A. marmelos*-related terms. Out of 120 publications found, 62 were eligible, laying the groundwork for investigating the pharmacological properties of *A. marmelos*. Phytochemical screening revealed diverse compounds, including alkaloids, flavonoids and terpenoids. *In vitro* as well as *in vivo* studies underscore its antioxidant, analgesic, anti-inflammatory and antimicrobial properties, validating its historical medicinal uses and highlighting its potential for future therapeutic interventions.

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