



AEGLE MARMELOS: AN OVERVIEW ON ITS PHARMACOLOGICAL PROPERTIES

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Abstract : *Aegle marmelos* also known as Bael, is a plant with significant medicinal properties from the family Rutaceae. *A. marmelos* is recognized in traditional medicine for its numerous therapeutic properties and is used to treat various diseases. In recent years, there has been a lot of research to investigate the medicinal qualities of *A. marmelos* using advanced scientific techniques. This has resulted in extracting and examining several bioactive compounds from various parts of the plant for their pharmacological impacts. This review focuses on the therapeutic uses of various parts of the Bael tree, including the root, bark, fruit, leaf, and flower. The present review provides an overview of the existing scientific research on the pharmacological effects of *Aegle marmelos*.

Keywords - *Aegle marmelos*, Phytochemical components, Pharmacological activities.

INTRODUCTION

For thousands of years, people have used plants as a natural supply of therapeutic chemicals. Many plants and products made from them are used by humans as remedies and treatments for a wide range of medical and psychological conditions. 25% of commonly used medications are derived from plants. [1]

Over the last few years, researchers have attempted to uncover and validate plant-derived compounds for the treatment of numerous ailments. [2]

Many pharmacologically active principles and chemicals found in Indian medicinal plants are thought to be abundant and are frequently utilized in home treatments for a variety of illnesses. [3]

Aegle marmelos Linn, often known as Bael, is a member of the Rutaceae family. Because of its many medicinal uses, the native Indian medical system has regularly used this plant. *A. marmelos* Linn (Rutaceae) is also known as Bengal quince, Bilva, Indian quince, Golden apple, Holy fruit, Bel, Belwa, Sriphal, Stone apple, and Maredu in India. [4] Bael is widely distributed throughout India, with the northern districts of Bengal holding an extensive range of variations in bael species. Bael is widely distributed throughout India, specifically in Burma, Bengal, Central, and chromosomeSub-Himalayan forests. [5]

India's most significant medicinal plant, Bael (*Aegle marmelos*), has been recognized since Charak's time (1500 B.C.). The Bael tree is used in various ayurvedic treatments, with every part such as the stem, bark, root, leaf, flower, seed oil, and fruits in any stage of ripening and maturity being utilized. [5] Numerous phytochemical components, including phenols, flavonoids, alkaloids, cardiac glycosides, saponins, terpenoids, steroids, and tannins, have been identified from different plant sections. These compounds are well known for their biological and pharmacological efficacy against a variety of chronic diseases, including cancer, cardiovascular, and gastrointestinal disorders. [6]

PLANT PROFILE**TAXONOMICAL CLASSIFICATION [7, 4]****Table 1:** Taxonomical classification

TAXONOMICAL CLASSIFICATION	
Sub-kingdom	Plantae
Sub-kingdom	Tracheobionta
Super division	Spermatophyta
Division-	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Sapindales
Family	Rutaceae
Genus	<i>Aegle</i>
Species	<i>marmelos</i>
Botanical name	<i>Aegle marmelos</i>

BOTANICAL DESCRIPTION

The *Aegle marmelos* is a tree of medium size, growing at a slow pace and can reach heights of 12 to 15 meters. It has a short trunk, thick, soft bark that flakes, and spreading, occasionally prickly branches, with the bottom branches drooping. There are many rigid, straight spines on young suckers. From injured branches, a transparent, sticky fluid that resembles gum Arabic drips down in long threads and gradually solidifies. It tastes delicious at first, but soon it irritates the throat. [8]. The leaves are arranged alternately, usually in a trifoliate pattern, with three to five leaflets per leaflet, each measuring four to ten centimeters in length and two to five centimetres in width. The color of young leaves is lighter green, while older leaves become a darker shade of green. [9] The bark is delicate, light grey, and exfoliates in irregular flakes. The flowers are greenish white, sweet-scented. The leaf axil holds some lateral panicles which contain ten flowers. [10]

CHEMICAL CONSTITUENTS [11-13]

From the different parts of *Aegle marmelos*, several phytoconstituents have been identified, these can be categorized as shown in **Table 2**

A. marmelos contains phytoconstituents such as

- Alkaloids: Aegeline, fragrine, aegelenine, rutacine, ysitosterol, marmeline, dictamine, cinnamide.
- Coumarins: Marmin, Marmelide, Psoralen, Imperatonin, marmesin, umbeliferone, Xanthotoxol, impertonin, scoporone, scopoletin, psoralen.
- Terpenoids: Cineol, Caryophyllene.
- Polysaccharides: Galactose, arabinose, L-rhamanose.

Table 2: Phytoconstituents that have been extracted from different components of *Aegle marmelos*.

SL NO	PART	PHYTOCONSTITUENTS
1	Leaf	Skimmianine, Aegeline, Lupeol, Cineol, Citral, Citronella, Cuminaldehyde, Eugenol, Marmesinine, Rutin, Y-sitosterol, β -sitosterol, Flavone, Glycoside, O-isopentenyl, Halfordiol.
2	Fruit	Marmelosin, Luvangetin, Aurapten, Psoralen, Marmelide, Tannin
3	Bark	Skimmianine, Fagarine, Marmin
4	Seed	Essential oil: P-cymene, cineol, citronellal, citral, D-limonene, A-D-phellandrene, and cumin aldehyde

Biological activities of isolated Bael compounds [4,11]

Various parts of the *Aegle marmelos* tree have yielded numerous chemical constituents, but only a small number have undergone investigation for their biological activity. The bioactive compound and their biological activity are shown in **Table 3**

Table 3: The bioactive compound from *Aegle marmelos* is listed along with their corresponding biological activity.

Bioactive compounds isolated from different parts of <i>Aegle marmelos</i>	Reported biological Activity
Aegelin	Anti-diabetic
Auraptene	Inhibition of heart rate
Cineol	Expectorant, Disinfectant, antiulcer
Citral	Antibacterial, antifungal, antiallergic and antiparasitic
Citronellal	Anticancer, antiseptic
Cumin aldehyde	Antibacterial
D-limonene	Dissolve containing gallstones
Eugenol	Antibacterial, hepatoprotective, Antiulcer, analgesic and anti-oxidant
Fagarine	Abortifacient
Flavone	Antifungal
Imperatorin	Antiviral
Luvangetin	Antiulcer
Lupeol	Cardioactive, Anti-inflammatory
Marmin	Antiulcer
Psoralen	Antispasmodic
P-cymene	Anti-viral, antitumor, antibacterial and antifungal
Psoralen	Cytotoxic, antispasmodic
Rutin	Antioxidant, anti-inflammatory
skimmianine	Sedative, anticonvulsive, analgesic, anticancer, hypnotic, antipyretic, antidiuretic, antimalarial.
β Sitosterol	Antioxidant

PHARMACOLOGICAL USES OF *AEGLE MARMELLOS*

A. marmelos is a common medicinal and nutritional plant in the Rutaceae family. In recent history, this plant has been recognized for a variety of medical characteristics. [14]

1. ANTIOXIDANT ACTIVITY

Free radicals destroy macromolecules such as DNA, proteins, and lipids in the body through oxidative stress caused by metabolic processes or exposure to environmental or chemical stimuli. Oxidative stress contributes to diseases such as cancer and diabetes. Natural products have been shown to contain a high concentration of antioxidants other than Vitamin C, E, and carotenoids. Antioxidants slow or inhibit free radical-catalyzed processes. Medicinal plants' high phenolic and flavonoid content gives them antioxidant qualities. Many reports have indicated that *A. marmelos* has antioxidant action against a range of free radicals. [16]

Vanitha R P., et.al., stated that *Aegle marmelos* (AM) contains tocopherols, glutathione, ascorbic acid, and flavonoids. The leaves of AM were extracted with methanol (ME), ethanol (EE) and water (WE), Water extract (WE) of *Aegle marmelos* showed maximum radical scavenging activity. *Aegle marmelos* water extract showed a significantly higher ($p \leq 0.01$) Radical scavenging activity. [17]

Raman G., et.al., conducted a study to evaluate the antioxidant activity of ethanolic extract of *Aegle marmelos* root and leaves against CCl₄-induced toxicity in animal models. The study found that CCl₄ considerably increased ($p < 0.001$) the levels of MDA (malondialdehyde) in lipid peroxidation and decreased the activity of antioxidant enzymes such as CAT (catalase) and SOD (superoxide dismutase) in the liver in contrast to healthy control. Root and leaf extract of *Aegle marmelos* (100 mg/kg, p.o.) and gallic acid, a standard medication, significantly ($p < 0.001$) reduced the increased MDA levels. *Aegle marmelos* root ($p < 0.001$) and leaf ($p < 0.05$) significantly increased SOD and catalase activity. [18]

Sharmila et.al., conducted a study to evaluate the hypoglycaemic and antioxidant effect of aqueous extract of *Aegle marmelos* leaves (AML). It was observed that there was an increased oxidative stress in diabetic rats as evidenced by higher MDA (erythrocyte malondialdehyde) and lower GSH (Erythrocyte Glutathione) compared to controls. Administration of AML extract decreased MDA levels and increased GSH levels and *A. marmelos* treatment was found to decrease the liver lipid peroxidation level significantly at $p < 0.001$. Thus, AML reduces oxidative stress. [19]

2. ANTI-MICROBIAL ACTIVITY

The concerning rise in the prevalence of infections caused by microbes resistant to antibiotics has compelled scientists to explore substances possessing possible antimicrobial properties. Research on the effects of plant extracts on microorganisms has been conducted all over the world.

Mujeeb F., et.al., A study was conducted aimed at evaluating the phytochemical potential and antibacterial activity of *Aegle marmelos* aqueous and methanolic leaf extracts. The extracts demonstrated strong antibacterial activity against microbes. The aqueous extract showed the maximum inhibitory action against *S. epidermidis*, whereas the methanolic extract was most effective against *S. aureus* at a dosage of 40 mg/mL. [20]

Priyadarshini P., et.al., conducted a study to test the antimicrobial potential of in-vitro and in-vivo derived callus against 12 phytopathogens. The diffusion test demonstrated that the chloroform and methanol extract of *A. marmelos* roots exhibited antimicrobial activity by effectively inhibiting the growth of test pathogens. Two of the phytopathogens that were tested showed growth inhibition, *Alternaria helianthi* and *Sclerotium rolfsii*. The chloroform extract of *A. marmelos* calli exhibited the most significant antibacterial activity, with a MIC (minimum inhibitory concentration) of 2.0 μ L, resulting in a 94.45% inhibition. [21]

Suresh K, et.al., evaluated the anti-microbial activity of the different parts of *Aegle marmelos* plant like leaves and flowers, and were subjected to extraction by using methanol as a solvent. They showed greater inhibitory effects against gram-negative and gram-positive organisms. The organisms used were *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Salmonella typhi*, and *Staphylococcus aureus*. Antibacterial activity of Methanolic leaf and flower extract of *Aegle marmelos* was maximum in *salmonella typhi* and *staphylococcus aureus* respectively. [22]

Yogeshwar, et.al., evaluated the antifungal activity of acetone, ethanol, methanol and chloroform leaf and fruit extracts of *Aegle marmelos* and other medicinal plants against soil-borne fungi, *Pythium debaryanum*. *A. marmelos* leaves and fruits methanol extract was found to have the most inhibitory effect on fungal growth. [23]

3. ANTI-DIABETIC ACTIVITY

Diabetes mellitus is a diverse metabolic condition as old as mankind, and its incidence is estimated to be high (4-5%) around the world. Medicinal plants may be a valuable source of new oral hypoglycemic chemicals for the development of pharmaceutical products.[24]

Achyut N K., et.al., reported that *Aegle marmelos* aqueous seed extract had been shown to improve blood glucose levels as well as hyperlipidemia caused by diabetes. The study reveals that *Aegle marmelos* aqueous seed extract significantly ($p < 0.05$) reduces glucose levels in both normal and severely diabetic rats and increases glucose tolerance in sub and moderate-diabetic animals. [25]

Sevugan A., et.al., conducted a study, that was aimed at assessing the potential of calluses from *A. marmelos* leaf explants for diabetes treatment compared to other plant materials. Extracts from leaf and callus significantly reduced ($p < 0.05$) blood sugar levels in streptozotocin-diabetic rabbits. The methanol extracts of the leaf and callus had the most anti-diabetic efficacy.[26]

Kamalakkannan N., et.al., conducted a study to evaluate the anti-diabetic and anti-oxidant activity of aqueous extract *Aegle marmelos* fruit in streptozotocin (STZ) induced diabetic rats. When *Aegle marmelos* fruit extract was administered to STZ-diabetic rats, there was a significant increase ($p < 0.05$) in plasma insulin and a considerable decrease ($p < 0.05$) in blood glucose. This extract also exhibited an antioxidative effect in STZ-diabetes rats. [27]

Kumar V., et.al., The study was conducted to evaluate the antidiabetic, antihyperlipidemic and antioxidant oxidative stress of umbelliferone β -D-galactopyranoside (UFG) from stem bark of *Aegle marmelos* Correa. in STZ (streptozotocin) induced diabetic rats. Daily oral treatment of UFG for 28 days resulted in a significant ($P < 0.001$) decrease in fasting blood glucose and improved plasma insulin levels compared to the diabetes control group. UFG may work via increasing pancreatic insulin output and affecting antioxidant markers.[28]

Research Through Innovation

4. ANTI-INFLAMMATORY ACTIVITY

Inflammation is an essential aspect of the body's defence process. Acute inflammation is characterized by vasodilation, plasma exudation, the production of numerous inflammatory mediators, cytokines, growth factors, and leukocyte emigration. Chronic inflammation is characterized by mononuclear cell infiltration, fibroblast proliferation, blood vessel dilation, and enhanced connective tissue development. An instance of an inflammatory response is a tissue infection. Anti-inflammatory medications inhibit the various stages of inflammation.

Benni J M., et.al., conducted a study to evaluate anti-inflammatory activity of the aqueous root bark extract of *Aegle marmelos*. *Aegle marmelos* had shown considerable anti-inflammatory efficacy in the models examined. The animal models used to investigate the in vivo anti-inflammatory activity were acute (paw

edema induced by carrageenan) and chronic (granuloma induced by cotton pellet). In the acute model, bilwa (100mg/kg) and indomethacin both exhibited highly significant activity ($p<0.001$). Anti-inflammatory activity is observed as percentage inhibition (PI), the PI of Bilwa and Indomethacin were 35.7% and 51.5% respectively; however, in the chronic condition, there was a trend of anti-inflammatory action, Bilwa did not show significant anti-inflammatory activity ($p>0.05$). Bilwa and Indomethacin showed a percentage inhibition of 9.2% and 24.7%, respectively. [29]

Kumari K D., et.al., evaluated the anti-inflammatory effect of the water extract and ethanolic extract of dried flowers of *Aegle marmelos* (WEAM). The dose of 200 mg/kg at 2 hours resulted in the highest percentage inhibition of paw oedema. WEAM 200 mg/kg was the most effective dose at suppressing paw oedema (69.9%). Ethanolic extract of *Aegle marmelos* EEAM (25 mg/kg) decreased paw oedema by 69.3% at 2 hours, while indomethacin reduced it by 71.9% at the same time. EEAM and indomethacin were shown to be statistically significant ($p<0.05$). [30]

Rao C V., et.al., conducted a study to evaluate the anti-inflammatory activity of the ethanolic extract of unripe fruit of *Aegle marmelos*. Inflammation was induced by injecting 0.1ml of 1% carrageenan into the subplantar side of the left hind paw. After the administration of the extract the inflammation was significantly reduced ($p<0.1$ to $p<0.001$) equivalent to 37.14% to 65.71% protection. [31]

Ghangale G R., et.a., evaluated anti-inflammatory activity of *Aegle marmelos* leaf extract in rats. The animals were treated with aqueous extract of *Aegle marmelos* with aspirin as standard drug. *Aegle marmelos* leaf extract (200mg/kg B.W.) significantly reduced acute inflammation ($p<0.01$) compared to aspirin, the conventional medication. It was concluded that *Aegle marmelos* has anti-inflammatory properties. [32]

5. HEPATOPROTECTIVE ACTIVITY

The liver is the primary organ for detoxifying and disposing of endogenous chemicals. It is constantly and widely exposed to xenobiotics, hepatotoxins, and chemotherapeutic drugs, which cause impairment of its functioning.

Singan V., et.al., Essential biochemical indicators were used to assess the hepatoprotective impact of Bael leaves on alcohol-induced liver damage in albino rats. In animals treated with herbal drugs, alcohol-impaired animals, and healthy animals, the observed levels of TBARS (thiobarbituric acid reactive compounds) were 121.35, 235.68, and 141.85 g/g tissue, respectively. The outcomes were contrasted with silymarin (133.04 g/g tissue), a standard herbal medication. The study results showed that bael leaves have a significant hepatoprotective effect.[33]

Singh R., et.al., aimed to investigate the protective effect of *Aegle marmelos* fruits on CCl₄-induced liver damage in rats. When rats were given fruit pulp/seed aqueous extract, there was a significant reduction ($p<0.05$) in the elevation of plasma enzyme and bilirubin levels induced by CCl₄. This study implies that treating rats with fruit pulp/seed extracts can lessen the liver damage caused by CCl₄. [34]

Siddique N A., et.al., Rats intoxicated with carbon tetrachloride (CCl₄) were used in the investigation to test the hepatoprotective potential of the methanolic extract of *Aegle marmelos* leaves (MEAML). Sterol, aegelin, and skimianinc are present in the leaves. Rats treated with CCl₄ were given MEAML at varying doses (50, 100, 200 mg/kg body weight) and standard silymarin (40mg/kg body weight). The effect of these treatments was examined on serum enzymes. Varying doses of MEAM significantly reduced ($p<0.001$) AST (aspartate transaminase), ALT (alanine transaminase), ALP (alkaline phosphatase), and bilirubin. Treatment with MEAML reduced TBARS (thiobarbituric acid) and increased GSH (reduced glutathione) levels significantly at $p<0.001$. The results of this study demonstrated that the MEAML exhibits strong hepatoprotective action by reducing cellular oxidative stress caused by CCl₄ and reversed the induction in hepatic disorder. [35]

Jayachandra K., et.al., Potentiation of *A. marmelos* hepatoprotective effect with piperine co-administration was studied. An oral dosage of 400 mg/kg of paracetamol was given for seven days to cause hepatotoxicity. Treatment with *A. marmelos* reduced the harmful effects of paracetamol in a dose-dependent manner. Co-administration of *A. marmelos* dose of 25 mg/kg and piperine at a dose of 20 mg/kg (sub hepatoprotective dose) significantly ($p < 0.001$) decreased the AST, ALT, ALP and LDH levels as compared to paracetamol group. Piperine co-administration enhanced hepatoprotective effects. Piperine enhances the antioxidant and anti-inflammatory characteristics of *A. marmelos*, which contribute to its hepatoprotective activity. [36]

6. ANTI-DIARRHEAL

Common health issues like cholera and dysentery are caused by enter pathogens like *Vibrio cholerae*, *E. coli*, etc., mainly in tropical and subtropical developing nations. The majority of infectious diseases in the world are diarrheal. [37]

Das G., et.al., Hot water soluble pectic polysaccharide (HWSPP), which was extracted from the aqueous extract of semiripe *Aegle marmelos* fruit pulp, was assessed for antidiarrheal properties. In mice, the HWSPP exhibited a dose-dependent antidiarrheal action, with a significant decrease ($p < 0.05$) in defecation noted at a dose of 5 mg/kg body weight in comparison to the control group. [38]

Mehesare S S., et.al., A study was conducted to investigate the antidiarrhoeal activity of the ethanolic extract from the fruit of *A. marmelos*. The antidiarrheal activity was evaluated on castor oil-induced. The Ethanolic extract of *A. marmelos* considerably reduced diarrhea in mice ($p < 0.05$). The extract of unripe fruits of *Aegle marmelos* at 400 mg/kg and 800 mg/kg significantly reduced ($p < 0.01$) the frequency of defecation (mean percentage inhibition determined to be 67.44% and 70.93%, respectively). Whereas loperamide (3mg/kg) significantly reduced the frequency of defecation by 86.00%. The extract of unripe fruits of *Aegle marmelos* effectively treated castor oil-induced diarrhea in mice. [39]

7. ANTIULCER ACTIVITY

Peptic ulcers are a severe gastrointestinal erosion condition that penetrates the muscle mucosa and affects the whole mucosal thickness. It is widely acknowledged that an imbalance between defensive and aggressive variables causes ulcers. Gram-negative *Helicobacter pylori* infection, increased hydrochloric acid production, insufficient mucosal defense against stomach acid, and medications such as cholinergic drugs are the main causes of peptic ulcers.[40]

Sharmin R D., et.al., The protective activity of the ethanolic extract from *Aegle marmelos* leaves was studied at a dosage of 400mg/kg body weight using the ethanol-induced gastric ulcer method. It exhibited significant ($p < 0.001$) anti-ulcer activity in the ethanol-induced gastric ulcer model. The percentage protection of ulcers with ethanolic extract of *Aegle marmelos* was 56.33% compared to the standard anti-ulcer drug omeprazole (50.44%). [41]

Sharma G N., et.al., Methanolic and aqueous extracts of *Aegle marmelos* seeds were studied for ulcer protective activity using indomethacin-induced ulceration, stress-induced ulceration, and pylorus ligation-induced ulceration. Ranitidine (50 mg/kg) was used as a standard antiulcer agent. Methanolic extract showed significant ($p < 0.01$) ulcer protective action at the doses of 200 and 400mg/kg b.w. in all animal models. It was discovered that the aqueous extract, at the same doses as the methanolic extract, had significant ($p < 0.05$) ulcer healing properties. [42]

Madhu C., et.al., investigated the anti-ulcer activity of aqueous extract of *Aegle marmelos* on an indomethacin-induced ulcer model in Wistar rats. In comparison to the control, the extracts at doses of 175 mg/kg and 350 mg/kg significantly ($p < 0.01$) reduced the stomach gastric volume, free acidity, and ulcer

index. The results suggested that the extract was found to possess antiulcerogenic as well as ulcer healing property. [43]

8. ANTIPYRETIC

Fever or pyrexia can result from secondary effects such as infection, inflammation, tissue damage, graft rejection, cancer, or other medical conditions.

Ramachandra YL., et al., Rats were used in a study to evaluate the antipyretic effects of *Aegle marmelos* leaf extracts at a dose of 200 mg/kg body weight. Petroleum ether, ethanol, and aqueous extracts of the leaves were chosen for the above pharmacological screening. The petroleum ether extract of the leaf showed significant antipyretic activity ($p < 0.05$) at 30 min and more significant antipyretic activity ($p < 0.01$) at 90 min after drug administration. At an interval of 3hrs petroleum ether extract of the leaf showed significant activity whereas ethanol extract and aqueous extract of the leaf failed to exhibit this property. [44]

Vyas A., et.al., Ethanolic extracts as well as aqueous extracts of *Aegle marmelos* (L.) Correa leaves (200 mg/kg body weight and 400 mg/kg body wt.) showed a significant ($p < 0.001$) antipyretic effect in yeast-provoked elevation of body temperature in rats. [45]

9. ANTICANCER ACTIVITY

Cancer is a complex hereditary disease that results from abnormal cells proliferating and dividing uncontrollably within the body, and then these abnormal cells spreading to other bodily regions. Cancer ranks as the second most prevalent reason for death globally.

Jagetia G C., et.al., A study was conducted using Swiss albino mice with Ehrlich ascites carcinoma to investigate the potential anticancer effects of the hydroalcoholic extract of *Aegle marmelos* (AME). Administering AME intraperitoneally at an equimolar dose resulted in superior antineoplastic activity compared to oral administration. Administration of AME once daily for six days to tumor-bearing mice resulted in dose-dependent tumor regression ($p < 0.05$) at 400 mg/kg body weight, with higher dosages causing toxic effects. [46]

Akhouri V., et.al., Research was conducted to study the anticancer activity of *Aegle marmelos* fruit extract on 7,12-dimethylbenz(a)anthracene (DMBA) induced breast cancer in rats. Female Charles Foster rats were used to induce breast cancer using DMBA (20mg/ml dissolved in olive oil). *Aegle marmelos* ethanolic fruit extract (200mg/kg b.w/day) was orally administered for 5 weeks. There was a significant reduction ($p < 0.05$) in mammary tumor volume, and also a significant reduction ($p < 0.0001$) in serum biomarkers such as TNF- α level, serum malondialdehyde (MDA) level, and glucose levels. [47]

Kumar A., et.al., A study was conducted to evaluate the anticancer activity of *Aegle marmelos* fruit pulp extract on Benzo [A] pyrene-induced lung cancer in rats. Animals weighing (150-180g) were induced with Benzo[A] pyrene (25mg/kg dissolved in olive oil) orally for 14 days and left for 3 months. *A marmelos* fruit pulp extract at the dose of 250mg/Kg body weight was administered to the rats for 5 weeks. After the treatment significant reduction ($p < 0.05$) in the lung tumor size was observed. [48]

10. IMMUNOMODULATORY ACTIVITY

The body's immune system protects it from infections, diseases, and foreign substances. It is a complex system of cells, tissues, and organs that combine to identify and eliminate unwanted invaders. However, the immune system's response might be too weak, leaving the body vulnerable to infections, or too strong, resulting in autoimmune illnesses in which the body's own tissues are attacked. Immunomodulatory effects refer to the ability of certain substances to modify or regulate one or more functions of the immune system.

Patel P., et.al., conducted a study to investigate the immunomodulatory action of the methanolic extract of *Aegle marmelos* fruit (FEAM) in an experimental immunity model. The neutrophil adhesion test and the carbon clearance assay were used to evaluate cellular immunity, while the mouse lethality test and the indirect haemagglutination assay were used to assess humoral immunity. In the carbon clearance experiment, FEAM at 100 and 500 mg/kg significantly increased ($p < 0.001$) neutrophil adhesion and phagocytic index. In the indirect haemagglutination test, animals treated with FEAM showed considerably higher circulating antibody titers. [49]

Govinda HV., et.al., evaluated the immunomodulatory potential of the methanolic extract of *Aegle marmelos* in an animal model of cellular and humoral immunity. The administration of methanol extract of *Aegle marmelos* (500 and 1000 mg/kg, p.o) resulted in a significant increase ($p < 0.001$) in neutrophil adhesion and phagocytic index in the carbon clearance experiment. However, cellular immunity was more effectively increased by low doses of *Aegle marmelos* methanol extract, whereas high doses more strongly influenced humoral immunity.[50]

11. ANTIFERTILITY ACTIVITY

Antifertility activity is defined as the ability of some drugs to diminish or suppress fertility, hence preventing pregnancy. This activity can be accomplished through numerous mechanisms and is used in the development of contraceptives and treatments for reproductive health disorders.

Agarwal SS., et.al., evaluated *Aegle marmelos* bark extracts for male antifertility activity in albino wistar rats. The methanolic bark extract of *Aegle marmelos* showed dose and duration-dependent infertility by significant reduction ($p < 0.01$) in reproductive organ weight and serum testosterone levels. The findings of the sperm examination revealed a decrease in sperm motility, density, viability, and acrosomal integrity without affecting libido or the body weight of essential organs.[51]

Chauhan A., et.al., tested the antifertility activity of *Aegle marmelos*. Oral administration of an aqueous extract to male rats significantly decreased ($p \leq 0.01$) the weights of their testes, epididymis, seminal vesicle, ventral prostate, and vas deferens. Sperm motility and density in the cauda epididymis decreased considerably, resulting in a 70% reduction in fertility rates. The testes and reproductive tissues showed decreased sialic acid, protein, glycogen, fructose, and ascorbic acid levels, but testicular cholesterol levels increased considerably. [52]

Kumar DU., et.al., evaluated the effect of *Aegle marmelos* leaf aqueous extract on testicular activities in rats. At a dose of 50 mg/100 g body weight, essential testicular steroidogenic enzymes were significantly reduced ($p < 0.01$), resulting in low plasma testosterone levels and relative weights of sex organs compared to the control group. The administered dose did not exhibit any toxicity in the liver and kidney. Thus, it was reported that the aqueous extract of *Aegle marmelos* leaf has a potent anti-testicular effect. [53]

Kumar B S., et.al., total alkaloids were isolated from the leaves of *Aegle marmelos* and studied their effect on fertility of adult male albino rats. Three dosages (20, 40, and 80 mg/kg body weight) of total alkaloids were delivered orally to mature male albino rats. Treatment with the total alkaloidal fraction of *A. marmelos* resulted in significant decreases ($p < 0.05$) in the weights of reproductive organs, accessory glands, and sperm counts, indicating antifertility activity. Serological parameters showed no significant changes in treated animals at the tested dose levels, indicating the safety of long-term use. [54]

12. NEPHROPROTECTIVE ACTIVITY

Nephroprotectivity refers to the ability of certain substances to protect or maintain kidney function. This protection is essential because the kidneys filter waste products from the blood, regulate fluid balance, and maintain electrolyte levels. Nephroprotective drugs can help prevent or treat kidney damage caused by a variety of factors, including toxins, medications, illnesses, and oxidative stress.

Kalita B., et.al., A study was conducted to evaluate the nephroprotective and nephrocurative effect of *Aegle marmelos* in gentamycin-induced nephrotoxicity. There was a significant decrease ($p < 0.01$) in nephrotoxicity after oral administration of aqueous extract of *Aegle marmelos*. [55]

Dwivedi J., et.al., evaluated the nephroprotective activity of hydro-alcoholic (HAEAM) and ethyl acetate (EAEAM) extracts of *Aegle marmelos* leaves against cisplatin-induced nephrotoxicity in Wistar rats. EAEAM (400 mg/kg) reduced creatinine levels from 2.29 ± 0.387 to 0.96 ± 0.095 mg/dL. The treatment reduced BUN levels from 92.06 ± 7.949 to 38.18 ± 5.686 mg/dL, restored renal antioxidant enzyme activity, reduced LPO levels from 158.70 ± 3.542 to 106.91 ± 5.876 $\mu\text{M/g}$, increased SOD levels from 12.59 ± 0.463 to 29.95 ± 5.222 Ug^{-1} , and glutathione (GSH) levels from 0.24 ± 0.029 to 0.57 ± 0.048 $\mu\text{M/g}$ and catalase (CAT) from 1.14 ± 0.067 to 3.27 ± 0.296 Umg^{-1} with $p < 0.01$. [56]

Ahmad R., et.al., The methanolic extract of *Aegle marmelos* leaves was evaluated against cisplatin-induced nephrotoxicity in rats. The serum/blood levels of urea, creatinine, uric acid, sodium, and potassium were measured, as well as TBARS (Thiobarbituric acid reactive substances), reduced glutathione (GSH), superoxide dismutase, and catalase in kidney tissue homogenate. At all doses, the extract significantly enhanced serum parameters, decreasing the high level of TBARS while increasing the reduced amount of GSH, superoxide dismutase, and catalase at $p < 0.05$. The *A. marmelos* extract was found to have nephroprotective and anti-oxidant properties. [57]

13. MYOCARDIAL INFARCTION

Myocardial infarction (MI), often known as a heart attack, occurs when blood supply to a portion of the heart is interrupted, resulting in heart muscle injury or death. The main cause of this blockage in the coronary arteries is an accumulation of plaque called atherosclerosis, which can rupture and generate a blood clot.

Prince PS., et al. investigated the preventative impact of an aqueous *Aegle marmelos* leaf extract (AMLEt) in isoprenaline-induced myocardial infarction. Isoprenaline treatment significantly increased CK and LDH activity in serum but lowered it in the heart. AMLEt therapy decreased serum CK and LDH activity while increasing it in the heart at a significant level ($p < 0.05$). [58]

Rajadurai M., et.al., evaluated the effect of *Aegle marmelos* leaf extract (AMLEt) and alphatocopherol on plasma lipids, lipid peroxides, and marker enzymes in rats with isoproterenol (ISO)- induced myocardial infarction. Treatment with AMLEt at doses of 100 mg/kg and 200 mg/kg bodyweight for 35 days significantly improved ($p < 0.05$) the activities of ISO-treated rats, showed changes in marker enzymes, lipid peroxides, lipids, lipoproteins, and antioxidant enzymes. The effect of AMLEt 200 mg/kg was similar to that of alpha-tocopherol 60 mg/kg. *Aegle marmelos* leaves showed antihyperlipidemic effects in rats with ISO-induced myocardial infarction.[59]

Ramachandra Y., et.al., evaluated the cardioprotective activity of petroleum ether, ethanol, and aqueous extract of leaf, stem, and root extract of *A. marmelos*. The animal group administered with aqueous leaf extract showed significant cardioprotective effects ($p < 0.05$) compared to standard treatment and petroleum ether and ethanol extract of the leaf. Petroleum ether, ethanol, and an aqueous extract of *A. marmelos* stem and root did not show any cardioprotective effects against myocardial infarction caused by isoproterenol. [60]

Jagetia G C., et.al., The effect of hydroalcoholic effect of *Aegle marmelos* (AME) was evaluated against doxorubicin-induced cardiotoxicity in mice. Doxorubicin (DOX) treatment showed a significant elevation in the glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), creatine kinase (CK-MB) and lactate dehydrogenase (LDH) activities in the serum of animals killed at 30 h after DOX treatment. Mice treated with AME before DOX injection had significantly reduced ($p < 0.05$) serum levels of CK-MB, LDH, GPT, and GOT, suggesting that AME protected the mice from the acute cardiotoxicity induced by DOX. [61]

14. ANTI-OBESITY

Obesity is a medical disorder defined by an excessive accumulation of body fat, which can have a severe impact on health. It is commonly measured using the body mass index (BMI), with a BMI of 30 or more being classified as obese.

Karmase A., et.al., A study was conducted to evaluate the potential anti-obesity properties of *Aegle marmelos* leaf extract. The lipolytic activity of *A. marmelos* leaf extracts was investigated using dichloromethane (DCM), ethyl acetate (EtOAc), and n-butanol. The most active compounds, umbelliferone and esculetin, were tested for antiobesity activity in vivo in a high-fat diet (HFD)-induced obese rat model. Umbelliferone and esculetin significantly ($p < 0.05$) decreased body weight, total triglycerides (TG), total cholesterol (TC), and glucose levels in their respective HFD groups. *A. marmelos* DCM extract and its isolated components reduced obesity by promoting lipolysis in adipocytes. [62]

Garg A., et.al., evaluated the antiobesity Activity of aqueous (AmAe) and Ethanol (AmEe) Extracts of *Aegle Marmelos* Leaves in High Fat Diet (HFD) Induced Obese Rats. AmEe and AmAe at 200, 400, 250, and 500 mg/kg orally significantly reduced oxidative stress ($P < 0.005$) and morphological parameters such as body weight growth, BMI and Waist hip ratio (WHR) with ($p < 0.05$) also obesity index, and adiposity index ($p < 0.01$) compared to the HFD control group. Likewise, serum glucose, triglycerides, and total cholesterol levels were found to be lower ($p < 0.01$) compared to the HFD control group. AmEe and AmAe have shown antiobesity effects by reducing fat pad accumulation, adipocyte differentiation, or adipocyte hypertrophy in high-fat diet-induced obesity rats. [63]

15. ANTITHYROID ACTIVITY

Thyroid hormones play a vital role in the growth, development, metabolism, and regulation of body temperature in humans. Changes in these hormone levels cause a variety of health issues in addition to changes in basal metabolic rate. Hyperthyroidism is the most common endocrine disease in women and hypothyroidism may occur in individuals of all ages affecting several different organs and system.

Shrivastava S., et.al., evaluated the antithyroid effect from the aqueous extract of *Aegle marmelos* leaves on the L-thyroxine (L-T4) induced hyperthyroidism and propylthiouracil-induced hypothyroidism. A change in the levels of serum T3 and T4 was observed in rats treated with L-thyroxine (0.5 mg/kg) and propylthiouracil (10 mg/kg). When 250 mg/kg/d (p.o.) of *Aegle marmelos* leaf extract was given to hyperthyroid mice for 15 days, their levels of T3 and T4 decreased by 78% and 54%, respectively, at a significance level ($p < 0.05$).

However, in animals treated with propylthiouracil, there was no change in the levels of T3 and T4. [64]

16. ANXIOLYTIC ACTIVITY

Anxiety is a type of psychiatric illness characterized by experiences of fear, restlessness, nervousness, tension, apprehension, panic, and agitation. Conditions like generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social phobia, specific phobias, and acute stress disorders fall under the category of anxiety disorders.

Bagga H., et.al., conducted a study to evaluate the anxiolytic activity. The effects were compared with the standard drug diazepam. *Aegle marmelos* extract demonstrated anxiolytic effects in both the elevated plus-maze (EPM) and Y-maze models. Both the 100 mg/kg and 200 mg/kg, p.o. dosages of *A. marmelos* extract significantly increased ($p < 0.001$) open arm activity in EPM, increasing time spent and number of entries

while decreasing the number of trips in the Y-maze, as compared to the control. Hence, the study found that *Aegle marmelos* has anxiolytic effects. [65]

Kothari S., et.al., evaluated the anxiolytic and antidepressant activities of methanol extract of *Aegle marmelos* (AM) leaves in mice. A photoactometer was used to measure the effects of AM (75, 150, and 300 mg/kg p.o) on locomotor activity. Results showed that AM significantly and dose-dependently ($p < 0.05$) increased time spent and the number of entries into open arms while decreasing the number of stretches attend postures and head dips in closed arms. AM-treated mice exhibited a dose-dependent and statistically significant ($P < 0.05$) anti-immobility effect. [66]

17. RADIOPROTECTIVITY

Radioprotectivity refers to the ability of certain substances or interventions to protect cells and tissues from the damaging effects of ionizing radiation. This protection is crucial in various contexts, such as medical treatments (like radiation therapy for cancer), occupational exposure, and accidental radiation exposure.

Jagetia GC., et.al., evaluated the radioprotective effect of *Aegle marmelos* (AME) leaf extract in mice. Animals were administered different doses of AME (0, 5, 10, 15, 20 and 40 mg/kg) once daily consecutively for 5 days before exposure to 10 Gy⁶⁰ Co γ -radiation. Up to 30 days after radiation, the animals were observed for signs of radiation sickness and mortality. On day 31 post-irradiation, glutathione and lipid peroxidation levels were measured in the surviving mice of both groups. Radiation-induced symptoms of illness decreased and survival rates increased with AME treatment. The radioprotective effect could be attributed to the increase in glutathione as well as the arrest of lipid peroxidation and the scavenging of free radicals. [67]

Jagetia GC., et.al., The hydroalcoholic extract of *Aegle marmelos* (AME) was tested for radioprotective effects on cultured human peripheral blood lymphocytes (HPBLs) using the micronucleus assay. The frequency of radiation-induced micronuclei was significantly decreased ($p < 0.01$) in HPBLs treated with varying doses of AME, with a significant reduction in micronucleus induction being observed for 5 mg/ml AME. Therefore, it was determined that this dosage of AME was ideal for radioprotection. [68]

18. NEUROPROTECTIVITY

Seth E., et.al., conducted a study to investigate the potential of leaf extract of *Aegle marmelos* (AM) against cadmium-induced oxidative stress. An evaluation of AM protective effect against CdSO₄ (5 mg/kg body weight i.p. for 5 days) induced neurotoxicity was conducted by estimating biochemical and histopathological parameters in mice that received prophylactic and therapeutic treatments (pre and post) at two different doses (250 and 500 mg/kg body weight). Significant alterations in the structure of neural tissue were brought about by cadmium exposure, which also resulted in a decrease in non-enzymatic antioxidants (reduced glutathione) and enzymatic antioxidants (catalase, superoxide dismutase, glutathione reductase, and glutathione-S-transferase). Pretreatment with AM considerably reversed enhanced lipid peroxidation at $p \leq 0.01$ and reduced enzymatic antioxidants at $p \leq 0.05$. Additionally, AM pretreatment preserved the histoarchitecture of neural tissue activity. [69]

19. DIURETIC ACTIVITY

Diuretics are substances that enhance urine production and excretion, hence eliminating excess fluid from the body. They are frequently used to treat hypertension, heart failure, kidney disease, and edema.

Singh S., et.al., conducted a study to evaluate the diuretic activity of ethanolic extracts and its fractions (petroleum ether fraction, chloroform fraction, ethyl acetate fraction) of *Aegle marmelos* fruit in experimental animals. Experimental rats received intraperitoneal injections of ethanolic extracts and its

fractions of ripe *Aegle marmelos* fruit at doses of 300, 400, and 500 mg/kg i.p. The standard group received Furosemide at a dose of 100 mg/kg. Among all the test compounds assessed, the petroleum ether fraction demonstrated the highest activity, with a urine volume of 35 ± 1.732 ml/kg and a concentration of excreted Na^+ ions at 97 ± 1 mEq/L when administered at 300 mg/kg. This difference was found to be statistically significant compared to the control group at $p < 0.05$. Results from this study suggest that the extract of *Aegle marmelos* possesses diuretic activity. [70]

20. WOUND HEALING ACTIVITY

The process of wound healing involves multiple stages and encompasses a range of biological processes aimed at repairing tissue integrity.

Gautam MK., et.al., A study was conducted to evaluate wound healing potential of *Aegle marmelos* fruit pulp extract (AME) on incision, excision and dead space wound models in rats. AME (200 mg/kg) was given orally once a day for varying durations based on the kind of wound ulcer studied. AME reduced mean epithelization period and scar size while increasing wound breaking strength as compared to the control. Granulation tissue had greater levels of antioxidants (13.0-38.8%, $p < 0.05$ -0.001) and collagen determinants (33.7-64.4%, $p < 0.001$), in the group treated with AME, there was a decrease in oxidative stress markers (55.0 to 55.6%, $p < 0.001$) and myeloperoxidase (21.3%, $p < 0.001$). *Aegle marmelos* appeared to promote wound healing by increasing connective tissue formation and antioxidant status, while lowering free radicals and myeloperoxidase, both of which cause tissue damage. [71]

Sharma GN., et.al., A study was aimed to evaluate wound healing activity of *Aegle marmelos* seed extract. The ointment with methanolic and aqueous extract was prepared in white soft paraffin separately at 5% and 10% (w/w) concentrations, and it was applied to an excision and incision wound model. There was a significant increase in the proportion of tensile strength, wound contraction and reduction in the epithelialization duration. The ointment made from methanolic extract demonstrated significant effectiveness in healing wounds ($p < 0.01$) when used at 5% and 10% w/w concentrations in all animal models. Also, significant wound healing properties ($p < 0.05$) were seen at the same concentration. [72]

Jaswanth A., et.al., Methanolic extract of the root of *Aegle marmelos* was evaluated for its wound-healing effect. It was evaluated as an ointment with two concentrations (5% and 10% w/w in a simple ointment base) in excision and insicion wound model in rats. The extract ointment significantly improved ($p < 0.001$) wound contraction, closure time, and overall healing in both wound types examined at both dosages as evidenced by its wound contracting ability, wound closure time, and increase in the tensile strength. [73]

CONCLUSION

This review has highlighted the therapeutic potential of *Aegle marmelos* in managing a variety of health conditions. The plant's rich phytochemical composition, including compounds like alkaloids, tannins, and essential oils, underlies its diverse pharmacological activities, such as anti-inflammatory, antimicrobial, and antioxidant properties, etc. Despite the promising findings, more comprehensive research is required to fully understand the mechanisms of action, refine therapeutic applications, and validate efficacy and safety through rigorous clinical trials. In summary, *Aegle marmelos* holds immense promise for future therapeutic applications. With continued research and sustainable management, this versatile plant can significantly contribute to advancing healthcare and improving well-being.

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