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# Therapeutic potential of *Aegle marmelos* (L.)-An overview

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PEER REVIEW

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**Comments**

This paper is a good review paper on therapeutic potential of *A. marmelos*. Citations used are also good resources for reviewing and very informative to all the traditional medical practitioners.
Details on Page 75

ABSTRACT

Medicinal plants are used in herbalism. They form the easily available source for healthcare purposes in rural and tribal areas. In the present review, an attempt has been made to congregate the phytochemical and pharmacological studies done on an important medicinal plant *Aegle marmelos*. Extensive experimental and clinical studies prove that *Aegle marmelos* possesses antidiarrhoeal, antimicrobial, antiviral, radioprotective, anticancer, chemopreventive, antipyretic, ulcer healing, antigenotoxic, diuretic, antifertility and anti-inflammatory properties, which help it to play role in prevention and treatment of many disease. Therefore, it is worthwhile to review its therapeutic properties to give an overview of its status to scientist both modern and ancient. This review also encompasses on the potential application of the above plant in the pharmaceutical field due to its wide pharmacological activities.

KEYWORDS

*Aegle marmelos*, Phytochemistry, Pharmacological properties, Therapeutic potential, Toxicological studies

## 1. Introduction

Nature has provided a complete storehouse of remedies to cure ailment of mankind. About 80% of the world's population depends wholly or partially on traditional medicine for its primary health care needs[1,2]. According to a survey (1993) of World Health Organization, the practitioners of traditional system of medicine treat about 80% of patients in India, 85% in Burma and 90% in Bangladesh[3]. Herbal medicines, as the major remedy in traditional medical systems, have been used in medical practice for thousands of years and have made a great contribution to maintain human health[4]. The medicinal plants are rich in secondary metabolites (which are potential sources of drugs) and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability[5].

*Aegle marmelos* (L.) Correa (*A. marmelos*), commonly known as Bael belonging to the family Rutaceae, has been widely used in indigenous systems of Indian medicine due to its various medicinal properties. *A. marmelos* is native to Northern India, but widely found throughout the Indian Peninsula and in Ceylon, Burma, Bangladesh, Thailand and Indo-China[6]. It is a medium to large sized deciduous glabrous, armed tree with the axillary and 2.5 cm long alternate trifoliate leaves, short flower and globular fruits[7].

## 2. Phytochemistry of *A. marmelos*

*A. marmelos* has been reported to contain several phytoconstituents mainly marmenol, marmin, marmelosin, marmelide, psoralen, alloimperatorin, rutaretin, scopoletin, aegelin, marmelin, fagarine, anhydromarmelin, limonene,

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â-phellandrene, betulinic acid, marmesin, imperatorin, marmelosin, luvangentin and auroptene[8]. Yadav *et al*. have determined the contents of tannin (0.985%) and riboflavin (0.005%)[9]. Various organic acids including oxalic, tartaric, malic and ascorbic acids were separated and quantified using a RP-HPLC[8]. Dhan *et al*. have characterized the 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) through LC-MS and LC-MS/MS scans and HPLC studies[10]. In 2008, Suvimol *et al*. have used SPME/GC/MS system to find *A. marmelos*. They found hexanal, isoamyl acetate, limonene, β-phellandrene, p-cymene, acetoin, (E)-2-octenal, (E,E)-2,4-heptadienal, dehydro-p-cymene, linalool oxide, 3,5-octadiene-2-one, α-Cubebene, *trans-p*-mentha-2,8-dienol, citronellal, β-cubebene, β-caryophyllene, hexadecane, pulegone, α-Humulene, verbenone, carvone, carvyl acetate, dihydro-β-Ionone, (E)-6,10-dimethyl-5,9-undecadien-2-one, β-Ionone, caryophyllene oxide, humulene oxide and hexadecanoic acid[11]. Seed oil composed of palmitic, stearic, oleic, linoleic and linolenic acid[12]. Apart from these, seed oil has been found to contain 12.5% of an unusual fatty acid, ricinoleic acid along with other normal fatty acids[13].

## 3. Pharmacological properties of *A. marmelos*

### 3.1. Antidiarrhoeal activity

Mazumder *et al*. performed *in vitro* and *in vivo* antidiarrhoeal potential of chloroform extract of the root of *A. marmelos*. *In vitro* study was found that the extract was comparable to that of ciprofloxacin and mostly active against the strains of *Vibrio cholerae*, followed by *Escherichia coli* (*E. coli*) and *Shigella* spp[14]. Also it was found that methanol extract of the fruits of *A. marmelos* decreased the intestinal propulsion in rats[15].

The unripe fruit pulp of *A. marmelos* affected the bacterial colonization to gut epithelium and production and action of certain enterotoxins. These suggest the varied possible modes of action of *A. marmelos* in infectious forms of diarrhoea thereby validating its mention in the ancient Indian texts and continued use by local communities for the treatment of diarrhoeal diseases[6,16].

### 3.2. Antimicrobial and antiviral activity

The essential oil isolated from the leaves of *A. marmelos* tree has proved to have antifungal activity against animal and human fungi like *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, *Microsporum audounii*, *Microsporum cookie*, *Epidermophyton floccosum*, *Aspergillus niger*, *Aspergillus flavus* and *Histoplasma capsulatum*[12]. Balakumar *et al*. showed *A. marmelos* leaf extracts and fractions have fungicidal activity against various clinical isolates of dermatophytic fungi. The MIC and MFC were found to be high in water and ethyl alcohol extracts and methanol fractions (200 μg/mL) against dermatophytic fungi studied[17]. The essential oil from the *A. marmelos* leaves may interfere with the $Ca^{2+}$ dipicolinic acid metabolism pathway and possibly inhibit spore germination. $Ca^{2+}$ ion uptake and utilization by spore is one of the prime factors that determine whether the spore will germinate or remain dormant. Thus *A. marmelos* may exhibit the antifungal activity by lowering the vegetative fungal body inside the host or in solid medium. This is the possible mechanism of the protective role of *A. marmelos* leaf oil against fungal infection[12,18].

Various extracts of *A. marmelos* leaves, roots and fruits have been reported to be active against many bacterial strains. There are several reports in the literature regarding the antimicrobial activity of crude extracts prepared from plants[19-21]. In 2009, Venkatesan *et al*. showed that aqueous and ethanolic extract has activity against *E. coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*. The ethanolic extract showed considerably more activity than the aqueous extract. Maximum antibacterial activity was shown against *Bacillus subtilis* followed by *Staphylococcus aureus*, *E. coli* and *Pseudomonas aeruginosa*[22]. Jyothi and Rao showed that hexane, cold methanol and hot methanol extracts have inhibited *Klebsiella pneumoniae*, *Micrococcus luteus*, *Entercococcus faecalis* and *Streptococcus faecalis* groth *in vitro*. They also found that these three extracts have no effect on *E. coli* and *Proteus vulgaris*[23].

The alcoholic extracts of the *A. marmelos* seeds and leaves have been tested *in vivo* and *in vitro* for antimalarial activity against the NK65 strain of *Plasmodium berghei*. The seeds have shown schizontocidal activity in both the system, whereas, the leaves have shown activity only in the *in vitro* system[12].

The *in vitro* viral activity of various parts of *A. marmelos* tree has been evaluated for their efficacy against human coxsackie viruses B1-B6. The $IC_{50}$ of leaves, stem and stem bark, fruit, root and root bark and pure compound marmelide are 1 000, 500 to 1 000, 250 to 500, and 62.5 μg/mL, respectively, whereas, the $IC_{50}$ of ribavirin, a standard antiviral agent, is 2 000 μg/mL for the same viruses and at the same time period[24]. Balasubramanian *et al*. showed that *A. marmelos* extracts against white spot syndrome virus in shrimp at the concentration of 150 mg/kg of animal body weight[25].

It seems that *A. marmelos* has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents (that is ribavirin), which usually act in the later stages of viral replication and have potent side effect[12].

### 3.3. Radioprotective effects

The effective use of radiotherapy in cancer cure and palliation is compromised by the side-effects resulting

from radiosensitivity of bordering normal tissues, which are invariably exposed to the cytotoxic effects of ionizing radiation during treatment. In this situation, use of radioprotective compounds that can protect normal tissues against radiation injury are of immense use. Radiation ill-effects are principally the result of generation of free radicals, and the antioxidant compounds that counter them are supposed to be of immense use in preventing them[26].

In 2004, Jagetia *et al.* showed that intraperitoneally used hydroalcoholic leaf extract of *A. marmelos* in mice increases its survival rate when the mice are exposed to lethal dose of 10 Gy of g-radiation[27]. Pretreatment of mice with 15 mg/kg before exposure to different doses of radiation (6, 7, 8, 9, 10, or 11 Gy of γ-radiation) delayed or reduced the severity of radiation sickness and the onset of radiation-induced mortality, compared with the concurrent placebo treated radiation group[27]. The leaf extract is better than both the fruit extract and the positive control (2-mercaptopropionylglycine). Leaf extracts give protection against gastrointestinal damage and hematopoietic damage[26]. Bonemarrow stem cells are more sensitive than intestinal crypt cells to the deleterious effects of ionizing radiation. However, as peripheral blood cells have a longer transit time than intestinal cells, the onset of a gastrointestinal syndrome occurs earlier than a bone-marrow syndrome[28]. The deleterious effects of radiation occur as a result of direct ionization of DNA and other cellular targets and via an indirect effect, in which reactive oxygen species (ROS) are generated through water radiolysis[29]. When DNA is damaged, it is followed by altered cell division, enhanced cell death, depletion of stem cell pools, and organ-system dysfunction, and if the radiation dose is lethal, the organism will die. Radiation induces mitotic cell death in dividing cells and activates pathways that lead to death by apoptosis in interphase cells and differentiated cells[30]. *In vitro* studies have shown that the leaf extract of *A. marmelos* is a scavenger of ROS and reactive nitrogen species. The fruit is also reported to have potent free-radical scavenging and antioxidant effects. Recently, Abdullakasim *et al.* have observed that *A. marmelos* fruit drink had high quantities of total phenolic compounds and was a good antioxidant[31]. *A. marmelos* leaf extract reduced radiation-induced DNA damage in cultured human peripheral blood lymphocytes and in mouse bone-marrow cells, indicating that *A. marmelos* is an efficient anticlastogen[32]. Transitional metals like iron, undergo redox cycling, resulting in production of ROS. *A. marmelos* is a good chelator, and this might have contributed, at least in part, to these observed antioxidant and radioprotective effects[26].

Inhibition of lipid peroxidation is important in disease processes involving free radicals, and studies have shown that both leaf and fruit extracts prevented radiation-induced lipid peroxidation in the livers, kidneys, intestines, and spleens of mice. *A. marmelos* caused a concentration-dependent inhibition of $H_2O_2$ and iron-induced lipid peroxidation in mice brain homogenate[26]. Administration of *A. marmelos* leaf extract increased activities of the antioxidant enzymes SOD, catalase, and glutathione peroxidase in normal mice as well as in diabetic rats[33].

Radiation triggers an inflammatory response via mediators and activates significant physiologic and immunologic processes. Loss of immunity is associated with depletion of immunocompetent cells that can cause infection by opportunistic microbes. Immune activation is a protective approach, and immunostimulants enhance the overall immunity of a host by presenting a nonspecific immune response against microbial pathogens. *A. marmelos* leaf extract increased peritoneal macrophages and splenic lymphocyte counts in mice, suggesting it produces immunomodulatory effects[26].

### 3.4. Anticancer activity

Cancer is a major public health problem, being the second highest cause of death in both men and women in developed as well as developing countries[34]. In 2008, approximately 12.7 million new cancer cases (56% of which were in developing regions of the world) and 7.6 million cancer deaths (63% in less developed regions) occurred. By the year 2020, predictions report the incidence of cancer will increase 3-fold, with a disproportionate rise in cancer cases and deaths in developing countries with limited resources to tackle the problem[35].

Preclinical studies have shown that *A. marmelos* leaf extracts were effective in inhibiting the growth of leukemic K562, T-lymphoid Jurkat, B-lymphoid Raji, erythroleukemic HEL, melanoma Colo38, and breast cancer cell lines MCF7 and MDA-MB-231[36]. *A. marmelos* extracts may increase ERa gene expression in MDA-MB-231 (ERα-negative breast cancer cells) and inhibited cell proliferation[35]. *A. marmelos* leaf extract is also shown to have antineoplastic effects on the Ehrlich ascites carcinoma in Swiss albino mice[37]. The ethanolic fruit extract has cytotoxic effect on SKBR3 cells *in vitro*[38]. Experiments have shown that the phytochemicals such as lupeol, eugenol, citral, cineole and d-limonene present in *A. marmelos* possess antineoplastic effects[35].

1-hydroxy-5,7-dimethoxy-2-naphthalene-carboxaldehyde (Marmelin) present in *A. marmelos* inhibiting the growth of epithelial cancer cells (HCT-116 colon and HEp-2, alveolar epithelial carcinoma cells), but not normal cells (mouse embryo fibroblasts). Marmelin induced TNF-α, TNFR1, and TRADD mRNA and protein expression, G1 cell cycle arrest, and mediated apoptosis through activated caspase-3, which was abrogated when pretreated with caspase-3 inhibitors. Marmelin also caused activation of caspase-8 and Bid, with release of cytochrome C, suggesting the existence of a cross-talk between death receptor and the mitochondrial pathways. Marmelin also inhibited AKT and extracellular signal regulated kinase phosphorylation both in cells in culture and in tumor xenografts. AKT plays a key role in tumor cell survival, proliferation, and invasiveness, which is frequently altered in certain cancers. Some tumor

cells have constantly active AKT and may depend on it for survival. By reducing the AKT levels, marmelin decreases the cell survival, proliferation, and invasiveness[35,39].

Lupeol, another compound present in *A. marmelos*, possesses antineoplastic effects on various human neoplastic cell lines (human melanoma 451Lu cells, WM35 cells, B162F2 cells; human pancreatic adenocarcinoma cells AsPC-120, human epidermoid carcinoma A431 cells, hepatocellular carcinoma SMMC7721 cells, prostate carcinoma cell lines LNCaP, CWR22Rγ1, and PC-3)[35]. Lupeol caused G1-S phase cell cycle arrest and decreased expression of cyclin D1, cyclin D2, and cdk2 with increase in expression of p21 (cyclin-dependent kinase inhibitor, involved in regulation of cell cycle progression) protein in PC-3 cells. By decreasing cyclin D1, cyclin D2 and cdk2 expression and by increasing p21, lupeol mediates the cell cycle arrest[40]. Lupeol modulate and/or increase the expression of Bax protein, ErbB2, tissue inhibitor of metalloproteinases-3, cyclin D1, Fas associated protein with death domain (FADD mRNA) and matrix metalloproteinase (MMP)-2 genes, 14-3-3σ genes in various cells (SMMC7721, LNCaP and PC-3 cells). It reduces and/or inhibits the expression of PI3K/Akt, MAPK proteins p38 and Erk1/2, and phosphorylation of IkBa and NF-κB/p65, death receptor 3 (DR3), cyclin B, cdc25C, and plk1. Lupeol is also shown to induce apoptosis by downregulating Bcl2 (an anti-apoptotic protein), upregulating Bax (a pro-apoptotic protein), activating caspase-3, caspase-9, and apaf1 genes, and inducing poly (ADP) ribose polymerase cleavage in the CWR22Rnu1 and PC-3 neoplastic cells. Lupeol treatment increases reactive oxygen species, causes loss of mitochondrial membrane potential, and induces DNA fragmentation in PC-3 cells[35].

Other compounds like eugenol and citral present in *A. marmelos* has anti proliferative activities. Eugenol shows cytotoxic effects against salivary gland tumor cell line (HSG), normal human gingival fibroblast (HGF), malignant HepG2 hepatoma cells, malignant Caco-2 colon cells, human melanoma cell line, WM1205Lu and B16, and nonmalignant human VH10 fibroblasts[41]. Citral (3,7-dimethyl-2,6-octadien-1-al) has been recently shown to induce apoptosis in several hematopoietic cancer cell lines. Recent report showed that citral possessed antiproliferative effects, inhibited cell cycle progression in G2/M phase, induced apoptosis of the human breast cancer cell line MCF-7, and decreased the prostaglandin E(2) synthesis[42].

### 3.5. Chemopreventive action

Numerous experimental and epidemiological studies show that chemoprevention has the potential of providing an important means for cancer prevention[43]. Gupta *et al.* showed that *A. marmelos* fruit extracts has chemopreventive role against DMBA-induced skin carcinogenesis in mice[44]. Khan and Sultana have reported that the methanolic extract of *A. marmelos* (25 and 50 mg/kg body weight) was effective in inhibiting the diethylnitrosamine initiated and 2-acetyl aminofluorene promoted hepatocarcinogenesis in Wistar rats[45]. Studies have also shown that the phytochemicals present in *A. marmelos*, such as lupeol, eugenol, limonene, citral, rutin, and anthocyanins have been reported to possess chemopreventive effects. The presence of these compounds in the extract may have contributed to the observed effects[35].

### 3.6. Antipyretic potential

Shukla *et al.* evaluated the antipyretic property of *A. marmelos* on Brewer's yeast induced pyrexia in albino rats. They reveal that the ethanolic extract, at dose of 200 mg/kg body weight and 400 mg/kg body weight, produced significant ($P<0.001$) reduction in elevated body temperature in a dose dependent manner. This antipyretic effect of extracts was comparable to that of paracetamol (100 mg/kg body weight)[46,47].

### 3.7. Ulcer healing potential

Sharma *et al.* investigated anti-ulcer activity of methanolic and aqueous extract of *A. marmelos* seeds using indomethacin induced ulceration, stressed induced ulceration and pylorus ligation induced ulcerations. Methanolic extract showed significant ($P<0.01$) ulcer protective action at the doses of 200 and 400 mg/kg body weight in all animal model. The aqueous extract was also found to possess significant ($P<0.05$) ulcer healing property at the same doses as of methanolic extract. A significant reduction in volume of gastric juice, free acidity and total acidity, along with increase in pH was observed in pylorus ligated rats. The antiulcer property of both the extracts was attributed due to the presence of quercetin like (flavonoid) contents[48]. Another study indicated that *A. marmelos* fruit pulp extract treated albino rats show a significant decrease in mucosal thickness, superoxide dismutage, catalase activity and glutathione level. A significant increase in ulcer index, aspartate aminotransferase, alanine aminotransferase, lipid peroxidation activity was also observed. These results suggest that gastro duodenal protective and antiulcerogenic properties of *A. marmelos* may also depend on antioxidant mechanism[7,49].

### 3.8. Antigenotoxic activity

Antigenotoxic activity of *A. marmelos* fruit extracts were tested by Kaur *et al.* using *E. coli* PQ37 (SOS chromotest) and the peripheral human blood lymphocytes (Comet assay)[50]. Methanol and acetone extract are effective in decreasing the SOS response induced by hydrogen peroxide and aflatoxin B1 in the SOS chromotest. Methanol extract inhibited the genotoxicity of $H_2O_2$ by 70.48% and that of aflatoxin B1 by 84.65%. The extracts showed significant decrease in the tail moment induced by hydrogen peroxide (9 μmol/L) in the single cell gel electrophoresis assay. The antigenotoxic

activity exhibited by the extracts may be attributed the various polyphenolic constituents present in these extracts. These polyphenolic constituents possess the potential to protect DNA from reactive oxygen species and S9 dependent mutagens. Various reports showed that polyphenolic rich extracts can reduce the activity of enzymes involved in aflatoxin B1 metabolism[51]. The marked inhibitory effect against aflatoxin B1 may be due to inhibition of activity of cytochrome P450 dependent enzymes involved in the activation of aflatoxin B1 [50].

### 3.9. Diuretic activity

Singh *et al.* investigated the diuretic activity of various organic extracts and their fractions of *A. marmelos* fruit in experimental models. The extracts were administered to experimental rats intraperitonealy at doses of 300, 400 and 500 mg/kg. They evaluated diuretic effect by measuring urine volume and sodium content in urine. They found that ethanolic extract produce significant increase in excretion of sodium at the higher dose (500 mg/kg). Petroleum ether, chloroform and ethyl acetate fractions are also effective[52].

### 3.10. Antifertility activity

*A. marmelos* leaf, seed and fruit is known to affect male fertility in reversible manner. *A. marmelos* bark extract is a rich source of marmin and fagarine known for reducing male fertility. Agrawal *et al.* found that methanolic extract of *A. marmelos* causes a dose and duration dependent infertility via reducing reproductive organ weight and serum testosterone levels. They also report reduction in sperm density, motility, viability and sperm acrosomal integrity. Exfoliation of elongated spermatids, nuclear chromatin condensation and degeneration were found in testes histopathological studies and presence of spaces within the germinal epithelium signifying testicular cytotoxicity and necrosis. Finally time dependent complete infertility was observed in that study. The authors also reported that after the withdrawal of treatment, complete restoration of the morphological as well as physiological parameters in extract treated rats[53]. These findings suggest that *A. marmelos* extract is a strong candidate for male contraceptive via its ability to produce complete inhibition of pregnancy, rapid restoration of fertility after withdrawal from treatment[54].

### 3.11. Anti-inflammatory activity

Different organic extracts of the *A. marmelos* leaves possess highly significant acute and subacute anti-inflammatory activity[12]. In acute and chronic inflammatory animal models, *A. marmelos* showed significant anti-inflammatory activity and it can be a promising anti-inflammatory agent[55]. These activities may be due to the presence of lupeol and skimmianine in the leaves because both the compounds have shown the same potentialities in pure form. Activation of histamine receptor is essential for allergic and asthmatic manifestation. The alcoholic extract of *A. marmelos* leaves antagonized the histamine induced contractions and demonstrated positive relaxant effect in isolated guinea pig ileum and tracheal chain, suggesting inhibition of H1 receptor activity this extract may underlie these effects[12].

### 3.12. Toxicological studies

Generally, *A. marmelos* considered safe and few studies have been carried out with respect to its toxicity. Veerappan *et al.* studied toxic effects of *A. marmelos* leaves. They found no remarkable changes in histopathological studies of heart, liver, kidney, testis, spleen and brain after 50 mg/kg body weight of the extracts of *A. marmelos* administered intraperitoneally for 14 d successively. Pathologically, neither gross abnormalities nor histopathological changes were observed. These researchers also found that intraperitoneal administration of the extracts of the leaves of *A. marmelos* at doses of 50, 70, 90 and 100 mg/kg body weight for 14-consecutive day to male and female Wistar rats did not induce any short-term toxicity[56]. In addition the aqueous extract of *A. marmelos* fruit has been reported to be non mutagenic to *Salmonella typhimurium* strain TA 100 in the ames assay[57]. But no animal studies were reported. Pharmacological studies on animal models also repeated that doses of *A. marmelos* fruit extract over a period of up to 30 d have not reported any adverse effect up to a maximum dose of 250 mg/kg body weight[12,58].

## Conflict of interest statement

We declare that we have no conflict of interest.

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## Comments

### Background

The authors performed an interesting review regarding therapeutic potential of *A. marmelos*. The pharmacological effects exhibited by this plant have been elaborated in depth with citations from studies that have been conducted using this medicenal plant.

### Research frontiers

There is no lab experiment being done in this manuscript

since it is a review paper. However, the authors cited recent publications on works done in this particular field which bring the readers to the recent approach for pharmacological potential of this plant.

### *Related reports*

The authors cited different papers in this manuscript to support the therapeutic potential of *A. marmelos*. Past studies mostly presented the pharmacological activities of this plant done *in vitro* and *in vivo*.

### *Innovations & breakthroughs*

This is not a research article. Here authors summarized various research article in a good manure to give an overview about the therapeutic potential of *A. marmelos*.

### *Applications*

This review summarizes researches conducted on *A. marmelos*, specifically in medicinal field. It is a good source of literature survey for researchers who intended to do studies in this particular field.

### *Peer review*

This paper is a good review paper on therapeutic potential of *A. marmelos*. Citations used are also good resources for reviewing and very informative to all the traditional medical practitioners.

## References


[1] Gangadhar M, Shraddha K, Ganesh M. Antimicrobial screening of garlic (*Allium sativum*) extracts and their effect on glucoamylase activity *in-vitro*. *J Appl Pharm Sci* 2012; **2**(01): 106-108.

[2] Rahman MS, Salehin MF, Jamal M, Parvin A, Alam MK. Antibacterial activity of *Argemone mexicana* L. against water borne microbes. *Res J Med Plant* 2011; **5**(5): 621-626.

[3] Meena A, Rao M, Kandale A, Sannd R, Kiran NU, Yadav A. Standardisation of desmodium gangeticum-a tradition ayurvedic plant. *Drug Invention Today* 2010; **2**(2): 182.

[4] Kumar T, Chandrashekar K. *Bauhinia purpurea* Linn.: A review of its ethnobotany, phytochemical and pharmacological profile. *Res J Med Plant* 2011; **5**(4): 420-431.

[5] Beidokhti MN, Prakash D. Antioxidant and anti-inflammatory potential of selected medicinal plants of Lamiaceae family. *Int J Pharm Pharm Sci* 2013; **5**(Suppl 1): 100-104.

[6] Brijesh S, Daswani P, Tetali P, Antia N, Birdi T. Studies on the antidiarrhoeal activity of *Aegle marmelos* unripe fruit: validating its traditional usage. *BMC Complement Altern Med* 2009; **9**(1): 47.

[7] Das SK, Roy C. The protective role of *Aegle marmelos* on aspirin-induced gastro-duodenal ulceration in albino rat model: a possible involvement of antioxidants. *Saudi J Gastroenterol* 2012; **18**(3): 188-194.

[8] Bansal Y, Bansal G. Analytical methods for standardization of *Aegle marmelos*: A review. *J Pharm Educ Res* 2011; **2**(2): 37-44.

[9] Yadav N, Tyagi G, Jangir DK, Mehrotra R. Rapid determination of polyphenol, vitamins, organic acids and sugars in *Aegle marmelos* using reverse phase-high performance liquid chromatography. *J Pharm Res* 2011; **4**(3): 717-719.

[10] Prakash D, Upadhyay G, Pushpangadan P, Gupta C. Antioxidant and free radical scavenging activities of some fruits. *J Complement Integr Med* 2011; **8**: doi: 10.2202/1553-3840.1513.

[11] Charoensiddhi S, Anprung P. Bioactive compounds and volatile compounds of Thai bael fruit (*Aegle marmelos* (L.) Correa) as a valuable source for functional food ingredients. *Int Food Res J* 2008; **15**(3): 287-295.

[12] Dhankhar S, Ruhil S, Balhara M, Dhankhar S, Chhillar A. *Aegle marmelos* (Linn.) Correa: A potential source of phytomedicine. *J Med Plant Res* 2011; **5**(9): 1497-1507.

[13] Katagi KS, Munnolli RS, Hosamani KM. Unique occurrence of unusual fatty acid in the seed oil of *Aegle marmelos* Corre: screening the rich source of seed oil for bio-energy production. *Appl Energ* 2011; **88**(5): 1797-1802.

[14] Mazumder R, Bhattacharya S, Mazumder A, Pattnaik AK, Tiwary PM, Chaudhary S. Antidiarrhoeal evaluation of *Aegle marmelos* (Correa) Linn. root extract. *Phytother Res* 2006; **20**(1): 82-84.

[15] Gutiérrez SP, Sánchez MA, González CP, García LA. Antidiarrhoeal activity of different plants used in traditional medicine. *Afr J Biotechnol* 2007; **6**(25): 2988-2994.

[16] Dhuley J. Investigation on the gastroprotective and antidiarrhoeal properties of *Aegle marmelos* unripe fruit extract. *Hindustan Antibiot Bull* 2003; **45-46**(1-4): 41-46.

[17] Balakumar S, Rajan S, Thirunalasundari T, Jeeva S. Antifungal activity of *Aegle marmelos* (L.) Correa (Rutaceae) leaf extract on dermatophytes. *Asian Pac J Trop Biomed* 2011; **1**(4): 309-312.

[18] Rana B, Singh U, Taneja V. Antifungal activity and kinetics of inhibition by essential oil isolated from leaves of *Aegle marmelos*. *J Ethnopharmacol* 1997; **57**(1): 29-34.

[19] Rojas R, Bustamante B, Bauer J, Fernández I, Albán J, Lock O. Antimicrobial activity of selected Peruvian medicinal plants. *J Ethnopharmacol* 2003; **88**(2): 199-204.

[20] Duraipandiyan V, Ayyanar M, Ignacimuthu S. Antimicrobial activity of some ethnomedicinal plants used by Paliyar tribe from Tamil Nadu, India. *BMC Complement Altern Med* 2006; **6**(1): 35.

[21] Parekh J, Chanda SV. *In vitro* antimicrobial activity and phytochemical analysis of some Indian medicinal plants. *Turk J Biol* 2007; **31**(1): 53-58.

[22] Venkatesan D, Karunakaran M, Kumar SS, Palaniswamy P, Ramesh G. Antimicrobial activity of *Aegle marmelos* against pathogenic organism compared with control drug. *Ethnobotanical Leaflets* 2009; **13**: 968-974.

[23] Jyothi KS, Rao BS. Antibacterial activity of extracts from *Aegle marmelos* against standard pathogenic bacterial strains. *Int J PharmTech Res* 2010; **2**(3): 1824-1826.

[24] Badam L, Bedekar S, Sonawane KB, Joshi SP. *In vitro* antiviral activity of bael (*Aegle marmelos* Corr) upon human coxsackieviruses B1-B6. *J Commun Dis* 2002; **34**(2): 88-99.

[25] Balasubramanian G, Sarathi M, Kumar SR, Hameed AS. Screening the antiviral activity of Indian medicinal plants against white spot syndrome virus in shrimp. *Aquaculture* 2007; **263**(1-4): 15-19.

[26] Baliga MS, Bhat HP, Pereira MM, Mathias N, Venkatesh P. Radioprotective effects of *Aegle marmelos* (L.) Correa (Bael): a

concise review. *J Altern Complement Med* 2010; **16**(10): 1109-1116.

[27] Jagetia G, Venkatesh P, Baliga M. Evaluation of the radioprotective effect of bael leaf (*Aegle marmelos*) extract in mice. *Int J Radiat Biol* 2004; **80**(4): 281-290.

[28] Jagetia GC, Venkatesh P. Radioprotection by oral administration of *Aegle marmelos* (L.) Correa *in vivo*. *J Environ Pathol Toxicol Oncol* 2005; **24**(4): 315-332.

[29] Devasagayam T, Tilak J, Boloor K, Sane K, Ghaskadbi S, Lele R. Free radicals and antioxidants in human health: current status and future prospects. *J Assoc Physicians India* 2004; **52**: 794-804.

[30] Borek C. Antioxidants and radiation therapy. *J Nutr* 2004; **134**(11): 3207-3209.

[31] Abdullakasim P, Songchitsomboon S, Techagumpuch M, Balee N, Swatsitang P, Sungpuag P. Antioxidant capacity, total phenolics and sugar content of selected Thai health beverages. *Int J Food Sci Nut* 2007; **58**(1): 77-85.

[32] Jagetia GC, Venkatesh P. Inhibition of radiation-induced clastogenicity by *Aegle marmelos* (L.) Correa in mice bone marrow exposed to different doses of γ-radiation. *Hum Exp Toxicol* 2007; **26**(2): 111-124.

[33] Tiku AB, Abraham SK, Kale RK. Eugenol as an *in vivo* radioprotective agent. *J Radiat Res* 2004; **45**(3): 435-440.

[34] Agrawal A, Jahan S, Soyal D, Goyal E, Goyal PK. Amelioration of chemical-induced skin carcinogenesis by *Aegle marmelos*, an Indian medicinal plant, fruit extract. *Integr Cancer Ther* 2012; **11**(3): 257-266.

[35] Baliga MS, Thilakchand KR, Rai MP, Rao S, Venkatesh P. *Aegle marmelos* (L.) Correa (Bael) and its phytochemicals in the treatment and prevention of cancer. *Integr Cancer Ther* 2012; **12**(3): 187-196.

[36] Lampronti I, Martello D, Bianchi N, Borgatti M, Lambertini E, Piva R, et al. *In vitro* antiproliferative effects on human tumor cell lines of extracts from the Bangladeshi medicinal plant *Aegle marmelos* Correa. *Phytomedicine* 2003; **10**(4): 300-308.

[37] Jagetia GC, Venkatesh P, Baliga MS. *Aegle marmelos* (L.) Correa inhibits the proliferation of transplanted Ehrlich ascites carcinoma in mice. *Biol Pharm Bull* 2005; **28**(1): 58-64.

[38] Moongkarndi P, Kosem N, Luanratana O, Jongsomboonkusol S, Pongpan N. Antiproliferative activity of Thai medicinal plant extracts on human breast adenocarcinoma cell line. *Fitoterapia* 2004; **75**(3-4): 375-377.

[39] Subramaniam D, Giridharan P, Murmu N, Shankaranarayanan NP, May R, Houchen CW, et al. Activation of apoptosis by 1-hydroxy-5, 7-dimethoxy-2-naphthalene-carboxaldehyde, a novel compound from *Aegle marmelos*. *Cancer Res* 2008; **68**(20): 8573-8581.

[40] Prasad S, Nigam N, Kalra N, Shukla Y. Regulation of signaling pathways involved in lupeol induced inhibition of proliferation and induction of apoptosis in human prostate cancer cells. *Mol Carcinog* 2008; **47**(12): 916-924.

[41] Slameňová D, Horváthová E, Wsólová L, Šramková M, Navarová J. Investigation of anti-oxidative, cytotoxic, DNA-damaging and DNA-protective effects of plant volatiles eugenol and borneol in human-derived HepG2, Caco-2 and VH10 cell lines. *Mutat Res* 2009; **677**(1): 46-52.

[42] Chaouki W, Leger DY, Liagre B, Beneytout JL, Hmamouchi M. Citral inhibits cell proliferation and induces apoptosis and cell cycle arrest in MCF-7 cells. *Fundam Clin Pharmacol* 2009; **23**(5): 549-556.

[43] Agrawal A, Verma P, Goyal P. Chemomodulatory effects of *Aegle marmelos* against DMBA-induced skin tumorigenesis in Swiss albino mice. *Asian Pac J Cancer Prev* 2010; **11**: 1311-1314.

[44] Gupta N, Agrawal R, Shrivastava V, Roy A, Prasad P. Chemopreventive potential of *Aegle marmelos* fruit extract against 7, 12-Dimethylbenz (a) anthracene-induced skin papillomagenesis in mice. *Res J Pharmacol Pharmacodynamics* 2012; **4**(2): 87-90.

[45] Khan HT, Sultana S. Effect of *Aegle marmelos* on DEN initiated and 2-AAF promoted hepatocarcinogenesis: a chemopreventive study. *Toxicol Mech Methods* 2011; **21**(6): 453-462.

[46] Atul NP, Nilesh VD, Akkatai AR, Kamlakar SK. A review on *Aegle marmelos*: a potential medicinal tree. *Int Res J Pharm* 2012; **3**(8): 86-91.

[47] Vyas A, Bhargava S, Bhargava P, Shukla S, Pandey R, Bhadauria R. Evaluation of antipyretic potential of *Aegle marmelos* (L.) Correa leaves. *Orient J Chem* 2011; **27**(1): 253-257.

[48] Sharma GN, Dubey SK, Sati N, Sanadya J. Ulcer healing potential of *Aegle marmelos* fruit seed. *Asian J Pharm Life Sci* 2011; **1**(2): 172-178.

[49] Madhu C, Hindu K, Sudeepthi C, Maneela P, Reddy KV, Sree BB. Anti ulcer activity of aqueous extract of *Aegle marmelos* leaves on rats. *Asian J Pharm Res* 2012; **2**(4): 132-135.

[50] Kaur P, Walia A, Kumar S, Kaur S. Antigenotoxic activity of polyphenolic rich extracts from *Aegle marmelos* (L.) Correa in human blood lymphocytes and *E. coli* PQ 37. *Nat Prod Rec* 2009; **3**: 68-75.

[51] Ammar RB, Bouhlel I, Valenti K, Sghaier MB, Kilani S, Mariotte AM, et al. Transcriptional response of genes involved in cell defense system in human cells stressed by $H_2O_2$ and pre-treated with (Tunisian) *Rhamnus alaternus* extracts: combination with polyphenolic compounds and classic *in vitro* assays. *Chem Biol Interact* 2007; **168**(3): 171-183.

[52] Singh S, Singh SK, Srivastava S, Singh P, Trivedi M, Shanker P, et al. Experimental evaluation of diuretic activity of *Aegle marmelos* in rats. *Int J Pharm Biol Sci* 2013; **3**(1): 98-102.

[53] Agrawal SS, Kumar A, Gullaiya S, Dubey V, Nagar A, Tiwari P, et al. Antifertility activity of methanolic bark extract of *Aegle marmelos* (L.) in male wistar rats. *Daru* 2012; **20**(1): 94.

[54] Chauhan A, Agarwal M. Reversible changes in the antifertility induced by *Aegle marmelos* in male albino rats. *Syst Biol Reprod Med* 2008; **54**(6): 240-246.

[55] Benni JM, Jayanthi M, Suresha R. Evaluation of the anti-inflammatory activity of *Aegle marmelos* (Bilwa) root. *Indian J Pharmacol* 2011; **43**(4): 393-397.

[56] Veerappan A, Miyazaki S, Kadarkaraisamy M, Ranganathan D. Acute and subacute toxicity studies of *Aegle marmelos* Corr., an Indian medicinal plant. *Phytomedicine* 2007; **14**(2-3): 209-215.

[57] Kruawan K, Kangsadalampai K. Antioxidant activity, phenolic compound contents and antimutagenic activity of some water extract of herbs. *Thai J Pharm Sci* 2006; **30**: 28-35.

[58] Jagetia GC, Venkatesh P, Baliga MS. Evaluation of the radioprotective effect of *Aegle marmelos* (L.) Correa in cultured human peripheral blood lymphocytes exposed to different doses of γ-radiation: a micronucleus study. *Mutagenesis* 2003; **18**(4): 387-393.