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 phytocomstituents mainly marmenol, marmin, marmelosin, marmelide, psoralen, alloimperatorin, rutaretin, scopoletin, aegelin, marmelin, fagarine, anhydromarmelin, limonene,
and linolenic acid[12]. Apart from these, seed oil has been
found to contain 12.5% of an unusual fatty acid, ricinoleic
acid[11]. Seed oil composed of palmitic, stearic, oleic, linoleic
acid[12]. Balakumar
et al. have determined the contents of tannin (0.985%) and riboflavin
(0.005g%)[8]. Various organic acids including oxalic, tartaric,
malic and ascorbic acids were separated and quantified
using a RP–HPLC[18]. 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, β–cubebene,
trans–p–mentha–2,8–dienol, citronellal, β–caryophyllene, hexadecane, pulegone,
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 ripe 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
has been found to have antifungal activity against animal
and human fungi like Trichophyton mentagrophytes, Trichophyton rubrum, Microsporum gypseum, Microsporum
audouini, Microsporum cookie, Epidermophyton floccosum,
Asperillus niger, Asperillus 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⁺ dipicolinic acid metabolism
pathway and possibly inhibit spore germination. Ca⁺ 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, Enterococcus
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 IC₅₀ of leaves, stem and stem
hark, fruit, root and root hark and pure compound marmelide
are 1 000, 500 to 1 000, 250 to 500, and 62.5 µg/mL, respectively,
whereas, the IC₅₀ 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[28]. Bone marrow 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, Abdullahakasim 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[30].

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 H2O2 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 leukemia 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 ERα 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, B16F2 cells; human pancreatic adenocarcinoma cells AsPC–120, human epidermoid carcinoma A431 cells, hepatocellular carcinoma SMMC7721 cells, prostate carcinoma cell lines LNCaP, CWR22Rv1, and PC-3[38]). 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, Erk2, tissue inhibitor of metalloproteinases–3, cyclin D1, Fas associated protein with death domain (FADD mRNA) and matrix metalloproteinase (MMP)–2 genes, 14–3–3 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 IκBα 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 apafl1 genes, and inducing poly (ADP) ribose polymerase cleavage in the CWR22Rv1 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–acetylaminofluorene 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<0.01) 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 queretin like (flavonoid) contents[48]. Another study indicated that A. marmelos fruit pulp extract treated albino rats show a significant decrease in mucosal thickness, superoxide dismutate, 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 PQ87 (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 H2O2 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 to 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 experimental models and their fractions of A. marmelos fruit in experimental rats. The extracts were administered to experimental rats intraperitoneal 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 medicinal 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 information 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**

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


