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Review Article

Biological activities of crude extracts and chemical constituents of Bael, *Aegle marmelos* (L.) Corr.[#]

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Bael (*Aegle marmelos* (L.) Corr.) is an important medicinal plant of India. Leaves, fruits, stem and roots of *A. marmelos* have been used in ethno medicine to exploit its' medicinal properties including astringent, antidiarrheal antidysenteric, demulcent, antipyretic and anti-inflammatory activities. Compounds purified from bael have been proven to be biologically active against several major diseases including cancer, diabetes and cardiovascular diseases. Preclinical studies indicate the therapeutic potential of crude extracts of *A. marmelos* in the treatment of many microbial diseases, diabetes and gastric ulcer. This review covers the biological activities of some isolated chemical constituents of *A.marmelos* and preclinical studies on some crude extracts and pure compounds to explore novel bioactive compounds for therapeutic application.

Keywords: *Aegle marmelos*, Antibacterial, Anticancer, Antidiabetic, Antifungal, Antihyperlipidaemic, Antioxidant, Antiulcer, Antiviral, Bael, Radioprotective

Over the last few years, researchers have aimed at identifying and validating plant-derived substances for the treatment of various diseases[1-3]. Interestingly, it is estimated that more than 25% of modern medicines are directly or indirectly derived from plants[1-3]. In this context, it is worth mentioning that Indian medicinal plants are considered a vast source of several pharmacologically active principles and compounds and that are commonly used in home remedies against multiple ailments[4,5]. Neem and turmeric are quite popular among these important medicinal plants and several pharmacologically active compounds have already been isolated and extracted from these plants[4-9]. Bael (*Aegle marmelos* (L.) Corr.) is another Indian plant, which has enormous traditional uses against various diseases and many bioactive compounds have been isolated from this plant also[10,11].

Bael is a medium-sized, armed, deciduous tree from the family Rutaceae. This tree was originated in India and is presently growing in most of the countries of Southeast Asia. In India, it grows wild, especially in dry forest, outer Himalayas, Shivaliks, South Indian plateau with altitudes ranging from 250-1200 m and also cultivated throughout Indian sub continent for its fruits. It prefers dry and sunny or warm parts of the hill slopes with well-drained loamy soil[12]. Leaves, fruits, stem and roots of this tree at all stages of maturity are used as ethno medicines against various human ailments[10]. Extensive chemical investigations on various parts of the tree have been carried out and more than 100 compounds have been isolated[11]. Many of these compounds including skimmianine, aegelin, lupeol, cineole, citral, citronellal, cuminaldehyde (4-isopropylbenzal-dehyde), eugenol, marmesinin, marmelosin, luvangetin, aurapten, psoralen, marmelide, fagarine, marmin and tanin have been proved to be biologically active against various major and minor diseases including cancer, malaria and gastroduodenal disorders[10,13-20]. Various crude extracts of this plant have shown activities including antiulcer, antidiabetic,

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antihyperlipidaemic, antioxidant, anticancer, antimicrobial, radioprotective, anti-inflammatory, antipyretic, analgesic and antispermatogenic effects on various animal models[10,14,21-57]. All the compounds present in the extracts responsible for these activities have not been identified so far. Presently, there is no published source that can provide the available information compiling all the active compounds of bael. Therefore, in this article, a brief but all-encompassing discussion has been presented on the bioactive compounds isolated from this plant, their pharmacological activities and preclinical studies. This article will enhance the existing knowledge of the bael, and also create the awareness of possible new therapeutic uses for the development of pharmaceutical entities or dietary adjuncts for better health care in the near future.

Biological activities of purified bael compounds

A large number of compounds have been isolated from various parts of the bael tree and a few of them have been studied for their biological activity (Table 1). The structures of some of these bioactive compounds are presented in Fig.1. The bioactive compounds isolated from the various parts of this tree and their biological activities are:

Leaf

Several compounds such as skimmianine, aegelin, lupeol, cineole, citral, citronellal, cuminaldehyde, eugenol and marmesinin have been purified from bael leaves[14,17,19,21-23,25-29,56,61,62,67-71]. Skimmianine (**1**) ($C_{14}H_{13}NO_4$), an alkaloid, is also found in the immature bark of the tree. It has shown anticancer activity in A2780 human ovarian cancer

Table 1 — Bioactive compounds isolated from various parts of bael

Bael compound	Source	Biological activity	Reference for biological activity	Reference for structure
Skimmianine (**1**)	Leaf, Immature bark	Anticancer	13	121,122
		Anti-methamphetamine	22	
		Sedative, Hypnotic, Analgesic, Anticonvulsive, Antipyretic, Hypothermic, Antidiuretic,	20, 21	
		Antimalarial	16	
Aegelin(**2**)	Leaf	Cardioactive Antihyperglycemic Antidislipidemic	60, 61,72	121
Lupeol(**3**)	Leaf	Cardioactive,	60, 61	122
		Anti-inflammatory	24	
Cineol(**4**)	Leaf	Antiulcer	18, 25, 26, 66	122
Citral(**5**)	Leaf	Antiallergic	67	122
		Antiseptic	68	
Citronellal (**6**)	Leaf	Antiseptic	68	121,122
Cuminaldehyde (**7**)	Leaf	Antibacterial	27	122
Eugenol (**8**)	Leaf	Antioxidant	25, 69, 70	122
		Antibacterial	28	
		Hepatoprotective	55	
		Antiulcer	18	
Marmesinin (**9**)	Leaf	Antioxidant, Cardioprotective	61	122
Marmelosin (**10**)	Fruit	Antihelminthic, Antibacterial	73-75	122
Luvangetin (**11**)	Fruit	Antiulcer	19, 73	121,122
Aurapten (**12**)	Fruit	Heart beat inhibitor	23	121,122
Psoralen (**13**)	Fruit	Antispasmodic	76	122
		Artemicide, Cytotoxic	77	
Marmelide (**14**)	Fruit	Antiviral	10	21
Fagarine (**15**)	Mature bark	Abortifacient	27	122
Marmin **(16)**	Immature bark	Antiulcer	12	121,122
Tannin	Unripe fruit	Anti-diarrhoea, Astringent	75	

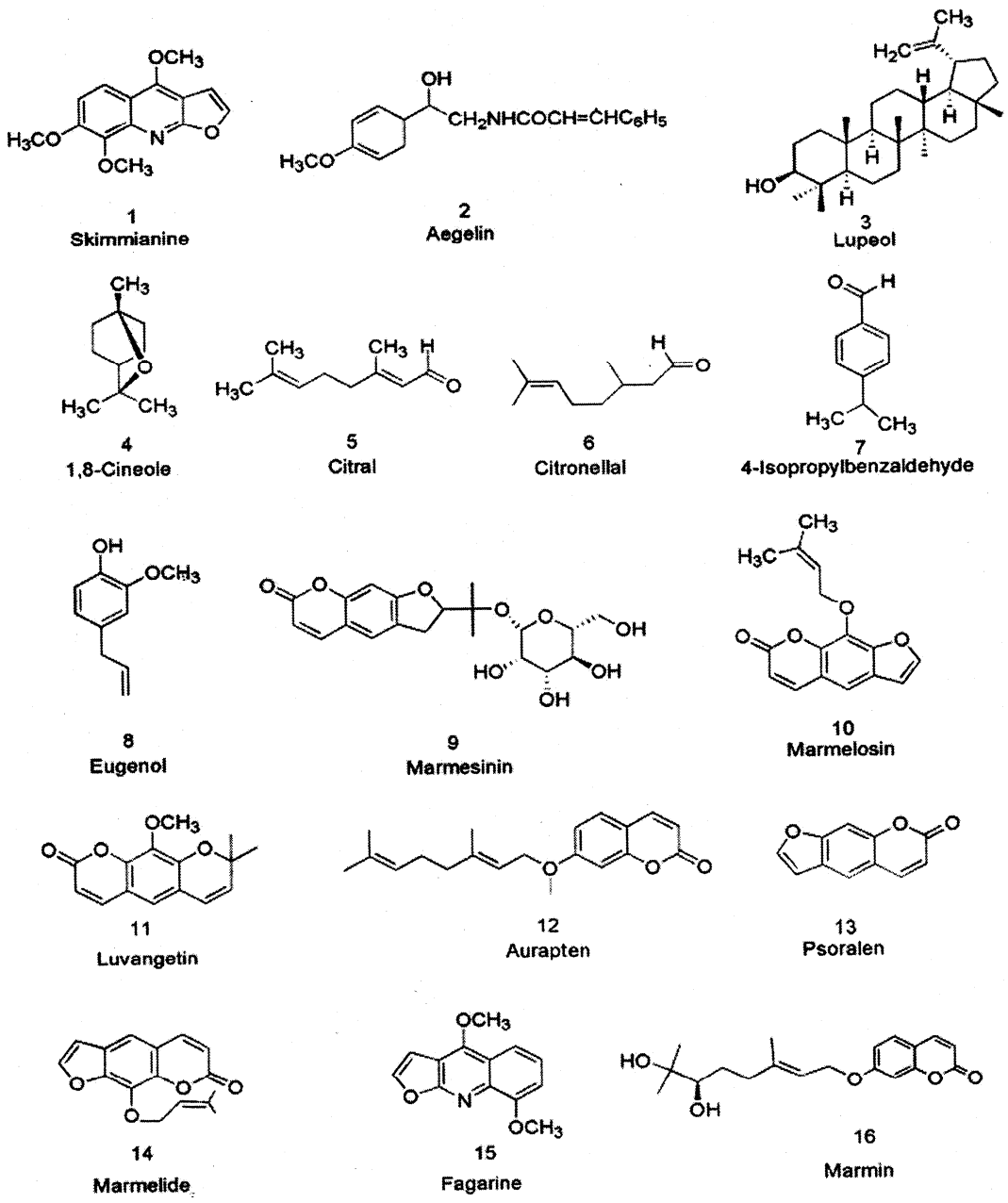

Fig. 1— Structures of purified bioactive compounds from bael (references given in Table 1).

cell line[14]. It also inhibits spontaneous motor activity, exploratory behavior, cataleptogenic activity and conditioned avoidance response in animals[23]. In various experimental animal models, skimmianine has shown sedative, hypnotic, analgesic, anticonvulsive, antipyretic, hypothermic and antidiuretic effects[21,22]. It also exhibits anti-malarial activity through the inhibition of *Plasmodium falciparum* growth *in vitro* (IC_{50}=48.2 μg/ml)[17]. Aegelin (**2**) ($C_{18}H_{18}O_4$) is a potent cardioactive compound[61,62] and has antihyperglycemic activity[72]. Lupeol (**3**) ($C_{30}H_{50}O$) is also a potent cardioactive compound[61,62] and shows anti-inflammatory property[25]. Development of oxidative stress[54,63] and neutrophil infiltration are common for inflammatory diseases[55,64]. It is now accepted that gastric ulcer is mainly caused by oxidative stress[6,8,65, 66]. Cineole (**4**) ($C_{10}H_{18}O$) exhibits antioxidant property by restoring ethanol associated depletion of non-protein sulfhydryl (NPSH) level to normal in the stomach indicating that it can prevent the generation of reactive oxygen species (ROS) and prevent ethanol induced gastric injury in rats[19,26,27,67].

At higher doses, cineol also inhibited pylorus-ligation induced gastric acid secretion[67]. Citral (**5**) ($C_{10}H_{16}O$) has shown antiallergic[68] and antiseptic activities[69]. Citronellal (**6**) ($C_{10}H_{18}O$) has also been used for its antiseptic activity[69]. Cuminaldehyde (**7**) ($C_{10}H_{12}O$) has been found to have antibacterial activity[28]. Eugenol (**8**) ($C_{10}H_{12}O_2$) has potent antioxidant property[26,70,71] and inhibits lipid peroxidation[71,73]. It also has antiperoxidative activity on Fe^{2+}-ascorbate and Fe^{2+}-H_2O_2-induced lipid peroxidation in rat liver mitochondria[74]. Eugenol offers antibacterial activity[29], hepatoprotective activity against CCl_4-induced hepatic damage[56] and prevents ethanol and platelet-activating factor (PAF) induced gastric damage in a dose-dependent fashion[19,27,67]. Furanocoumarin marmesinin (**9**) ($C_{20}H_{24}O_9$), at a dose of 200 mg/kg protects the heart against damage caused by experimental myocardial injury in rats[62]. Treatment with marmesinin (oral) for two consecutive days before and during isoproterenol administration decreases the extent of lipid peroxidation in rats[62]. Marmesinin has also been shown to have a membrane stabilizing action by inhibiting the release of β-glucuronidase from the subcellular fractions[62].

Fruit

The bioactive compounds isolated from beal fruits are marmelosin, luvangetin, aurapten, psoralen, marmelide and tannin[10,20,24,75-79]. Marmelosin (**10**) ($C_{16}H_{14}O_4$) has shown antihelmintic as well as antibacterial activities[75-77]. Luvangetin (**11**) ($C_{15}H_{14}O_4$), a pyranocoumarin isolated from the seeds of bael fruit protects against multiple models of gastric ulceration in rodents[20,75]. Aurapten (**12**) ($C_{19}H_{22}O_3$) inhibits (IC_{50} = 0.6 μg/ml) the chronotrophic effects on cardiac tissue and thus may be useful in treatment of hypertension[24]. Psoralen (**13**) ($C_{11}H_6O_3$) shows various activities such as antispasmodic[78], artemicide (LD_{50} = 5.93 μg/ml) and cytotoxic[79]. Marmelide (**14**) ($C_{16}H_{14}O_4$) is very effective against viruses and is found to influence the early stages of replicative cycle such as adsorption, penetration, etc.[10]. Tannin, present in the unripe fruit of this plant, has astringent property and is an excellent remedy for diarrhoea[77].

Bark

Among the important bioactive compounds isolated from bark are fagarine and marmin[13,28]. Fagarine (**15**) ($C_{13}H_{11}NO_3$) is present in the mature bark and possesses abortifacient activity[28]. Marmin (**16**) ($C_{19}H_{24}O_5$), is found in the immature bark of the tree. It shows antiulcer activity in experimental ulcer models[13]. Oral administration of marmin at a dose of 10-50 mg/kg in rats has inhibited the occurrence of ethanol induced gastric haemorrhagic lesions in a dose dependent manner with ED_{50} of 17.2 μg/kg. Intragastric administration of marmin at a dose of 25 mg/kg body weight also significantly inhibited gastric motility[13].

Traditional uses and Pre clinical studies on bael

Crude extracts from multiple parts of the bael plant are used to treat various disorders in different Indian traditional systems[80]. Roots are used to cure cardiac malfunction, abdominal pain, fever, urinary troubles, hypochondriasis and melancholia[81]. Leaves are used as an astringent, laxative, digestive and febrifuge when fresh. They are also useful in opthalmia, hearing loss and inflammation[81]. The unripe fruit is also helpful in curing dysentery. The ripe fruit is used as an astringent, appetizer, laxative, tonic, restorative, febrifuge and also used in biliousness[81]. Different parts of this plant are used to cure various diseases in folklore medicine. A number of ethno-medicinal uses of bael tree have already been documented[11, 80].

Antiulcer activity

Gastroduodenal ulcer is a common disorder of the gastrointestinal tract[6]. It is now considered that gastroduodenal ulcer is a disease of multifactorial origin but its detailed etiology is still not clear[82]. Development of oxidative stress[6,8,66,84], lowering of gastroprotection, decrement of mucosal blood flow, delayed restitution and regeneration etc. play dominant role in the pathogenesis of ulcer[66,83]. Ulcer develops when there is imbalance between the defensive and aggressive factors on the mucosa resulting from either potentiation of aggressive factors and/or lowering of mucosal protection[66,83]. Stress, non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* are the most common causes of ulceration[6]. Cigarette smoking and alcohol ingestion are other inducers of this disease[65,82]. Current medicinal therapy with proton pump inhibitors and selective H_2 receptor blockers can efficiently cure ulcers. But none of these are devoid of side effects and execute their action within a limit. Moreover, the recurrence of ulcer after stopping the medication is very high. About 70% of ulcers could recur after stopping medication[86]. These drawbacks of the currently available antiulcer medicines necessitate the development of newer generation phytogenic drugs.

Many Indian medicinal plants like turmeric and neem have already shown antiulcer activity and various active compounds have been isolated from these plants[4-9,85,87]. Bael is another Indian indigenous plant which also has prominent gastroprotective effect. Pretreatment of rats with unripe bael fruit extract produced a significant inhibition of absolute ethanol induced gastric mucosal damage[88]. This activity may be due to the compound luvangetin present in the fruit. Gastric ulcer is basically mediated by the development of oxidative stress and the compounds preventing ulcer formation may act through inhibition of oxidative stress in the gastroduodenal mucosa. The phenolic compounds are potent antioxidants[57] and have powerful antiulcer activities[6]. These compounds contain an OH group linked with the aromatic ring and thus may possess potent antioxidant and antiulcer activities. The pathway for antiulcer efficacy and possible mode of action are presented in Fig. 2.

Antidiabetic activity

Diabetes mellitus is a common metabolic disease around the world. A large percentage of the global population is suffering from this disorder. The disease is induced by stressful lifestyle, fast food eating, lack of exercise and genetic makeup. Diabetes and its related complications are closely related with oxidative stress of the body[89,90]. Diabetes is closely inter-linked with cardiovascular as well as renal disorder at advanced stage and creates fatal disease syndromes. Oral, as well as intraperitoneal administrations of the aqueous extract of bael fruit exhibited hypoglycemic effect against streptozotocin-induced diabetic rats[32,33,91]. The antidiabetic mode of action is of multidirectional as the extract can significantly lower the levels of blood glucose and glycosylated hemoglobin and increased the plasma insulin as well as liver glycogen in diabetic rats[91]. The fruit extract at a dose of 250 mg/kg exhibited to be more effective than glibenclamide, a well-known hypoglycemic drug[33]. This antidiabetic effect is probably due to the presence of coumarins in the fruit extract, which potentiate the insulin secretion from existing beta cells of the Islets of Langerhans[32]. The aqueous extract of bael seeds reduced the blood glucose level in normal as well as in severe diabetic rat[92]. In a number of pre-clinical trials it has been found that the methanolic, alcoholic and aqueous extracts of bael leaves have antidiabetic action. These extracts significantly decreased the serum glucose level, improved the ability to utilize the external glucose load and increased the plasma insulin levels in artificially induced diabetic animal models[35,93-97]. Figure 3 represents a composite diagram of the antidiabetic activity of bael extracts. Oral administration of aqueous and alcoholic extracts of bael leaves in doses of 500 mg/kg significantly induced hypoglycaemia in normal fasted rabbits[98]. The crude leaf extract administered orally to streptozotocin-diabetic rats at a dose of 1g/kg weight at 24 h intervals for a period of two weeks was found to be as effective as insulin in restoring blood glucose and body weight to normal levels[99]. The mechanism of action could be either stimulation of glucose uptake or enhancement of insulin secretion or both[93]. The unique glucose lowering activity occurs without altering the serum cortisol concentration[100]. The treatment of leaf extract on diabetic pancreas showed improved functional state of beta cells and also helped in the regeneration of parts of the pancreas damaged by streptozotocin[101]. In an uncontrolled clinical trial the administration of leaf extract for 15 days significantly reduced blood cholesterol levels with slight lowering of blood glucose in some patients with diabetes mellitus[102].

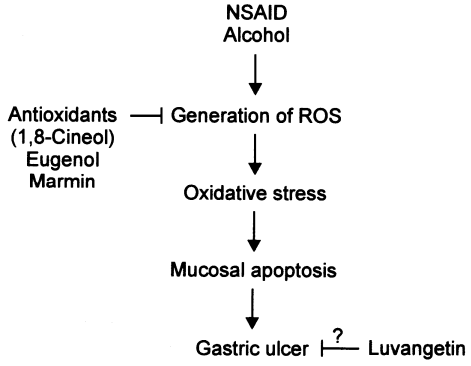

Fig. 2— Possible mode of antiulcer action of bael extracts. (? = not confirmed ; –= inhibition)

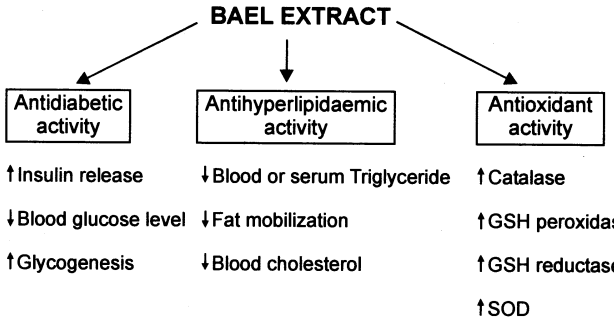

Fig. 3— Diagrammatic representation of the possible antidiabetic, antihyperlipidaemic and antioxidant activities of bael. (↑= increase; ↓=decrease)

Antihyperlipidaemic activity

A higher concentration of blood triglyceride, fatty acid and cholesterol level leads to atherosclerosis by arterial damage and may lead to ischemic heart disease, myocardial infarction and cerebro vascular accidents. Although modern drugs are effective in preventing cardiovascular disorders, their use is very limited because of their side effects. Pretreatment with bael leaf extract at 100 mg/kg and 200 mg/kg doses for 35 days have shown significant improvement on the activities of marker enzymes, decrement of lipid peroxides, plasma lipids and lipoproteins in isoproterenol-treated rats, suggesting its antihyperlipidaemic effect[103]. Oral administration of the aqueous extract of bael fruits and seeds separately at a dose of 250 mg/kg to streptozotocin-induced diabetic rats significantly lowered the serum and tissue lipid profile[32,92]. Ethanolic extract of bael leaves also inhibited the elevation of serum cholesterol and triglycerides level in Triton WR 1339 treated hyperlipidaemic rat[104]. Reduction of serum lipids may be due to decreased fat mobilization from the peripheral depots as well as their synthesis. This extract activates hydrolysis of triglycerides and decreases circulatory level of blood cholesterol by decreasing fat mobilization from peripheral adipose tissues (Fig. 3). This extract also potentiates glucose utilization. The higher level of fatty acid and their metabolites such as acyl carnitine and long chain acyl CoA, usually interfere with Na^+/K^+-ATPase activity level[32]. Thus a lower level of circulatory fatty acid may favor the restoration of normal function of Na^+/K^+-ATPase path, an essential gateway for proper burning of glucose at cellular level in diabetic animals.

Antioxidant activity

Oxidative stress is produced during normal metabolic processes in the body as well as induced by a variety of environmental and chemical factors, which cause generation of various reactive free radicals and subsequent damage to macromolecules like DNA, proteins and lipids. In artificially induced diabetic animals, the levels of lipid peroxidation, hydroperoxides (HP), conjugated diene, thiobarbituric acid reactive substances (TBARS), creatine kinase (CK) and lactate dehydrogenase (LDH) increased considerably, and then decreased after treatment with the various extracts of bael leaves and fruits[35-37]. On the other hand, antioxidative parameters like reduced glutathione, glutathione peroxidase, glutathione reductase, superoxide dismutase (SOD) and catalase have shown a dose-related increase in their level/activity and a decrease in lipid peroxidation following the treatment with bael leaf extract (Fig. 3)[35,37,105]. The fruit extract at a dose of 250 mg/kg body weight is more effective than glibenclamide (300 μg/kg)[36]. Leaf extract (200 mg/kg) is as effective as alpha-tocopherol (60mg/kg) in isoproterenol (ISO)-treated rats[103]. The antioxidative phytochemicals such as flavonoids, alkaloids, sterols, tannins, phlobatannins and flavonoid glycosides present in the leaf extract possess this free radical scavenging activity[21,26,103,106-109]. Glutathione (GSH) is reduced in erythrocyte whereas plasma glutathione-S-transferase (GST) and malondialdehyde (MDA) are increased in male albino rats with diabetes. However, these alterations returned to normal level with bael leaf extract administration, suggesting antioxidant potential of bael leaves[101]. Eugenol and marmesinin may be responsible for such activity because these compounds have independently shown their activity against oxidative stress[26,62,70,71]. Figure 3 summarizes the potential antioxidant activity of bael extract.

Anticancer activity

Most of the potent antineoplastic drugs available are expensive, mutagenic and teratogenic including drugs derived from natural sources (paclitaxel)[14,110]. Hence, attention is being given to develop inexpensive and non-toxic drugs from alternative sources. The hydroalcoholic extract of bael leaves has shown anticancer effect in the animal model of Ehrlich ascites carcinoma[14]. Administration of the extract (400 mg/kg) has shown the greatest anti-tumor effect. The exact mechanism of this extract is yet to be established[14]. The plant extract exhibits cytotoxicity against tumor cell lines in brine shrimp lethality assay and methyl thiazolyl tetrazolium (MTT) based assay[15]. The extract also possesses anti-proliferative activity on MCF7 and MDA-MB-231 breast cancer cell lines[16]. Induction of apoptosis may be due to the presence of skimmianine in the leaf extract which may have killed the tumor cells[14].

Antifungal activity

Fungal diseases including candidiasis and ring worm infection are cosmetic problems that may become fatal due to secondary or super infection as

commonly occurs in AIDS patients. There are many synthetic antifungal drugs available, but attention is now been paid to discover herbal drugs by using natural resources directly or by using them to manufacture other products. The essential oil isolated from the leaves of the bael tree has proved its antifungal activity against many animal and human fungi like *Trichophyton mentagrophytes, T.rubrum, Microsporum gypseum, M. audouinii, M. cookei*, *Epidermophyton floccosum, Aspergillus niger, A. flavus,* and *Histoplasma capsulatum*[47,48,111-113]. The unsaponifiable matter of the seed has exhibited considerable *in vitro* activity against various fungi *viz. Trichophyton rubrum, T. terrestre, Epidermophyton floccosum, Aspergillus fumigatus, A. niger* and *A. flavus*[45,47]. The ethanolic extract of the root has shown activity against *Aspergillus fumigatus* and *Trichophyton mentagrophytes*[42]. The germination of any spore (i.e. bacterial or fungal) is related to Ca^{2+} – dipicolonate and/or free Ca^{2+} ions availability in the medium as well as within cytoplasm of microbes. This Ca^{2+} ion uptake and utilization by spore is one of the prime factors that determine whether the spore will germinate or remain dormant[114]. The essential oil from the bael leaves may interfere with the Ca^{2+} – dipicolonic acid metabolism pathway and possibly inhibit spore germination. Thus it exhibits 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 bael leaf oil against fungal infection[50]. However, its curative role is yet to be explored. A generalized scheme for antifungal activity of bael extracts is presented in Fig. 4.

Antibacterial activity

Bacteria are the most versatile unicellular pathogens, which are normally transmitted through soil, water, air and food and cause diseases in human beings and animals. Such types of diseases could be treated with various natural products including bael. Various extracts of bael leaves, roots and fruits have been reported to be active against many bacterial strains. Leaf extracts have shown activity against *Escherichia coli*[38,39]. The essential oil obtained from the leaves exhibited activity against *Aeromonas* sp., *Escherichia coli, Pseudomonas salanacearum* and *Xanthomonas vesicatoria*[40,41]. The ethanolic extract of the root has shown activity against *Vibrio cholerae, Salmonella typhimurium*, *Klebsiella pneumoniae, Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus*[42,43]. The ethyl acetate extract of the plant has exhibited activity against *Vibrio cholerae, Salmonella typhimurium, Staphylococcus aureus, Pseudomonas putida* and *Bacillus anthracis*[44]. Methanol and aqueous extracts of bael fruits have shown strong activity against multi drug resistant *Salmonella typhi*. Methanolic extract is more potent than the aqueous extract. The minimum inhibitory concentration (MIC) value of the methanolic extract is around 256 μg/ml. The unsaponifiable matter of the seed has shown considerable *in vitro* activity against *Escherichia coli, Salmonella typhi, Salmonella paratyphi, Proteus vulgaris, Streptococcus faecalis, Vibrio cholerae, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*[45]. Both the oil and the unsaponifiable matter of the seed have also been found to be active against *Bacillus subtilis, Escherichia coli, Klebsiella aerogenes, Salmonella typhi, Salmonella paratyphi, Staphylococcus aureus, Erwinia carotovora, Pseudomonas solanacearum, Xanthomonas citri,* and *Xantha malvacearum*[47]. Thus it is evident that bael has antibacterial activity and the mechanism of action may be the blockage of protein synthesis either at transcription or translation level and/or peptido-glycan synthesis at membrane level. The antibacterial activity of the leaf extracts may be due to the presence of cuminaldehyde and eugenol because these compounds have already shown their activities against various bacterial strains[28,29]. Figure 4 represents the possible mode of antibacterial action of bael extract.

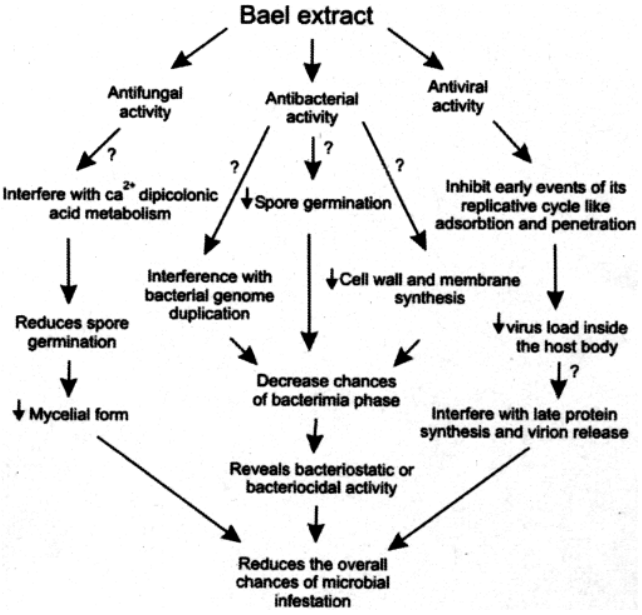

Fig. 4— Diagrammatic representation of the antifungal, antibacterial and antiviral activities of bael extracts. (↑= increase; ↓=decrease; ?=not confirmed)

Antiviral activity

Virus is the smallest pathogen with its dual form: a living entity inside the host body and non-living inert form outside the host. This causes various seasonal outbreaks including conjunctivitis and influenza and usually does not respond to any synthetic drugs. It is very important to develop antiviral drugs from natural bio-resources to overcome these problems. The *in vitro* antiviral activities of various parts of the bael tree have 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 the pure compound marmelide are 1000, 1000, 500-1000, 250-500 and 62.5 μg /ml, respectively, whereas, the IC_{50} of ribavirin, a standard antiviral agent, is 2000 μg/ml for the same viruses and at the same time period[10]. Marmelide is the most effective virucidal agent interfering with early events of its replicative cycle[10]. It seems that bael has antiviral activities in the early stages of viral replication with minimum host cytotoxicity in contrast to modern virucidal chemotherapeutic agents (i.e. ribavirin), which usually act in the later stages of viral replication and have potent side effects[51]. The effect of bael extracts also on the late protein synthesis need to be studied to evaluate its degree of potentiality as an antiviral agent. The 50% ethanolic extract of the fruits has shown antiviral activity against Ranikhet disease virus[52]. The fruit extract has exhibited interferon-like activity against the same virus but not against vaccinia virus[53]. Thus bael has better viricidal potential and may be exploited as a potent antiviral agent in near future. Figure 4 summarizes the antiviral action of bael extracts.

Radioprotective activity

Recently radiotherapy is one of the most important therapies to cure cancer particularly for those who are suffering from vital visceral malignancies. A large number of cancer patients are regularly being cured all over the world with this treatment. However, the radiotherapy also has some side effects. It causes alteration in genome base pair(s) and has a very slow, deep and long term effect on exposed persons. High doses of radiation lead to severe esophagitis in lung cancer and acute mucositis and pharyngitis in head and neck cancer, respectively[27]. The radio protective chemicals, which are currently in use exhibit severe toxicity and undesirable side effects and hence their uses are very restricted. The radio protective effect of hydroalcoholic extract of bael leaves has been evaluated in cultured human peripheral blood lymphocytes (HPBLs). The irradiation of $HPBL_S$ with different doses of gamma-radiation caused a dose-dependent increase in the frequency of lymphocytes bearing one, two and multiple micronuclei. Treatment of HPBLs with 5 μg/ml leaf extract significantly reduced the frequency of lymphocytes bearing one, two and multiple micronuclei when compared with the irradiated control. The mechanism of this type of radioprotective activity of the leaf extract may be due to the scavenging of radiation-induced free radicals[26]. Radioprotective activity of bael leaf extract has also been studied in Swiss albino male mice. The mice were administered with various intraperitoneal single doses of the extract. The optimum radioprotective dose of the extract has been found to be five consecutive doses of 15 mg/kg body weight[115]. Irradiation caused a dose dependent decline in the level of glutathione accompanied by an elevation in lipid peroxidation. Bael leaf extract arrested glutathione decline and lipid peroxidation significantly[108]. Hydroalcoholic extract of the bael fruits has also been studied for its radioprotective effect in mice exposed to various doses of gamma radiation. The extract (20 mg/kg) administered intraperitoneally for 5 consecutive days before irradiation of gamma ray has been found to afford maximum protection as evidenced by the highest number of survivors after 30 days post-radiation[27]. Symptoms of sickness and mortality of the animals are due to irradiation resulting in a dose-dependent elevation in lipid peroxidation in liver, kidney, stomach and intestine as well as depletion in GSH concentration. Treatment of animals with the bael fruit extract before irradiation caused a significant decrease in the lipid peroxidation accompanied by a significant elevation in the GSH concentration in liver, kidney, stomach and intestine of mice[27].

Miscellaneous activities

Inflammation is the basic strategy of any host defense mechanism to combat or overcome the invader pathogen and/or foreign particles. There are several cardinal signs of inflammation like redness, swelling, heat, pain, loss of function. The severity of infection is expressed by these signs involving organs or host body as a whole[116,117]. Different organic extracts of the bael leaves possess highly significant acute and sub-acute anti-inflammatory, analgesic and antipyretic activities[30]. 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[21,22,25]. Activation of histamine receptor is essential for allergic and asthamatic manifestation[118]. The alcoholic extract of bael 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 by this extract may underlie these effects[119]. This activity may be due to the presence of some anti-inflammatory and anti-allergenic constituents, such as lupeol and citral present in the alcoholic extract, as most of the anti-inflammatory and anti-allergenic compounds act through inhibition of histamine mediated signaling[25,68]. The protozoal diseases like malaria are one of the most troublesome problems in tropical countries. Malaria caused by *Plasmodium falciparum* causes about 2 million deaths annually[58,59]. Development of resistance to existing anti-malarial drugs has led to complications in treating this dreadful disease[60]. Thus, identification of novel molecules to treat this multidrug resistant malaria is vital[59]**.** The alcoholic extracts of the bael 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 systems, whereas, the leaves have shown activity only in the *in vitro* system[18]. Population explosion is one of the major global crises in the present century for the resource management and utilization. A number of chemical and hormonal treatments as well as physical processes have been developed to control the birth rate, but none of these are hundred percent successful and all are with some side effects. Hence, it is very essential to develop some cost effective herbal drugs without or less side effects to combat this burning problem. The ethanolic extract of bael leaves has shown antispermatogenic activity in albino rats in the form of significant decrease in the weight of primary as well as some accessory sex organs and reduced sperm count[31]. Another study demonstrated that the aqueous extract of the same has no adverse effect on male body and testicular weights as well as on cauda epididymal sperm counts of rats. No notable changes in sperm morphology and motility have also been observed[120]. This contradictory effect may be explained in such a way that the aqueous extract probably lacks the bioactive ingredients present in the ethanolic extract.

Conclusion

It is quite evident that bael contains several important bioactive compounds and some have already shown their therapeutic potential. Unfortunately, most of the compounds have not properly been evaluated for the exploration of new lead molecule or pharmacophore. Moreover, mechanisms of action of a few bioactive compounds have been identified so far. Hence, extensive research is required to find out the mechanisms of action as well as bioactivity of other compounds in crude extracts and to exploit their therapeutic potential to combat various diseases. A drug development programme can be developed through extensive investigation of the bioactivity of various compounds, their mechanism of action, pharmacotherapeutics, toxicity, standardization and clinical trials. Thus in near future bael may play a very important role in modern system of medicine.

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