Clinical Journal of Diabetes Care and Control
ISSN: 2642-0872

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Review Article *Volume 6 Issue 1*

Antidiabetic Effect of Bael *Aegle Marmelos Correa* Family Rutaceae

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Received Date: May 09, 2024; **Published Date:** June 10, 2024

Abstract

Natural remedies have played a pivotal role in human healthcare since time immemorial and continue to be part of the treatment of various diseases. Bael (*Aegle Marmelos Correa*) is an angiosperm that has been credited to possess treatment capability to cure diarrhea, chronic dysentery, constipation, gonorrhea, catarrh, diabetes, deafness, inflammations, ulcerated intestinal mucosa, intermittent fever, melancholia, and heart palpitation. The review deals with the antidiabetic action of Bael in experimental and clinical conditions. The data were collected by searching on Google, Google Scholar, Science Direct, Pubmed, and consulting published material on Bael. The Bael contains several secondary metabolites including anthocyanins, cardiac glycosides, alkaloids, coumarins, flavonoids, lignins, saponins, steroids, terpenoids, tannins, and quinones. The experimental evaluation has indicated that Bael is non-toxic and well-tolerated. Diabetes has been increasing due to lifestyle alterations and it is the ninth killer disease in the world. Bael exerts its antidiabetic action by increasing glycated hemoglobin, insulin, and β-cell function, and reducing HOMA-IR (Homeostatic Model Assessment of Insulin Resistance). Bael elevated reduced glutathione, glutathione peroxidase, glutathione-S-transferase, catalase, and superoxide dismutase and reduced lipid peroxidation, and cholesterol. The antidiabetic action of Bael is mediated by a rise in PPAR-γ and consequent inhibition of TNF-α, NF-κB, Hsp70, PI3K/AKT, HIF-1α, IFN-γ and IL-8, IL-1β, IL-6, IL-10, IL-17, MIP-1α, COX-I, COX-II, STAT-3, AKT, tyrosinase, and galectin-3 and consequently increase of PI3K, IL-2, JAK-STAT3, and DT-diaphorase. The review deals with the antidiabetic action of Bael (*Aegle Marmelos Correa*).

Keywords: *Aegle Marmelos Correa*; HOMA-IR; Antidiabetic; Super Oxide Dismutase

Abbreviations: GST: Glutathione-S-Transferase; SOD: Super Oxide Dismutase; GPx: Glutathione Peroxidase; LDL-c: Low-Density Lipoprotein Cholesterol; LDH: Lactate Dehydrogenase; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; PPAR- γ: Peroxisome Proliferator Activated Receptor; AGEs: Advance Glycation End Products; BUN: Blood Urea Nitrogen; ACAT: A Cholesterol Acyl Transferase; HO1: Heme Oxygenase-1; GR: Glutathione Reductase; ARE: Antioxidant Response Element; NQO1: NAD[P]H: Quinone Oxidoreductase-1; CAT: Catalase.

Introduction

Diabetes is caused by hormonal dysregulation and defects in cellular capabilities that lead to improved fasting blood glucose leading to hyperglycemia and glucose intolerance. Generally, the subjects displaying fasting blood glucose levels higher than 110 mg/ dL (6.1 mmol) and postprandial glucose levels of 200 mg/dL (11.1 mmol) are diabetic [1]. The glucose levels in the human blood is regulated by insulin in concordance with glucagon, corticosteroids, epinephrine,

and growth hormone [2]. Diabetes results from both the cessation of insulin production and dysregulated action of insulin owing to the nonfunctional and/or damaged pancreas. Diabetes is divided into four types depending on the etiology and clinical presentation. Insulin-dependent diabetes mellitus or Type I (IDDM, Type I) and Type II diabetes- a non-insulin-dependent diabetes mellitus (NIDDM, Type II). In addition, the other types of diabetes are gestational diabetes, and other specific types [3-5]. IDDM or Type I diabetes is an autoimmune disorder caused by the carnage of β-cells of islets of Langerhans by the body's T-lymphocytes that leads to local inflammation and inhibition of insulin secretion. IDDM usually needs insulin replacement therapy [2,6,7]. IDDM is more prevalent in children than in adults. The IDDM occurs due to genetic predisposition and its incidence is increasing [8,9]. NIDDM or Type II is the most frequent type of diabetes in adult humans. NIDDM is a metabolic disorder that develops as a result of inadequate secretion of insulin by the β cells of the pancreas and/or the insulin-sensitive tissues that do not respond to insulin secretion. The glucose homeostasis, insulin release, and the mechanisms involved in insulin synthesis and its release are meticulously controlled; however dysregulation of these mechanisms leads to diabetic disorders [10]. The NIDDM exhibits intermediate stages of impaired fasting glucose and impaired glucose tolerance, therefore it is also known as prediabetes.

Obesity is one of the major causes of Type II diabetes and 85-95% of diabetic patients suffer from Type II diabetes [5,11]. Diabetes is characterized by polyuria, polydipsia, polyphagia, fatigue, blurred visions, dry mouth, burning sensation, numbness of feet, acanthoses nigricans, erectile dysfunction, hunger, hyperglycemia, itching, excess thirst, and weight loss [4,5,12]. Several treatment modalities are available for the treatment of both type I and II diabetes in modern medicine. Diabetes leads to various complications including, cerebrovascular disorders cardiomyopathies, neuropathy, nephrotoxicity, and delayed wound healing [13,14]. Type II diabetes is a lifestyle disease and changing lifestyle can reduce the incidence of this disorder [15,16].

One in every ten individuals is suffering from diabetes and 10.5% world's population is suffering from diabetes which is ranked as the 9th killer disease in the world. Several other complications arise in diabetic patients. In the year 2021, 537 million individuals in the age group of 20 to 79 years were afflicted with diabetes and it is estimated that this figure will rise to 643 by the year 2030. The projected rise of diabetic patients worldwide by the year 2045 will be 783 million. It is estimated that 6.4 million individuals (1 individual 5 every second) died of diabetes in the year 2021. The maximum number of diabetic patients is in China, which has 140.9 million individuals living with diabetes. India stands second to China with 74.2 million individuals afflicted with diabetes in the year 2021. Pakistan ranked third in the occurrence of diabetes with 33 million diabetic patients and USA ranked fourth in the number of diabetic patients having about 32.2 million individuals living with diabetes in the year 2021. This indicates that diabetes is a major health concern in the world including the US. Diabetes has already emerged as one of the major public health problems in the world and the healthcare cost for diabetes in the year 2021 has been around 966 billion USD globally [5]. Modern medicine offers several treatment modalities for both type I and II diabetes. Ayurveda an ancient system of medicine gives a detailed account of the treatment of diabetes using various herbs or their formulation however I will focus on the use of Bael (*Aegle marmelos Correa*) in the treatment of diabetes.

Scientific Position

Bael *Aegle marmelos* belongs to Kingdom: Plantae, Subkingdom: Tracheobionta, Super division: Spermatophyta, Division: Magnoliophyta: Class: Magnoliopsida, Subclass: Rosidae, Order: Sapindales, Family: Rutaceae, Genus Aegle Correa, Species marmelos (L.) Correa. Bael is scientifically known as *Aegle marmelos* and is also known as *Belou marmelos* (L.) Lyons, *Bilacus marmelos* (L.) Kuntze, Crateva marmelos L., *Crateva religiosa* Ainslie, and *Feronia pellucida* Roth.

Distribution

Bael is a subtropical plant native to the Indian subcontinent and Southeast Asia including Bangladesh, Myanmar, Pakistan, Thailand, Nepal, China, Cambodia, Fiji, Laos, Indonesia, Malaysia, Philippines, Tibet, Java, Vietnam, and Sri Lanka [17-19]. Bael originated in the Eastern Ghats and central India. It grows in dry forests, plains, and hilly areas including the outer Himalayas, Shivalik hills, and South India up to an altitude of 250-1200 m above sea level. It has a remarkable ability to adapt to a wide range of habitats and is grown worldwide. Bael grows in all Indian states from north to south and east to west including Himachal Pradesh, Jammu and Kashmir, Haryana, Punjab, Uttar Pradesh, Uttarakhand, Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Chhattisgarh, Bihar, Jharkhand, West Bengal, Assam, Andhra Pradesh, Karnataka, Kerala, Tamil Nadu and Andaman Islands. It is usually planted near temples in India due to its religious and mythological importance. Hindus consider it a holy tree and its leaves are considered sacred and offered to lord Shiva during worship [20,21].

Botanical Profile

Bael is a slow-growing spiny tree that reaches up to a height of 12-15 m and 90-120 cm in girth (Figure 1). The trunk of the Bael is short with thick bark, which is soft and flaking (Figure

2). Leaves of Bael are alternate, 4-10 cm long, 2-5 cm wide, deciduous, pointed, pinnate, or ternate having a long petiole. The leaflets are broad, oblong, lanceolate, and crenulated. The leaves are thick, smooth, shining, green, or dark green colored with an aromatic smell. New developing leaves are pinkish maroon and glossy (Figure 3). The inflorescence of Bael consists of tiny fragrant flowers that are 4-7 in number along with young branchlets having 4 recurved fleshy petals which are yellowish inside and greenish outside. The flowers are 2 cm wide, stalked, erect, and lax, with a sweet aroma that appears axillary or as terminal cymes. The flowers have shallow calyces that are short five with broad teeth and are pubescent. The ovary is ovoid to oblong tapering into a thick short style and the stigma is capitate and stamens are 50 or more in number (Figure 4) [19,22,23]. Bael fruits are 5-20 cm in diameter of different sizes and round, ovoid, oblong, or pyriform in shape. The fruit rind is very hard and becomes stony when dry (hence the name wood apple), almost smooth, and light yellow, brown, or cherry red. The pulp of Bael fruit is firm brownish-red colored with 12 stony carpels containing one or more hairy seeds. The cavity between the carpel and surrounding seed contains a reddish-brown colored, transparent gluten-like or gummy resinous mass that becomes hard after drying (Figure 5). The fruit pulp is sweet or astringent having an agreeable aromatic odor. The seeds are flattened-oblong shaped, 1 cm long, 10-50 in number, and are encased in a gummy or transparent mucilaginous substance that becomes solid after drying (Figure 5) [23].

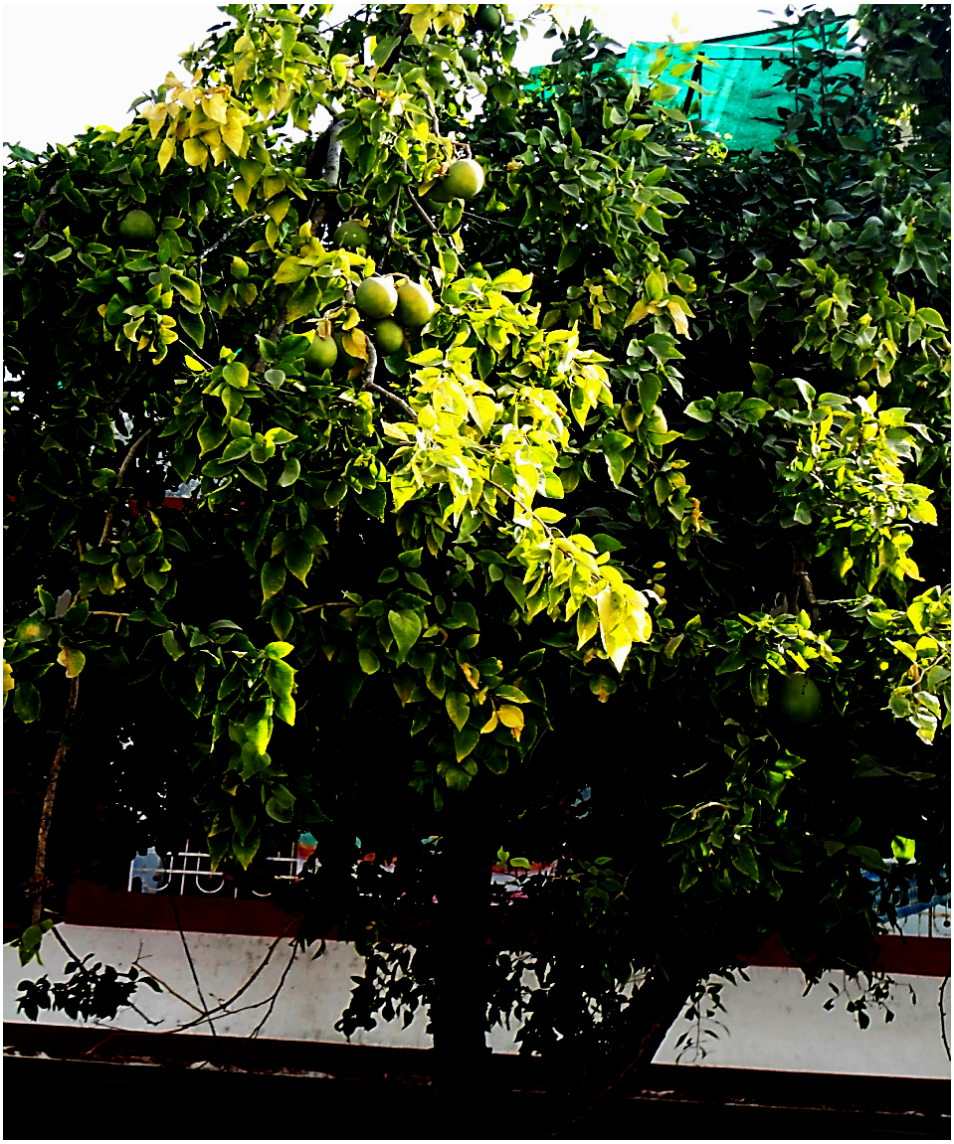

Figure 1: Bael, *Aegle marmelos* tree in its natural habitat.

Figure 2: Bael, *Aegle marmelos* stem and its bark.

Figure 3: Bael, *Aegle marmelos* leaves. a: mature leaves and b: new leaves.

Figure 4: Bael, *Aegle marmelos* flower. a: in native form and b: flower closeup.

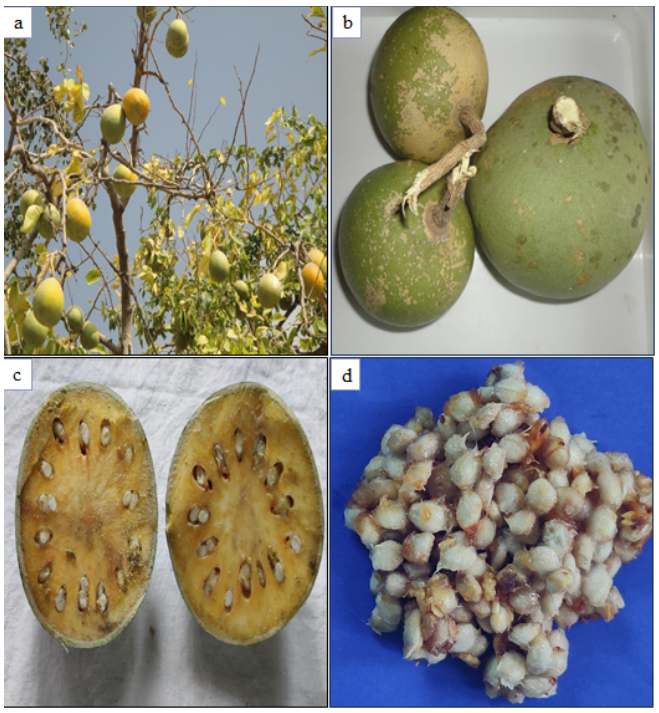

Figure 5: Bael, *Aegle marmelos* fruit. a: fruits in native form, b: fruits and c: opened fruit and d: seeds.

Colloquial Names

Commonly *Aegle marmelos* is known as Bael fruit, Bael fruit tree, Bael tree, Ball tree, Bel fruit, Bela tree, Bengal quince, Elephant apple, Golden apple, Holy fruit, Indian Bael, Indian quince, Maredoo, Quince-apple of India, Stone apple, and Wood apple in English. *Aegle marmelos* is known as Bel, Bela, Bel patra, Villi, Shivadume, Shriphal in Hindi; Bilva, Bilvam, Bilva-phalam, Duraruha, Mahura, Nilamallika, Shivaphala, Shivadruma, Sriphal, Pootivat, Pattraśreṣṭha; Satyaphala, Shaelpatra, Lakshmiputra, Shivestha in Sanskrit; Malura in Pali; Bel and Bael in Urdu; Bel in Assamese; Bel, Bilivaohal, and Billi in Gujarati; Bael, Bela, and Shriphal in Bengali; Bilpatra, Malura, and Kumbala in Kannada; Gorakamli in Konkani; Bela, Maredu, and Kaveeth in Marathi; Baela koovalam, Kuvalam, Maaredy, and Vilvam in Malayalam; Belo, Baela in Oriya; Beel, and Bil in Panjabi; Katori in Sindhi; Bilva, Bilvamu, Bilva-pandu, Maradu-pandu, Malu-remu-chettu and Sandiliyamu in Telugu, Bilva, Bilubam, Kuuviram, Villuvam, Vilvam, Vilvama, Vilva-maram, and Vilva-pazham in Tamil [19,24-29].

Aegle marmelos is called as Safarjale-hindi, and Shul in Arabic; Ohshit, and Opesheet in Burmese, Mu ju, Yin du gou qi, and Ying pi ju in Chinese; Slijmappelboom in Dutch; Bel indien, Cognassier du Bengal, Coing de l'Inde, Oranger de Malabar, and Oranger du Malaba in French; Belbaum, Bengalische quitte, Indische quitte, and Schleimapfelbaum

in German; Maja batuh, and Maja in Indonesian; Modjo in Javanese; Cotogno del Bengala, and Cotogno d'India in Italian; Berunoki, and Igure marumerozu in Japanese; Phneou, and Pnoi in Khmer; Toum in Laotian (Sino Tibetan); Bel, Bila, Bilak, Maja, Maja batuh, and Maja pahit in Malay; Belapatra, and Belpatra in Nepali; Bah hindi, Safarjal-e-hindi, and Shull in Persian; Marmeleiro-da-India in Portuguese; Beli in Sinhalese; Bela, and Milva in Spanish; Bael in Tagalog; Mapin, and Matum in Thai; Hind ayva agh in Turkish; Bau nau, and Tráimam in Vietnamese [19,28-31].

Traditional Medicine

The Bael has been used as medicine since ancient times in Ayurveda in India and other Southeast Asian countries. The Bael has been used as a medicine for 5000 years and it has been cited in Ramayan, Charak Samhita, Upvana Vinod, and Yajur Veda [20,32-34]. According to Charaka (1500 BC), the medicinal values of Bael have been appreciated by Indians for a very long time. Traditionally Bael has been used to control fertility, treatment of intestinal disorders, and intermittent fever, and is given after childbirth. It is also used as a fish poison [35]. Bael is also used to treat asthma, acute bronchitis, abdominal discomfort, burning sensation, brain fever, jaundice, constipation, stomachache, febrile delirium, high blood pressure, indigestion, inflammations, snakebite, leporsy, myalgia, mental illnesses, nausea, smallpox sores, swelling, thirst, thyroid disorders, tumors, ulcers and upper respiratory tract infections, anemia, fractures, healing of wounds, swoliing of joints.

The vomiting in pregnant women can be stopped by giving unripe fruit pulp of Bael in boiled rice water twice daily. The urinogenital disorders can be cured by giving unripe Bael fruit mixed with milk and sugar. The half-roasted unripe Bael fruit pulp mixed with sugar cures abscesses and dysentery in humans [28]. The unripe fruits of Bael act as astringent digestive, demulcent, and stomachic, and help to relieve piles. A mixture of one part of dried fruit powder and 2 parts of mustard oil is applied to treat burn wounds in Southern Chhattisgarh by traditional healers. Chronic dysentery, diarrhea, constipation, gonorrhea, and ulcerated intestinal mucosa are treated with ripe fruits which are also used as a tonic for the heart and brain. Ripe fruits act as laxative, and antiviral, and are used to treat epilepsy and parasitic infections. The melancholia, intermittent fever, and heart palpitation are treated by giving root decoction. Bael roots are one of the essential ingredients of dashmool' an Ayurvedic medicine. The sharbat prepared from Bael fruits helps to treat frequent micturition and consumption of Bael fruit juice removes toxins from the body [34,36].

The Bael leaves are bitter, astringent, expectorant, febrifuge, and laxative and are topically applied on the inflamed parts. The ulcers and ophthalmic disorders are treated by applying a 'poultice' prepared from Bael leaves. Fresh leaves help to mitigate the weakness of the heart, beriberi, and dropsy and their juice is laxative and treats asthmatic complaints, eye affections, and ophthalmia [34]. The leaves are used in the treatment of catarrh, diabetes, deafness, and inflammations. Eating young leaves of Bael causes sterility in males and abortions in females. The regular application of oil prepared by heating one teaspoon of Bael leaf juice, an equal quantity of sesame oil, a few black pepper seeds, and half a teaspoon of kalonji (*Nigella sativa*) on the scalp increases the resistance against cough and cold. This filtered oil can be stored for later use. The medicated Bael leaf oil relieves recurrent colds and arrests respiratory infections. Bael flower distillate acts as an antidysenteric, and expectorant. It is used as a tonic for the intestine and stomach, as a local anesthetic, and in the treatment of epilepsy [30,33,34].

Phytochemistry

Flavonoids, phenols, total carotenoids, and ascorbic acid were detected in Bael fresh fruit pulp [37]. The alcoholic extract of fruit pulp of Bael contains alkaloids, flavonoids, steroids, terpenoids, tannins, lignins, inulin, proteins, carbohydrates, amino acids, reducing sugars, fat, and oils, whereas saponins and cardiac glycosides were also detected in aqueous extract in addition to all these phytoconstituents except alkaloids [38]. The alkaloids, glycosides, phenols, saponins, tannins, terpenoids, proteins, and carbohydrates were found in the ethanol fruit pulp extract whereas the aqueous extract was devoid of saponins, and tannins but contained sterols [39]). The fruit pulp extracted in petroleum ether showed flavonoids, saponins, sterols, and tannins, whereas, in addition, the benzene extract contained saponins, alkaloids, and proteins but not the sterols [40]. Fruit extract of Bael in ethanol, methanol, hexane, phosphate buffer, and water contained flavonoids and phenols and the maximum quantity was found in the hexane extract and least in the aqueous extract [41]. Fruit pulp showed the presence of reducing and nonreducing sugars, gallotannic acid, and oxalates [42]. Alkaloids, flavonoids, glycosides, saponins, tannins, phenols, and carbohydrates were detected in the ethanol extract of Bael fruit, whereas the aqueous extract showed the presence of flavonoids, glycosides, saponins, and polyphenols [43].

Aqueous fruit extract showed the presence of alkaloids, flavonoids, glycosides, sterols, terpenoids, phenolic compounds, saponins, proteins, carbohydrates, and amino acids [44]. Extraction of unripe Bael fruit in chloroform, ethyl acetate, methanol, and water led to the detection of alkaloids, flavonoids, glycosides, terpenoids, saponins, proteins, carbohydrates, and amino acids in all extracts except saponins in aqueous extract. The triterpenoids were also detected in the methanol extract, whereas petroleum

ether extract contained steroids as well as triterpenoids [45]. The aqueous and methanol ripe Bael fruit pulp extracts showed the presence of alkaloids, coumarins, flavonoids, glycosides, phenolics, saponins, tannins, and proteins [46]. Hydroethanolic extract of Bael fruit and peel showed the presence of alkaloids, coumarin, glycoside phenol, tannins, terpenoids, resins, carbohydrates, and proteins [47]. Alkaloids, flavonoids, glycosides, terpenoids, phlobatannins, and reducing sugars in the aqueous extract of Bael fruit [48].

Total phenol and flavonoid contents were least in the Bael root (1.7281 ± 0.049 and 1.087 ± 0.002 mg/g), more in the stem (7.4693 ± 0.047 and 1.400 ± 0.029 mg/g), and maximum (9.8367 ± 0.0235 and 8.248 ± 0.029) in the leaf all extracted in methanol [49]. The Bael leaves extracted in n-hexane showed the presence of cardiac glycosides, steroids, triterpenoids, and pseudotannins, whereas the aqueous extract possessed alkaloids, anthraquinone glycosides, catechins, fixed oils, fats, furanoids, proteins, phenolics and saponins [50]. Phytochemical analysis of chloroform Bael leaf extract led to the detection of alkaloids, amino acids, anthocyanins, cardio glycosides, coumarins, diterpenes, emodins, fatty acids, flavonoids, phlobatannins, glycosides, phenols, saponins, tannin, carbohydrates and proteins [51]. The alkaloids, flavonoids, saponins, tannins, terpenoids, carotenoids, cardiac glycosides, and reducing sugars were identified in the aqueous and methanol Bael leaf extracts [52]. Bael leaf extracted in ethanol, methanol, ethyl acetate, phosphate buffer, and water showed the presence of flavonoids and phenols, and the maximum quantity was found in the methanol extract followed by the ethanol extract and least in the aqueous extract [41]. Cardiac glycosides, saponins, and tannins were detected in ethanol, chloroform, and water extracts of Bael leaf, whereas flavonoids were detected in both chloroform and water extracts, and steroids were found only in ethanol extract [53]. Phytochemical analysis of methanol, chloroform, petroleum ether, and aqueous extracts showed the presence of alkaloids in all fractions of Bael leaf and seed extracts but not in aqueous and chloroform extracts, whereas tannins were absent in all leaf extracts except chloroform and petroleum ether seed extracts of the Bael [54]. Flavonoids, phenol, tannins, and carbohydrates were detected in the ethanol extract of Bael leaf [55].

Quantitative estimation of aqueous Bael leaf extract showed the presence of alkaloids (15.58 ±0.05 mg/g), flavonoids (64.0±0.05 mg/g), and phenolics (30.34±0.01 mg/g) [56]. The alkaloids, phenolic compounds, sterols, and tannins were detected in the aqueous and methanol leaf extracts of Bael [57]. The alkaloids, flavonoids, phenols, saponins, steroids, tannins, and carbohydrates were identified in the aqueous Bael leaf extract whereas saponins were absent in the acetone and ethanol extracts. The ethanol extract was devoid of tannins [58]. Alkaloids, terpenoids, tannins, saponins, steroids, coumarins, leucoanthocyanins, and carbohydrates were present in the aqueous and ethanol extracts of the leaves and stem bark of Bael. Proteins and reducing sugars were detected in the stem extract in addition to these phytochemicals, however, coumarins were absent [59]. Bael leaf methanol extract contains alkaloids, flavonoids, saponins, tannins, steroids, glycosides, phlobatannins, quinones, coumarins, and proteins, whereas ethanol extract showed the presence of all phytochemicals except flavonoids and sugars. The acetone extract showed terpenoids in addition to all the phytochemicals detected for methanol extract but not the steroids. The terpenoids, flavonoids, saponins, tannins, steroids, glycosides, phlobatannins, quinones coumarins, sugars, and proteins were detected in the chloroform extract [60]. The ethyl acetate extract of the Bael stem showed the presence of alkaloids [61].

The aqueous leaf extract of Bael contained alkaloids, flavonoids, phenolic compounds, and saponins [62]. The aqueous extract of Bael leaf consisted of 16.36 mg rutin equivalent total flavonoids and 31.38 gallic acid equivalent total phenolics [63]. The ethanol and aqueous extracts of Bael root have been reported to contain alkaloids, flavonoids, saponins proteins, and tannins [64]). The aqueous and methanol seed extracts of Bael possessed alkaloids, flavonoids, glycosides, phenolics, steroids, tannins, carbohydrates, proteins, amino acids, volatile oils, and fats [65]. Alkaloids, flavonoids, glycosides, phenols, tannins, sterols, terpenoids, carbohydrates, proteins, and amino acids were present in the ethanol, ethyl acetate, and aqueous extracts of stem bark of Bael [66]. The Bael root and small twigs extracted in ethanol and water showed the presence of phenols, quinones, reducing sugars, saponins, sugars, tannins, and triterpenoids (except aqueous extracts). The aqueous extracts also contained alkaloids and the ethanol extracts showed the presence of coumarins additionally [67]. Anthocyanins, alkaloids, cardiac glycosides, flavonoids, saponins, tannins, and terpenoids have been reported from the 60% ethanol extract of Bael leaf [68]. The methanol extract of Bael leaf showed the presence of alkaloids, flavonoids, glycosides, phenols, and carbohydrates however phytosterols could not be detected in it [69].

Safety Evaluation

The safety evaluation of any pharmacophore is of utmost importance before its human application and Bael has been reported to be non-toxic at the doses for human use as indicated by numerous preclinical investigations. Swiss albino mice administered intraperitoneally with 1000, 1500, 1750, 2000, 2125, 2250, 2375, and 2500 mg/kg of 50% ethanol Bael leaf extract did not induce mortality up to 1750 mg/kg. A further increase in the leaf extract dose to 2000, 2125, 2250,

and 2375 mg/kg led to an increase in mortality by 10, 20, 50, and 80%, respectively and all animals died at a dose of 2500 mg/kg in acute toxicity studies. The lethal dose (LD) 50 was found to be 2250 mg/kg body weight in mice [70]. The acute toxicity of hydroethanolic (50%) Bael fruit extract was tested in mice where the intraperitoneal administration of 1, 2, 3, 4, 5, and 6 g/kg body weight extract did not induce mortality even at 6 g/kg and hence it was considered safe [71]. Acute toxicity studies of total ethanol, methanol, total aqueous, and whole aqueous extracts of Bael leaf administered (intraperitoneally) at a dose of 1000, 1500, 2000, and 2500 mg/kg body weight in Wistar rats led to LD_{50} of 1660, 1445, 1549, and 1318 mg/kg body weight for total alcohol, total aqueous, whole aqueous and methanol Bael leaf extracts, respectively. The acute toxicity studies did not show any adverse effect except the stoppage of the heart in a systolic stand-still. The daily intraperitoneal administration of 50, 70, 90, and 100 mg/kg body weight of each extract for 14 days in Wistar rats did not cause any toxicity in rats [72]. Intraperitoneal administration of 1, 1.2, 1.5, and 2 g/kg aqueous Bael fruit extract led to the LD_{50} of 1.6 g/kg in Swiss albino mice [73].

The oral administration of 2000 mg/kg body weight of aqueous Bael leaf extract did not produce any toxicity as there was no alteration in the food and water intake. The extract also did not induce mortality [74]. The methanol fruit extract of Bael was found to be nontoxic at a dose of 5000 mg/kg body weight in rats after oral administration. The hematological profile, liver, spleen, kidney, and body weight remained unaltered indicating the safety of Bael fruit extract [75]. The methanol extract of (70:30 methanol and water) extract of Bael fruit administered orally at graded doses of 500, 1000, 2500, 5000, and 7500 mg/kg body weight in Swiss albino mice did not produce any behavioral and physiological changes in the animals during the observation period of 24 h. All test animals survived even after a dose of 7500 mg/kg indicating the safety of fruit extract [76]. The oral administration of ethanol extract of Bael fruit produced mortality at a dose of 2 g/kg body weight in Swiss albino mice and LD_{50} was greater than 1250 mg/kg, which did not exert any toxicity [77]. Mice orally administered with 500, 1000, and 2000 mg/kg body weight of hydroalcoholic (60% ethanol and 40% water) extract of unripe fruits did not exhibit visible signs of toxicity and also did not produce mortality even at 2000 mg/kg [78]. In another study, oral administration of methanol Bael leaf extract did not produce toxicity up to 2000 mg/kg in albino rats [79]. Administration of 820, 880, 970, 1100, 1230, and 1450 mg/kg of Bael leaf oil in Swiss albino mice resulted in an LD_{50} of 1051.96 mg/kg [80].

Antidiabetic

The water extract of Bael leaves administered for 30 days in alloxan-induced diabetic Wistar albino rats led to an increase in glucose tolerance, and a significant reduction in blood glucose, blood urea, and serum cholesterol levels [81]. The aqueous leaf extract of Bael (100 mg/kg body weight) once daily for 10 days reduced plasma glucose and increased insulin levels in streptozotocin-induced diabetic rats [82]. The aqueous fruit extract of Bael fruit given twice daily for 30 days orally decreased blood glucose levels, improved oral glucose tolerance, and increased glycogen and glycated hemoglobin (HbA1c) in streptozotocin-induced diabetic Wistar rats [83]. Similarly, the aqueous extract of fruit attenuated lipid peroxidation (LOO), hydroperoxides, cernloplasmin, and α-tocopherol and significantly increased plasma reduced glutathione (GSH) and Vitamin C [84]. Significant attrition in the blood glucose, plasma glutathione-S-transferase (GST), and LOO accompanied by a rise in the GSH levels has been detected in the erythrocytes at the end of 4th week in alloxan-induced diabetic albino rats receiving 100 mg of aqueous leaf extract of Bael for four weeks [85]. The methanol Bael leaf extract reduced serum glucose, serum, and liver LOO, and hydroperoxides in alloxan-induced diabetic rats on 12-day post-treatment followed by an elevation in the superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) in the blood and liver on 12 days [86]. The methanol Bael leaf extract reduced serum glucose, serum, and liver LOO, and hydroperoxides in alloxan-induced diabetic rats on 12-day post-treatment followed by an elevation in the SOD, catalase, and GPx in the blood and liver on 12 days [86].

The aqueous extract of Bael fruit reduced blood glucose levels at different post-treatment times in streptozotocin-induced diabetic Wistar rats. The seed extract depleted fasting blood glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-c), and elevated high-density lipoprotein cholesterol (HDL-c) in diabetic rats [87]. The aqueous leaf extract of Bael administered intraperitoneally once daily for 30 days caused a significant decline in fasting and postprandial blood glucose levels in alloxan-induced diabetic rats [88]. Aegeline, an alkaloid extracted from Bael leaves significantly depleted blood glucose levels in sucrose-challenged streptozotocin-induced diabetic albino rats from 90 min to 24 h [89]. The methanol extract of leaf and leaf callus of Bael orally administered at a dose of 1 g/kg once daily attenuated the serum glucose level in streptozotocin-induced diabetes in rabbits on day 20 after administration, which was maintained at this level even up to 90 days [90].

Administration of Bael leaf ethanol extract orally for 30 days in streptozotocin-induced diabetic Wistar rats resulted in a significant decline in blood glucose, hemoglobin, and HbA1c. The extract also reduced the plasma and pancreatic LOO accompanied by an increase in catalase, SOD, and GPx activities in the pancreas. The extract also caused a rise in the GSH level in the plasma and pancreas. There has been an increase in vitamin C and vitamin E and a decline in the

ceruloplasmin in the plasma of diabetic rats by leaf extract [91]. The Bael leaves extracted in ethanol reduced fasting serum glucose, total cholesterol, LOO, and the activity of lactate dehydrogenase (LDH) and creatinine kinase, in the alloxan-induced diabetic Wistar rats. The extract increased GSH levels and activity of catalase and SOD dose dependently [92]. The high fat diet fed streptozotocin-induced Wistar rat given 250, 500, and 1000 mg/kg body weight of aqueous extract of Bael fruit once daily for 21 days showed a significant reduction in serum glucose, HOMA-IR (Homeostatic Model Assessment of insulin resistance), and increase in HOMA-B (β-cell function) dose dependently at 21 days. The total cholesterol, triglycerides, LDL-c, declined and HDL-c elevated on day 21 in diabetic rats administered with fruit extract. The Bael fruit extract reduced pancreatic LOO and increased SOD activity dose dependently. There was a dose dependent rise in the peroxisome proliferator activated receptor (PPAR-γ) expression in the liver in fruit extract-treated diabetic rats [93]. The blood glucose (14, 21, and 28 days), and total proteins were reduced whereas HbA1c, and plasma insulin levels increased on day 28 in streptozotocin-induced diabetic Wistar rats administered with 200 and 400 mg/kg body weight methanol stem bark extract of Bael for 30 days. Bael extract alleviated AST, ALT, ALP, hexokinase, glucose-6-phosphatase, and fructose 1, 6 bi phosphatase and liver glycogen at 30 days in streptozotocin-induced diabetic Wistar rats [94].

Administration of marmelosin separated from Bael and its derivatives including 9-[(2-methylprop-1-en-1-yl)peroxy]-5-nitro-7H-furo[3,2-g]chromen-7-one, 9-[(2-methylprop-1-en-1-yl)peroxy]-5-nitro-7H-furo[3,2-g]chromen-7-one, 9-[(2-methyl prop-1-en-1-yl) peroxy]-7-oxo-7H-furo[3,2-g] chromene-5- sulfonic acid and 5-bromo-9-[(2-methylprop-1-en-1-yl)peroxy]-7H-furo[3,2-g]chromen-7-one significantly depleted blood glucose level in alloxan-induced diabetes in Wistar rats indicating their antidiabetic potential [95]. Chloroform leaf extract of Bael (150/300 µg/kg for 60 days) decreased blood glucose, HbA1c, serum creatinine, blood urea glucose, and urine albumin significantly in streptozotocin-induced diabetic male Wistar rats. The leaf extract also inhibited the formation of total advance glycation end products (AGEs) and pentosidine, a specific AGE significantly in tail collagen and it also depleted the bovine serum albumin and protein carbonyl formation [96]. Administration of 500 mg/kg body weight of Bael flower aqueous extract reduced serum glucose levels in alloxan-induced diabetic rats at 7, 21, and 42 days [97]. The administration of 200 and 400 mg/kg body weight of ethanol and methanol extracts of Bael leaves for 14 days resulted in the attrition of blood glucose, total cholesterol, triglycerides, LDL, and elevation in the HDL significantly in alloxan-induced diabetic Wistar rats [98]. Daily oral administration of Bael leaf ethanol extract for 20 days reduced serum glucose, protein, triglyceride, urea, and plasma insulin levels in alloxan-induced diabetic Wistar albino rats [99]. The daily administration of 2g/kg Bael leaf ethanol extract for 21 days in streptozotocin-induced diabetic Wistar rats significantly reduced blood glucose level on days 3, 6, 9, 12, 15, 18, and 21 [53].

The ethanol extract of Bael fruit significantly reduced body weight gain, blood glucose level, total cholesterol, triglyceride, LDL-c, and very low-density lipoprotein cholesterol (VLDL-c) dose dependently accompanied by a dose dependent rise in the serum insulin level and HDL-c in the alloxan-induced diabetic rats. The fruit extract also significantly reduced the alloxan-induced LOO and increased the GSH and SOD significantly in diabetic rats [100]. The hydromethanol (20% water) extract of Bael fruit pulp increased the glucose tolerance in a dose dependent manner and decreased blood glucose levels at 60, 120, and 180 min in streptozotocin-induced diabetic Wistar rats. The 400 mg/kg body weight of fruit pulp extract administered for 42 days increased the serum insulin level leading to a 10-fold rise in the insulinogenic index followed by an increase in the β-cell function and improved the architecture of pancreatic β-cells in diabetic rats at 43 days. The extract decreased the HbA1c level, triglycerides, cholesterol, HDL-c, and LDC-c significantly followed by an increase in the total antioxidant status after 42 days [101]. The ethanol leaf extract of Bael reduced fasting serum glucose level in streptozotocin-induced diabetes in Long Evans rats either administered singly (250 or 500 mg/kg body weight) or 250 mg/kg twice daily for 28 days. The extract also inhibited the absorption of sucrose in the intestine by inhibiting the disaccharidase enzyme activity [102]. Administration of 500 mg/kg body weight of aqueous leaf extract reduced fasting blood glucose levels in the fructose-fed rats. The extract reduced serum triglycerides, total cholesterol, LDL, VLDL, and insulin levels and increased HDL and HOMA-IR after 8 weeks in the fructose-fed rats. The leaf extract also inhibited fructose-induced hyperleptinemia. The Bael leaf reduced liver glycogen, hexokinase, glucose-6-phosphate dehydrogenase, and fructose 1,6 biphosphatase after 8 weeks. The leaf extract upregulated Janus Kinase –signal transducer and activator of transcription-3 (JAK-STAT3) and phosphatidylinositol-3-kinase (PI3K/AKT) in the rat liver when compared to fructose treatment at 8 weeks [103]. The aqueous leaf and fruit extracts of Bael administered for 21 days in streptozotocin-induce diabetic Long Evans rats caused a decline in blood glucose, insulin levels, HOMA-IR, and QUICKI significantly indicating that the extracts are effective against diabetes. However, both extracts did not change the lipid profile in diabetic rats [104]. The aqueous Bael leaf extract reduced hexokinase, phosphofructokinase, and phosphofructokinase significantly in the HepG2 cells fed with high fructose or glucose, except aldehyde dehydrogenase which increased in the glucose-fed cells. The extract significantly increased

the phosphatidylinositol-4, 5-bisphosphate 3-kinase (PI3K) responsible for insulin signaling in the Hep-G2 cell fed with a high fructose diet. The leaf extract down modulated the glucose and fructose-induced activation of signal transducer and activator of transcription-3 (STAT-3), hypoxia-inducing factor (HIF-1α), and tumor necrosis factor (TNF-α) in HepG2 cells indicating the usefulness of Bael in ameliorating diabetes [105].

The ethanol leaf extract administered for 4 weeks in alloxan-induced diabetic rats lowered serum glucose, uric acid, urea, creatinine, and albumin levels at the end of the experiment [106]. The blood glucose, aspartate aminotransferase (AST), alanine transaminase (ALT), total proteins, serum albumin, serum creatinine, and alkaline phosphatase (ALP) declined significantly in the alloxan-induced diabetic Wistar rats administered with 500 mg/kg of methanol extract of Bael leaves [107]. Methanol leaf extract at a dose of 100 and 250 mg/kg body weight reduced mean blood glucose, albumin, bilirubin, blood urea, blood urea nitrogen (BUN), calcium, direct bilirubin, globulin, glucose-6-phosphate, HbA1c, homocysteine, indirect bilirubin, inorganic phosphate, lipase, mean blood glucose, serum uric acid, and vitamin D3 followed by an increase in amylase activity in alloxan-induced diabetic rats [108].

The methanol Bael fruit extract has been reported to reduce blood glucose, serum and plasma insulin, C-peptide, HbA1c, triglycerides, total cholesterol, LDL-c, and VLD-cL in streptozotocin-induced diabetic rats. The fruit extract depleted the inflammatory cytokines including TNF-α, and IL-6 accompanied by a rise in IL-1β. The extract also elevated GSH and SOD levels and depleted catalase and LOO in diabetic rats [109]. The hydroalcoholic alkaloid-free extract of Bael leaves significantly reduced the plasma glucose level (oral glucose tolerance test) and restored it to normal in streptozotocin-induced diabetic mice. The extract reduced triglycerides, total cholesterol, and LDL and increased HDL (400 mg/kg). There has been a significant decline in the LOO and a rise in SOD, CAT, and glutathione peroxidase (GPx) in the extract treated diabetic mice. The methanol extract of Bael leaves significantly attenuated TNF-α, IL-6, and IL-1β profile in diabetic mice serum. The histological architecture of pancreatic β-cells has been restored by methanol Bael fruit extract [110]. The methanol extract of Bael fruit powder and coumarin rich extract has been reported to exert antidiabetic action by increasing α-amlylase activity in vitro. The coumarin rich extract (IC_{50} 23.85±0.78 µg) was moe efficient than the crude extract (IC_{50} 68.35±2.48 µg) [111].

Clinical Studies

The NIDDM patients given 2 g of Bael leaves twice a day for eight weeks reduced fasting and postprandial blood glucose levels from the second week of treatment until 8 weeks significantly indicating its potential as an antidiabetic medicine in humans [112]. Type-II diabetic (50) patients given 2 encapsulated 50 mg of leaf extract of Bael once daily after breakfast for 90 days revealed a reduction in fasting blood glucose level and HbA1c significantly on day 90 post-treatment [113]. Diabetic patients taking 2 g Bael fruit pulp powder once daily for 60 days exhibited a significant reduction in fasting blood glucose, HbA1c, total cholesterol, triglycerides, LDL-C, and VLDL-C [114]. In a randomized clinical trial of 60 (25 males/35 females) diabetic patients given Bael leaf juice (20 g/100 mL) for 8 weeks significantly reduced fasting blood glucose, postprandial blood glucose, HbA1c, total cholesterol, serum triglycerides, LDL, VLDL, AST, and ALT levels followed by an increase in serum HDL [115].

Antihyperlipidemic

The hydroethanolic (50%) extract of Bael leaves significantly reduced serum cholesterol and triglyceride levels in hyperlipidemic rats [116]. The aqueous Bael leaf extract depleted total cholesterol, triglycerides, LDL, and VLDL followed by a significant rise in the HDL dose dependently in streptozotocin-induced albino rats [117]. A significant decline in triglycerides, cholesterol, LDL, and VLDL and increased HDL was detected in hyperlipidemic Wistar rats treated with aqueous, ethanol, and chloroform extracts of Bael leaves [118]. The aqueous Bael leaf extract reduced 3-hydroxy-3 methyl glutaryl CoA (HMG-CoA) and reductase, acyl coenzyme-A cholesterol acyl transferase (ACAT) in liver microsomes and triglycerides, cholesterol, LDL, VLDL accompanied by a significant rise in HDL in the serum of hyperlipidemic Wistar rats [119]. Bael leaf extract lowered serum total cholesterol, triglycerides, LDL, HDL, and VLDL in hyperlipidemic rats significantly [120]. The hyperlipidemic albino rats fed with 125 and 250 mg/kg in the diet for 60 days showed a significant decline in the serum cholesterol, free cholesterol, cholesterol ester, triglycerides, and LDL accompanied by a rise in the HDL at 30 and 60 days [56].

Side Effects of Bael

Consumption of Bael is safe and does not cause any known adverse side effects. However, eating massive amounts of Bael fruit or its powder may cause hypoglycemia, stomach upset, indigestion, throat burn, abdominal pain, nausea, diarrhea, and vomiting (https://nootropicsplanet.com/bael/).

Mechanism

The actual mechanism of antidiabetic action of Bael is not clearly understood. It is plausible that Bael may have used several cellular pathways to control diabetes (Figure 6,7). The dysregulation of the (Nuclear factor E2-related factor 2) Nrf2/Keap1/ARE (Antioxidant Response Element) signaling

pathway is reported in diabetes [121,122] and Bael seems to operate this pathway by segregation of Nrf2/Keap1 that causes translocation of Nrf2 into the nucleus where Nrf2 activates ARE leading to the stimulation of heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1) as a result antioxidants like GSH, GPx, glutathione reductase (GR), catalase, SOD, glutathione-s-transferase (GST) are raised by Bael in diabetic condition and also reduce lipid peroxidation [86,100].

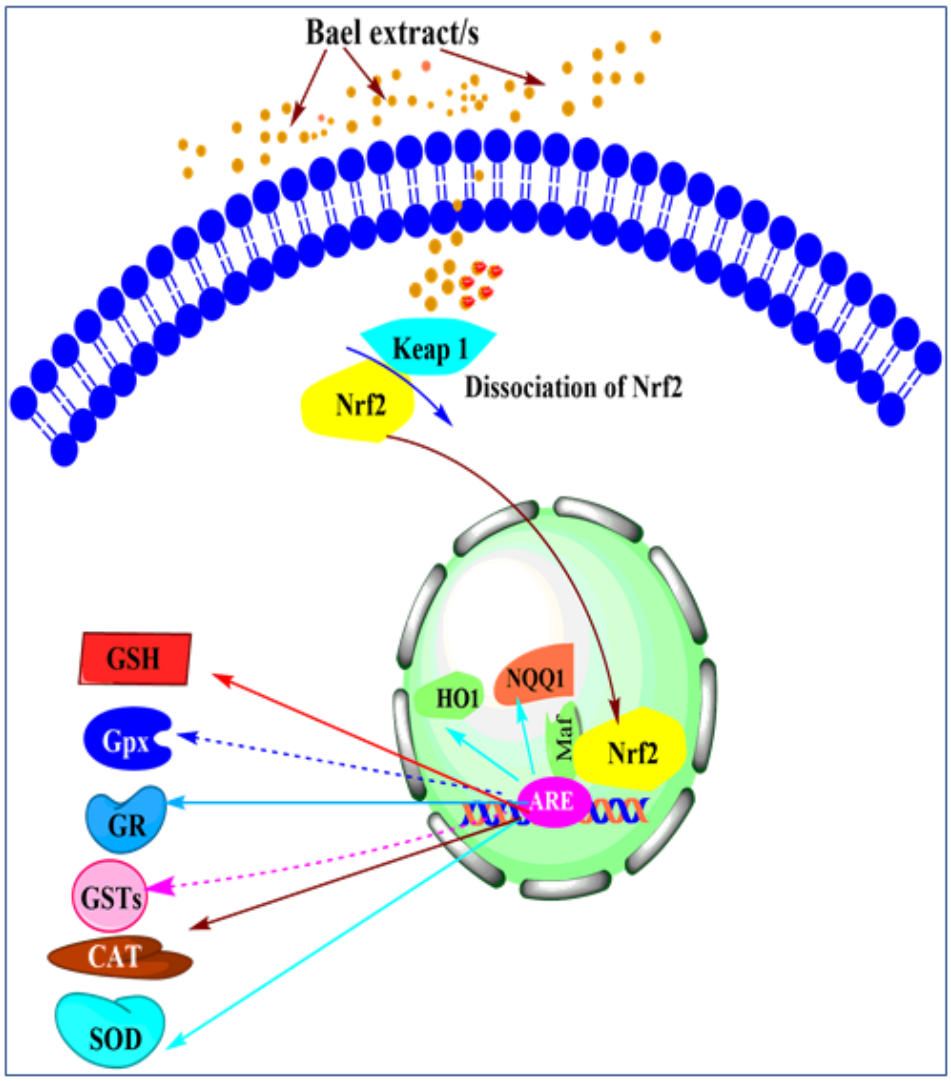

Figure 6: The scavenging of free radicals (reactive oxygen species ROS) by Bael causes dissociation (nuclear factor E2-related factor 2) of Nrf2/Keap1 leading to the translocation of Nrf2 into the nucleus. Once Nrf2 is in the nucleus it activates antioxidant response element (ARE), heme oxygenase-1 (HO1) and NAD[P]H: quinone oxidoreductase-1 (NQO1) which increases glutathione (GSH), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-s-transferase (GST), super oxide dismutase (SOD) and catalase (CAT) and reduces lipid peroxidation (LOO).

Bael is known to activate PPAR-γ that leads to suppression of TNF-α, NF-κB, Hsp70, PI3K/AKT, HIF-1α, IFN-γ and IL-8, IL-1β, IL-6, IL-10, IL-17, MIP-1α, COX-I, COX-II, STAT-3, AKT, tyrosinase, and galectin-3 and consequently increase of PI3K, AKT, IL-2, JAK-STAT3, and DT-diaphorase by Bael and its active components seem to arrest the inflammatory pathways [94,105,109,110,123,124]. In addition to this Bael may also activate mechanisms that are still unknown to exert its antidiabetic action.

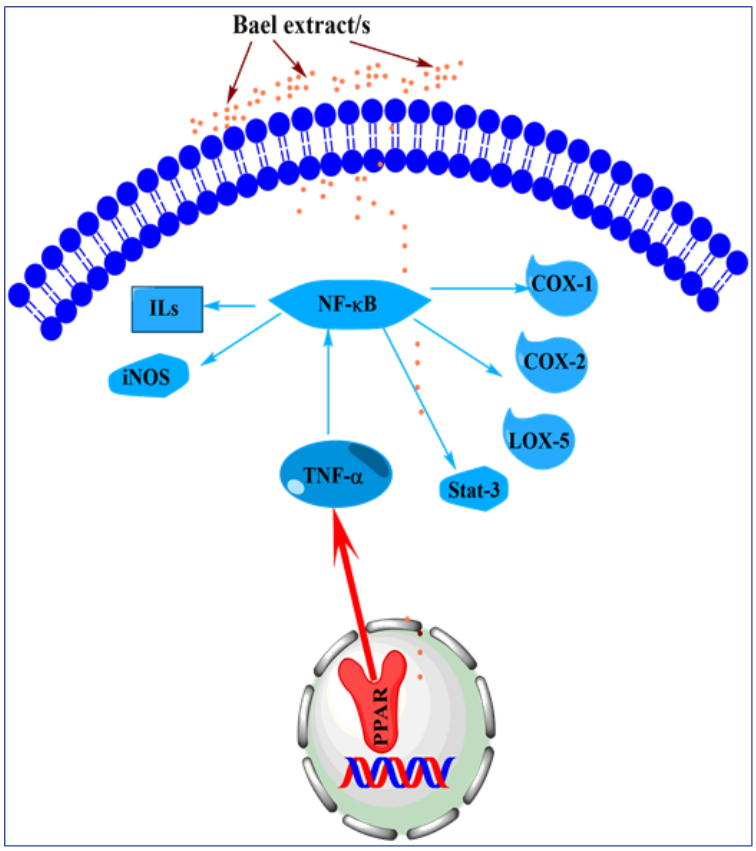

Figure 7: The activation of PPAR by Bael causes downmodulation of TNF-α, NF-κB, COX-I, COX-II, LOX-5, iNOS and various interleukins that leads to antidiabetic action as well as protection of various tissues.

Conclusion

Bael is a native of the Indian subcontinent and Southeast Asia. Its fruits are edible, eaten fresh, or in the form of sharbat and Jams. Bael possesses alkaloids, anthocyanins, flavonoids, glycosides, phenols, tannins, sterols, terpenoids, carbohydrates, proteins, quinones, reducing sugars, saponins, and phenols. Bael is non-toxic and exerts antidiabetic effects by decreasing HOMA-IR, and elevating HbA1c and HOMA-B. The antidiabetic activity of Bael is due to its ability to scavenge free radicals, reduce LOO, LDH, ODC, AST, ALT, ALP, creatinine kinase, creatinine, urea, blood glucose, BUN, triglycerides, cholesterol, LDL, VLDL, HOMA-IR, hexokinase, glucose-6-phosphatase, fructose 1, 6 bi phosphatase and glycogen. Bael increases insulin, HDL, catalase, SOD, GPx, GST, GR, GSH. Bael inhibits inflammatory pathways by downregulating TNF-α, NF-κB, Hsp 70, HIF-1α IFN-γ and IL-8, IL-1β, IL-6, IL-10, IL-17, MIP-1α, COX-I, COX-II, STAT-3, and simultaneously activating at PI3K, AKT, IL-2, JAK-STAT3, PPAR-γ, DT-diaphorase molecular level. Future research needs to be carried out to unfurl the molecular mechanisms in more detail so that Bael can be used to control diabetes in patients accompanied by the comprehensive safety and the risk-benefit profile guided studies of Bael extracts in diabetic patients.

Acknowledgments

The author is grateful to his wife Mrs. Mangla Jagetia for her unstinted support and patience during the writing of this manuscript. The financial assistance from the University Grant's Commission, New Delhi, India vide grant no. F4-10/2010(BSR) is thankfully acknowledged.

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