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Review Article

Bioactive Phytoconstituents and Medicinal Properties of Jamun (*Syzygium cumini*)

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Abstract

Natural products have been used effectively to treat different ailments since the advent of human history. Angiosperms contain numerous bioactive molecules that have been applied as medicines to treat various human diseases, including cancer. Jamun (*Syzygium cumini*) is an angiosperm belonging to the Myrtaceae family. This comprehensive review on Jamun includes information collected from Google Scholar, SciFinder, PubMed, ScienceDirect, and other websites on the internet, giving an account of its botanical profile, chemical composition, and medicinal properties. Ethnomedicinally, various parts of Jamun are used to treat various conditions and have been administered since ancient times in Ayurveda to treat arthritis, obesity, urinary diseases, asthma, bowel spasms, stomach pain, flatulence, diabetes, and dysentery. Several scientific studies also have demonstrated the pluripotent medicinal properties of Jamun, including anti-oxidant, anti-allergic, antiretinitis, antipyretic, antidiarrheal, antinociceptive, anticancer, antidiabetic, anti-obesity, antihyperlipidemic, anti-inflammatory, antimicrobial, diuretic, cardioprotective, chemopreventive, gastroprotective, immunomodulatory, hepatoprotective, wound healing, anthelmintic, and radioprotective. Jamun contains alkaloids, anthraquinones, catechins, cardiac glycosides, flavonoids, glycosides, steroids, phenols, tannins, and saponins. Numerous active phytochemicals have been isolated from its roots, stems, leaves, flowers, fruits, and seeds. Jamun increases glutathione, glutathione peroxidase, catalase, and superoxide dismutase expression and reduces lipid peroxidation levels to exert its beneficial effects on important organs and tissues. Jamun also protects against DNA damage induced by toxic agents including metals, chemicals and ionizing radiation. Jamun activates peroxisome proliferator-activated receptors alpha and gamma and increases fatty acid and glucose metabolism. Additionally, Jamun suppresses various genes at the molecular level. Thus, the scientific evaluation of Jamun is a step forward in validating its traditional use to treat various disorders and may pave the way for translational research for its medicinal use.

Introduction

Angiosperms are a diverse group of plants encompassing more than 300,000–400,000 species, which represent about 80% of all living green plants on Earth.[1,2] The World Health Organization has identified 21,000 medicinal plants, and India is an abode for 2,500 important medicinal plants in the world.[3] Angiosperms have the unique ability to synthesize numerous bioactive compounds that can be of medicinal and healthcare importance to humans.[1] The use of plants and natural products dates back at least 5,000 years, and the Atharva Veda lists at least 50 plants used for the treatment of different ailments.[4,5] The Myrtaceae family consists of 121 genera and 5,800 species of perennial trees and shrubs that are distributed widely in the subtropical and tropical regions of the world. This family consists of plants that bear edible fruits, which are a berry type with pulp. The plants have a characteristic aroma and are of great agro-industrial importance.[6,7]

Jamun is native to India and has 400–500 varieties; however, only a few varieties of Jamun produce edible fruits. Jamun can be found along the roadside in tropical and subtropical regions in the Indian subcontinent. It has a remarkable ability to adapt to a variety of climatic conditions, including alkaline soils (pH 10.5); therefore, it is widely planted in semi-arid regions. Jamun is grown as a minor commercial crop in different parts of India and throughout the world for its fruits/timber. Usually, two varieties of Jamun, namely Rama Jamun and Raja Jamun, are cultivated in northern India for their fruits and seeds. These varieties have small seeds and large quantities of pulp. Another seedless variety is commonly grown in Varanasi. The Jamun fruits have a sub-acidic spicy fla-

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vor and are used to prepare squashes, juices, jams, jellies, pickles, wines, and cookies. Jamun fruit squash is a highly refreshing drink to quench thirst during the summer. Jamun is a rich source of various nutrients like proteins and iron.[8] The alkaloid jambosin, the glucoside jambolin, and antimalin from its seeds reduce the conversion of starch and sugars. Seeds (10–47% of the total mass) are one of the important byproducts left after the processing of Jamun. The seeds are a rich source of minerals, carbohydrates, proteins, lipids, and vitamins, and they serve as important ingredients for the food industry. Jamun syrup cures diarrhea, and Jamun vinegar has cooling, carminative, diuretic, stomachic, and digestive properties. The foliage of Jamun is used as feed for cattle, while Jamun wood is used in buildings, agricultural implements, and railway sleepers.[9–11]

Natural products have been used to treat several human disorders since time immemorial. Trial-and-error experimentation for many centuries by traditional medicinal practitioners has established the medicinal importance of natural products in the treatment of human diseases and their nontoxic nature. The medicinal activities of plants and herbs are due to their ability to synthesize numerous secondary metabolites that are medicinally bioactive once they reach into the human body. This is reflected in the fact that 75% of modern marketed drugs have a natural origin and are used for the treatment of almost all human diseases, including infectious diseases, inflammatory conditions, cardiovascular disorders, and even cancer.[12,13] Ayurveda is an ancient system of medicine that mainly uses natural products for the treatment of all diseases.[14,15] The application of scientific research and new modern analytical methods, including genome profiling, molecular profiling, chemoprofiling, and metabolite fingerprinting, in natural products research has established the utility of natural products in the treatment of various human diseases. Furthermore, the advent of molecular biology techniques and their application in natural product research has provided new insights into the molecular mechanisms of action of natural products in various human disorders.[16,17] This comprehensive review on Jamun includes information collected from Google, Google Scholar, SciFinder, PubMed, ScienceDirect, and other websites on the internet as well as several individual publications. Importantly, this review focuses on the chemical composition, pharmacology, and medicinal properties of Jamun (*Syzygium cumini*), which has been used to treat various human disorders in India since Vedic times.

Profile of Jamun

The scientific and colloquial names of Jamun in different languages of the world are listed in Table 1.[18–21]

Botanical description

The scientific classification of Jamun is as follows: kingdom, Plantae; subkingdom, Viridiplantae; infrakingdom, Streptophyta; division, Tracheophyta; subdivision, Spermatophytina; infradivision, Angiospermae; class, Magnoliopsida; superorder, Rosanae; order, Myrtales; family, Myrtaceae; genus, *Syzygium*; and species, *cumini*. Jamun grows profusely in the Indian subcontinent, especially India, Ceylon, Bangladesh, Pakistan, Myanmar, and Madagascar. The well-drained, deep, and loamy soils are most suitable for the growth of Jamun. The USA, Israel, and the West Indies grow Jamun for its fruits and timber.[21–23] It takes 40 years for the Jamun tree to become fully grown. Jamun reaches a height of 100 feet (30 m), and its canopy spreads up to 36 feet (11 m) with a trunk diameter of 2–3 feet (0.6–0.9 m) (Fig. 1). Jamun branches out at a short distance from the ground, and its stem bark is discolored at the lower end and becomes smooth and light gray at higher levels. The stem bark of Jamun is rough, cracked, and flaking (Fig. 1). The leaves are 8–10 inches long, up to 4 inches wide, oblong, oval, or elliptically shaped, opposite, blunt, or tapering at the apex, and grow 5–10 inches long (5–25 cm) (Fig. 1). The leaves are pink colored when young and become leathery, glossy, and dark green above, and lighter beneath with yellowish midrib when fully mature with a turpentine smell. Jamun flowers are scented, occur in clusters of a few or 10–50 or more, and each cluster is 1–4 inches long (2.5–10 cm). The flowers are round to oblong, funnel-shaped, 1/2 inch (12.7 mm) wide, and 0.16 inch (4 mm) long, and they bloom during March–April. The flowers bear 4–5 petals, which are united as a small disk with a toothed calyx (Fig. 1). The flowers are greenish-white when young and become rose-pink later.[10,21,24] Jamun begins to fruit in June–July, and the fruits ripen in the summer. The fruits are round to oblong, initially green colored but become light to dark purple or even black colored when fully ripened, and their size varies between 1/2 and 2 inches (1.2–5 cm) and 1–2.8 cm wide (Fig. 2).[10,20,21,23,24] Jamun fruits are sweetish sour in taste, and eating Jamun fruits turns the tongue purple. The seeds of the Jamun are oblong in shape, whitish purple colored, and turn brown when dried (Fig. 2). The Hindus and Buddhists consider Jamun a holy tree, and it is commonly grown in the compounds of Hindu temples. The Jamun fruits and leaves are commonly offered to Lord Ganesha (Elephant God) during worship, and it is loved by Lord Krishna (*Jamboo phala saara bhakshitam*).[20]

Phytochemical analysis

Different parts of Jamun, including the roots, stems, leaves, fruits, and seeds, are reported to synthesize several phytochemicals (Table 2).25–48 The water, ethanol, chloroform, ethyl acetate, hexane petroleum ether, and methanol extracts of Jamun leaves contain high-to-low amounts of anthraquinones, alkaloids, cardiac glycosides, flavonoids, glycosides, phenols, steroids, saponins, tannins, proteins, triterpenoids, phytosterols, mucilage, amino acids, carbohydrates, fixed oils, volatile oil, terpenoids, and fats. Additionally, Jamun leaves contain calcium, copper, iron, magnesium, manganese, nitrogen, phosphorus, potassium, sulfur, and zinc as micronutrients.[25–32] Carbohydrates, flavonoids, terpenoids, and tannins have been reported to be present in the Jamun ethanol leaf extract; whereas only carbohydrates have been detected in the ethyl acetate, methanol, and chloroform extracts.[33] The acetone extract of Jamun leaf contains glycosides, phenols, resins saponins, and proteins; while flavonoids and alkaloids have been detected in the acetone stem bark extract. Flavonoids, alkaloids. glycosides, phenols, saponins, resins, and proteins have been reported in the acetone root extract. Alkaloids, steroids, and proteins are present in the chloroform Jamun leaf and root extracts. The Jamun seed extract has shown the presence of phenols, alkaloids, tannins, carbohydrates, and proteins; while alkaloids and tannins have been detected in the chloroform stem bark extract. The Jamun leaf and stem bark methanol extracts contain glycosides, flavonoids, alkaloids, phenols, saponins, steroids, tannins, resins, and carbohydrates; while the root extract contains proteins in addition to all other phytochemicals. The stem bark extracted in *n*-hexane showed the presence of alkaloids, proteins, and tannins; but only alkaloids were detected in the leaf extract. The root extract has been reported to contain alkaloids, resins, and carbohydrates; whereas the seed extract contains proteins.[34] Flavonoids, glycosides, phenolics, saponins, tannins, triterpenoids, steroids, lipids,

Table 1. Names of Jamun (*Syzygium cumini*) in various languages[18–21]

S. No.	Language/country	Names
1	Scientific names	*Syzygium cumini* (L.) Skeels, *Syzygium jambolana* (Lam.) DC., *Calyptranthes oneillii* Lundell, Eugenia cumini Druce, *Syzygium jambolanum* DC, *Syzygium caryophyllifolium* (Lam.) DC., *Eugenia djouat* Perr. *Calyptranthes jambolana* Willd. *Eugenia caryophyllifolia* Lam., *Eugenia jambolana* Lam., and *Myrtus cumini* L.
2	English	Indian blackberry, black plum, jambolan, Java plum, purple plum, Malabar plum, jambul, jamblang, Damson plum, Duhat plum, Jambolan plum, rose-apple and Portuguese plum
3	Hindi	Jamun, jaman, duhat and jam
4	Sanskrit	Jambu, jambuphalam, phalendra, mahaskandha, raja-jambuh, or meghamodini
5	Prakrit	Jambu in Pali; jambulo, and jammulo
6	Assamese	Jamu and kala jamu
7	Bengali	Kala jam
8	Gujrati	Jambu, and jaambu
9	Kannada	Nerale hannu, jambunerale, jumnerale, nainerale, jambuva, naayinaerale and neeram
10	Manipuri	Gulamchat and jam
11	Malayalam	Gnaval, naga, naivil, palamper, perinnaralnjara, njaval, perin-njara, and naval-pazham
12	Mizo	Hmuipui and Lenhmui
13	Oriya	Jam, jaman, jambul, rajale, rajjambula and thorajambula in Marathi; Jamkoli
14	Punjabi	Jaman
15	Tamil	Areconitamaram, arugadam, arukatam, caccanam, cattuvalam, nampu, neretu, kavarkalimaram, turavam, and turkolum
16	Tangkhul	Chomshathei
17	Telegu	Goyya-pandu, jam-pandu, jamba, jambu, naredu and raacahnaeredu
18	Urdu	Jaman, jamun and poast jamun
19	Brazil	Azeitona, jambol, jambulao, jamelao, Murta and jalao
20	Cambodia	Pring bai
21	Khmer	Pring bai, Pring das krebey
22	Cook Islands	Paramu (Aitutaki); Damson plum in Jamaica; Pistati and ka'ika
23	France	Jamélongue, jambolanier, jamelongier, faux-pistachier and jamelon-guier
24	Germany	Jambolanapflaume, rosenapfel and wachsjambuse
25	Fiji	Duhat in Guam; Kavika ni India and jammun
26	Indonesia	Jambhool, Duwet, Djoowet, and jamblang
27	Bali	Jambul, Jambulan, Jambulana,Jumbul, Jiwat, Juwet
28	Italy	Pomo della Malesia and Aceituna dulce
29	Laos	Va
30	Japan	Janboran, Murasaki futo momo, Madan
31	Madagascar	Rotra
32	Malaysia	Jambolan, obah jambulana, and jiwat
33	Nepal	Jaamun, kaalo jaamun, phanir, jaambu and jamunaa
34	New Caledonia	Jamelonguier
35	Palau	Mesekerrak and mesigerak
36	Philippines	Lomboi and Duhat
37	Portugal	Jamboleiro and jambolão

(continued)

Table 1. *(continued)*

S. No.	Language/country	Names
38	Russia	Sitsigiui dzhamboza
39	Spain	Guayabo pesgua and yambolana
40	Costa Rica	Ciruelo de Java, and Jambolan
41	Sri Lanka	Jambu, jambul, madan and naval
42	Surinam	Koeli, jamoen and druif
43	Sweden	Jambolanäpplein
44	Thailand	Thabyay-hypyoo in Myanmar; Hakhiphae, lukwa, ma-ha, and wa
45	Tibet	Dza mbu, dzam-bu, and ka ka dz mbu in
46	Kenya, Uganda and Tanzania	Msambarau and mzambarau
47	Venezuela	Guayabo pesjua and pesjua extranjera
48	Vietnam	Va in Laos, Trâm môc, and voi rung
49	West Indies	Indian blackberry in Jamaica; Jambol

Fig. 1. Photos of Jamun (*Syzygium cumini*). (a) Tree in its natural habitat; (b) Matured stem and bark; (c) Leaves; and (d) Flowers.

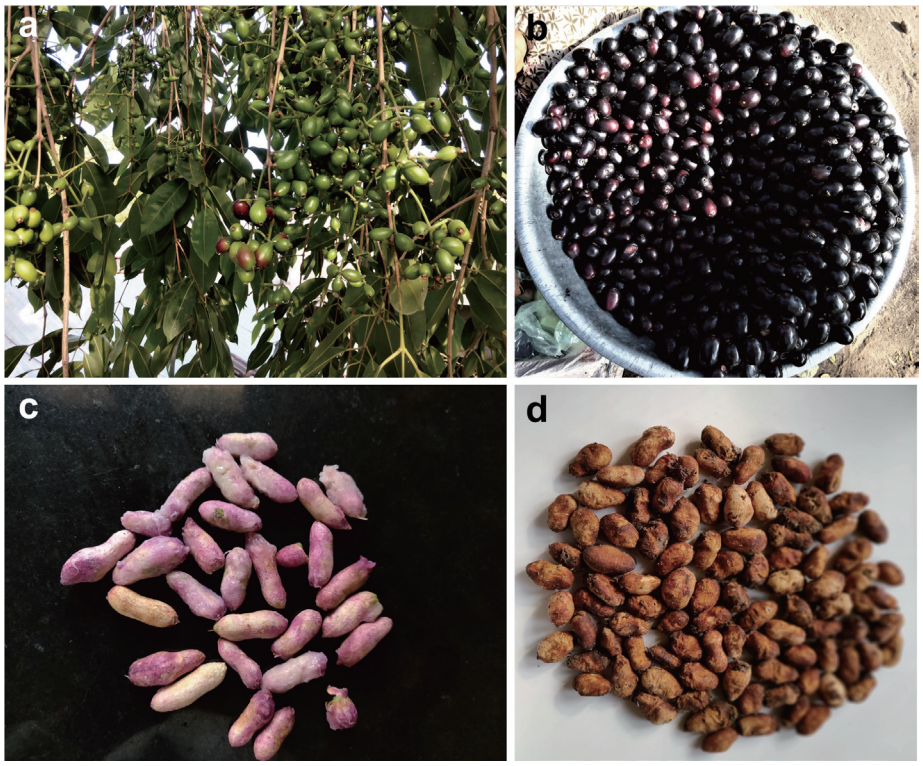

Fig. 2. Photos of Jamun (*Syzygium cumini*) fruit. (a) Fruits in their natural form on the tree; (b) Ripened fruits; (c) Fresh seeds; and (d) Dried seeds.

and sugars were detected in the aqueous and alcoholic leaf extracts of Jamun.[35,36] Catechins, flavonoids, phenols, and quinones are present in the aqueous Jamun stem bark extract.[37] The methanol extract of Jamun fruits and its subsequent extraction in n-hexane, chloroform, ethyl acetate, and n-butanol exhibited the presence of alkaloids, flavonoids, glycosides, steroids, phenols, saponins, tannins, fatty acids, carbohydrates, and reducing sugars.[38]

Alkaloids, flavonoids, phytosterols, phenols, saponins, tannins, and amino acids have been found in the aqueous and methanol extracts of Jamun seeds.[39] The analysis of ethanol, methanol, and water extracts of Jamun seeds has shown the presence of glycosides, alkaloids, proanthocyanidins, flavonoids, terpenoids, phenol, steroids, saponins, tannins, reducing sugars, and reducing monosaccharides. However, glycosides, alkaloids, steroids, and saponins have not been found in the chloroform extract. Proanthocyanidins, flavonoids, tannins, phenols, reducing sugars, and monosaccharides have been detected in the Jamun seed diethyl ether extract. Flavonoids and steroids have been detected in the *n*-hexane extract of Jamun seeds; whereas the benzene extract has shown the presence of terpenoids in addition to flavonoids.[40] Alkaloids, flavonoids, glycosides, saponins, steroids, triterpenoids, and tannins have been detected in the ethyl acetate and methanol extracts of Jamun seeds.[41] Anthocyanins, alkaloids, flavonoids, cardiac glycosides, proanthocyanins, phenols, saponins, terpe-

Table 2. Phytochemical constituents of Jamun (*Syzygium cumini*)

S.No.	Parts used	Extract type	Phytochemicals	Reference
1	Leaves	Methanol, ethanol, aqueous, chloroform petroleum ether, acetone and hexane	Alkaloids, anthraquinones, flavonoids, glycosides, steroids, phenols, tannins, saponins, phenols, steroids triterpenoids, cardiac glycosides, phytosterols, resins	25–36,47,48
2	Stem bark	Aqueous, ethanol, methanol, hexane and chloroform	Terpenoids, flavonoids anthraquinone glycosides, alkaloids, catechins, phenols, quinones, saponins, phytosterols, quinones steroids tannins and amino acids and flavonoids,	34,35,37
3	Seed and fruit pulp	Ethyl acetate, methanol, ethanol, hydroalcoholic	Alkaloids, anthocyanins, tannins, cardiac glycosides, flavonoids, phenols, terpenoids, glycosides, steroids, saponins, reducing monosaccharides, reducing sugars and proanthocyanidins, proanthocyanins, saponins, steroids, tannins and phenolic, amino acid, and phytosterols	36–46
4	Root	Hexane, Aqueous	Alkaloids and resins and carbohydrates Volatile oil, alkaloids, flavonoids, glycosides, saponins, steroids, tannins, terpenoids, carbohydrates and mucilage	32,34

noids, tannins, steroids, phytosterols, and amino acids have been found in the ethanol extract of Jamun fruit pulp and seeds.[42–44] Flavonoids, alkaloids, tannins, and steroids have been detected in the hydroalcoholic Jamun seed extract.[45] Glycosides, alkaloids, flavonoids, steroids, saponins, tannins, volatile oils, terpenoids, carbohydrates, and mucilage have been reported in the aqueous root extract of Jamun.[32] The aqueous and methanol extracts of Jamun seeds showed the presence of alkaloids, flavonoids, phenols, saponins, tannins and terpenoids. However, the terpenoids were absent in the aqueous extract.[46] The leaves of Jamun have been found to contain alkaloids, flavonoids, glycosides, resins, tannins, saponins and protein.[47,48]

Specific active phytochemicals

Jamun synthesizes numerous specific chemical molecules, which have been isolated from various parts including the leaf, stem, roots, flowers, fruits, and seeds (Table 3).[32,45,49–87] The medicinal activity of Jamun may be due to these phytochemicals. The chemical structures of some important active bioactive secondary metabolites synthesized by Jamun are depicted in Figure 3.

Root

Flavonoid glycosides, isorhamnetin 3-*O*-rutinoside; myrecetine glycoside (5-((3,4-dihydroxy-5-(((3,4,5-trihydroxytetrahydro-2-furanyl)methoxy)methyl)tetrahydro-2-furanyl)methoxy)-3,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-4-chromenone; myrecetine gentobioes (2-(3,4-di-hydroxy-5-((3,4,5-trihydroxy-6-(((3,4,5,6-tetrahydroxy-tetrahydro-2*H*-2-pyranyl) methoxy) methyl)tetrahydro-2*H*-2pyranyl)methoxy)phenyl)-3,5,7-trihydroxy-4-oxo-4*H*-chromenium); 4-(2-amino-2-(2-(2-hydroxy-3 methylbutyl) octahydropyrrolo [1,2-a]pyrazin-7-yl) ethyl)-2-ethyl-phenol; 9-((2-hydroxy-5-m-tolylpentan-2-yloxy)methyl)-2,10-dimethoxy-icosahydro-1*H*-phenanthro[2,1-f]chromene-1,9-diol; (*E*)-1-(3-aminophenyl)-7-hydroxy-6-methoxy-3-methyl-7-(1,3,11-trimethoxy-2,4,4,13,14-pentamethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)oct-4-en-3-yl acetate; 6-(6-acetyl-2-(11-acetyl-8a-(1-amino-ethyl)-4,4,6a,6b,11-pentamethyl-14-oxo 1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yloxy)-4,5-dihydroxy tetrahydro-2*H*pyran-3-yloxy)-3,4,5-trihydroxytetra-hydro-2*H*-pyran-2-carboxylic acid; 14-hydroxy-11-methoxy-10-(2-methoxypropoxy)-4,6a,6b, 12,14b-pentamethyl-8a-(methylamino)-4-(1-(2,4,8-trimethyl-2,5,6,7,8,8a-hexahydro-1*H*-pyrido [3,4-d1,3]oxazin-6-yloxy)ethyl)octadecahydro-1*H*-phenanthro[1,2-h]isochromen-3(4*H*)-one and 6-(17-(4,6-dihydroxy-5-methoxy-2-(methylperoxy)-tetrahydro-2H-pyran-3-yloxy)-1,12-di-methoxy-4,5,8,10,12,13,14,17-octahydro-1*H*-cyclopenta[a]phenanthren-3-yloxy)-2-(methylper- oxy)-3,4-dihydro-2*H*-pyran-3,4,5-triol have been obtained from the Jamun roots.[32,49]

Stem

Bergenins; eugenin; friedelin; epi-friedelanol; β-sitosterol, and fatty acid ester of epi-friedelanol have been extracted from the stem bark of Jamun.[45] In addition, the Jamun stem contains quercetin; kaempferol; myricetin; 11-*O*-galloylbergenin; ellagitannin; betulinic acid; ellagic acid and gallic acid.[50–53] 2-butoxy-ethanol; cyclohexanone; 1,2,3,5-tetramethyl-benzene; cyclohexasiloxane, dodecamethyl; 2-butenoic acid, 2-methyl-1,1a,1b,4,4a,5,7a,7b,8,9-decahydro-4a,7b-dihydroxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-5-oxo-9a*H*-cyclopropa[3,4]- benz[1,2-e]azulene-9,9a-diyl ester, [1aR-[1a.alpha.,1b.beta.,4a.beta., 7a.α.,7b.αa.,8.α.,9.β.(*E*); 9a.α.(*E*)]]-; 2,4-imidazolidinedione, 5-[3,4-bis[(trimethylsilyl) oxy]phenyl]-3-methyl-5-phenyl-1-(trimethylsilyl)-; psi.,.psi.-carotene,3,3′, 4,4′-tetradehydro-1,1′,2,2′-tetrahydro-1-hydroxy-1′-methoxy-; 9,10-anthracenedione, 1-(methylamino)-4-[(4-methylphenyl)amino]; acetic acid, 1,1′,4′-triacetoxy-5,5′-diisopropyl-6,7,6′,7′-tetramethoxy-3,3′-dimethyl-[2,2′]binaphthalenyl-4-yl ester; 3,9.beta.;14,15-diepoxypregn-16-en-20-one,3,11.β.,18-triacetoxy-; canthaxanthin; cephalontaxine, 11-(acetyloxy)-, acetate (ester), (11.α.); 1H-cyclopent[c]isoxazole, 1-[2,3:5,6-bis-*O*-(1-methylethylidene)-α-d-mannofuranosyl]hexahydro-4,5,6-tris(phenylmeth-oxy)-, [3a*R* -(3a.α.,4.α.,.β.; 9-15 desoxo-9-x-acetoxy-3,8,12-tri-*O*-acety-lingol; spiro[9,9′]-difluorene, 2,2′-(2,5,8,11-tetraoxadodecane-1,12-diyl)-; 3,8,12-tri-*O*-acety-lingol 7-phenylacetate; 2H-1,4-benzo-diazepin-2-one,7-chloro-1,3-dihydro-1-methyl-5-[4-[(trimethylsilyl)oxy]phenyl]-; α-lumi colchicine; pregn-16-en-20-one,11,18-bis(acetyloxy)-3,9-epoxy-3-methoxy-, (3.α.,5.β.,11.α.)-; 3-hydroxybromoazepam, bis(trimethylsilyl)-deriv; 6,6′-diacetyl-7,7′-dihydroxy-2,2′,4,4′,5,5′-hexamethoxy-1,1′-binaphthalene; pregnane-11,20-dione, 3,17,21-tris[(trimethyl-silyl) oxy]-, 20-[*O*-(phenylmethyl)oxime], (3α,5α)- and silane, [[(3.β., 5.α.,11.β.,20S)-pregnane-3,11,17,20,21-pentayl]pentakis(oxy)] pentakis[trimethyl- have been extracted from the methanol stem bark extract of Jamun.[54]

Leaves

Jamun leaves show the presence of myricetin; mycaminose; myricetin 3-*O*-(4″-acetyl)-α-L-rhamnopyranosides; *n*-nonacosane; noctacosanol; quercetin; *n*-dotricontanol; *n*-hentriacontane; *n*-hepatcosane; β-sitosterol; *n*-triacontano; betulinic acid; crategolic (maslinic) acid; eicosane; octacosane; octadecane; quercetin 3-*O*-rutinoside; prenylbenzoic acid 4-β-D-glucoside; morolic acid 3-*O*-caffeate; 5,4′-dihydroxy, 7-methoxy, 6-methylflavone; 3,4,5-trihydroxybenzoic acid, isoetin-7-*O*-β-D-glucopyranoside, and (4′-hydroxy-3′-methoxyphenol-β-D-[6-*O*-(4″-hydroxy-3″,5″-dimethoxylbenzoate)]glucopyranoside).[55–58] Diferulic acid; butin; methyl gallate; cianidanol; kaempferide, 4′-hydroxyflavan; taxifolin; palmitic acid; punicic acid; cedrol; caffeic acid; 3 (3hydroxyphenyl) propanoic acid; xanthoxylin; ferulic acid; quinic acid; astragalin; 6-*O*-feruloyl-d-glucose; gallic acid; isoquercetin, and 3,5,7,4′-tetra-hydroxy- 6-(3-hydroxy- 3-methylbutyl) flavone have been isolated from the aqueous Jamun leaf extract.[59]

Essential oils

Jamun leaves contain several essential oils, including alloocimene; cineole; caryophyllene; caryophyllene oxide; L-limonene; eucarvone; geranyl acetone; α-myrtenal; pinocarvone; pinocarveol; α-terpeneol; myrtenol; muurolol; α-pinene; α-terpineol; α-bornyl acetate; 2-β-pinene; α-humulene, and α-terpineolene.[60–62] (*E*)-caryophyllene; α-humulene; α-zingiberene; hydroxytoluene butylated; caryophyllene alcohol; caryolan-8-ol; thujopsan-2-α-ol, and *n*-heneicosane are also present in Jamun leaves.[63] The presence of δ-cadinene; τ-cadinol; τ-muurolol; β-eudesmol; globulol; β-pinene; γ-cadinene; camphene; α-terpinenol; camphor; humulene 6,7-epoxide; cubeban-11-ol; α-muurolene; epicubenol; α-copaene; viridiflorene; β-guanine; β-bourbonene; terpinen-4-ol; endoborneol; levoverbenone isobornyl acetate, and 4-methylene-2,8,8-trimethyl-2-vinyl-bicyclo[5.2.0]nonane also has been confirmed in Jamun leaves.[64] In addition, Jamun leaves contain β-farnesene; caryophyllenol; β-myrcene; fenchol; cis-β-ocimene; 1,3,6-heptatriene; and 3,5-heptadienal, 2-ethylidene-6-methyl-.[65]

Flowers

Different phytochemicals, including kaempferol; isoquercetin; quercetin; myricetin-(quercetin-3-glucoside); isoquercetin

Table 3. Different active phytochemicals isolated from different parts of Jamun (*Syzygium cumini*)

S.No.	Parts	Isolated compounds	Reference
1	Roots	Flavonoid glycosides, isorhamnetin 3-O-rutinoside, myrecetine glycoside (5-((3,4-dihydroxy-5-(((3,4,5-trihydroxytetrahydro-2-furanyl)methoxy)methyl) tetrahydro -2-furanyl)methoxy)-3,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-4H-4-chromenone); myrecetine gentobioes (2-(3,4-dihydroxy-5-((3,4,5-trihydroxy-6-(((3,4,5,6-tetrahydroxy tetrahydro-2H-2-pyranyl)methoxy) methyl) tetrahydro-2H-2pyranyl) methoxy) phenyl)-3,5,7-trihydroxy-4-oxo-4H-chromenium) and 4-(2-amino-2 -(2-(2-hydroxy-3-methyl butyl) octahydropyrrolo-[1,2-a] pyrazin-7-yl)-ethyl)-2- ethylphenol; 9-((2-hydroxy-5-m-tolylpentan-2-yloxy)methyl)-2,10-dimethoxy-icosahydro-1*H*-phen-anthro[2,1-f]chromene-1,9-diol; (*E*)-1-(3-aminophenyl)-7-hydroxy-6-methoxy-3-methyl-7-(1,3,11-trimethoxy-2,4,4,13,14-pentamethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-17-yl) oct-4-en-3-yl acetate; 6-(6-acetyl-2-(11-acetyl-8a-(1-amino-ethyl)-4,4,6a,6b,11-pentamethyl-14-oxo 1,2,3,4,4a,5,6,6a,6b,7,8,8 a,9,10,11,12,12a,14,14a,14b-icosahydropicen-3-yloxy)-4,5-dihydroxy tetrahydro-2*H*pyran-3-yloxy)-3,4,5-trihydroxytetra-hydro-2*H*-pyran-2-carboxylic acid; 14-hydroxy-11-methoxy-10-(2-methoxypropoxy)-4,6a,6b, 12,14b-pentamethyl-8a-(methylamino)-4-(1-(2,4,8-trimethyl-2,5,6,7,8,8a-hexahydro-1*H*-pyrido [3,4-d1,3]oxazin-6-yloxy)ethyl)octadecahydro-1*H*-phenanthro[1,2-h] isochromen-3(4*H*)-one and 6-(17-(4,6-dihydroxy-5-methoxy-2-(methylperoxy)-tetrahydro-2H-pyran-3-yloxy)-1,12-di-methoxy-4,5,8,10,12,13,14,17-octahydro-1*H*-cyclopenta[a]- phenanthren-3-yloxy)-2-(methylper- oxy)-3,4-dihydro-2*H*-pyran-3,4,5-triol.	32,49
2	Stem	Bergenins; eugenin; friedelin; epi-friedelanol; fatty acid ester of epi-friedelanol; quercetin; β-sitosterol; kaempferol;, myricetin; 11-O-galloylbergenin; ellagitannin; betulinic acid; ellagic acid; gallic acid; 2-butoxyethanol, cyclohexanone, 1,2,3,5-tetra-methyl-benzene, cyclohexasiloxane, dodecamethyl, 2-butenoic acid,2-methyl-,1,1a,1b,4, 4a,5,7a,7b,8,9-decahydro-4a,7b-dihydr-oxy-3-(hydroxymethyl)-1,1,6,8-tetramethyl-5-oxo-9aH-cyclopropa [3,4]-benz[1,2-e]azulene-9,9a-diylester,[1aR-[1a.α., 1b.β., 4a.β.,7a.α., 7b.αa., 8.α.,9.β. (E),9a.α.(E)]]-2,4-imidazolidinedione, 5-[3,4-bis-[(trimethylsilyl) oxy]phenyl]-3-methyl-5-phenyl-1-(trimethylsilyl)-; psi.,.psi.-carotene,3,3′, 4,4′-tetradehydro-1,1′,2,2′-tetrahydro-1-hydroxy-1′-methoxy-, 9,10-anthracenedione, 1-(methylamino)-4-[(4-methylphenyl)amino]; acetic acid, 1,1′,4′-triacetoxy-5,5′-diisopropyl-6,7,6′,7′-tetrameth-oxy-3,3′-dimethyl[2,2′]binaphthal-enyl-4-yl ester, 3,9.β.;14,15-diepoxypregn-16-en-20-one,3,11.β.,18-triacetoxy-; canthaxanthin; cephalotaxine, 11-(acetyloxy)-, acetate (ester), (11.α.)-; 1H-cyclo-pent[c]isoxazole, 1-[2,3:5,6-bis-O-(1-methyl-ethylidene)-.α.-d-mannofuranosyl]-hexa-hydro-4,5,6-tris-(phenylmeth-oxy)-,[3aR -(3a.α.,4.α.,5.β.; 9-15des-oxo-9-x-acet-oxy-3,8,12-tri-O-acety-lingol, spiro[9,9′]-difluorene, 2,2′-(2,5,8,11-tetraoxadodecane-1,12-diyl)-; 3,8,12-tri-O-acety-lingol 7-phenyl-acetate; 2H-1,4-benzodiazepin-2-one, 7-chloro-1,3-dihydro-1-methyl-5-[4-[(trimethylsilyl)oxy] phenyl]-; α-lumicol-chicine pregn-16-en-20-one,11,18-bis(acetyl-oxy)-3,9-epoxy-3-methoxy-, (3.α.,5.β.,11.α.)-; 3-hydroxybromo- azepam, bis(tri-methylsilyl)-deriv; 6,6′-diacetyl-7,7′-dihydroxy-2,2′,4,4′,5,5′-hexa methoxy-1,1′-binaphthalene; pregnane-11,20-dione, 3,17,21-tris[(trimethyl-silyl)oxy]-, 20-[O-(phenylmethyl)-oxime], (3.α., 5.α.)- , and silane [[(3.β.,5.α.,11.β.,20S)-pregnane-3,11,17,2 0,21-pentayl]-pentakis-(oxy)]pentakis[trimethyl-.	45,50–54
3	Leaves	Myricetin; mycaminose; myricetin 3-O-(4″-acetyl)-α-L- rhamno-pyranosides; n-nonacosane; noctacosanol; quercetin; n-dotricontanol; n-hentriacontane; n-hepatcosane; β-sitosterol; n-triacontanol; betulinic acid; crategolic (maslinic) acid; triterpenoids tannins eicosane; octacosane; octadecane; quercetin3-O-rutinoside; prenylbenzoic acid 4-β-D-glucoside; morolic acid 3-O-caffeate; 5,4′-dihydroxy, 7-methoxy, 6-methyl-flavone; 3,4,5-trihydroxybenzoic acid; isoetin-7-O-β-D-glucopyranoside and (4′-hydroxy-3′-methoxyphenol-β-D-[6-O-(4″-hydroxy-3″,5″-dimethoxylbenzoate)] glucopyranoside).	55–59
4	Essential oils	Alloocimene; α-cadinol; cineole; caryophyllene; caryophyllene oxide; L-limonene; eucarvone; geranyl acetone; α-myrtenal; pinocarvone; pinocarveol; myrtenol; muurolol; α-pinene; α-terpineol; α-bornyl acetate; 2-β-pinene; α-humulene; α-terpineolene; (E)-caryophyllene; α-humulene; α-zingiberene; hydroxytoluene butylated; caryophyllene alcohol; caryolan-8-ol; thujopsan-2-α-ol; n-heneicosane; τ-cadinol; τ-muurolol; globulol; δ-cadinene; β-eudesmol; β-pinene; γ-cadinene; camphene; α-terpinenol; camphor; humulene 6,7-epoxide; cubeban-11-ol; α-muurolene; epicubenol; α-copaene; viridiflorene; β-guanine; β-bourbonene; terpinen-4-ol; endoborneol; levoverbenone isobornyl acetate; 4-methylene-2,8,8-trimethyl-2-vinyl-bicyclo[5.2.0]nonane; β-farnesene; caryophyllenol; β-myrcene; fenchol; cis-β-ocimene; 1,3,6-heptatriene, and 3,5-heptadienal, 2-ethylidene-6-methyl-.	60–65

(continued)

Table 3. *(continued)*

S.No.	Parts	Isolated compounds	Reference
5	Flowers	Kaempferol; isoquercetin; quercetin; myricetin-(quercetin3-glucoside); isoquercetin (quercetin- 3 -glucoside); myricetin-3-L-arabinoside; quercetin-3-D-galactoside; ellagic acids; dihydromyricetin; oleanolic acid; acetyl oleanolic acid; eugenol-triterpenoid A and eugenol-triterpenoid B.	66
6	Fruits	Cyanidin 3-glucoside; cyanidin 3,5-diglucoside; delphinidin 3-glucoside; delphinidin 3,5-diglucoside; malvidin 3,5-diglucoside; malvidin 3-glucoside; petunidin 3,5-diglucoside; peonidin 3,5-diglucoside; delphinidin acetyl-diglucoside; petunidin 3-glucoside; dihydromyricetin diglucoside; galloyl-glucose ester; dihydro-quercetin diglucoside; methyldihydromyricetin; gallic acid; dimethyl-dihydromyricetin diglucoside; myricetin glucoside; myricetin pentoside; myricetin rhamnoside; myricetin acetyl-rhamnoside; myricetin; cyanidin-3,5-diglycoside; peonidin-3,5-diglycoside; delphinidin-3,5-diglycoside; petunidin-3,5-diglycoside; delphinidin-3,5-diglucoside; delphinidin; petunidin; peonidin; delphinidin di-glucoside; petunidin di-glucoside; malvidin di-glucoside; malvidin; malvidin-3,5-diglycoside; cyanidin 3-glucoside; cyanidin 3-xyloside; cyanidin 3-rutinoside; cyanidin 3-dioxalylglucoside; cyanidin 3-malonyl-glucoside; quercetin 3-rutinoside; quercetin 3-glucoside; quercetin 3-galactoside; quercetin 3-glucosylpentoside; quercetin 3-glucuronide; lambertianin C isomer; quercetin 3-O-[6″-(3-hydroxy-3-methylglutaroyl)]-b-galactoside; quercetin 3-oxalylpentoside; quercetin 3-rhamnoside; quercetin; sanguiin H-6 lambertianin A; galloyl-bis-HHDP glucose isomer; ellagic acid; peonidin-3,5-diglucoside; liquitrigenin; scopoletin; umbelliferon; catechin; quinic acid; chlorogenic acid; rosmanol, caffeic acid; gibb-3-ene-1,10-dicarboxylic acid; 2,4adihydroxy-1-methyl-8-methylene-; 1,4alactone, 10-methyl ester, (1a,2a,4aa,4b,10a)-; 18,19-secoyohimban-19-oi acid,16,17,20,21- tetradehydro-16-(hydroxymethyl)-,methyl ester, (15a,16E)-; carda-5,20 (22)-dienolide, 3-[(6-deoxy-a-L manno pyranosyl)oxy]-14-hydroxy-, (3a)-; spirostan-9-ol,3-amino-, (3a,5a,25R)-; acetic acid,17-acetoxy-3-hydroxyimino-4,4,13- trimethyl- hexadecahydrocyclopenta(a)phenanthren-10-ylmethyl ester; aspidosermidin-17-ol, 1-acetyl-19,21-epoxy15,16-dimethoxy and cholestan-3-ol,2-methylene-, (3a,5a)-.	62,67–78
7	Seeds	Jamboline; 7-hydroxycalamenene; (6′methyl, 2′-1-hydroxyisopropene-1-yl)4,5,6 H pyran; jambosine; methyl-β-orsellinate; β-sitosterol; oleanolic acid; 3-hydroxy androstane [16,17-C](6′methyl, 2′-1-hydroxy -isopropene-1-yl) 4,5,6 H pyran; hexahydroxydiphenoyl glucose; hexahydroxydiphenic acid; 1-galloylglucose; brevifolin; δ-cadinene; 1,2,3-benzenetriol; bicyclogermacrene; (1a,3a,4a)-3,4-bis[dimethyl(4-methylphenyl) silyl]cyclopentan-1-yl acetate; shahamin B; ellagic acid; ellagitannins; oxirane; β caryophyllene; 2,3-dimethyl, caryophyllene, 5-(hydroxymethyl) 2-furancarbxaldehde; 3,7-dimethyl-1,3,6-octatriene; germacrene; 5,10-dichloro-5,10-dimethyl-tricyclo [7.1.0.0(4,6)]decane; cadinene; 2-isopropenyl-5-isopropyl-7,7 methylbicyclo[4.1.0]hept-3-ene; 1-methyl-2-methylenecyclo- heptanol; bicyclo[2.2.1]heptan-2-one; 3-(3-butenyl)-2,2-dimethyl cyclopropane carboxylic acid; caryophyllene oxide, bicyclo(4.4.o)decane; 4-methylene cyclohexane methanol; β-pinenoxid; 8,11,14-eicosatrieonic acid; capric acid; methylheptanoate; 3-thujanol; cis,cis-4,6-octadienol; 5, 9-dimethyl 1-decanol; 2-methylpentanal; hexadecanoic acid (methyl ester); tetradecanoic acid (methyl ester); 4-dodecen-1-ol acetate; 2-methyl pentanol; propyl spiropentane; 3-ethyl-2,2-dimethyl-oxirane; 1,10-decandiol; caryophyllene oxide; 4,11,11-trimethyl-8-methylene; isogeraniol; 3(2H)-furanone dihydroxy-2-methyl; 2-methyl-3-isobutenyl-4-penten-2-ol, 5(hydroxymethyl)-2-furaldehyde; decahydro-4A-methyl-1-methylene-7-(1-methylethenyl); 12-methyl-E,E-2,13-octadecadien-1-ol, nondecanoic acid; guaiol; limonene oxide; 3-methyl-4-hexyn-3-ol; thujanol; tannic acid; gallic acid; ellagic acid; caffeic acid; catechin; epicatechin; quercetin; ρ-coumaric acid; cuscohygrine (alkaloid); naringin; rutin; myricetin (flavonoids); epoxy caryophyllanone (terpenoid); 5-acetamido-4,7-dioxo-4,7-di-hydrobenzofurazan; oxetane, 2,4-dimethyl-,trans-, ethanamine,2-methoxy-, (S)-2-hydroxy-propanoic acid; glycerin; 1-dimethyl- (pentafluorophenyl)silyloxycyclopentane; hydroperoxide, 1-methyl-pentyl; benzene-1,2,3-triol; phthalic acid; heptyl pentyl ester, 9,9-dimethoxybicyclo[3.3.1]nona-2,4-dione; 1,1-dodecanediol; hexa-tricontane, nonadecane, 1- chlorodotriacontane, 1-heptadecanamme, cyclohexane; 1-(l,5-dimethyl-hexy)l-4-(4-methyl-pentyl); N-hexa-decanoic acid; hexadecanoic acid ethyl ester; t-butyl cyclopentane- eperoxycarboxylate; 5-isopropyl-6-methyl-hepta-,35-dien-2-ol; 2,3-anhydro-Dmanosan; 2,3-anhydro-D-galactosan; α-cadinol; τ-muurolol; ledene oxide (II); 1,1-dodecanediol diacetate; l ,6;3,4-dianhydro-2-deoxy-β-D-lyxo-hexopyranose; l-hexyl-2-nitrocyclohexane; oleic acid; eicosanoic acid; l,6;2,3-dianhydro-4-O-acetylβ-D-allopyranose; α-cadinol; pregnan-3,l l-diol-20-one; propanal,2,3-dihydroxy and diglycerol.	70,79–87

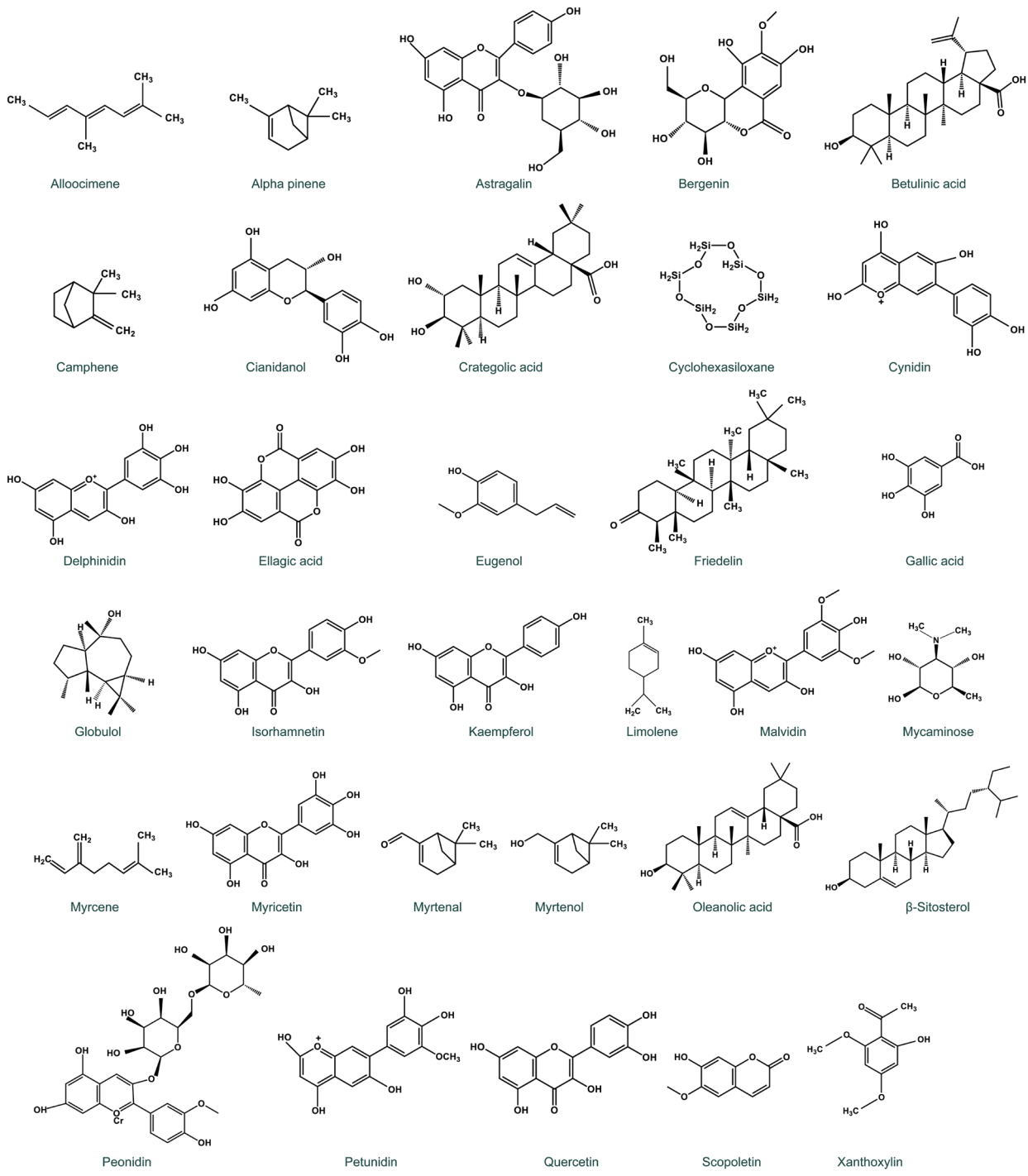

Fig. 3. Chemical structures of some important bioactive phytochemicals present in the different parts of Jamun (*Syzygium cumini*).

(quercetin-3-glucoside); myricetin-3-L-arabinoside; quercetin-3-D-galactoside; ellagic acids; dihydromyricetin; oleanolic acid; acetyl oleanolic acid; eugenol-triterpenoid A, and eugenol-triterpenoid B have been isolated from the flowers of Jamun.[66]

Fruit

Anthocyanins including cyanidin 3,5-diglucoside; delphinidin; cyanidin 3-glucoside; delphinidin di-glucoside; malvidin; delphinidin 3-glucoside; delphinidin 3,5-diglucoside; malvidin 3,5-diglucoside; malvidin 3-glucoside; malvidin di-glucoside; malvidin-3,5-glycoside; petunidin 3,5-diglucoside; peonidin 3,5-diglucoside; delphinidin acetyldiglucoside; petunidin; petunidin 3-glucoside; petunidin diglucoside; petunidin-3,5-diglycoside; peonidin, and peonidin-3,5-diglycoside impart a peculiar color to

Jamun fruits. Jamun fruits also contain nonanthocyanin phenolic compounds, including dihydromyricetin diglucoside (flavanonol); galloylglucose ester (phenolic acid); methyldihydromyricetin; dihydroquercetin diglucoside (flavanonol); dimethyl-dihydromyricetin diglucoside (flavanonol); gallic acid (phenolic acid); myricetin glucoside (flavonol); myricetin pentoside (flavonol); myricetin rhamnoside (flavonol); myricetin acetyl-rhamnoside (flavonol); and myricetin (flavonol). The fruit pulp also shows the presence of cyanidin 3-glucoside; cyanidin 3-xyloside; cyanidin 3-rutinoside; cyanidin 3-dioxalylglucoside; cyanidin 3-malonyl-glucoside; quercetin 3-rutinoside; quercetin 3-glucoside; quercetin 3-galactoside; quercetin 3-glucosylpentoside; quercetin 3-glucuronide; lambertianin C isomer; quercetin 3-*O*-[6″-(3-hydroxy-3-methylglutaroyl)]-β-galactoside; quercetin 3-rhamnoside; quercetin 3-oxalyl-pentoside; quercetin; galloyl-bis-HHDP glucose isomer; sanguiin H-6 lambertianin A, and ellagic acid.[62,67–74] Peonidin-3,5-diglucoside; rosmanol; delphinidin-3-glucoside; myricetin; scopoletin; liquitrigenin; umbelliferon; catechin; quinic acid; chlorogenic acid, and caffeic acid also have been detected in the methanol fruit extract.[75,76] The aqueous fruit extract of Jamun contains gibb-3-ene-1,10-dicarboxylic acid, 2,4-adihydroxy-1-methyl-8-methylene-, 1,4alactone,10-methyl ester, (1a,2a,4aa,4b,10a)-,)-; 18,19-secoyohimban-19-oi acid,16,17,20,21-tetradehydro-16-(hydroxymethyl)-,methyl ester,(15a,16E)-,)-; carda-5,20 (22)-dienolide, 3-[(6-deoxy-a-lmanno- pyranosyl)oxy]-14-hydroxy-, (3a)-,)-; spirostan-9-ol,3-amino-, (3a,5a,25*R*)-,)-; acetic acid, 17-acetoxy-3-hydroxyimino-4,4,13- trimethylhexadecahydro-cyclopenta(a) phenanthren-10-ylmethyl ester; aspidosermidin-17-ol, 1-acetyl-19,21-epoxy15,16-dimethoxy, and cholestan-3-ol,2-methylene-, (3a,5a)-. The acidified aqueous extract of Jamun fruit pulp and the peel extract show ρ-coumaric acid; ferulic acid; gallic acid; vanillic acid; caffeic acid; (phenolic acid); epicatechin; catechin; myricetin (flavonoids), 3,5-diglucosides of petunidin; malvidin, and delphinidin anthocyanins.[77,78]

Seeds

Jamboline; 7-hydroxycalamenene, (6′methyl, 2′-1-hydroxyisopropene-1-yl)4,5,6-*H*-pyran, jambosine; methyl-β-orsellinate; β-sitosterol; oleanolic acid; 3-hydroxy androstane [16,17-*C*] (6′methyl, 2′-1-hydroxyisopropene-1-yl) 4,5,6-*H*-pyran; hexahydroxydiphenoyl glucose; hexahydroxydiphenic acid; 1-galloylglucose and brevifolin have been separated from the ethanol Jamun seed extract.[70,79,80] Jamun seed contains δ-cadinene; 1,2,3-benzenetriol; bicyclo-germacrene; (1a,3a,4a)-3,4-bis[dimethyl(4-methylphenyl)silyl]cyclopentan-1-yl acetate; ellagic acid; shahamin B and ellagitannins.[70,81] The Jamun methanol seed extract shows the presence of oxirane; β caryophyllene; 2,3-dimethyl, caryophyllene; 5-(hydroxymethyl) 2-furan-carbxaldehde; 3,7-dimethyl-1,3,6-octatriene; germacrene; 5,10-dichloro-5,10-dimethyl-tricyclo- [7.1.0.0(4,6)]-decane; cadinene; 2-isopropenyl-5-isopropyl-7,7methylbicyclo[4.1.0]hept-3-ene; 1-methyl-2-methylenecycloheptanol; bicyclo[2.2.1]heptan-2-one; 3-(3-butenyl)-2,2-dimethyl cyclopropane carboxylic acid; caryophyllene oxide; bicyclo(4.4.O)decane; 4-methylene cyclohexane methanol; β-pinenoxid; 8,11,14-eicosatrieonic acid; capric acid; methylheptanoate; 3-thujanol, cis,cis-4,6-octadienol; 5, 9-dimethyl 1-decanol; 2-methylpentanal; hexadecanoic acid (methyl ester); tetradecanoic acid (methyl ester); 4-dodecen-1-ol acetate; 2-methyl pentanol; propyl spiropentane; 3-ethyl-2,2-dimethyloxirane, and 1,10-decandiol. Caryophyllene oxide; 4,11,11-trimethyl-8-methylene; isogeraniol; 3(2*H*)-furanone dihydroxy-2-methyl; 2-methyl-3-isobutenyl-4-penten-2-ol; 5(hydroxymethyl)-2-furaldehyde; decahydro-4 A-methyl-1-methylene-7-(1-methylethenyl); 12-methyl-*E,E*-2,13-octadecadien-1-ol, nondecanoic acid, guaiol, limonene oxide, 3-methyl-4-hexyn-3-ol, and thujanol have been detected in the ethanol extract.[82] The aqueous Jamun seed extract contains tannic acid; gallic acid; ellagic acid; caffeic acid; catechin; epicatechin; quercetin, and ρ-coumaric acid; whereas the ethyl acetate fraction of Jamun seed extract shows the presence of cuscohygrine (alkaloid); naringin; rutin; myricetin (flavonoids), and epoxycaryophyllanone (terpenoid).[83,84] 5-Acetamido-4,7-dioxo-4,7-di-hydrobenzofurazan; oxetane; 2,4-dimethyl-transethanamine; 2-methoxy-, (*S*)-2-hydroxy-propanoic acid; glycerin; 1-dimethyl-(penta-fluorophenyl)silyloxycyclopentane; hydroperoxide, 1-methylpentyl; benzene-1,2,3-triol; phthalic acid; heptyl pentyl ester, and 9,9-dimethoxy- bicyclo[3.3.1]nona-2,4-dione have been isolated from the methanol Jamun seed extract.[85] Gas chromatography–mass spectrometry analysis of the Jamun seed ethanol extract led to the isolation of 1,1-dodecanediol; hexatricontane; nonadecane; 1-chloro-dotriacontane; 1-hepta-decanamme; cyclohexane; 1-(l,5-dimethyl-hexy)l-4-(4-methyl-pentyl); *N*-hexadecanoic acid; hexa-decanoic acid ethyl ester; *t*-butyl cyclopentane eperoxycarboxylate; α-cadinol; τ-muurolol; 5-isopropyl-6-methyl-hepta-,35-dien-2-ol; 2,3-anhydro-Dmanosan; 2,3-anhydro-D-galactosan; ledene oxide (II); 1,1-dodecanediol diacetate; l,6;3,4-dianhydro-2-deoxy-β-D-lyxohexo-pyranose; l-hexyl -2-nitrocyclohexane; eicosanoic acid; oleic acid; l,6;2,3-dianhydro-4-*O*-acetylβ-D-allopyranose; α-cadinol; pregnan-3,l, l-diol-20-one; propanal, 2,3-dihydroxy, and diglycerol.[86,87]

Nutritional profile

The Jamun fruit pulp has been analyzed for its nutritional value, which may vary depending on the region and season of analysis (Table 4). [21,88–92] The moisture contents in the Jamun fruit pulp were found to be 79.21–86.12% and 1.03 ± 0.08%, respectively. The Jamun fruit pulp has shown the presence of the following: total soluble sugars, 1.4 ± 0.15 (degree Brix); total dissolved solids, 217 ± 1.15 (ppm); total solids, 47.75 ± 3.17%; total carbohydrates, 89.68 ± 0.29%; total sugars, 5.54 ± 0.69%; fats, 1.28 ± 0.11%; pectin, 4.7 ± 0.13%; proteins, 0.65 ± 0.03%; fiber, 0.18 ± 0.02%; antioxidant capacity (1,1-diphenyl-2-picrylhydrazyl; DPPH), 31.29 ± 1.53%; tannins, 94.52 ± 9.19 (mg/100 g); anthocyanins, 195.58 ± 6.15 (mg/100 g); and polyphenols, 203.76 ± 9.84 (mg/g gallic acid equivalents). The minerals (mg/100 g) present in the Jamun fruit pulp include the following: sodium, 1.73 ± 1.70–8.75 ± 0.25; potassium, 172.4 ± 17.23–358.5 ± 5.0; calcium, 54.55 ± 4.78–81.4 ± 11.15; phosphorous, 152.65 ± 15.38; zinc, 0.46 ± 0.06–1.215 ± 0.1; iron, 4.66 ± 0.81–33.2 ± 1.0; magnesium, 27.13 ± 3.43–166.7 ± 7.10; manganese, 0.2 ± 0.007; copper, 1.8 ± 0.41–8.75 ± 0.25; lead, 0.33 ± 0.13; chromium, 1.06 ± 0.13; sulfur, 13, and chlorine, 8. The following vitamins (mg/100 g) have been detected in the Jamun fruit pulp: ascorbic acid, 49.78 ± 2.17; niacin, 8; choline, 7; folic acid, 3 µg; riboflavin, 0.01–0.06; thiamine, 0.03–0.12; and vitamin A, 80 IU. The pH of Jamun fruit pulp has been measured as 3.87 ± 0.01, with an acidity of 2.65 ± 0.21.[21,88–92]

The moisture and ash contents in Jamun seeds are reported to be 52.24 ± 3.17% and 3.13 ± 0.16%, respectively. Jamun seeds have shown the presence of the following: total soluble sugars, 1.4 ± 0.15 (degree Brix); total dissolved solids, 217 ± 1.15 (ppm); total solids, 47.75 ± 3.17%; total carbohydrates, 89.68 ± 0.29%; total sugars, 5.54 ± 0.69%; fats, 1.28 ± 0.11%; proteins, 4.68 ± 0.35%; fiber, 1.21 ± 0.06%; antioxidant capacity (DPPH), 48.23 ± 2.98%; tannins, 388.99 ± 7.34 (mg/100 g); anthocyanins, 18.47

Table 4. Nutritional profile of Jamun (*Syzygium cumini*) fruit pulp and seeds[21,88–92]

S. No.	Parameters	Fruit pulp	Seeds
1	Moisture	79.21 to 86.12%	52.24 ± 3.17% 3.13 ± 0.16%
2	Ash	1.03 ± 0.08%	3.13 ± 0.16%
3	Acidity	2.65 ± 0.21	0.04 ± 0.001
4	pH	3.87 ± 0.01	2.5 ± 0.1
5	Total soluble sugars	14.86 ± 1.47	1.4 ± 0.15 (degree Brix)
6	Total dissolved solids	615 ± 0.21	217 ± 1.15 (ppm)
7	Total solids	20.33 ± 0.34	47.75 ± 3.17
8	Total carbohydrate	97.59 ± 0.09%	89.68 ± 0.29%
9	Total sugars	7.88 ± 0.41%	5.54 ± 0.69%
10	Fats	0.18 ± 0.02	1.28 ± 0.11
11	Pectin	4.7 ± 0.13%	–
12	Proteins	0.65 ± 0.03 %	4.68 ± 0.35%
13	Fiber	0.18 ± 0.02%	1.21 ± 0.06%
14	Antioxidants capacity (DPPH)	31.29 ± 1.53%	48.23 ± 2.98%
15	Tannins	94.52 ± 9.19 (mg/100g)	388.99 ± 7.34 (mg/100g)
16	Anthocyanins	195.58 ± 6.15 (mg/100g)	18.47 ± 1.99 (mg/100g)
17	Polyphenols (mg/g gallic acid equivalent)	203.76 ± 9.84	386.51 ± 10.25
	Minerals (mg/100 g)		
18	Sodium	8.75 ± 0.25- 1.73 ± 1.70	43.86 ± 12.09
19	Potassium	172.4 ± 17.23–358.5 ± 5.0	606.46 ± 69.37
20	Calcium	54.55 ± 4.78–81.4 ± 11.15	135.86 ± 26.81
21	Phosphorous	152.65 ± 15.38	–
22	Zinc	0.46 ± 0.06–1.215 ± 0.1	0.46 ± 0.17
23	Iron	4.66 ± 0.81–33.2 ± 1.0	4.2 ± 0.80
24	Magnesium	27.13 ± 3.43–166.7 ± 7.10	111.6 ± 18.06
25	Manganese	0.2 ± 0.007	0.4 ± 0.11
26	Copper	1.8 ± 0.41–8.75 ± 0.25	2.13 ± 0.86
27	Lead	0.33 ± 0.13	0.66 ± 0.06
28	Chromium	1.06 ± 0.13	1.4 ± 0.61
29	Sulphur	13	–
30	Chlorine	8	–
	Vitamins (mg/100 g)		
31	Ascorbic acid	49.78 ± 2.17	–
32	Niacin	8	–
33	Choline	7	–
34	Riboflavin	0.01 to 0.06	–
35	Thiamine	0.03–0.12	–
36	Folic acid	3 µg	–
37	Vitamin A	80 IU	–

± 1.99 (mg/100 g); and polyphenols, 386.51 ± 10.25 (mg/g gallic acid equivalents). The minerals (mg/100 g) present in Jamun seeds include the following: sodium, 43.86 ± 12.09; potassium, 606.46 ± 69.37; calcium, 135.86 ± 26.81; zinc, 0.46 ± 0.17; iron, 4.2 ± 0.80; magnesium, 111.6 ± 18.06; manganese, 0.4 ± 0.11; copper, 2.13 ± 0.86; lead, 0.66 ± 0.06; and chromium. The pH of Jamun fruit pulp was estimated to be 2.5 ± 0.1, with an acidity of 0.04 ± 0.001.[88–90]

Traditional medicinal uses

For centuries, Jamun has been used in diverse ethnomedicinal practices to treat a variety of human diseases.[20,93] According to Verse 140 of Charak Sutrasthana, 27 Jamun is medicinally characterized as madhura (sweet), kashaya (slightly astringent), amla (sour) in taste, guru (heavy), ruksha (dry), vishtambhi (producing wind in the abdomen, causing bloating), sheetala (cooling), grahi (absorbent, bowel binding), vatakara (aggravates vata, i.e., subtle energy associated with movement), balances pitta (related to body's metabolism) and kapha (related to body structure), pramehagna (cures urinary diseases including diabetes), and medoroga (obesity).[94] Jamun purifies the blood and is a good general health tonic for humans. The Jamun stem bark is astringent, constipating, antibacterial, anthelmintic, digestive, carminative, diuretic, febrifuge, stomachic refrigerant, and sweet. In Ayurveda, Jamun is used to treat cold, anorexia, cough, diabetes, worm infestation, emaciation, diarrhea, dysentery, dental, digestive, liver, skin, erectile disorders, and wheezing difficulty. The patients are orally administered with 1–3 g of dried Jamun seed powder to treat diabetes in Ayurvedic medicine. In the traditional system of medicine, various parts of Jamun are used in the treatment of diabetes, dysentery, mouth blisters, digestive complaints, colic, stomachache, cancer, diarrhea, pimples, and piles.[95] The administration of 2.5–10 mL (half to two teaspoons) of ripe Jamun fruit juice thrice a day to patients cures diabetes.[96,97] Traditionally, Jamun fruits and seeds are utilized to treat diabetes, bronchitis, asthma, and splenopathy.[20,24,98–101] The application of the seed powder of Jamun removes blemishes left by acne as well as blackheads on the skin. Eating a mixture of fresh Jamun fruit pulp and honey keeps the body healthy. Enlarged spleen and urinary problems are treated by the use of Jamun fruit juice.[20,101] Eating Jamun seed powder mixed with jaggery relieves dysentery and diarrhea.[20] The topical application of the poultice prepared from Jamun leaf juice is a good remedy to treat skin disorders and dysentery.[102,103] The bleeding gums can be cured by topical application of Jamun leaf ash, which also keeps teeth healthy.[20,91] One teaspoon of Jamun seed powder with water prevents bed wetting in children. Metrorrhagia in women can be treated by consuming 3 g of seed powder. The cataract can also be treated by consuming tablets prepared from Jamun seed powder and honey (1:1 ratio) with milk. The decoction prepared from Jamun leaves relieves conjunctivitis.[97]

The Jamun is a liver tonic in Unani medicine, and the application of leaf paste heals wounds. Jamun strengthens teeth and gums, enriches the blood, and disinfects ringworm and head lice infection.[20,104] Hemorrhoids can be treated by eating Jamun for 2–4 months, and gingivitis is treated with Jamun fruit pulp.[20] The decoction of Jamun stem bark, root bark, or dried seeds treats dyspepsia, diarrhea, and dysentery as well as acts as an enema.[20,103] A mixture of dried stem bark powder and yogurt is used to treat menorrhagia.[20,96] Jamun stem bark powder mixed with its fruit juice is a good remedy for cough and cold. Furthermore, a mixture of half a teaspoon of stem bark powder in one glass of Jamun fruit juice taken daily is useful against infections of the urinary tract and urinary diseases. Strychnine poisoning is cured by giving Jamun seed powder in India.[20,103] Asthma and bronchitis are treated by administering Jamun stem bark decoction.[105] Spongy gums, mouth ulcerations, and stomatitis are treated using Jamun stem bark decoction, which also acts as a good mouthwash.[20,101,103] A mixture of Jamun stem bark ash and oil is applied to treat burns, and its mixture with water acts as an anti-inflammatory agent.[20,101] The decoction prepared from Jamun seeds relieves strain and fatigue.[20] Looking into traditional uses, various investigators have scientifically investigated the application of different parts of Jamun to exploit its pleiotropic medicinal properties and substantiate the claims of traditional healers.

Toxicity evaluation

Safety evaluation of any drug is critical for human use. As such, Jamun has been reported to be safe in various preclinical models, which also justifies the traditional claim that it is a nontoxic remedy. Single intraperitoneal administration of 100, 200, 300, and 400 mg/kg body weight of 1:1 dichloromethane and methanol leaf extract of Jamun did not induce any changes in animal behavior or mortality; hence, a dose of 400 mg/kg is considered safe. The median lethal dose (LD_{50}) could not be determined because higher doses could not be administered.[106] Similarly, a dose of 1,000 mg/kg body weight was found to be safe in Swiss albino mice administered with 250, 500, 750, or 1,000 mg/kg body weight of 50% hydroethanolic Jamun seed extract as none of these doses could alter the behavior or induce mortality in mice in acute toxicity studies. It was not possible to determine the LD_{50} as higher doses could not be administered.[107] The methanol leaf extract has been reported to be nontoxic up to 3.5 g in oral acute toxicity studies in mice, with an LD_{50} of 3.873 mg/kg body weight, and oral administration of hydroalcoholic leaf extract did not induce toxicity up to 6 g/kg body weight in mice. The intraperitoneal administration of methanol leaf extract was toxic, with an LD_{50} of 489 mg/kg body weight in mice.[108] The oral administration of aqueous extract of Jamun stem bark at doses of 300, 2,000, or 5,000 mg/kg body weight in rats was safe up to 5 g/kg body weight, and repeated oral administration of 300, 1,000, or 2,000 mg/kg body weight of aqueous extract of Jamun stem bark for 28 days did not produce any toxicity in the rats.[109] Likewise, 70% methanol stem bark extract of Jamun was nontoxic up to 5,000 mg given orally in mice, and an LD_{50} of 3.873 mg/kg was reported for the leaf extract.[110]

The oral administration of a single dose (acute toxicity) of the ethanol leaf extract of Jamun was nontoxic up to 5 g/kg body weight in rats. Furthermore, the oral administration of 1,250, 2,500, or 5,000 mg/kg for 28 days also did not induce toxicity in rats.[111] The administration of aqueous Jamun seed extract and polymeric nanoparticles prepared from the seed extract given to Wistar rats was found to be nontoxic in acute toxicity studies as they did not induce mortality or alteration in the biochemical or hematological profiles after 14 days.[112] Similarly, the oral administration of Jamun leaves, stem bark, root, or seeds extracted in methanol (except seeds) was found to be nontoxic up to 2,000 mg/kg in rats, and the administration of 100 and 500 mg/kg body weight aqueous leaf extract for 30 days in rats in drinking water was nontoxic as no significant changes were observed in the organ or body weights of male Wistar rats.[113] The 70% ethanol seed extract of Jamun was nontoxic up to 2 g/kg orally in acute toxicity studies in rats, whereas the daily oral administration of 250, 500, or 1,000 mg/kg of extract once daily for 28 days did not produce any toxic effects.[114]

Antioxidant activity

The increased oxidative stress by various reactive oxygen species is the major cause of numerous human diseases. Jamun has been reported to possess antioxidant activity, where different parts of Jamun passivated free radicals *in vitro*. Concentration-dependent inhibition of nitric oxide (NO•) free radicals has been reported for the dichloromethane, methanol, and 50% hydroalcoholic extracts of Jamun leaves and seeds.[115] The methanol leaf extract and its ethyl acetate, chloroform, *n*-hexane, and water fractions scavenged DPPH radicals and increased the ferric reducing antioxidant power (FRAP).[116] The ethanol extract of Jamun leaves scavenged DPPH radicals and increased the reducing power concentration dependently.[117] The dichloromethane and methanol (1:1) extract of Jamun leaves scavenged the radicals of hydroxyl (•OH), superoxide ($O_2^{-\bullet}$), DPPH, and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid ($ABTS^{+\bullet}$), depending on the concentration.[118] The dichloromethane and methanol leaf extracts of Jamun passivated DPPH free radical generation and elevated FRAP.[119] The generation of •OH, NO•, and DPPH free radicals was inhibited in a concentration-dependent manner by the methanol and aqueous Jamun leaf extracts, which also increased FRAP in a similar manner.[120] Concentration-dependent passivation of •OH, NO•, and $ABTS^{+\bullet}$ radicals has been detected with the acetone and aqueous leaf extracts of Jamun.[121] The methanol extracts of Jamun leaves, fruit pulp, and seeds increased FRAP, and the leaf extract was more effective than the seed and fruit pulp extracts.[122] The Jamun aqueous leaf and seed extracts reduced DPPH, NO• radicals, and H_2O_2 formation as well as increased FRAP, depending on their concentration. The leaf extract was more effective than the seed extract.[123] Ethyl acetate:methanol (3:1), ethyl acetate:methanol (1:1), ethyl acetate:methanol (1:3), and pure methanol extracts of Jamun leaves inhibited DPPH radical production.[124]

The formation of •OH, $O_2^{-\bullet}$, and DPPH free radicals was reduced by the aqueous extract of Jamun fruit skin.[125] The concentration-dependent alleviation has been detected in the generation of DPPH, •OH, and $O_2^{-\bullet}$ radicals by ethanol extracts of Jamun fruit pulp, kernels, and seed coat. The fruit pulp extract resulted in half-maximal inhibitory concentration (IC_{50}) values of 158 ± 5, 310 ± 10, and 1,703 ± 9 µg/mL for DPPH, •OH, and $O_2^{-\bullet}$ radicals, respectively. The IC_{50} values for the kernel extract were 8.6 ± 3, 151 ± 5, and 85 ± 5 µg/mL; whereas the IC_{50} values for the seed extract were 48 ± 9, 261 ± 4, and 759 ± 14,261 µg/mL for DPPH, •OH, and $O_2^{-\bullet}$ radicals, respectively.[126] The Jamun fruit extract rich in anthocyanin neutralized $ABTS^{+\bullet}$ and peroxy radicals efficiently.[68] The seed and fruit pulp of Jamun extracted in acidified ethanol inhibited the generation of DPPH and $ABTS^{+\bullet}$ free radicals and also exhibited iron-chelating activity.[71] The methanol stem bark extract of Jamun increased the scavenging of DPPH and •OH radicals as well as the FRAP.[127] The acetone extract of Jamun seeds passivated the DPPH, NO•, and $ABTS^{+\bullet}$ radicals as well as H_2O_2 and increased the antioxidant activity and FRAP concentration dependently.[128]

Antibacterial and antifungal activity

Bacterial and fungal infections lead to numerous infectious diseases in humans, and Jamun can act against bacterial and fungal infections. The growth of *Bacillus sphaericus*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium* has been reported to be inhibited by the essential oils from Jamun leaves.[61] Antibiotic-resistant bacteria, including *Klebsiella pneumoniae*, *P. aeruginosa*, *S. aureus*, *Enterococcus faecalis*, *E. coli*, *Kocuria rhizophila*, and *Neisseria gonorrhoeae*, and the fungus *Candida krusei* were effectively killed by the hydroalcoholic extract of Jamun leaves.[129] The 70% methanol leaf extract and leaf oil suppressed the growth of *E. coli, S. aureus*, *Salmonella typhii*, and *Bacillus subtilis* bacteria and *Candida albicans* fungi.[110] The growth of *Vibrio cholerae* serogroups *Ogawa* and *Inaba* was suppressed by Jamun leaf ethanol extract.[130] The methanol and methylene chloride extracts and essential oils from the leaf of Jamun prevented the growth of *E. coli*, *P. aeruginosa*, *S. aureus*, *N. gonorrhoeae*, *B. subtilis*, *S. aureus*, and *E. faecalis*, and the methanol extract was more effective than the methylene chloride extract and essential leaf oils.[119] The essential leaf oils were also active against the fungi *Aspergillus flavus*, *Aspergillus niger*, *Fusarium solani*, and *Rhizopus solani.*[66]

The Jamun fruit ethanol extract attenuated the growth of *S. aureus* and *Staphylococcus epidermidis* (Gram-positive) as well as *P. aeruginosa* (Gram-negative) bacteria and *C. albicans*, *C. krusei*, *Candida parapsilosis*, and *Cryptococcus neoformans* fungi, indicating its antibacterial and antifungal potential.[131] Jamun leaf, stem bark, pulp, and seeds extracted in 70% ethanol restricted the growth of *Bacillus cereus*, *B. subtilis*, *S. aureus* (Gram-positive), *P. aeruginosa, Shigella flexneri,* and *V. cholera* (Gram-negative) bacteria. The leaf and bark extracts of Jamun were more effective than the pulp and seed extracts.[43] *B. subtilis*, *E. coli*, *P. aeruginosa*, and *S. aureus* growth was suppressed by Jamun seed ethanol extract.[132] The diethyl ether, methanol, and aqueous extracts of Jamun fruit arrested the growth of *S. epidermidis*, *B. cereus*, *Micrococcus luteus*, and *Salmonella typhi*, respectively.[48]

The aqueous extract of the stem and leaves of Jamun was active against *S. aureus*, *E. coli*, *Staphylococcus saprophyticus*, *Proteus vulgaris*, and *P. aeruginosa*, and the fruit extract effectively suppressed the growth of *P. aeruginosa* and the fungi *Penicillium chrysogenum* and *C. albicans*.[133] The growth of the Gram-positive *Bacillus amyloliquefaciens* and the Gram-negative *S. aureus* was restrained by the methanol extract of Jamun stem bark; whereas the ethanol extract of Jamun roots was active against *E. coli*, *Streptococcus suis*, *S. aureus*, *S. epidermidis*, *Salmonella* spp., and *Corynebacterium diphtheriae*, and greater growth inhibition was seen for the Gram-positive than the Gram-negative bacteria.[134] The growth of *E. coli, S. aureus,* and *C. albicans* was inhibited by the chloroform and ethyl acetate leaf extracts of Jamun.[36] The growth inhibitory activity of aqueous Jamun seed extract and polymeric nanoparticles formulated from seed extract has been reported against *C. krusei*, *C. albicans*, *Candida haemulonii*, *Candida guilliermondii*, and *Cryptococcus* sp.[135] In addition, the fruit juice of Jamun effectively arrested the growth of *Salmonella typhimurium, S. aureus*, *S. flexneri*, and enterotoxigenic *E. coli*; whereas it did not have any effect on *Lactobacillus acidophilus* or *Lactobacillus bulgaricus*.[136]

The ethanol and methanol extracts of Jamun stem bark killed *B. amyloliquefaciens*, *S. aureus*, *E. coli*, and *P. aeruginosa*; whereas the aqueous extract was ineffective against these bacteria.[137] The Jamun seed extracted in ethanol exhibited antibacterial activity against *Streptococcus agalactiae*, *S. aureus*, *B. cereus*, *E. faecalis*, *Clostridium perfringens*, *Listeria monocytogenes*, *S. typhimurium*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *Aeromonas hydrophila*; however, it was most effective against *B. cereus*.[44] The ethyl acetate extract of Jamun fruits acted against the Gram-negative bacterial strains *E. coli*, *Salmonella*, *P. aeruginosa*, and *S. typhi* as well as the two Gram-positive strains *S. aureus* and *Streptococcus*.[138] The aqueous, 80% ethanol, methanol, acetone, and hexane extracts of Jamun leaves arrested the growth of methicillin-resistant *S. aureus* and inducible clindamycin-resistant *S. aureus*, depending on the

concentration; the aqueous extract was the most effective, whereas the hexane extract was ineffective.[44] The methanol extracts of ripe fruit pulp, ripe fruit seeds, unripe fruit pulp, and unripe fruit seeds attenuated the growth of *E. coli*, *B. subtilis*, and *S. typhi* bacteria as well as *A. niger*, *Penicillium notatum*, and *Alternaria alternata* fungi, where 0.1% was effective against all bacterial and fungal species.[139] The aqueous and methanol seed extract inhibited the growth of *Salmonella enteritidis.*[47]

Anti-inflammatory activity

Inflammation is related to several diseases, including cancer, and Jamun has been experimentally shown to be active against acute and chronic inflammation. The chloroform and ethanol extracts of Jamun seeds arrested carrageenan (acute) as well as kaolin-carrageenan (subacute)-induced paw edema in rats; moreover, they arrested exudation of proteins, dye leakage in peritoneal inflammation, and leukocyte migration.[140] The anti-inflammatory activity of aqueous, methanol, and ethyl acetate Jamun seed extracts has been reported in human neutrophils and carrageenan-induced rat paw edema, and the extracts also reduced ectonucleotidase, adenosine deaminase (ADA), acetylcholinesterase, and dipeptidyl peptidase IV activities and NO formation.[141,142] The Jamun stem bark ethanol extract arrested the carrageenan (acute), kaolin-carrageenan (subacute), and formaldehyde (subacute)-induced rat paw edema and chronic cotton pellet granuloma.[143] Carrageenan-induced paw edema also was attenuated in Wistar rats by the methanol, ethyl acetate, and aqueous extracts of Jamun seeds, with the aqueous extract being more potent than the methanol extract.[142,144] The Jamun leaves extracted in ethyl acetate and methanol alleviated carrageenan-induced paw edema in Wistar rats.[145]

Acute and chronic inflammation was arrested by Jamun leaf methanol extract in histamine, carrageenan, and serotonin-induced rat paw edema as well as cotton pellet-induced granuloma.[146] In addition, the migration of rat eosinophils was attenuated by essential oils from Jamun leaves, indicating their anti-inflammatory potential.[147] The aqueous leaf extract of Jamun decreased the indomethacin-induced inflammatory changes by decreasing the expression of cyclooxygenase 1 and 2 (COX1 and COX2), tumor necrosis factor-alpha (TNF-α), and inducible nitric oxide synthase (iNOS) in mice.[121] Furthermore, Jamun leaf essential oils reduced chronic granulomatous inflammation in BALB/c mice induced by an intravenous injection of *Mycobacterium bovis* and *Bacillo calmet* Guerin.[148] Importantly, hepatitis B vaccine antigen-induced inflammation was arrested in human neutrophils, lymphocytes, and monocytes by the Jamun leaf flavonoid fraction.[149] Likewise, Jamun root aqueous and ethanol extracts depleted interleukin 6 (IL6) production in RAW 264.7 macrophages, indicating their anti-inflammatory activity.[134]

The inoculation of *C. albicans* into Wistar rats increased the inflammatory response by increasing the expression of IL1, IL6, TNF-α, and interferon gamma (IFN-γ) and decreasing the expression of IL10, an anti-inflammatory cytokine. The treatment of rats with aqueous Jamun seed extract and polymeric nanoparticles formulated from the seed extract administered once daily for 21 subsequent days significantly attenuated the inflammatory cytokines TNF-α, interferon gamma, dipeptidyl peptidase IV, IL1, and IL6 and elevated the anti-inflammatory cytokine IL10. The inoculation of *C. albicans* in rats led to an increase in the hydrolysis of adenosine diphosphate (ADP), adenosine triphosphate (ATP), and adenosine monophosphate (AMP) and raised the ADA activity in serum and platelets; whereas the administration of the aqueous Jamun seed extract and polymeric nanoparticles prepared from the seed extract for 21 days significantly depleted ATP, ADP, and AMP and ADA activity.[135] The methanol extract of Jamun leaves suppressed the carrageenan-induced paw edema in the hind legs of rabbits in a dose-dependent manner.[31] The methanol extract of Jamun fruits inhibited the formaldehyde, carrageenan, and prostaglandin E2-induced paw edema in mice as well as *in vitro*, whereas 50% methanol and dichloromethane extract showed weak anti-inflammatory activity. Similarly, the Jamun fruit methanol extract attenuated glutamate and formaldehyde-induced paw licking in Swiss albino mice.[76] The aqueous Jamun leaf extract inhibited carrageenan-induced paw edema in mice.[150]

Anti-allergic activity

The hypersensitive response elicited by the immune system against certain substances leads to allergic reactions, and different extracts of Jamun have been found to act against allergic reactions. The aqueous leaf extract alleviated mast-cell degranulator C48/80 or OVA-induced anaphylaxis edema in mice and also hindered the accumulation of eosinophils in the pleural cavity, indicating its anti-allergic potential. The rats given 1 µg/mL Jamun leaf extract before C48/80 treatment attenuated histamine delivery into the peritoneal mast cells as a result of attrition of the allergic reaction.[151] The aqueous methanol and methanol fractions of the aqueous extract of Jamun roots suppressed the catalepsy induced by clonidine in mice by preventing the histamine release triggered by mast cell degranulation. The milk-induced eosinophilia was also alleviated in mice by the above extracts.[152]

Hepatoprotective activity

Treatment of albino rats with aqueous leaf extract of Jamun for 7 days before carbon tetrachloride (CCl_4) treatment reduced aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, indicating its hepatoprotective activity.[153] In addition, the anthocyanin-rich ethanol extract and Jamun fruit peel aqueous extract have been reported to protect cultured rat hepatocytes against CCl_4-induced toxicity and elevate reduced glutathione (GSH) and glutathione peroxidase (GPx) levels accompanied by a subsequent decline in lipid peroxidation and lactate dehydrogenase, in which the former was more effective than the latter.[154] The ethanol extract of Jamun fruit pulp, when administered for eight consecutive days before paracetamol treatment, attenuated AST, ALT, alkaline phosphatase (ALP), total bilirubin, total proteins, and albumin levels in the rat liver. It also protected the rat liver against paracetamol-induced pathological changes.[155] The methanol Jamun seed extract protected rats against the CCl_4-induced hepatoxicity by alleviating the acid phosphatase (ACP), ALP, AST, and ALT activities and reduced bilirubin dose dependently.[156] The methanol Jamun fruit extract reduced damage to hepatocytes, decreased hepatic fibrosis and macrophage infiltration induced after bile duct ligation in C57BL/6 male mice, and also decreased lipid peroxidation. The extract attenuated mRNA expression of intercellular adhesion molecule 1 (ICAM1) and chemokine (C-X-C motif) ligand (CXCL2) genes. The methanol extract also reduced IL6, IL1β, iNOS, and nuclear factor kappa B (NF-κB) transcriptional activation in the mouse liver.[157] The ethanol extract of Jamun leaves protects rat liver against CCl_4-induced hepatotoxicity by lowering AST, ALT, ALP, and bilirubin and gradually bringing them to normal levels.[117]

The administration of aqueous seed extract protected the liver of alloxan-induced diabetic mice by lowering the AST, ALT, and

bilirubin levels and histological damage.[158] The administration of 100 or 200 mg/kg body weight ethanol extract of Jamun seeds depleted serum gamma-glutamyl transferase (GGT) and AST in rats. Similarly, the water extract of Jamun seeds protected liver damage by decreasing AST, ALT, ALP, and GGT activities in streptozotocin-induced diabetic rats and also restored the liver histology to normal.[159] The rats administered with the methanol Jamun seed extract for 14 days before CCl_4 administration protected the rat liver by decreasing the AST, ALT, and ALP activities and reducing histological damage in the liver.[160] The methanol extract of Jamun leaves protected against CCl_4-induced hepatotoxicity in Sprague-Dawley rats by decreasing AST, ALT, total bilirubin, total cholesterol, and total triglycerides. The extract increased the GSH concentration and superoxide dismutase (SOD) activity and decreased lipid peroxidation in the Sprague-Dawley rat liver.[161] The 90% ethanol Jamun seed extract protected against cypermethrin-induced liver hypertrophy, hyperchromatic nuclei, foamy cytoplasm with a few vacuoles, and mitochondrial swelling in Wistar rats. The extract also protected against the dilated sinusoids filled with glycogen at a few places, degeneration of hepatocytes, focal necrosis, and formation of binucleated cells in the livers of cypermethrin-treated Wistar rats.[162] The methanol, ethanol, and aqueous seed extracts of Jamun protected against arsenic-induced hepatotoxicity by reducing AST, ALT, and ALP levels in the rat serum.[163] Aqueous fruit extract of Jamun protected the mice liver against chromium-induced steatosis, fibrosis, dehydration, and atrophy.[164]

Gastroprotective activity

Different parts of Jamun have been found to relieve gastric disorders. The tannins obtained from Jamun stem bark suppressed ethanol and HCl-induced gastric ulcers in Sprague-Dawley rats by reducing gastric mucosal damage, free radicals, and ulceration of the gastric mucosa.[165] The hydroalcoholic extract of Jamun fruit has been reported to prevent acetylcholine, serotonin, histamine, and calcium-induced rabbit ileum contraction.[166] In addition, the oral administration of 95% ethanol seed extract once daily for 10 days inhibited the aspirin, cold restrain (2 h), and ethanol-induced ulcer index, gastric ulcers, acid-pepsin secretion, and cell shedding and increased mucin and mucosal glycoprotein expression.[167] The Jamun seed ethanol extract reduced peptic ulcers and the acid-pepsin output in diabetic rats. It also reduced indomethacin and ethanol-induced peptic ulcers in streptozotocin-induced diabetic rats.[168,169] The indomethacin-induced gastric ulcers in mice were suppressed by the aqueous leaf extract of Jamun, which also attenuated TNF-α, NF-κB, iNOS, COX1, and COX2 expression. The aqueous leaf extract of Jamun elevated GPx activity and reduced oxidized glutathione and NO levels in the gastric mucosa, whereas lipid peroxidation decreased in both the gastric mucosa and serum.[121]

Cardioprotective activity

Cardiac ailments rank number one in terms of human mortality, and Jamun has been found to protect against cardiac diseases in various preclinical studies. The oral administration of 500 mg/kg methanol extract of Jamun seeds daily for 30 days protected against isoproterenol-induced myocardial damage in rats.[170] In addition, the daily administration of ethanol extract of Jamun seed powder 1 h before doxorubicin treatment for 15 days protected Wistar rats against the cardiotoxic effect of doxorubicin. Moreover, the ethanol seed extract decreased the activity of creatinine phosphokinase, ALT, AST, and lactate dehydrogenase in the rat heart.[171] Furthermore, H9C2 cardio myoblast cells were protected against glucose-induced stress by the methanol, ethanol, and aqueous seed extracts of Jamun.[172,173]

The hydroalcoholic extract of Jamun fruit pulp protected rats against isoproterenol-induced cardiotoxicity by decreasing the serum levels of AST, creatine kinase-myocardial band (CK-MB), cardiac troponin I, TNF-α, IL6, and C-reactive protein as well as increasing the SOD and GSH levels. The extract also increased B-cell lymphoma 2 (Bcl2) and reduced Bcl2-associated X (Bax) in the rat heart tissue, along with decreased myonecrosis, contraction of myofibrils, vacuolization, and inflammation in myocytes.[174] In addition, the administration of 0.5 g of hydroalcoholic extract of Jamun leaves daily orally for 8 weeks to hypertensive rats decreased hypertension.[175] Meanwhile, the orogastric administration of 90% ethanol Jamun fruit extract reduced spontaneous hypertension in rats.[176] Jamun seed powder also reduced blood pressure in a randomized double-blind placebo control clinical trial when given orally before meals twice daily for 90 days.[177] The freeze-dried fruit extract of Jamun induced hypotension, bradycardia, and vasorelaxation in Wistar rats by activation of potassium channels.[178] Recently, methanol Jamun seed extract was found to reduce glucose-induced (25 mM) cardiomyopathy in cultured H9C2 cells by inhibiting gelatinase activity. The Jamun extract suppressed the expression of gelatinase B mRNA, TNF-α, IL6, and translocation of NF-κB.[179]

Renoprotective activity

The different extracts of Jamun have been found to reduce kidney toxicity induced by various agents. The ethanol extract of fruits and aqueous extract of seeds of Jamun reduced urea nitrogen, urinary protein, serum creatinine, serum total proteins, and lipid peroxidation in cisplatin-treated rats. These extracts also attenuated paracetamol-induced ALT, AST, ACP, ALP, urea, and creatinine levels. The administration of albino rats with ethanol extract of fruits and aqueous extract of seeds of Jamun restored the catalase and GPx activities as well as reduced histological damage in the kidneys.[180–182]

The ethanol stem bark of Jamun protected the kidneys against calcium oxalate stone-induced urolithiasis.[183] Sprague Dawley rats treated with betulinic acid, which is found in Jamun leaves, protected kidneys against anti-Fx1A antiserum-induced passive Heymann nephritis. Betulinic acid also decreased renal dysfunction, histopathological alterations, and immune complex deposition in the rat kidneys. The protection of the kidney by betulinic acid is mediated at the molecular level by the suppressed expression of NF-κB, iNOS, and TNF-α and upregulation of nuclear factor-erythroid factor 2-related factor 2 (Nrf2), heme oxygenase 1, and NAD[P]H quinone oxidoreductase 1 at the mRNA level.[184]

Antidiabetic activity

The number of diabetic patients has reached 537 million globally, and it is the world's ninth-leading disease causing death.[185] Diabetes results in numerous health complications, and India stands second to China in the occurrence of diabetes.[186] Ayurveda gives a detailed account to reduce high blood sugar levels in diabetes with Jamun seed powder, even though diabetes was not prevalent in ancient times in India. Western countries have conducted more than 130 clinical trials to control blood sugar levels in diabetes using Jamun, but the results have been inconclusive due to mixed respons-

es of patients against Jamun therapy. In these trials, many patients responded well to the treatment, but others did not.[20,24,100,186,187]

Preclinical studies

There are a couple of reports in which Jamun was found to be ineffective in treating diabetes in preclinical animal models. Alloxan-induced diabetic rats fed with Jamun seed extract did not show a reduction in blood sugar levels.[188] Similarly, lyophilized Jamun fruit pulp extract administered to streptozotocin-induced diabetes rats did not show any decline in their raised blood sugar levels in a Brazilian study.[189] However, studies reporting that Jamun reduces blood sugar levels in preclinical and clinical conditions outnumber the studies that found Jamun to be ineffective in controlling diabetes.[24,100,186] The rabbits administered with aqueous Jamun seed extract did exhibit a lowering of the blood glucose level.[190,191] In addition, the blood glucose levels declined significantly in the spontaneous diabetic rats fed with Jamun ethanol stem bark extract.[192,193] Moreover, Jamun seed powder decreased the blood glucose levels after 3 h in rabbits orally fed with 1, 2, 4, and 6 g/kg body weight aqueous suspension, and the oral administration of Jamun seed powder at 4 g/kg was found to be the most effective dose. A 42.64% alleviation in the blood glucose level was reported in rats orally given an aqueous Jamun seed powder suspension at 4 g/kg.[194] The alloxan-induced diabetic rats fed with 2.5 and 5 g/kg body weight Jamun seed aqueous extract daily for 6 weeks showed a decline in the blood glucose level.[195] Similarly, the blood glucose levels were reduced in the diabetic rats fed with Jamun fruit pulp within 30 min, whereas the hypoglycemic effect of the seed extract was evident by 24 h.[196]

The ethanol and aqueous extracts of Jamun seeds depleted blood glucose and increased insulin levels in the rats fed with a high-fructose diet.[197] A decline in the serum blood glucose levels was detected in streptozotocin-induced diabetic mice administered with aqueous Jamun seed extract.[198] Feeding of 15% unextracted, 15% defatted Jamun seed extract, and 6% water-soluble gummy fiber diets to alloxan-induced diabetic rats for 21 days effectively reduced the blood glucose level and increased the glucose tolerance.[199] The streptozotocin-induced Wistar rats fed with 250, 500, and 1,000 mg/kg of Jamun seed powder for 15 days decreased the fasting blood glucose level, especially at 500 and 1,000 mg/kg.[200] Attrition in the fasting blood glucose level has been reported in alloxan-induced mild and severe diabetic rabbits given 100 mg/kg ethanol extract of Jamun seeds/kernel daily for 15 days.[201] Streptozotocin-induced diabetic rats administered with 100 mg/kg Jamun seed kernel ethanol extract for 30 days exhibited a significant reduction in the blood glucose, urea, AST, ALT, and cholesterol levels. It also brought the SOD, catalase, GPx, and GSH levels to normal and decreased lipid peroxidation in the kidney and liver of streptozotocin-induced diabetic rats.[202–204] Sprague Dawley rats given 100 and 200 mg/kg of ethanol Jamun seed extract once daily for 8 weeks reduced blood sugar level and glycated hemoglobin at 4 and 8 weeks significantly.[205] The administration of 200 or 400 mg/kg ethyl acetate and methanol extracts of Jamun seeds or 50 mg/kg mycaminose (an isolated compound from seeds) for 15 days lowered the blood glucose levels in the streptozotocin-induced diabetic rats.[206]

A decline in serum blood sugar has been reported in streptozotocin-induced type-2 diabetic Long Evans rats orally given 1.25 g/kg Jamun seed powder and ethanol extract for 21 days.[207] A decline in the serum glucose levels also was found in the alloxan-induced mild and severe diabetes rats fed for 21 days with 10 mg/kg body weight active principles isolated from the ethanol fraction of seed extract of Jamun.[208,209] The oral administration of 100, 200, and 400 mg/kg aqueous seed extract of Jamun for 21 days lowered the blood glucose level to near normal in streptozotocin-induced type-II diabetic rats and raised peroxisome proliferator-activated receptor (PPAR) alpha and gamma gene expression in the streptozotocin-induced type-II diabetic rat liver.[210] The oral administration of 50, 100, and 200 mg/kg body weight of aqueous and ethanol extracts of Jamun fruit pulp or 25 mg of partially purified water extract to alloxan-induced diabetic rabbits lowered the blood glucose levels, and the aqueous extract was more effective than the ethanol extract.[211] The aqueous extract of the Jamun fruit pulp administered at a dose of 200 mg/kg daily for 15 days depleted the glucose level in the serum of streptozotocin-induced diabetes female Wistar rats, and its combination with the stem bark extract of *Cinnamon zeylanicum* in the ratio of 1:1 was more effective than either treatment alone.[212]

Feeding 50 or 100 mg/kg aqueous and methanol extracts of Jamun leaves, stem bark, root, and seeds for 21 days to alloxan-induced diabetic male Sprague Dawley rats decreased the serum glucose level. The maximum decline in serum glucose was detected for the leaf extract, which also restored the normal architecture of the islets of Langerhans.[213] Intraperitoneal administration of 150 and 250 mg/kg body weight of aqueous Jamun seed extract in alloxan-induced diabetic mice for 21 days significantly depleted the serum glucose levels.[214] The methanol extract of Jamun fruit pulp, seed, and kernel from different locations of Gujarat at a concentration of 0.1–300 µg inhibited porcine pancreatic α-amylase activity *in vitro*, and maximum inhibition of α-amylase activity was recorded for the kernel extract *in vitro*.[215] Sprague Dawley rats fed with a diet containing 3% aqueous ethanol extract (50%) of Jamun fruits and seeds for 60 days showed a decrease in the serum glucose levels and an increase in the insulin levels.[216] The alloxan-induced Wistar albino diabetic rats fed with different doses of methanol extract of Jamun seeds for 14 days reduced the serum glucose level significantly on days 9, 11, and 14.[217]

The streptozotocin-induced diabetic Wistar albino rats fed with 100, 200, and 400 mg/kg/day aqueous Jamun seed extract once daily for 21 consecutive days showed a decline in the serum insulin, glucose, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and TNF-α levels ensued by a rise in PPARγ and PPARα expression in the liver. The aqueous seed extract also elevated catalase, SOD, and GPx activities and reduced streptozotocin-induced pancreatic β-cell damage and lipid peroxidation in the rat pancreas.[218] Feeding of 100 mg/kg body weight Jamun fruit extract rich in triterpenoids once daily for ten days to streptozotocin-induced diabetic C57BL/6 mice resulted in a decline in the fasting serum glucose as well as damage to the pancreas and increased insulin levels and HOMA-β index. The triterpenoid-enriched Jamun fruit extract-treated diabetic mouse liver showed increased phosphorylation of serine/threonine kinase (AKT) and p-AKT/AKT and decreased Forkhead box protein 1, PPARγ coactivator 1-alpha, glucose-6-phosphatase, and phosphoenolpyruvate carboxykinase.[219] Streptozotocin-induced diabetic rats administered with 200 and 400 mg/kg of aqueous Jamun root extract or its isolated compound 4-(2-amino-2-(2-(2-hydroxy-3 methyl butyl) octahydropyrrolo[1,2-a] pyrazin-7-yl) ethyl)-2-ethylphenol daily for 15 days exhibited a decline in the serum glucose level.[32] The examination of *in-vitro* α-amylase and α-glucosidase activities against the *n*-hexane, ethyl acetate, and ethanol extracts of Jamun pulp and seed, respectively, showed IC_{50} values of 75.85 mg/mL and 74.72 mg/mL (for α-amylase activity) and 55.79 mg/mL and 59.85 mg/mL (for α-glucosidase activity), indicating the antidia-

betic action of Jamun.[220] Feeding of streptoazotocin-induced diabetic rats with 5 and 10% Jamun fruit in diet for 2 months reduced fasting blood glucose levels at 15, 30, 45 and 60 days.[221] The aqueous extract of Jamun fruit exerted antidiabetic action by inhibiting α-amylase and α-glucosidase. The extract also inhibited lipase and increased SOD activity.[222]

Clinical studies

The serum ADA activity and glucose levels declined in diabetic patients treated with aqueous Jamun leaf extract.[223] In another study, attrition in ADA, 5′-nucleotidase, glucose, triglycerides, and lipid peroxidation levels followed by a rise in the catalase activity was observed in diabetic patients given 80% ethanol leaf extract.[224] In addition, human diabetic patients fed with Jamun seed powder for 30 days had reduced fasting and postprandial blood glucose levels in their serum.[225] A decline in serum glucose was found in 99 diabetic patients given 5 g of seed powder before meals for 90 days twice daily in a randomized double-blind placebo-controlled clinical trial.[226] Similarly, 2 g of roasted Jamun seed powder given for 60 days to type-II diabetic patients caused a decline in their serum glucose level.[227] A similar effect was observed in another double-blind clinical study carried out between March 2018 and March 2019.[177] The feeding of 6 g of Jamun seeds to prediabetic individuals of both sexes reduced fasting blood glucose levels.[228] The preclinical and clinical studies described above indicate that Jamun is an effective treatment to control diabetes.

Antihyperlipidemic activity

Diabetes is usually linked with hyperlipidemia and is the major cause of cardiovascular morbidity, and different parts of Jamun are useful in bringing down the serum cholesterol levels. The ethanol extract of Jamun seed has been reported to decrease the total serum cholesterol/high-density lipoprotein cholesterol (HDL-c) ratio, serum low-density lipoprotein cholesterol (LDL-c), and 3-hydroxy-3 methyl glutaryl CoA (HMG-CoA) reductase activity in alloxan-induced diabetic rabbits.[201] The streptozotocin-induced diabetic rats administered with Jamun seed kernel ethanol extract exhibited a decline in the LDL-c and very-low-density lipoprotein cholesterol followed by an increase in HDL-c levels.[208] A decrease in serum triglycerides and total cholesterol as well as increased HDL-c levels has been detected in streptozotocin-induced diabetic rats intraperitoneally administered with 200 mg/kg aqueous Jamun fruit pulp extract.[212]

Attrition in the triglycerides and total cholesterol as well as a rise in the HDL-c levels was observed in alloxan-induced diabetic rabbits given 10 mg/kg of active compounds separated from the ethanol seed extract fraction of Jamun for 21 days.[209] Alloxan-induced diabetic Swiss albino mice administered with 150 and 200 mg/kg body weight of Jamun seed aqueous extract reduced hyperlipidemia by restoring triglycerides and total cholesterol to normal and increased the HDL-c level.[214] A depletion in triglycerides and LDL-c followed by an increase in HDL-c was observed in rats fed with a high-cholesterol diet for 30 days and administered with 3% ethanol extract of seeds and fruits of Jamun for 60 days continuously.[229] The streptozotocin-induced diabetic C57BL/6 mice treated with 100 mg/kg body weight of Jamun fruit extract enriched with triterpenoid once daily for 10 days resulted in a decline in the triglyceride and free fatty acid levels in the serum and liver of diabetic mice accompanied by a decline in the mRNA levels of acetyl-CoA carboxylase 1 (ACC1), cluster of differentiation 36 (CD36), stearoyl-CoA desaturase-1 (Scd1), and fatty acid synthase as well as ACC1 expression at the protein level. Jamun fruit extract raised p-ACC1 protein expression and normalized extracellular signal-regulated kinase (Erk1/2) and p-Erk1/2 expression in diabetic mice.[219]

The diabetic patients given 2 g of Jamun seed powder daily for 60 days showed a significant depletion in serum cholesterol, very-low-density lipoprotein, LDL, cholesterol, and triglycerides.[227] Hyperglycemic patients treated with 4.5 g of encapsulated Jamun seed powder once daily for 84 days showed a significant decline in the cholesterol and LDL-c levels.[230]

Anti-obesity activity

Obesity (body mass index > 30 kg/m^2) is one of the major problems in the world today, and there has been a 39% increase in the obese population throughout the world between 1975 and 2020; approximately 764 million individuals were obese in 2020, and the number is constantly on the rise and will reach to more than 1 billion by 2030 (https://www.worldobesity.org/about/about-obesity/prevalence-of-obesity). The various parts of Jamun have been found to reduce obesity in several preclinical studies. The high-carbohydrate and high-fat diet-fed obese Wistar rats given 2.5% Jamun seed powder for 56 days showed a significant decrease in body weight gain, accumulation of white adipose tissue, blood glucose, serum insulin, total cholesterol, LDL-c, triglycerides, and lipid peroxidation in the plasma. It normalized the AST, ALT, and ALP levels in obese rats. In addition, the feeding of Jamun seed powder restored the levels of HDL-c, GSH, SOD, and catalase in the plasma of obese rats, followed by a decline in the advanced protein oxidation products, myeloperoxidase, NO generation, lipid peroxidation, and elevated catalase, GSH, and SOD levels in the obese rat liver.[231]

The C57BL/6 obese mice fed with both ethanol and acetone Jamun fruit extracts returned the ratio of *Firmicutes* to *Bacteroidetes* in the gut to normal as well as inhibited body weight gain and white adipose tissue accumulation in epididymal, visceral, and subcutaneous tissues. The extracts also decreased the serum glucose and insulin levels in obese mice. The oral feeding of both ethanol and acetone Jamun fruit extracts led to normalization of the expression of p-AKT and phosphoinositide 3-kinase (p85) protein and a reduction in the phosphorylation of insulin receptor substrate 1 (p-IRS1) at Ser318, mRNA expression of ACC1, sterol regulatory element-binding protein 1c, FAS, PPARγ, and CD36 in the liver of obese mice. A decline in cholesterol, triglycerides, and free fatty acid levels was found in the liver and plasma of obese mice fed with ethanol and acetone Jamun fruit extracts; however, the plasma cholesterol level remained unaltered.[232]

Oral feeding of 0.5 or 1.0 g/kg/day of hydroalcoholic Jamun leaf extract daily for 8 weeks decreased the weight gain and white adipose tissue storage in the retroperitoneal and periepididymal regions of monosodium L-glutamate-induced obesity in newborn Wistar rats. Attrition in the serum glucose and free fatty acid levels and restoration of the total cholesterol and triglyceride levels to normal was evident in obese rats fed with the Jamun leaf extract. A regression in nonalcoholic fatty liver disease and a decline in AST activity were detected in the obese rats treated with hydroalcoholic Jamun leaf extract. The livers of obese rats fed with hydroalcoholic extract suppressed endoplasmic reticulum stress by arresting the G protein-coupled receptor 98 (GPR98) expression, translation of the endoplasmic reticulum protein retention receptor (KDEL) chaperone, and GPR78 expression marginally. The Jamun leaf hydroalcoholic extract also attenuated spliced microsomal triglyc-

eride transfer protein (MTP), X-box-binding protein (XBP) 1s, unspliced XBP1u, and protein disulfide isomerase (PDI) expression in the hepatocytes of the obese rats.[233]

Antipyretic activity

The antipyretic potential of Jamun also has been explored, with the chloroform fraction from the methanol seed extract and the ethanol extract of Jamun leaves reducing brewer's yeast-induced pyrexia in rats and bringing the body temperature to normal.[140,234,235]

Antidiarrheal activity

Diarrhea is a common occurrence, and everyone suffers from this disorder at some time in their life. Whatever the cause, diarrhea leads to discomfort to the individual suffering from it. Jamun has been used to control diarrhea for a long time. The oral administration of 125, 250, and 500 mg/kg body weight Jamun aqueous seed extract, given 30 min before castor oil treatment, reduced castor oil-induced diarrhea in mice.[236] In addition, the stem bark of Jamun extracted in ethanol controlled the castor oil-induced diarrhea in mice and rats.[237,238] Inhibition of castor oil-induced diarrhea has been observed in mice treated with the ethanol, chloroform, and petroleum ether fractions from the crude methanol extracts of Jamun leaves.[239,240]

Anti-Leishmania activity

Leishmaniasis is a tropical disease, and Kala-azar is the most serious form caused by the protozoan *Leishmania*, which is transmitted in humans by an infected female phlebotomine sandfly bite. Exposure of promastigotes of *Leishmania amazonensis* to the essential oil of Jamun for 24, 48, and 72 h led to their killing, and the 24-h exposure time was most effective, with an IC_{50} of 36 mg/L.[241] The essential oil and its constituent α-pinene from the Jamun leaves were effective against *L. amazonensis* promastigotes, with an IC_{50} of 19.7 µg/mL. α-Pinene was more effective against axenic and intracellular amastigotes, with IC_{50} values of 16.1 µg/mL and 15.6 µg/mL, respectively, whereas the essential oil had IC_{50} values of 43.9 µg/mL and 38.1 µg/mL against axenic and intracellular amastigotes, respectively. Increased phagocytic, lysosomal activity, and NO levels are responsible for this effect.[242]

Antispasmodic activity

Treatment of rat uterine smooth muscles with 936.55 µg/mL Jamun seed ethanol extract reduced potassium chloride-induced muscle contraction *in vitro*.[243] The exposure of rat uterus and jejunum to 27, 81, 243 and 729 µg/mL hydroalcoholic extract of Jamun fruit alleviated oxytocin or carbachol-induced muscle contraction. Similarly, it also reduced muscle contraction induced by potassium chloride and carbachol.[46] In addition, isolated guinea pig trachea exposed to 2.5, 5, 7.5, and 10 mg/mL macerated aqueous Jamun leaf extract showed an attenuated potassium chloride-induced contraction and caused tracheal relaxation concentration dependently.[244] A dose-dependent inhibition has been reported in acetylcholine, histamine, serotonin, and calcium-induced contraction in isolated rabbit ileum samples exposed to aqueous and ethanol extracts of Jamun fruits, whereby 3 mg/mL and 5 mg/mL extracts were more effective than 1 mg/mL and 2 mg/mL.[245] Hydroalcoholic (70%) ethanol extract of Jamun leaves attenuated potassium chloride, acetylcholine, and calcium chloride-induced jejunum contraction, depending on the concentration, and this was due to a reduction in the Ca^{++} level.[239] Exposure of the uterus and jejunum of Wistar rats to 70% ethanol extract of Jamun seeds inhibited the oxytocin and carbachol-induced contraction dose dependently.[246]

Antiretinitis activity

The mutagenic alteration in the X-linked retinitis pigmentosa gene is linked to loss of vision in humans, and there is no treatment for this disease presently. The antiretinitis effect of five anthocyanin compounds like cyanidin 3,5 diglucoside, delphinidin 3,5-diglucoside, petunidin 3,7-diglucoside, peonidin 3,5-diglucoside, and malvidin 3,5-diglucoside from Jamun fruit peel was evaluated on the X-linked retinitis pigmentosa gene by molecular docking studies, and cyanidin 3,5 diglucoside was found to be the most effective inhibitor of retinitis pigmentosa in humans compared to the other anthocyanin compounds.[247]

Anti-Alzheimer's disease (AD) activity

The methanol extract of Jamun fruits has been reported to protect against scopolamine-induced amnesia by reducing the activity of acetylcholine esterase and lipid peroxidation accompanied by an elevation in the activities of catalase and SOD in the rat brain.[248] The administration of Jamun seed methanol extract daily for 12 weeks to amyloid β1-40 induced AD in Wistar rats significantly increased their memory and reduced amyloid plaque formation in the cortex and hippocampus of the rat brain. The Jamun extract also reduced lipid peroxidation in the cortex and hippocampus of the brain and plasma of AD rats. A decline in TNF-α and a rise in brain-derived neurotrophic factor, postsynaptic density protein 95, tropomyosin receptor kinase B, and synaptosomal-associated protein 25 have been reported in the cortex and hippocampus of AD rats treated with Jamun extract.[249] A significant reduction in acetylcholinesterase and butyrylcholinesterase activities, hydroperoxides, and lipid peroxidation accompanied by a rise in the SOD, catalase, and glutathione-S-transferase activities and the GSH concentration were observed in the brain of alloxan-induced diabetic rats treated with polyphenols extracted from Jamun leaves and 80% acetone leaf extract of Jamun.[250]

Effect on the central nervous system

The methanol seed extract of Jamun acts as a sedative in mice, whereby it changes the overall behavior pattern and reduces the exploratory behavior pattern, spontaneous motility, hypothermia, pentobarbitone-induced hypnosis, analgesia, spontaneous locomotor activity, electric shock-induced fighting, muscle relaxant action, aggressive behavior, and exploratory behavior patterns. The methanol seed extract inhibited pentylenetetrazol and strychnine-induced convulsions and lethality. Furthermore, the Jamun seed extract decreased amphetamine-induced toxicity in mice, depending on the dose.[251] The methanol and ethyl acetate extracts of Jamun seeds reduced diazepam and chlorpromazine-induced central nervous system activity in mice.[252] The oral administration of Jamun seed extract for 12 weeks improved the memory and learning behavior in senile rats by decreasing lipid peroxidation in the hippocampus and cerebral cortex.[253] Moreover, the aqueous extract of Jamun leaves reduced the ADA activity in the cerebral cortex of Wistar rats.[254] The aqueous and ethanolic stem bark extracts of Jamun also protected rat pheochromocytoma PC-12 cells against 6-hydroxydopamine-induced toxicity *in vitro*.[137]

Antinociceptive activity

Pain is an unpleasant perception caused by numerous stimuli and tissue damage, and everyone experiences pain due to some or the other reason. The different parts of Jamun possess antinociceptive action and relieve pain. The hydroalcoholic extract of Jamun leaves exerted antinociceptive activity in a dose-dependent manner, as indicated by hot plate and formalin tests in rats, and also suppressed the release of excitatory amino acids, including prostaglandin E2, kinins, glutamate, protons, and NO.[255] The methanol extract of Jamun seed extract attenuated acetic acid-induced writhing in mice dose dependently.[256] In addition, the methanol extract of Jamun roots exerted analgesic action in the rats in the tail immersion test.[257] The petroleum ether, ethanol and chloroform root bark extracts of Jamun also exhibited a dose-dependent antinociceptive activity in mice as indicated by alleviation of acetic acid-induced writhing and formalin-induced pain.[258] Moreover, the administration of 50 and 100 mg/kg body weight methanol extract of Jamun leaves exerted analgesic action in rabbits.[31] The petroleum ether and chloroform fractions of the methanol extract of Jamun leaf exerted an analgesic effect in mice in a dose-dependent manner.[240] Furthermore, the methanol extract of Jamun fruit pulp exerted antinociceptive activity in a dose-dependent manner in mice against the formalin and glutamate-induced paw licking test, and the maximum effect was observed at 200 mg/kg Jamun extract.[77]

Anti-arthritic activity

Arthritis is tenderness and swelling of joints causing pain that increases with age. Its incidence has been increasing globally. Arthritis is categorized as osteoarthritis and rheumatoid arthritis, which is an autoimmune disorder. Jamun has been reported to be active against rheumatoid arthritis in preclinical models. The methanol seed extract of Jamun helped to attenuate Freund's complete adjuvant-induced arthritis in rats administered with 250 mg/kg and 500 mg/kg of the extract.[259] The oral administration of 50, 500, 750, and 1,000 mg/kg of petroleum ether extract of Jamun stem bark also attenuated Freund's complete adjuvant-induced arthritis in rats. The extract reduced the expression of rheumatoid factor and the arthritic index as well as increased the body weight dose dependently.[260]

Diuretic activity

The oral administration of chloroform, methanol, and aqueous extracts of stem bark of Jamun increased the urine output in Wistar albino rats, with the methanol extract being the most effective among all three extracts, whereas the chloroform extract was the least active.[261] The oral administration of the methanol seed extract of Jamun elevated the urine volume and the excretion of chlorine, sodium, and potassium electrolytes at 24 h compared to 5 h in Wistar rats.[262]

Anthelmintic activity

The exposure of *Pheretima posthuma* to 50–100 mg/mL benzene, methanol, chloroform, and *n*-hexane extracts of Jamun leaves killed the worms in a dose- and time-dependent manner, and the benzene extract was the least effective. The anthelmintic activity of the methanol, chloroform, and *n*-hexane extracts was better than the standard albendazole.[263] The aqueous and methanol extracts of the stem bark of Jamun paralyzed *P. posthuma* within 36.58 min after exposure to these extracts, and 100 mg/mL methanol extract killed all worms within 70.58 min after treatment.[264,265] The exposure of *P. posthuma* to 50–100 mg/mL 95% ethanol seed extract of Jamun paralyzed and killed worms dose and time dependently, and initiation of the effect was early for 100 mg/mL.[266] The oral feeding of Jamun leaf powder to sheep led to a 76.67% reduction in the eggs/g of the intestinal worm *Haemonchus contortus*, indicating its anthelmintic activity *in vivo*.[267] The treatment of *Lumbricus terestris* (earthworms), *Monnizia expansa*, (tapeworms), and *H. contortus* (red worms) with 6.25, 12.5, 25, 50, and 100 mg/mL methanol extract of Jamun leaves paralyzed and killed all the worms in a concentration and time-dependent manner. The higher the concentration, the less time was needed to paralyze and kill the worms with the methanol leaf extract.[268]

Immunomodulatory activity

The oral administration of the methanol seed extract of Jamun demonstrated immunomodulatory activity in mice and rats orally administered at doses of 100, 200, 300, 400, and 500 mg/kg. The methanol seed extract enhanced the carbon clearance and hemagglutination titer in mice and the delayed-type hypersensitivity reaction in rats in a dose-dependent manner. The seed extract elevated the white blood cell and lymphocyte counts significantly.[269]

Wound healing activity

Wounds are a common occurrence, and most individuals suffer from this type of injury during their life. Jamun has been found to heal wound injuries. The oral administration and topical application of the ethanol seed extract of Jamun healed punch wounds in streptozotocin-induced diabetic Sprague Dawley rats.[270] The topical application of Jamun honey on excision wounds healed wounds of normal and streptozotocin-induced diabetic rats by increasing re-epithelialization and collagen deposition as well as the expression of collagen I, III, hypoxia-inducible factor 1α, vascular endothelial growth factor (VEGF), and VEGF receptor II. Jamun honey also healed scratch wounds created on cultured primary fibroblasts of both normal and diabetic rats as well as increased the expression of collagen type I and II and alpha-smooth muscle actin.[271]

Metal toxicity protective activity

Metals like mercury and arsenic are present in the environment, and they cause health hazards in humans. The leaf and seed extracts of Jamun have been applied to reduce metal toxicity. The aqueous Jamun seed extract protected two-day-old neonate rats against mercury toxicity by lowering the methyl mercury-induced *N*-acetyl-β-D-glucosaminidase activity in the kidney and urine, lipid peroxidation levels in the liver, and ADA activity in the hippocampus, kidney, and liver.[272] The treatment of mice with the ethanol extract of Jamun leaves for 12 weeks protected mice against the arsenic-induced decline in the body weight and the organ-to-body weight ratio of the spleen, kidney, and liver. It also reduced the arsenic-induced rise in the ALT, ALP, lactate dehydrogenase, uric acid, and glucose levels in the mouse serum.[273] The oral administration of methanol, ethanol, and aqueous seed extracts of Jamun seeds for 60 days protected Wistar rats against arsenic-induced DNA damage and increased the serum AST, ALT, and ALP levels.[163] Treatment of rats with 70 ethanol extract of Jamun bark

reduced the arsenic induced rise in the glucose, albumin, blood urea, nitrogen, creatinine and total protein in plasma and AST and ALT in the serum.[274]

Hair growth stimulation

The topical application of Jamun fruit pulp and seed ethanol extract ointment induced hair growth in Swiss albino mice earlier than the control. The length and number of hairs were increased, and the time of appearance of hairs was also advanced in mice significantly. The Jamun fruit pulp extract was superior to the seed extract in accelerating hair growth in mice.[275]

Antimutagenic and antigenotoxic activities

Aqueous and ethanolic extracts of Jamun seeds protected pBR322 DNA against hydroxyl radical-induced strand breaks. Swiss albino mice administered with 1 or 1.5 g/kg of Jamun seed extract significantly protected mouse bone marrow cells against urethane and 7,12-dimethylbenz(*a*)anthracene (DMBA)-induced micronuclei formation and chromosomal aberrations. The seed extract also elevated the GSH concentration and the catalase, SOD, and glutathione-S-transferase activities as well as reduced lipid peroxidation.[276] The ethyl acetate Jamun seed extract (100 µg/mL) attenuated the sodium azide and methyl methanesulfonate-induced increase in the revertant's frequency in *S. typhimurium* tester strains. The extract also reduced methyl methanesulfonate-mediated DNA fragmentation and oxidation in lymphocytes as well as oxidative damage in pBR322 plasmid DNA.[85] The 70% ethanol seed extract of Jamun also showed an antimutagenic effect against *S. typhimurium* (TA 98 and TA 100) strains.[114]

Radioprotective activity

Cosmic radiation, air and space travel, background radiation, radiodiagnosis, and/or radiotherapy procedures are the main sources of human radiation exposure in their daily life. Ionizing radiation inflicts various types of deleterious effects and is known to cause liver, cardiovascular, kidney, pulmonary, and reproductive disorders in addition to cancers of all organs. The deleterious effects of ionizing radiation can be reduced by pharmacological intervention. The Jamun leaf extracted in 1:1 dichloromethane/methanol protected against micronuclei formation in a concentration-dependent manner in human lymphocytes exposed to 3 Gy of γ-radiation.[277] The administration of 5, 10, 20, 30, 40, 50, 60, and 80 mg/kg body weight of dichloromethane/methanol leaf extract protected mice against whole-body γ-irradiation-induced radiation sickness and mortality, with optimum protection at a dose of 30 mg/kg.[106] In addition, the hydroalcoholic Jamun seed extract protected mice against radiation-induced sickness and mortality, with optimum protection at a dose of 80 mg/kg body weight and a dose reduction factor of 1.24.[107]

The effect of 5, 10, 20, 30, 40, 50, 60, and 80 mg/kg body weight of dichloromethane/ methanol leaf extract alleviated radiation-induced damage in the intestine of mice exposed to different doses of γ-radiation, as indicated by the increased villus height, higher number of regenerating crypts, and reduction in the number of goblet cells and dead cells.[278] The mice administered intraperitoneally with 50 mg/kg body weight dichloromethane/methanol leaf extract had reduced micronuclei formation in an irradiation dose-dependent manner in the cytokinesis-blocked cultured splenocytes extracted from irradiated mice exposed to 0, 0.5, 1, 2, 3, and 4 Gy whole-body γ-radiation.[118] Ionizing radiation reduced the anti-oxidant status, and the intraperitoneal administration of 50 mg/kg body weight of dichloromethane/methanol Jamun leaf extract before exposure to 0, 0.5, 1, 2, 3, and 4 Gy whole-body γ-radiation elevated the GSH concentration and catalase and SOD activities as well as decreased radiation-induced lipid peroxidation in the mouse liver.[279]

Anticancer activity

Cancer is a noncommunicable disease, and it is the second-largest disease of the human population leading to death after cardiovascular diseases. Cancer is treated by surgery, radiotherapy, chemotherapy, or their various combinations. Chemotherapy is the only remedy to treat cancer in advanced stages; hence, it has emerged as one of the most important modalities for cancer treatment. Most chemotherapeutic drugs are of natural origin or their semisynthetic derivatives.[12,280] Different parts of Jamun have been investigated for their cytotoxic action in different cell lines *in vitro*. The methanol crude extract of Jamun fruit skin was cytotoxic to HeLa (human papillomavirus-18 positive) and SiHa (human papillomavirus-16 positive) cells by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and it was more cytotoxic to the former than the latter. The cytotoxicity of the extract was due to the induction of greater apoptosis in HeLa cells than in the SiHa cells.[281] Moreover, freeze-dried Jamun fruit pulp extract reduced the cell proliferation and growth of MCF-7 and MDA-MB-231 breast cancer cells in a concentration- and time-dependent manner, and the extract was less effective against nontumorigenic MCF-10A cells. The Jamun fruit pulp extract stimulated apoptotic cell death in both MCF-7 cells and MDA-MB-231 breast cancer cells, whereas it did not induce apoptosis in untransformed MCF-10A breast cancer cells.[282] Treatment of acute myeloid leukemia cells (immature monocytes) collected from the patients with 25, 50, and 100 µL of hexane, chloroform, ether, ethyl acetate, ethanol, and water extracts of Jamun fruits killed leukemia cells in a concentration-dependent manner, whereby the ethyl acetate and ethanol extracts were more cytotoxic than the other extracts.[283]

Treatment of MCF-7 cells with 62.5, 125, 250, 500, and 1,000 µg/mL methanol fruit pulp extract of Jamun triggered cytotoxicity, depending on the concentration, and 1,000 µg/mL pulp extract was the most cytotoxic, with an IC_{50} of 266.8 µg/mL.[284] The Jamun fruit acidified (0.1% HCl) methanol extract also has been reported to induce cytotoxicity in a concentration-dependent manner in HCT-116 colon cancer cells by the MTT assay and reduced colony formation in colon cancer stem cells, depending on the concentration. The Jamun fruit extract also induced apoptosis in HCT-116 and colon cancer stem cells by triggering DNA fragmentation and elevating the caspase 3 and caspase 7 activities.[285] The methanol extract of Jamun fruits triggered cytotoxicity by decreasing cell proliferation in H460 lung cancer cells, depending on the concentration, with an IC_{50} of 35.2 µg/mL.[286] Treatment of A459 lung cancer cells with 50, 100, 150, 200, and 250 µg/mL Jamun pulp and seed extracted in 75% ethanol also inhibited cell proliferation in a concentration-dependent manner as determined by an MTT assay.[71]

Exposure of CHO cells to 10–1,000 µg/mL aqueous ethanol Jamun fruit extract induced cytotoxicity, depending on the concentration, by an MTT assay, with an IC_{50} of 400 µg/mL.[132] Treatment of HT29 cells with 1, 5, 10, 50, 100, 250, 500, and 1,000 µg/mL freeze-dried fruit peel extract of Jamun increased the cytotoxicity in a concentration-dependent manner and decreased the

G_2+M phase cells, especially at a concentration of 1,000 µg/mL.[287] Non-small cell lung cancer cells (CP-H460) and human embryonic kidney cells (HEK-293) were treated with 0.01, 0.1, 1, and 2 µg/mL aqueous fruit extract, which increased the cytotoxic effect in a concentration-dependent manner, and 2 µg/mL was cytotoxic to 89% CP-H460 cells, which were more sensitive than HEK-293 cells.[288] Treatment of HT-29 cells with 62.5, 152, 250, 500, and 1,000 µg/mL 80% methanol fruit extract increased the cytotoxic effect, depending on the concentration, with an IC_{50} of 267.5 µg/mL, and also induced DNA damage. The fruit extract also inhibited cell migration as indicated by delayed healing of scratch wounds created on HT-29 cell cultures. The methanol fruit extract of Jamun suppressed the expression of anti-apoptotic Bcl2 mRNA and stimulated the expression of Bax mRNA in HT-29 cells.[289]

The ethyl acetate and methanol extracts of Jamun seeds reduced cell survival and increased the cytotoxicity in MCF-7 cells in a concentration-dependent manner, and the ethyl acetate extract was slightly better than the methanol extract. Almost similar results have been reported for DNA fragmentation, an indicator of apoptosis.[290] Oral squamous cancer cells from the tongue (SCC-25) exposed to 1, 3, 10, 30, 100, and 300 µg/mL methanol seed extract of Jamun showed a concentration-dependent increase in the cytotoxicity, with an IC_{50} of <50 µg/mL. The seed extract induced reactive oxygen species in SCC-25 cells that were detected by a dichlorodihydrofluorescein diacetate assay. The Jamun seed extract induced apoptosis as determined microscopically and by flow cytometry with a fluorescein isothiocyanate-conjugated annexin V binding assay. The seed extract increased the expression of cadherin 1 in SCC25 cells concentration dependently.[291] Additionally, the ethanol Jamun seed extract was cytotoxic in a brine shrimp assay, with an IC_{50} of 61.50 ± 7.17 µg/mL.[292] The ethanol extract of Jamun seeds at concentrations of 10, 100, and 1,000 µg/mL exerted a cytotoxic effect on MCF-7, A2780 (ovarian adenocarcinoma), PC-3 (prostate carcinoma), and H460 (non-small cell lung carcinoma) cells, depending on the concentration. The A2780 cells were most sensitive, with an IC_{50} of 49 µg/mL; whereas H460 cells were the least sensitive, with an IC_{50} of 165 µg/mL. The MCF-7 and PC-3 cells showed an intermediate sensitivity, with IC_{50} values of 110 µg/mL and 140 µg/mL, respectively.[293]

Exposure of Hep2 (human laryngeal epithelioma) cells to 8, 15.6, 31.25, 62.5, 125, 250, 500, and 1,000 µg/mL acetone, methanol, and ethanol seed extracts of Jamun resulted in a concentration-dependent rise in the cytotoxicity as studied by an MTT assay, and 50% of cell killing was detected at 125 µg/mL.[294] Treatment of MCF-7, T-47D (breast), SF-295 (central nervous system), HCT-116 (colon), A-549 (lung), MDA-MB-435 (melanoma), OVCAR-5 (ovary), PC-3 (prostate), and A-498 (renal) cells with 100 µg/mL methanol seed extract of Jamun showed the following growth inhibition percentages: 93% (SF-295 cells), 75% (A-498 cells), 74% (HCT-116 cells), 72% (A-549 and PC-3 cells), 71% (MDA-MB-435 cells), 65% (OVCAR-5 cells), 61% (MCF-7 cells), and 60% (T-47D cells). Exposure of A459 cells to 1, 10, 30, and 50 µg/mL seed extract was cytotoxic in a concentration-dependent manner, with an IC_{50} of 10 µg/mL.[295] Treatment of MCF-7 cells with 5, 10, 20, 40, and 80 µg/mL aqueous extract of Jamun leaves also induced cytotoxicity in a concentration-dependent manner as well as increased the reactive oxygen species production.[296]

T47D breast cancer cells treated with 100 µg/mL hexane:50% ethyl acetate, ethyl acetate, and ethyl acetate:25% methanol extracts of Jamun leaves were cytotoxic, and the hexane:50% ethyl acetate extracts showed 68% cytotoxicity compared to the ethyl acetate extract. The ethyl acetate and ethyl acetate:25% methanol extracts had cytotoxicity percentages of 56% and 50%, respectively.[124] The HT-29 cells treated with 20, 40, 60, 80, and 100 µg/mL ethanol extract of Jamun leaves resulted in a concentration-dependent rise in the cytotoxicity, with an IC_{50} of 90.42 µg/mL.[297] A concentration-dependent decline in cell proliferation was observed in HepG2, Caco2, and PC3 cells treated with different concentrations of methanol extract of ripe fruit pulp and seeds as well as unripe fruit pulp and seeds of Jamun. The IC_{50} values for the ripe fruit pulp, ripe fruit seeds, unripe fruit pulp, and unripe fruit seeds were 27.78, 89.1, 77.33, and 75.2 µg/mL for HepG2 cells, respectively. The IC_{50} values for Caco2 cells were 90.48, 39.48, 40.21, and 30.93 µg/mL, respectively, for ripe fruit pulp, ripe fruit seeds, unripe fruit pulp, and unripe fruit seeds. Similarly, IC_{50} values of 50.21, 38.3, 53,71, and 43.21 µg/mL were recorded for ripe fruit pulp, ripe fruit seeds, unripe fruit pulp, and unripe fruit seeds in PC3 cells, indicating that the cells respond differentially to the different fruit extracts of Jamun.[130] The exposure of HepG2 cells to 8, 15.6, 31.25, 62.5, 125, 250, 500, and 1,000 µg/mL acetone, ethanol, and methanol extracts of Jamun seeds inhibited cell proliferation, depending on the concentration, and the methanol seed extract was most active, with 50% of cells being killed at 125 µg/mL.[298] Treatment of MCF-7, MDA MB-231, and HCT 116 cells with 0, 0.1, 1, 10, 100, and 1,000 µg/mL Jamun leaf, fruit, seed, and flower extracted in methanol resulted in a concentration-dependent inhibition of cell proliferation. IC_{50} values of 1.24 ± 0.09 mg/mL and 1.42 ± 0.34 mg/mL were recorded for the seed and leaf extracts, respectively, in HCT-116 cells; whereas MDA-MB-231cells showed IC_{50} values of 5.86 ± 0.63 mg/mL and 6.97 ± 0.68 mg/mL for leaf and flower extracts, respectively.[299] Treatment of HT29 cells with 7.8, 15.6, 31.2, 62.5, 125, 250, 500, and 1,000 µg/mL fresh and dehydrated fruits of Jamun extracted in acetone resulted in a concentration-dependent rise in the cytotoxicity by an MTT assay, with growth inhibition percentages of 51.42% for the fresh fruit extracts (31.2 µg/mL) and 50.10% for the dehydrated fruit extracts (15.6 µg/mL). Similarly, hybrid fresh and hybrid dehydrated fruit acetone extracts resulted in 50.98% and 48.13% killing of HT29 cells at 125 µg/mL and 62.5 µg/mL, respectively. The acetone extract of dehydrated Jamun fruit was more effective than the other extracts.[300]

The anticancer activity of the Jamun stem bark methanol extract was evaluated in Ehrlich ascites carcinoma tumorized Swiss albino mice intraperitoneally administered with the extract at 25, 50, and 75 mg/kg per day. The methanol extract inhibited the tumor growth dose dependently, and 75 mg/kg extract caused maximum growth inhibition and increased the mean survival time of mice by approximately 12 days when compared to no extract-treated tumor-bearing mice. The methanol Jamun bark extract caused DNA fragmentation, induced apoptosis, increased p53 and proapoptotic Bax expression, and subsequently downregulated Bcl2 and NF-κB expression in Ehrlich ascites carcinoma cells.[54]

Chemopreventive activity

The Jamun fruit pulp and seed extracts have been found to inhibit chemically induced skin and breast carcinogenesis in preclinical studies. The mice orally administered with the hydroalcoholic extract of Jamun seeds at 125 and 250 mg/kg body weight until the termination of the experiment was found to reduce the tumor incidence, the tumor burden, and the average number of tumors, followed by an increase in the latency period for tumor formation in the DMBA-treated two-stage skin carcinogenesis model. The administration of 250 mg/kg hydroalcoholic extract reduced lipid

peroxidation and elevated GSH, vitamin C, and activities of SOD and catalase in the liver and skin of the DMBA-treated mice.[301,302] The feeding of a 5% Jamun fruit pulp powder diet to female ACI rats before 2 weeks of breast tumor induction by 17-β-estradiol delayed the appearance of breast tumors by 21 days and also reduced the tumor incidence, tumor burden, and tumor multiplicity in female rats. Jamun extract significantly reduced the progesterone levels as well as the expression of cyclin D1, estrogen receptor alpha, and proliferating cell nuclear antigen. Jamun also downregulated the mRNA levels of cyclin D1, cyclin D3, Fox1, Bcl2, and cyclin-dependent kinase 4 (Cdk4) in mammary tumors.[303]

Other activities

In addition to the above-listed activities, Jamun has been shown to possess anticoagulant, anti-aging, antimalarial and antiasthmatic properties.[304–307]

Adverse effects

Despite several salubrious effects, Jamun is known to cause a few adverse effects in humans because of its ability to lower blood sugar levels. Jamun fruits should not be eaten within one week before and a minimum of two weeks after surgery to avoid complications. Eating Jamun should be avoided on an empty stomach and immediately after drinking milk. Additionally, Jamun should not be eaten by breastfeeding mothers or pregnant women to avoid complications. Eating too large of a quantity of Jamun fruit causes cough, body ache, sputum accumulation in the lungs, or even fever in humans. Other side effects of Jamun are delayed digestion, flatulence, emphysema, and inflamed larynx and lungs. Common salt and *Piper nigram* may be used as a corrective measure to minimize the side effects of Jamun.[20]

Discussion

It is clear from the above studies that different parts of Jamun, including the root, stem, leaf, flower, fruit, and seed, show potential in the treatment of infection, inflammation, and oxidative stress-related diseases like diabetes, arthritis, neurodegeneration, cardiovascular disease, intestinal disorders, fibrosis, aging, obesity, carcinogenesis, and cancer. Jamun also protects against helminthic, bacterial, viral, fungal, and Leishmania infections, immunity-related disorders, metal-induced toxicity, kidney diseases, malaria, mutagenesis, pain, wound injury, and radiation-induced damage.[113–303] The seeds of Jamun are clinically used to treat diabetes, allergies, inflammation, gastric ulcers, and viral infections.[8] The medicinal properties of Jamun are due to its ability to produce various secondary metabolites that can be developed as future medicines with no adverse effects or few side effects, unlike modern synthetic drugs that have numerous side effects leading to secondary ailments.[32–87] The root, stem, leaf, flowers, fruits, and seeds of Jamun have the potential as future medicines to treat numerous diseases, as indicated above, but more systematic research on each disease state is needed.

Mechanism of action

The mechanism of protection against various disorders by Jamun is not well understood. The generation of free radicals in the human body is linked to numerous diseases, including arthritis, diabetes, autoimmune disorders, neurodegenerative diseases, cardiovascular diseases, fibrosis, aging, and cancer. The action of Jamun depends on the conditions of the target tissues. The scavenging of free radicals by Jamun and its active phytochemicals, including myricetin, quercetin, cyanidin, imperatorin, ellagic acid, and kaempferol, seems to be one of the important mechanisms of action to exert conducive effects.[115–122,125,128] The beneficial effects of Jamun on various organs may be due to its ability to activate Nrf2, which stimulates heme oxygenase and NAD[P]H quinone oxidoreductase 1 as well as increase the GSH, GPx, catalase, SOD, and glutathione-S-transferase levels and reduce lipid peroxidation (Fig. 4).[154,161,171,184,235] At the molecular level, Jamun and its active biomolecules myricetin and quercetin activate PPARα and PPARγ, which play a crucial role in fatty acid and glucose metabolism and reduce inflammation by suppressing NF-κB, IL6, COX1, and COX2, and subsequent events seem to protect various tissues and augment wound healing by increasing collagen type I, III, alpha-smooth muscle actin, hypoxia-inducible factor 1α, VEGF, and VEGF receptor II (Fig. 5).[121,158,180,185,210,219,230,271] The inhibition of ICAM1, CXCL2, iNOS, NF-κB, COX1, COX2, TNF-α, and Bax by Jamun and a consequent rise in Bcl2 seems to play a crucial role in apoptosis evasion, leading to its protective effect on various tissues. The reduction in AST, ALT, ALP, ACP, GGT, and bilirubin may be an important mechanism to protect the intestine, heart, liver, kidneys, and other tissues.[111,121,156–159,153,181] Jamun downregulates the mRNA expression of ACC1, Scd1, CD36, and FAS at the protein level, accompanied by a rise in the expression of p-ACC1 protein and normalized expression of Erk1/2 and p-Erk1/2 to reduce hyperlipidemia and diabetes.[219,232] The anti-obesity effect of Jamun seems to be due to the normalization of pAKT and phosphoinositide 3-kinase (p85) protein expression as well as attrition in the phosphorylation of p-IRS1, the mRNA levels of sterol regulatory element-binding protein 1c, ACC1, FAS, PPARγ, CD36, and the expression of KDEL, GPR78, XBP1s, XBP1u, MTP, and PDI.[232,233]

The cytotoxic and chemopreventive actions of Jamun and its active components like myricetin, quercetin, cyanidin, and imperatorin are mediated by the arrest of cells in the G_2+M phase, downregulation of cyclin D1, cyclin D3, Cdk4, Fox1 (Fig. 6), NF-κB, Nrf2, COX1, COX2, TNF-α, iNOS, and Bcl2, and a rise in the DNA damage and activation of the Bax gene.[54,287,289,308–312] Recently, NF-κB has been found in mitochondria, and suppression of NF-κB and COX leads to the release of cytochrome c from mitochondria, leading to the activation of Bax and p53 and the inhibition of the release of Bcl2, stimulating the intrinsic pathway of apoptosis in cancer cells, as shown in Figure 7.[308–313] The attenuation of TNF-α by Jamun seems to trigger apoptosis by activating the extrinsic pathway of apoptosis, as indicated in Figure 7.

Conclusions

Various medicinal properties of Jamun are due to the presence of anthraquinones, alkaloids, flavonoids, glycosides, cardiac glycosides, catechins, quinones phytosterols, tannins, saponins, phenols, resins, terpenoids, steroids, volatile oils, carbohydrates, proteins, and amino acids. Jamun acts by scavenging free radicals, suppressing ICAM1, CXCL2, iNOS, NF-κB, COX1, COX2, TNF-α, Bcl2, cyclin D1, cyclin D3, Cdk4, and Fox1 expression, and arresting cells in the G_2+M phase of the cell cycle. The decline of AST, ALT, ALP, ACP, GGT, and bilirubin levels as well as elevation of Bcl2 expression by Jamun seem to protect various tissues in preclinical models. Furthermore, Jamun activates PPARα, PPARγ, p53, and

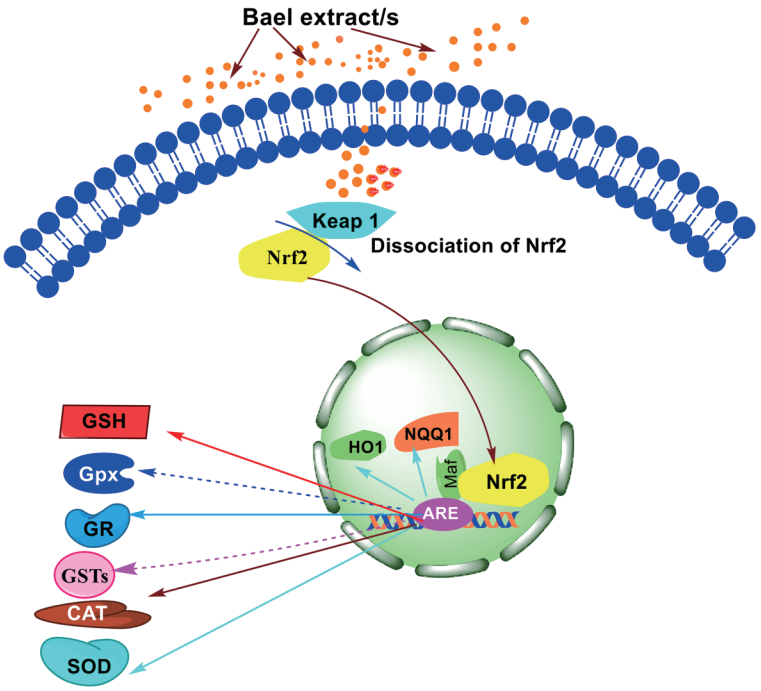

Fig. 4. The effects of Jamun on the antioxidant system. Activation of Nrf2 by different Jamun extracts and isolated active ingredients, such as quercetin, myricetin, ellagic acid, kaempferol, etc., activate the antioxidant system, including glutathione (GSH), glutathione peroxidase (Gpx), glutathione-s-transferase, glutathione reductase, and catalase as well as alleviate lipid peroxidation, thus protecting various organs as well as preventing diabetes and radiation-induced damage.

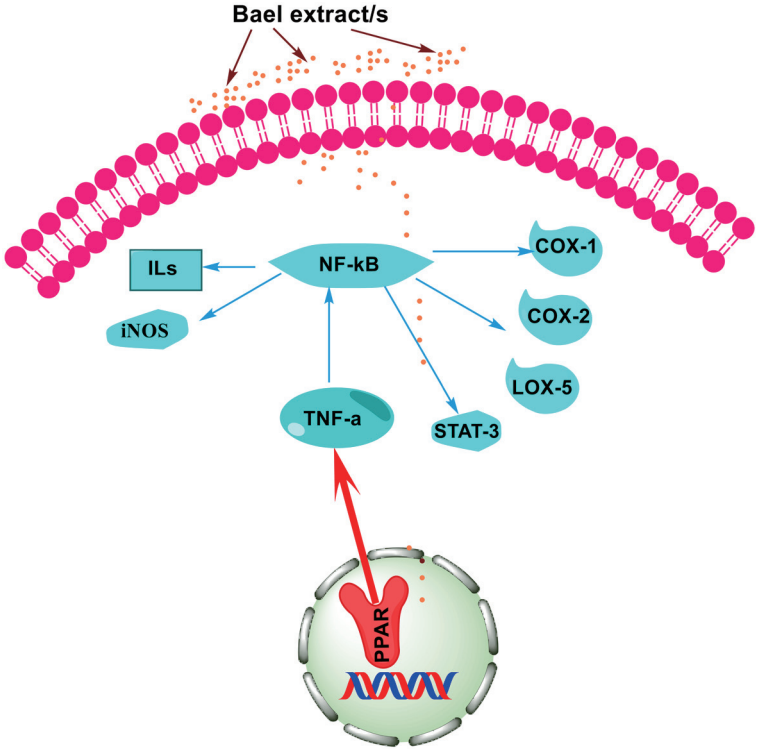

Fig. 5. The molecular pathways involved when cells are treated by Jamun extracts and its active phytochemicals myricetin, quercetin, and cyanidin. They activate peroxisome proliferator-activated receptor (PPAR), which inhibits the transactivation of nuclear factor kappa B (NF-κB), cyclooxygenase (COX) 1 and 2, interleukin (IL) 6, and inducible nitric oxide synthase (iNOS) to protect various organs as well as prevent inflammation and diabetes.

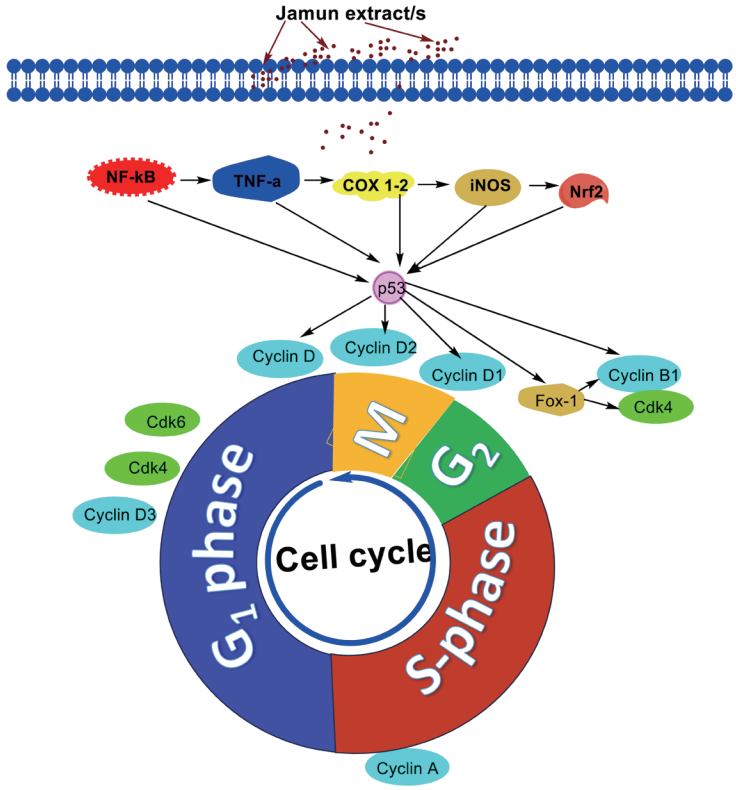

Fig. 6. The effects of Jamun on the cell cycle. Jamun and its active phytochemicals myricetin, quercetin, and cyanidin interfere with the cell cycle by suppressing cyclin D1, cyclin D3, and cyclin-dependent kinase 4 (Cdk4) and arresting cells in the G_2+M phase of the cell cycle. Inhibition of cyclin D3 and Cdk4 and elevation of p53 indicate that Jamun may also actively interfere with other cell cycle phases.

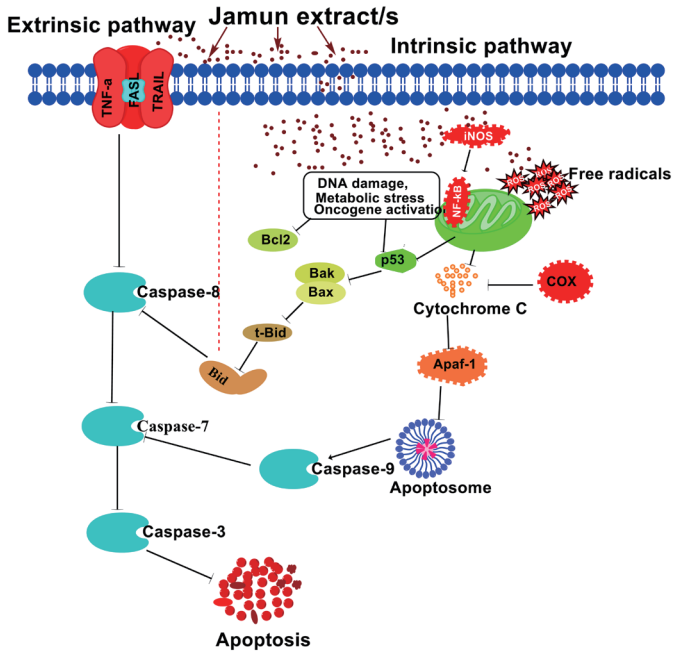

Fig. 7. The effects of Jamun on apoptosis. Jamun and its active phytochemicals myricetin, quercetin, and cyanidin increase reactive oxygen species formation and DNA damage as well as inhibit the transactivation of inducible nitric oxide synthase (iNOS), nuclear factor kappa B (NFκB), cyclooxygenase (COX) 1 and 2, Bcl2, and tumor necrosis factor (TNFα), leading to cytochrome c release from mitochondria and the activation of caspases and Bcl2-associated X (Bax), which subsequently triggers apoptosis to exert cytotoxic effects on neoplastic cells.

Bax and inhibits the expression of ACC1, stearoyl-CoA desaturase 1, CD36, FAS, p-IRS1, KDEL, GPR78, XBP1s, XBP1u, MTP, and PDI to exert its action on different tissues. All activities of Jamun are due to its ability to synthesize secondary metabolites, including myricetin, quercetin, cyanidin, imperatorin, ellagic acid, kaempferol, etc. Therefore, Jamun needs to be developed as the medicine of the future and tested clinically for the benefit of mankind.

The commercialization of Jamun becomes difficult as the phytochemicals in it may vary with the environment, soil composition of the region where it grows, and season of collection. This may compromise the medicinal activities of Jamun due to variations in the secondary metabolites synthesized by it. However, this problem can be solved by growing Jamun in tissue culture for medicinal purposes and incorporating quality control measures batchwise. Future studies need to be directed to unfurl the molecular mechanisms of action of the various medicinal activities of Jamun *in vitro* and *in vivo*.

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Conflict of interest

The author declares no conflict of interests.

Author contributions

GCJ is the sole author of the manuscript.

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