

Review article

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## Jamun Seed: A Review on Bioactive Constituents, Nutritional Value and Health Benefits

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Jamun fruit, a member of the Myrtaceae family, is commercially grown in tropical and subtropical areas of the world for its fruits with sweet, sour, and astringent luscious flesh. Seeds of jamun fruits are discarded as trash during the industrial processing of fruit pulp into beverages, jellies, jam, vinegar, wine, and squash. These seeds are a potential source of bioactive compounds including hydrolysable tannins, phenolic acids, flavonoids, other phenolics, terpenoids, phloroglucinol derivatives and saponins, which have been endorsed several biological activities, such as antidiabetic, anticancer, anti-inflammatory, antioxidant, antimicrobial, antihyperlipidemic and antihypercholesterolemic, as well as cardioprotective, hepatoprotective and neuroprotective properties. High contents of carbohydrates, dietary fiber, minerals, and ascorbic acid have also been found in jamun seeds. However, potential utilization of these seeds as innovative implements for health benefits has not yet been fully understood. We aim to compile scientific research and recent advances on jamun seed nutritional profile, bioactive compounds composition, bioactive properties, and their potential as an ingredient in functional food formulation.

# INTRODUCTION

Jamun (*Syzygium cumini* or *Syzygium jambolana* or *Eugenia jambolana* or *Eugenia cumini*) is a polyembryonic species of the Myrtaceae family grown for its fruit, timber, and ornamental values. Jamun blossoms in both tropical and subtropical regions and is mostly grown in deep loam and well-drained soils. Jamun, also known as Indian blackberry, Malabar plum, Portuguese plum, Java plum, black plum, or jambolan, is a native to the Indian subcontinent and spread across Southeast Asia, Latin America, and Africa [de Sousa Sabino *et al.*, 2018]. India is ranked second, accounting for around 15.4% of total global production, or 13.5 million tonnes [https://www.agrifarming.in/jamun-farming]. Jamun fruits are small, usually oval-shaped with a pink purple to

blue black colour when completely ripe, with a subtly sweet, astringent, and sour flavour, and a firm seed inside [Gajera *et al.*, 2018; de Sousa Sabino *et al.*, 2018; un Din *et al.*, 2020]. At fully ripen stage, jamun pulp contains sugars (glucose, fructose), free amino acids, minerals (Na, K, Ca, Mn, Mg), dietary fiber, ascorbic acid,  $\beta$ -carotene, organic acids [Gajera *et al.*, 2018; Seraglio *et al.*, 2018], phenolic compounds (anthocyanins, flavonols, ellagotannins and gallotannins) [Faria *et al.*, 2011; Lestario *et al.*, 2017], volatile compounds (*trans*-ocimene, *cis*-ocimene,  $\beta$ -myrcene, and  $\alpha$ -terpineol), and flavouring compounds (dihydrocarvyl acetate, geranyl butyrate, and terpinyl valerate) [Vijayanand *et al.*, 2001].

Because jamun fruits are highly perishable in nature, most of them are processed. Jam, jelly, vinegar, wine, squash, and non-fermented ready-to-drink beverages are some

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of the traditional jamun fruit products [de Sousa Sabino et al., 2018]. Moreover, the fruit pulp can be dried and used as a food colorant and as a nutritious and health-promoting additive for pasta, ice cream, etc. [Lestario et al., 2017; Panghal et al., 2019; Shelke et al., 2020; Singh et al., 2019]. However, since only the pulp is used in the processing of the jamun fruit, the rest generate the waste. Seeds are the main post--processing waste product. Their amount is large, because they constitute 10-47% of the total weight of the fruit [Benherlal & Arumughan, 2007; Gajera et al., 2018; un Din et al., 2020]. The generated waste causes problem for the industry and for the environment, but on the other hand, it has become a challenge for scientists. Jamun fruit waste has the potential to become a valuable by-product and open up avenues for the scientific and research community to assist industry and farmers in generating revenue. Jamun seeds have been utilized to treat diabetes and digestive problems in Ayurveda since ancient times. Currently, the health-promoting properties of jamun seeds are being confirmed and many bioactive compounds responsible for it, including phenolics, terpenoids, phloroglucinol derivatives and saponins, were identified [Liu et al., 2017a,b, 2018; Martin et al., 1998; Omar et al., 2012; Thiyagarajan et al., 2016]. Intensive research on biological potential is ongoing and the seed extracts, extract fractions and isolated compounds are being tested for antidiabetic, antioxidant, anti-inflammatory, anticancer, antimicrobial, cardioprotective, hepatoprotective, and neuroprotective properties. Moreover, the jamun seeds have been found to contain nutrients. They are rich in carbohydrates, dietary fiber, ascorbic acid, and some minerals [Benherlal & Arumughan, 2007; Ghosh et al., 2017; Kaur et al., 2011]. The nutritional and phytochemical profiles of jamun seeds revealed that they could be a novel source for pharmaceutical and food industries. This review mainly discusses the nutrients and phytochemicals of jamun seeds and recent research into their bioactive potential in the context of the possibility of using this jamun fruit processing by-product in the functional food formulation.

## **NUTRITIONAL PROFILE OF JAMUN SEEDS**

Proximate analysis indicated that moisture content of jamun fruit seeds ranged from 12.45 to 52.4 g/100 g and yielded crude protein, total lipids, total carbohydrates, and ash contents as 4.7–8.2 g/100 g, 0.35–1.28 g/100 g, 70.9–91.0 g/100 g, and 2.0–22.3 g/100 g on a dry matter (dm) basis, respectively [Benherlal & Arumughan, 2007; Ghosh *et al.*, 2017; Indrayan *et al.*, 2005].

# Carbohydrates

Carbohydrates are the main nutrient of the jamun seeds [Benherlal & Arumughan, 2007; Ghosh *et al.*, 2017; Indrayan *et al.*, 2005]. Among digestible carbohydrates, which provide the energy needed to support various metabolic processes in the human body, starch dominates with the content ranging from 23 g/100 g to 60 g/100 g dm of seed [Benherlal & Arumughan, 2007; Gajera *et al.*, 2018]. The content of total soluble sugars is negligible – 0.1–1.4 g/100 g [Gajera *et al.*, 2018; Ghosh *et al.*, 2017]. Moreover, jamun seeds were recognized

as the rich source of dietary fiber [Kaur et al., 2011], which together with lignin constituted non-digestible carbohydrates and represented nutritionally important, health-promoting food ingredient. The content of total dietary fiber of jamun seeds was evaluated at 27.7 g/100 g and the fraction of insoluble dietary fiber was significantly greater than that of the soluble dietary fiber (24.9 g/100 g and 2.8 g/100 g, respectively) [Kaur et al., 2011]. In turn, Pandey & Khan [2002] found water-soluble gums as the main fraction of non-digestible carbohydrates of jamun seeds with the content of 40 g/100 g of fresh matter, fm (moisture content of 5.9 g/100 g). The second non-digestible seed carbohydrate fraction was water--insoluble neutral detergent fiber (15 g/100 g fm) containing cellulose (6.9 g/100 g fm), hemicellulose (5.9 g/100 g fm), lignin (1.0 g/100 g fm), cutin (0.76 g/100 g fm), and silica (0.44 g/100 g fm). The profile of dietary fiber may determine its health benefits. As recently discussed in a review article by Cronin et al. [2021], the different type of dietary fiber can modulate the gut microbiota composition in various ways and thus alter the short chain fatty acid production and glucose and lipid metabolism which, if it is abnormal, is associated with a risk of chronic diseases.

Recently, many polysaccharides with biological activity, including antioxidant activity, and  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory properties, have been isolated from various parts of plants [Deng *et al.*, 2020; Oh & Yoon, 2018; Tan *et al.*, 2021]. Concerning the jamun seeds, Al-Dhabi & Ponmurugan [2020] isolated the water-soluble polysaccharide fraction free of reducing sugar, uronic acid, and starch. However, the biological activity of these polysaccharides has not been analysed.

## **Proteins**

Proteins constitute up to 8% of jamun seed dm [Benherlal & Arumughan, 2007; Indrayan et al., 2005], although some literature reports indicate a much higher protein content -19.96 g/100 g fm [Santos et al., 2020]. In addition to crude protein, free amino acids were reported in S. cumini seeds with the content of 4.84–9.90 mg/100 g [Gajera et al., 2018], but their profile has not been analysed. Recently, Binita et al. [2014] attempted to determine the protein profile of jamun seeds using two-dimensional gel electrophoresis (2D-PAGE) and matrix--assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) and identified 15 functional proteins including lactoferrin, chitinase1, sulphate transporter like protein, pectate lyases, β-tubulin, ABC transporter, phosphate binding protein, 1-aminocyclopropane-1-carboxylate oxidase, G protein coupled receptor, ADP-glucose pyrophosphorylase, and glutamate-ammonia ligase adenylyltransferase, which are important in plant defense mechanisms, metabolism, and transport of inorganic salts. Nevertheless, the jamun seed proteins are still very poorly understood and, to the best of our knowledge, there is a lack of data on their nutritional value, amino acid composition, digestibility, and possible use as food. More research is needed in this area.

### Lipids

The total lipid content of jamun seed is low (below 1.5 g/100 g) [Benherlal & Arumughan, 2007; Ghosh *et al.*,

2017], nevertheless fatty acid composition of lipids is healthy balanced. The saturated fatty acids (SFA) account for 50% and unsaturated fatty acids (UFA) including monounsaturated fatty acids and polyunsaturated fatty acids for 14% and 36% of total fatty acids, respectively [Bhaskar et al., 2021]. Among SFA, lauric acid (12:0; 2.8%), myristic acid (16:0; 31.7%), palmitic acid (16:0; 4.7%), and stearic acid (18:0; 6.5%) were determined. Oleic acid (18:1 *n*-9; 32.2%), linoleic (18:2 *n*-6; 16.1%), and epoxy and cyclopropenoid fatty acids, such as malvalic (1.2%), sterculic (1.8%), and vernolic (1.3%) acids, were also found in the fatty acid profile of jamun seed oil [Daulatabad et al., 1988]. In turn, Bhaskar et al. [2021] identified a few methyl esters of SFA (myristic acid, pentadecanoic acid, and heptadecanoic acid) and methyl esters of UFA (7,10,13-hexadecatrienoic acid, 8,11-octadecadienoic acid, 7,10-hexadecadienoic acid and 6,9,12,15-docosatetraenoic acid), together with fatty acid relevant compounds (3,7,11,15-tetramethyl-2-hexadecen--1-ol, docosyl acetate, 1-eicosene and 1,4-eicosadiene) in jamun seed oil using the GC-MS analysis. A low content of lipids and a high content of dietary fiber make the nutritional value of jamun seed low, raching only 267 kcal/100 g [Indrayan et al., 2005], which can be considered nutritionally beneficial in the context of the current global problem of overweight and obesity in humans.

### **Micronutrients**

Jamun seed contains ascorbic acid and a high amount of minerals, making it an attractive product for nutritionists [Ghosh *et al.*, 2017; Indrayan *et al.*, 2005].

Concerning the mineral composition of jamun seeds, Ravi et al. [2004a] found 9 dietary macro- and microelements. The dominant ones were manganese, potassium, iron, and chromium. Calcium and copper were determined in trace amounts, and sodium, zinc, and magnesium were detected with moderate levels. A similar qualitative profile was reported by Ghosh et al. [2017], although the ratios between the elements were different and the decreasing content was found for the following minerals: potassium (606 mg/100 g), calcium (136 mg/100 g), magnesium (112 mg/100 g), sodium (43.9 mg/100 g), iron (4.20 mg/100 g), copper (2.13 mg/100 g), chromium (1.40 mg/100 g), zinc (0.46 mg/100 g), and manganese (0.40 mg/100 g). The differences in the mineral composition may be due to different environmental conditions during plant growth and their soil-climate adaptation, varietal differences as well as harvest time [Granado-Rodríguez et al., 2021; Moussa et al., 2020]. Seraglio et al. [2018] found that the ripening process directly affected the contents of minerals of S. cumini fruit pulp and ripe fruits had significantly higher contents of potassium and calcium compared to these in intermediate ripe stage. It can be assumed that a similar phenomenon also applies to seeds, but this issue needs more extensive research.

Among vitamins and pro-vitamins, only ascorbic acid was determined in jamun seeds [Gajera *et al.*, 2018; Ghosh *et al.*, 2017]. Its content ranged from 90 mg/100 g to 137 mg/100 g for different genotypes and was higher compared to that in fruit pulp of each genotype [Gajera *et al.*, 2018]. A slightly lower content of ascorbic acid of jamun seeds was reported by Ghosh *et al.* [2017], which was 49.8 mg/100 g.

Although  $\beta$ -carotene along with other carotenoids has been determined in jamun fruit pulp [Faria *et al.*, 2011], its presence (and other fat-soluble vitamins) has not been confirmed in seeds. Gupta & Agrawal [1970] identified only  $\beta$ -sitosterol in the unsaponifiable fraction of the jamun seed oil.

### PHYTOCHEMICALS OF JAMUN SEEDS

Jamun seeds contain a variety of phytochemicals belonging to phenolic compounds, terpenes and terpenoids, sterols and saponins. The profile of these bioactive compounds of *S. cumini* seeds is summarised in Table 1.

## Phenolic compounds

Phenolic compounds are the most frequently recognised in jamum seeds and they are the most widely represented group of bioactive compounds (Table 1). The total phenolic content (TPC) has been determined as 55.54 mg gallic acid equivalents (GAE)/g dm of jamun seeds and 22.59 mg GAE/g fresh seeds at a moisture content of 62.25 g/100 g [Balyan & Sarkar, 2017; Shrikanta et al., 2015]. Lower TPC (26.9 mg GAE/g dried powdered seeds) was found by Aqil et al. [2012]. In turn, Mahindrakar & Rathod [2020a, 2020b] and Bajpai et al. [2005] reported higher values ranging from 79.89 to 108.7 mg GAE/ g dry seeds. Regarding jamun seed extracts, TPC of an aqueous extract of dried seed powder obtained under optimal extraction conditions (49.2°C, 89.4 min, and liquid-to-solid ratio 51.6:1, mL/g) with a yield 17.3% was 415 mg/g dried extract [Balyan & Sarkar, 2017]. This value was consistent with TPCs recorded for methanolic fractions obtained from seeds of various S. cumini genotypes (361.16– -496.26 mg/g extract), which were, in turn, 6.0-9.8 times higher than those determined for fruit pulps from the same genotypes [Gajera et al., 2017].

Phenolic acids, flavonoids (flavones, flavan-3-ols, flavonols, flavanonols and dihydrochalcones), stilbenoids, coumarins, lignans, hydrolysable tannins, and phloroglucinol derivatives are present in the profile of the phenolic compounds of jamun seeds (Table 1). Among them, two phenolic acids (gallic and ellagic acids), their simple derivatives and their polymeric forms (gallotannins and ellagitannins, respectively) are most often qualified and quantified [Bajpai et al., 2005; Balyan & Sarkar, 2017; Bhatia & Bajaj, 1975; Liu et al., 2018; Omar et al., 2012; Sawant et al., 2015]. It was found that tannic acid (gallotannin), gallic acid, and ellagic acid constituted 45.4%, 21.9% and 8.65% of the phenolic compounds of S. cumini seed aqueous extract, respectively [Balyan & Sarka, 2017]. The content of gallic acid was determined over a wide range from 0.65 to 6.24 mg/g dm of seeds and 90.8 mg/g extract, and the content of ellagic acid was reported as 0.038 mg/g dm and 36 mg/g extract [Bajpai et al., 2005; Balyan & Sarka, 2017; Shrikanta et al., 2015]. The use of liquid chromatography with tandem mass spectrometry (LC-MS/MS) and nuclear magnetic resonance (NMR) spectroscopy techniques has allowed to identify 9 gallotannins and 17 ellagitannins and other ellagic acid derivatives of jamun seeds [Bhatia & Bajaj, 1975; Elhawary et al., 2022; Liu et al., 2018; Omar et al., 2012; Sawant et al., 2015]. It is well known that hydrolysable tannins have a strong antioxidant

TABLE 1. Bioactive compounds identified in jamun seeds.

Class of compounds	Compound	Reference
r	Protocatechuic acid	Elhawary et al. [2022]
	p-Coumaric acid	Shrikanta <i>et al</i> . [2015]; Balyan & Sarkar [2017]
	Caffeic acid	Balyan & Sarkar [2017]; Gajera <i>et al.</i> [2017]; Abdin <i>et al.</i> [2019]; Elhawary <i>et al.</i> [2022]
	Ferulic acid Chlorogenic acid	Gajera <i>et al</i> . [2017]; Abdin <i>et al</i> . [2019]
Phenolic acids	Gallic acid	Bhatia & Bajaj [1975]; Bajpai et al. [2005]; Omar et al. [2012]; Sawant et al. [2015]; Shrikanta et al. [2015]; Balyan & Sarkar [2017]; Gajera et al. [2017]; Liu et al. [2018]; Abdin et al. [2019]; Elhawary et al. [2022]
	Syringic acid	Liu <i>et al</i> . [2018]
	5-Hydroxyveratric acid  Ellagic acid	Bhatia & Bajaj [1975]; Bajpai et al. [2005]; Aqil et al. [2012]; Omar et al. [2012]; Sawant et al. [2015]; Balyan &Sarkar [2017]; Gajera et al.
Stilbenoids	Resveratrol	[2017]; Liu et al. [2018]; Elhawary et al. [2022] Shrikanta et al.
	Quercetin	[2015]  Bhatia & Bajaj [1975]; Bajpai et al. [2005]; Sharma et al. [2008b]; Jadeja et al. [2012]; Balyan & Sarkar, [2017]; Elhawary et al. [2022]
	Rutin	Sharma <i>et al.</i> [2008b]; Jadeja <i>et al.</i> [2012]
Flavonols	Myricetin	Liu et al. [2018]
riavoliois	Myricetin 3- <i>O</i> -glucoside  Myricitrin  Syringetin  Syringetin 3- <i>O</i> -glucoside  Laricitrin  Quercitrin	Elhawary <i>et al</i> . [2022]
	Kaempferol	Bajpai <i>et al</i> . [2005]; Jadeja <i>et al</i> . [2012]; Abdin <i>et al</i> . [2019]; Elhawary <i>et al</i> . [2022]
Flavanonols	Dihydromyricetin	Elhawary <i>et al</i> . [2022]

TABLE 1 – continued

Class of compounds	Compound	Reference
	(+)-Catechin	Balyan & Sarkar, [2017]; Gajera et al. [2017]; Abdin et al. [2019]
Flavan-3-ols	(-)-Epicatechin	Shrikanta <i>et al.</i> [2015]; Balyan & Sarkar [2017]; Abdin <i>et al.</i> [2019]
	(-)-Epigallocatechin	Elhawary <i>et al</i> . [2022]
	Swertisin	Omar et al. [2012]
Flavones	Schaftoside	1
	Apigenin 6,8-di- <i>C</i> -β- -D-glucopyranoside	Liu <i>et al</i> . [2018]
	Tannic acid	Balyan & Sarkar [2017]
	1-Galloyl glucose 6-Galloyl glucose	Bhatia & Bajaj [1975]
Gallotannins	1,6-Digalloyl glucose 1,2,6-Trigalloyl glucose 1,2,3,6-Tetragalloyl glucose 1,2,3,4,6-Pentagalloyl glucose	Elhawary <i>et al</i> . [2022]
	Valoneic acid dilactone	Omar <i>et al.</i> [2012]; Sawant <i>et al.</i> [2015]; Liu <i>et al.</i> [2018]
	Jamutannin A and B	Omar et al. [2012]
	Corilagin	Bhatia & Bajaj [1975]; Elhawary et al. [2022]
	Eugeniin	Elhawary <i>et al</i> . [2022]
	3,6-Hexahydroxydiphenoyl glucose 4,6-Hexahydroxydiphenoyl glucose	Bhatia & Bajaj [1975]
	Iso-oenothein C	Omar <i>et al</i> . [2012]; Liu <i>et al</i> . [2018]
	Cornusiin B Phyllanthusiin E	Omar et al. [2012]
Ellagitannins	Rubuphenol	Sawant <i>et al.</i> [2015]; Liu <i>et al.</i> [2018]
and ellagic acid derivatives	Eschweilenol A and C Tergallic acid dilactone Ellagic acid 4-O-xylopyranoside 3'-O-Methyl ellagic acid 4-O-xylopyranoside 3-O-Methyl ellagic acid-4'O-α-L-rhamnopyranoside Ellagic acid-4-O-β-Dglucopyranoside Decarboxy ellagic acid 3,3',4'-Tri-O-methyl ellagic acid	Liu <i>et al</i> . [2018]  Bhatia & Bajaj [1975]; Liu <i>et al</i> . [2018]
	3,3'-Di- <i>O</i> -methyl ellagic acid	Bhatia & Bajaj [1975]

TABLE 1 - continued

Class of compounds	Compound	Reference
Coumarins	Brevifolin carboxylic acid	Omar et al. [2012]
Dihydrochalcones	Phloridzin	Liu et al. [2018]
Lignans	Medioresinol 4"-O-βglucoside (+)-Pinoresinol O-β-glucoside (+)-Syringaresinol O-β-glucoside Dihydrodehydrodiconiferyl alcohol 4"-O-β-glucoside	Martin <i>et al.</i> [1998]
Phloroglucinol derivatives	Jamunones A-O	Liu <i>et al.</i> [2017b]
Monoterpenes	Spiralisone C α-Pinene β-Pinene Limonene	Scharf <i>et al.</i> [2016]
Monoterpenoids	γ-Terpineol	Scharf <i>et al.</i> [2016]; Elhawary <i>et al.</i> [2022]
Sesquiterpenes	α-Copaene E-Caryophyllene α-Humulene δ-Cadinene α-Selinene Germacrene D	Scharf et al. [2016]
Sesquiterpenoids	Jambolanins A–K Sootepdienone Gibberodione Orientalol E Guaianediol Junipediol Cryptomeridiol Litseachromolaevanes A (4R)-4-Hydroxy-1,10-secomuurol-5-ene-1,10-dione (8R,9R)-Isocaryolane-8,9-diol Caryolandiol Clovane-2β,9α-diol Caryophyllenyl alcohol	Liu <i>et al</i> . [2017a]
Name	Caryophyllene oxide Caryophylla-4(12), 8(13)-dien-5-ol	Scharf et al. [2016]
Norses- quiterpenoids	Jambolanes A and B	Liu et al. [2017a]
Triterpenoids	Actinidic acid Oleanolic acid Ursolic acid Corosolic acid Arjunolic acid Asiatic acid Maslinic acid Betulinic acid	Liu <i>et al.</i> [2017a]  Sawant <i>et al.</i> [2015]  Elhawary <i>et al.</i> [2022]
Saponins	Vitalboside A	Thiyagarajan et al. [2016]
Sterols	β-Sitosterol	Gupta & Agrawal

and antibacterial activities [Karamać, 2009; Puljula *et al.*, 2020]. They can also affect the functioning of the digestive tract [Żary-Sikorska *et al.*, 2021]. In the case of jamun seeds, it was found that the ellagitannin-rich fraction of these seeds inhibited canonical Wnt signaling pathway in a human 293T cell line, suggesting its potential against colon carcinogenesis [Sharma *et al.*, 2010]. Moreover, the *in vitro* antioxidant activity of the jamun seed fraction containing ellagitannins and ellagic acid was reported and it was higher than that of the pulp with anthocyanins as the main component [Aqil *et al.*, 2012].

Among phenolic acids, apart from ellagic and gallic acids, also p-cumaric, caffeic, ferulic and chlorogenic acids were quantified in seeds of the same S. cumini genotypes and their contents were 14.06, 1.02–4.73, 1.50–8.21 and 0.89–6.80  $\mu$ g/g seed, respectively [Gajera et al., 2017; Shrikanta et al., 2015]. The presence of protocatechuic acid, syringic acid, and 5-hydroxyveratric acid was confirmed in the studies by Liu et al. [2018] and Elhawary et al. [2022].

Flavonoids are another class of phenolic compounds that are commonly distributed in plants. In jamun seeds, myricetin and its derivatives have been most widely represented including myricetin glycosides (myricetin 3-O-glucoside), O-methylated forms (syringetin, syringetin 3-O-glucoside, laricitrin), and dihydroxy derivatives (dihydromyricetin) [Elhawary et al., 2022; Liu et al., 2018]. In turn, (-)-epicatechin (129.20 μg/g dm), quercetin (98 μg/g dm), kaempferol  $(59 \mu g/g \text{ dm})$  and (+)-catechin  $(5.36-16.80 \mu g/g \text{ seed})$  were reported as the most abundant among flavonoids [Bajpai et al., 2005; Gajera et al., 2017; Shrikanta et al., 2015]. According to Sharma et al. [2008a,b] and Jadeja et al. [2012], rutin, quercetin and kaempferol present in standardized flavonoid-rich extracts of jamun seeds were responsible for their diverse bioactivity. The hypoglycemic and hypolipidemic effects and anti-atherogenic potential of such extracts were found. Flavone C-glycosides (swertisin, schaftoside and apigenin 6,8-di-C-β-D-glucopyranoside), that are limited in natural sources, have also been identified in jamun seeds [Liu et al., 2018; Omar et al., 2012]. Interestingly, jamun seeds do not contain the anthocyanins that are present in the pulp of the fruits [Aqil et al., 2012; Benherlal & Arumughan, 2007]. Lestario et al. [2017] reported that the content of pulp anthocyanins increased, but contents of flavonols, gallotannins, and ellagitannins decreased by 60%, 35%, and 11%, respectively, throughout fruit maturation. However, it has not been studied so far whether the seed phenolic profile changed during fruit ripening.

Other phenolic compounds detected in jamun seeds include stilbenoids (resveratrol), coumarins (brevifolin carboxylic acid), lignans (medioresinol 4"-O- $\beta$ -glucoside, (+)-pinoresinol O- $\beta$ -glucoside, (+)-syringaresinol O- $\beta$ -glucoside, and dihydrodehydrodiconiferyl alcohol 4"-O- $\beta$ -glucoside) and phloroglucinol derivatives (jamunones A–O and spiralisone C) [Liu *et al.*, 2017b; Martin *et al.*, 1998; Omar *et al.*, 2012; Shrikanta *et al.*, 2015]. Among them, only resveratrol was quantified at the level of 34.87  $\mu$ g/g dm [Shrikanta *et al.*, 2015]. In the mentioned publication, the authors suggested that resveratrol contributed significantly to the antioxidant capacity of jamun seeds. In turn, phloroglucinol derivatives of jamun seeds inhibited protein tyrosine phosphatase 1B

activity [Liu *et al.*, 2017a] and can therefore be considered as anti-diabetes and anti-obesity agents. The bioactivity of jamun seed coumarins and lignans has not been determined so far.

### Terpenes and terpenoids

Forty-five terpenes and terpenoids classified as monoterpenes, monoterpenoids, sesquiterpenes, sesquiterpenoids, norsesquiterpenoids and triterpenoids have been identified in jamun seeds [Elhawary *et al.*, 2022; Liu *et al.*, 2017a; Sawant *et al.*, 2015; Scharf *et al.*, 2016]. The names of these compounds are listed in Table 1.

Scharf et al. [2016] reported that two sesquiterpene hydrocarbons (*E*-caryophyllene and  $\alpha$ -humulene) were the major compounds of essential oil of fresh jamun seeds and their contents were 42.5% and 22.2% of the total essential oil, respectively. However, both the total essential oil content of the seeds and the essential oil profile changed during seed storage. The hydrodistillation yield decreased from 0.11% (w/w) for fresh seeds to 0.06% (w/w) for seeds after two-month storage. A successive decrease in the percentage of sesquiterpene hydrocarbons (from 74.1 to 21.0% after four months storage) and monoterpenes (from 7.8 to 1.3%), and an increase in the contribution of oxidized sesquiterpenes (from 12.3 to 70.5%) were noted in the profile of compounds. The major compounds of fresh seeds were partially oxidized to mainly caryophyllene oxide and humulene epoxide during storage.

Some of the jamun seed sesqutierepenoids were found to be biologically active [Liu et al., 2017b]. Among twelve isolated sesqutierepenoids, a mixture of jambolanins D and E as well as sootepdienone, guaianediol, cryptomeridiol, (4R)-4-hydroxy-1,10-seco-muurol-5-ene-1,10-dione, caryolandiol, and clovane-2 $\beta$ ,9 $\alpha$ -diol exhibited antimicrobial activity against *Staphylococcus aureus*. On the other hand, these compounds did not inhibit the proliferation of *Escherichia coli* and *Candida albicans* at the concentration  $100 \mu g/disk$ . In turn, Sawant et al. [2015] did not detect the aldose reductase (AR) inhibitory activity and protein tyrosine phosphatase 1B (PTP1B) inhibitory activity of maslinic acid isolated from jamun seeds when tested at concentration up to  $100 \mu g/mL$ .

## Other phytochemicals

Vitalboside A, a pentacyclic triterpene glycoside (saponin), was identified by NMR techniques and isolated using chromatographic methods from jamun seeds [Thiyagarajan et al., 2016]. The content of vitalboside A in the methanolic extract of jamun seeds was 0.8% (w/w). The antidiabetic and anti-adipogenic activities of the isolated compound were shown.

Another bioactive phytochemical detected in *S. cumini* seeds is  $\beta$ -sitosterol. It was identified in the unsaponifiable fraction of the jamun seed oil [Gupta & Agrawal, 1970]. Presence of sterol with an unidentified structure in the Sephadex LH-20 fraction of the ethanolic jamun seed extract was reported by Sharma *et al.* [2011a,b]. This fraction exhibited hypolipidemic and antidiabetic activity in alloxan-induced mildly diabetic and severely diabetic rabbits.

# EXTRACTION, PURIFICATION AND ISOLATION OF JAMUN SEED BIOACTIVE COMPOUNDS

Extraction is the first and most important step in the recovery of biological molecules from plant material. The solvent extraction with pure or aqueous methanol, ethanol and acetone was most commonly used to extract phenolics from jamun seeds [Liu et al., 2018; Elhawary et al., 2022; Sawant et al., 2015; Shrikanta et al., 2015]. Aqueous acetone was used in the first step of isolation of jamun seed sesquiterpenoids and phloroglucinol derivatives [Liu et al., 2017a,b], and water to recover polysaccharides with potential bioactivity [Al-Dhabi & Ponmurugan, 2020]. In the last-mentioned study, microwave treatment during extraction was successfully applied to increase extraction yield. In turn, ultrasonic--assisted extraction (UAE) was used to most effectively extract S. cumini seed phenolics [Mahindrakar & Rathod, 2020a]. Authors compared UAE with conventional, stirred batch extraction, and found that contents of (+)-catechin, gallic acid, total phenolic and total flavonoid as well as antioxidant activity (DPPH assay) were 3.6, 1.5, 1.3, 1.4 and 1.2 times higher, respectively, for the extract obtained by UAE. Both extractions were carried out under optimal conditions, which were as follows for UAE: 12 min of extraction time, 35°C of temperature, 1:15 of solid material to solvent ratio, 125 W of power, and 60% of duty cycle. The stirred batch extraction required longer extraction time, higher solvent volume and higher temperature than UAE by 8.8, 1.3 and 1.4 times, respectively. Abdin et al. [2019] used the response surface methodology (RSM) for optimization UAE of jamun seeds in terms of maximizing total phenolic content and for the inhibition of α-amylase and pancreatic lipase. The effects of extraction time (10–90 min), ethanol concentration (10–90%, v/v), and solvent to solid material ratio (10-70 mL/g) were investigated and the optimal UAE conditions were found as 59.8 min - extraction time, 63.1% (v/v) – ethanol concentration, and 43.8 mL/g – solvent to solid material ratio. The RSM was also applied to optimize the microwave-assisted extraction of polysaccharides from jamun seeds [Al-Dhabi & Ponmurugan, 2020]. Four--factor, five-step central composite rotary experimental design allowed to state that microwave power of 515 W, pH of 3.2, extraction time of 3.1 min, and solid material to solvent ratio of 1:15 g/mL were the most efficient conditions for the recovery of polysaccharides.

Fractionation of the crude extracts is a common step in the isolation of phytochemicals. Various techniques are used to obtain fractions rich in specific class of compounds, the most common are chromatographic separations. However, fractionation is often preceded by re-extraction of the crude extract with solvents of different polarities. Such a path was followed by Sawant *et al.* [2015], who partitioned methanolic extract of jamun seeds using water, ethyl acetate, and *n*-butanol sequentially to find AR and PTP1B inhibitory active compounds. The most active ethyl acetate extract was then purified by a multi-step column chromatography (with silica gel, Diaion HP-20 and Sephadex LH-20) until the compounds (valoneic acid dilactone, ellagic acid, and rubuphenol) responsible for the activity could be isolated by means of preparative high-performance liquid chromatography (HPLC).

Partition of the methanolic extract of jamun seeds with ethyl acetate and *n*-butanol was deployed to enable isolation of hydrolysable tannins [Omar et al., 2012]. In the next step, the *n*-butanol extract was separated by medium pressure liquid chromatography to five fractions and each of them was used to isolate pure compounds using different systems of column chromatography and semipreparative HPLC. In turn, sesquiterpenoids were isolated from a 70% (v/v) aqueous acetone extract of jamun seeds, which was partitioned with ethyl acetate and water, and thereafter an ethyl acetate part was fractionated by a combination of MCI gel CHP-20P, silica gel, and Sephadex LH-20 column chromatography, as well as semipreparative HPLC [Liu et al., 2017a]. Phloroglucinol derivatives and saponin (vitalboside A) were isolated from jamun seeds by similar techniques, by re-extracting the crude extract and then fractionating it using various chromatographic methods [Liu et al., 2017b; Thiyagarajan et al., 2016]. Another technique was harnessed by Jasmine et al. [2010] who loaded the crude methanolic extract into the silica gel column, from which the compounds were eluted with a gradient system of solvents of increasing polarity. In this way, five fractions were obtained and one of them was active against drug-resistant bacteria. Silica gel (60-120 mesh) column chromatography with 95% ethanol as a mobile phase and Sepahex LH-20 column chromatography with methanol were applied by Sharma et al. [2011a,b] to separate fractions rich in bioactive compounds directly from jamun seed methanolic crude extract.

Filtration techniques are another way to purify crude extracts. In the case of jamun seeds, an aqueous extract was subjected to integrated cross flow ultrafiltration (UF) and nanofiltration (NF) [Balyan & Sarkar, 2016]. These membrane processes allowed to clarify the extract and concentrate the phenolic compounds, respectively. UF with a membrane with molecular weight cutoff of 100 kDa under low pressures (below 450 kPa) recovered 65% of total phenolic content, increased DPPH radical scavenging activity from 75.5 to 90.2%, and enhanced the purity by 1.35 times. Furthermore, NF with 250 Da membrane of UF-clarified permeate resulted in about three-fold concentration of phenolic compounds.

# BIOLOGICAL ACTIVITIES OF JAMUN SEED EXTRACT

A range of pharmacological properties is possessed by various extracts of jamun which include antidiabetic, antihyperlipidemic, antihypercholesterolemic, anticancer, cardioprotective, hepatoprotective, neuroprotective, anti-inflammatory, antioxidant, and antimicrobial activities (Table 2), as established by scientific studies.

## **Antidiabetic activity**

The antidiabetic effect of many natural products is based on the inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase activities, which slow down starch digestion contributing to the reduction in blood glucose level [Alam *et al.*, 2019; Lee & Yoon, 2022]. The extracts of seeds of black jamun landraces inhibited  $\alpha$ -amylase activity in the range of 59.1–90.6% [Gajera *et al.*, 2017]. The water extract obtained

from jamun seed kernels showed inhibitory activity against  $\alpha$ -amylase and  $\alpha$ -glucosidase characterized by IC<sub>50</sub> values of 9.03 and 7.13 μg/mL, respectively [Mahindrakar & Rathod, 2020b]. The same authors, using a three-phase partitioning extraction, reported IC<sub>50</sub> of 9.33  $\mu$ g/mL for  $\alpha$ -amylase and 7.55 μg/mL for α-glucosidase [Mahindrakar & Rathod, 2021]. In turn, Abdin et al. [2019] determined 87.66% α-amylase inhibitory activity of the fraction of jamun seed aqueous ethanol extract containing (+)-catechin, (-)-epicatechin, kaempferol, gallic, chlorogenic, caffeic, and ferulic acids as main phenolics and tested at a concentration of 640  $\mu$ g/mL. Shinde *et al.* [2008] evaluated inhibitory activity of jamun seed extracts against microbial (Saccharomyces cerevisiae and Bacillus stearothermophilus, in vitro), and mammalian (in vivo on Goto-Kakizaki rat intestine, administration of 250 mg/kg body weight) α-glucosidase. Both acetone and 70% ethanol extracts exhibited inhibitory activity against enzyme of all three sources. Three hydrolysable tannins isolated from jamun seeds were the strong α-glucosidase inhibitors [Omar et al., 2012]. Their IC<sub>50</sub> values were as follows:  $8.2 \mu M$ (iso-oenothein C),  $12.2 \mu M$  (cornusin B), and  $75.1 \mu M$  (oenothein C). Liu *et al.* [2018] reported strong  $\alpha$ -glucosidase inhibitory activity of phenolic compounds isolated from jamun seeds and elucidated using modern spectroscopic methods. Among 21 isolated compounds, eight (mainly ellagitannins and ellagic acid derivatives) inhibited α-glucosidase better than acarbose - a clinical drug. Tergalic acid dilactone was found as the strongest inhibitor with the IC<sub>50</sub> value of 5  $\mu$ M.

In the diabetic state, hyperglycemia increases glucose metabolism via the polyol pathway [Alam et al., 2019]. Aldose reductase (AR) catalyzes the conversion of glucose to sorbitol. This polyol, generated at high levels, cannot diffuse across cell membranes and either accumulates or is converted to fructose. In turn, protein tyrosine phosphatase B1 (PTP1B) is a negative regulator of the insulin signaling pathway and is associated with risk of both type 1 and 2 diabetes [Alam et al., 2019]. Gallic acid, valoneic acid dilactone, rubuphenol, and ellagic acid separated from jamun seeds were found to inhibit AR with IC<sub>50</sub> values of 0.77, 0.075, 0.165, and  $0.12\mu g/mL$ , while valoneic acid dilactone, rubuphenol, and ellagic acid inhibited PTP1B with IC<sub>50</sub> values of 9.37, 28.14, and 25.96 µg/mL, respectively [Sawant et al., 2015]. Fourteen phloroglucinol derivatives isolated from jamun seeds inhibited PTP1B activity. The values of IC<sub>50</sub> were in the range of 0.42–3.2  $\mu$ M. The strongest inhibitory activity possessed jamunone E (C<sub>26</sub>H<sub>30</sub>O<sub>5</sub>) with 2,5,7-trihydroxy-2,3--dihydrochromone moiety [Liu et al. 2017b].

Several *in vivo* studies showed the antidiabetic activity of jamun seeds, their extracts and phytochemicals. Study revealed that jamun seed extract preferably improves various biochemical actions, such as glucose tolerance and glucose uptake, maintains glucose homeostasis in diabetic animals, and exhibits benefits in restoring β-cells [Sharma *et al.*, 2008a]. Addition of defatted jamun seeds as well as water-soluble fiber isolated from this material to the diet of diabetic rats exerted a hypoglycemic effect [Pandey & Khan, 2002]. The ethanolic extract of phenolic compounds obtained from jamun seeds reduced significantly the blood glucose level in rats [Yadav *et al.*, 2010]. The authors reported 41%

TABLE 2. Bioactivities of jamun seed extracts/phytochemicals - last decade studies.

Gir forest western Gujarat, India Konkan region  Methanol extract Aqueous extract obtained of Maharashtra, India India (industrial waste)  Extract obtained by three-phase (water, 20% ammonium sulfate and tert-butanol) partition  Afrelshiekh, Egypt  Fraction of aqueous ethanol extract  Gujarat, India  Isolated hydrolysable tannins  Isolated phenolics				
at, India an region tharashtra, India strial waste) strial waste) strial waste) at, India at, India	Inhibition of porcine pancreatic α-amylase in DNS assay	Antidiabetic activity	$\alpha\text{-Amylase}$ inhibitory activity of 59.1–90.6% (IC $_{50}-12.9\mu\text{g/mL})$	Gajera <i>et al.</i> [2017]
an region harashtra, India strial waste) strial waste) strial waste) at, India at, India	DPPH assay	Antioxidant activity	DPPH scavenging activity of 73.8-92.4%	
strial waste) strial waste) shiekh, Egypt at, India	nn DPPH assay	Antioxidant activity	$SC_{s_0}$ – 10.59 $\mu g/mL$	Mahindrakar & Rathod [2020a]
ite)	DNS assay, assay with $p$ -nitrophenyl $\alpha$ -D-glucopyranoside	Antidiabetic activity	$IC_{s_0}$ for $\alpha$ -amylase and $\alpha$ -glucosidase inhibitory activity – 9.03 and 7.13 mg/mL, respectively	Mahindrakar
ite)	DPPH assay	Antioxidant activity	$SC_{30} - 12.97  \mu g/mL$	& Natiou [20200]
ggypt	DNS assay, assay with <i>p</i> -nitrophenyl e α-D-glucopyranoside	Antidiabetic activity	$IC_{s_0}$ for $\alpha$ -amylase and $\alpha$ -glucosidase inhibitory activity – 9.33 and 7.55 mg/mL, respectively	Mahindrakar
Egypt	DPPH assay	Antioxidant activity	$SC_{50} - 12.15  \mu g/mL$	& Katnod [2021]
nd (9)	DNS assay, assay with p-nitrophenyl laurate	Antidiabetic and anti- obesity activity	Fraction of JSE inhibited 87.66% (conc. 640 $\mu$ g/mL) and 86.61% (conc. 1280 $\mu$ g/mL) of $\alpha$ -amylase and pancreatic lipase activities, respectively	Abdin <i>ot al</i> [2019]
	ABTS, DPPH, hydroxyl radical scavenging activity assays	Antioxidant activity	SC <sub>50</sub> of JSE fraction for ABTS *+ $-105.3 \mu g/mL$ , for DPPH *- $153.8 \mu g/mL$ , for hydroxyl radical $-501.6 \mu g/mL$	
	Assay with $p$ -nitrophenyl- $\alpha$ -D-glucopyranoside	Antidiabetic activity	IC <sub>30</sub> for $\alpha$ -glucosidase inhibitory activity of iso-oenothein C, cornusin B and oenothein C – 8.2, 12.2 and 75.1 $\mu$ M, respectively	Omar et al. [2012]
	Assay with <i>p</i> -nitrophenyl- α-D-glucopyranoside	Antidiabetic activity	Eight isolated phenolics (ellagitannins and ellagic acid derivatives) were very strong $\alpha$ -glucosidase inhibitors (IC $_{50}-5.0-21.2\mu M$ )	
	DPPH assay, inhibition of ROS production in murine RAW264.7 macrophages	Antioxidant activity	Nine most active isolated phenolics: $SC_{50}$ for DPPH – 25.0–87.2 $\mu$ M, 24–36% inhibition of ROS production in the RAW264.7 macrophages (conc. 20 $\mu$ M)	Liu et al. [2018]
Bangalore, India Fractions and isolated phenolics	Aldose reductase and PTP1B cs inhibition assays, <i>in vitro</i>	Antidiabetic activity	IC <sub>50</sub> for aldose reductase: $0.075  \mu g/mL$ (valoneic acid dilactone), $0.12  \mu g/mL$ (ellagic acid), $0.165  \mu g/mL$ (rubuphenol) and for PTP1B: $9.37  \mu g/mL$ (valoneic acid dilactone), $25.96  \mu g/mL$ (ellagic acid), $28.14  \mu g/mL$ (rubuphenol)	Sawant et al. [2015]
Gujarat, India Isolated phloroglucinol derivatives	PTP1B inhibition assays, <i>in vitro</i>	Antidiabetic activity	IC $_{50}$ of isolated phloroglucinol derivatives – 0.42–3.2 $\mu M$ and positive control (synthetic PTP1B inhibitor) – 2.0 $\mu M$	Liu <i>et al.</i> [2017a]

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Origin of jamun seeds	Type of extract/Class of compounds	Methods	Bioactivity	Mode of action/Key finding	References
Bangalore, India	Hydro-ethanolic extract	RIN-5F and L6 cells, in vitro	Antidiabetic activity	Glucose uptake by L6 myoblast cells was increased (19.91% at $40 \mu g$ extract/mL) as compared to vehicle control; JCE showed enhancement of insulin release (2.8-fold at $40 \mu g$ /mL)	Assan Aliyar et al. [2021]
Local market, Faisalabad, Pakistan	50% (v/v) Aqueous ethanol extract	In vivo model (male Sprague Dawley hyperglycemic/diabetic rats)	Antihyperglycemic activity	In normal and hyperglycemic mice, JSE lowered glucose by 7.04% and 14.36%, respectively, and increased insulin level by 3.56% and 7.24%, respectively	Raza <i>et al.</i> [2017]
Local market, Karnataka, India	80% (v/v) Ethanol extract	DPPH assay; assay based on the reduction of Mo(VI) to Mo(V) (total antioxidant capacity)	Antioxidant activity	DPPH· SC <sub>50</sub> – 0.40 mg/mL and total antioxidant capacity – 3.33 mmol GAE/g extract	Shrikanta <i>et al.</i> [2015]
Garden of NIPER, S.A.S. Nagar, India	75% (v/v) Aqueous ethanol with 10 mM HCl extract; additionally, hydrolysed with 2M HCl	ORAC, FRAP, DPPH and ABTS assays	Antioxidant activity	SC <sub>30</sub> for DPPH <sup>-</sup> – 6.3 and 19.8 μg/mL (crude and hydrolyzed extract respectively) and for ABTS <sup>+</sup> – 4.6 μg/mL (both extracts); FRAP (concentration giving 50% reduction of ferric iron) – 23.6 and 24.7 μg/mL (crude and hydrolyzed extract, respectively); ORAC – 3.379±151 μmol TE/g (both extracts)	Aqil <i>et al.</i> [2012]
		Human non-small-cell lung carcinoma cell line A549	Antiproliferative activity	Hydrolyzed JSE showed higher antiproliferative activity (IC $_{\rm S0}$ of 38 $\mu {\rm g/mL}$ ) then unhydrolyzed JSE (IC $_{\rm S0}$ of 64 $\mu {\rm g/mL}$ )	
Santa Maria, Rio Grande do Sul, Brazil	Aqueous extract (powder and nanoparticles)	Candida albicans-infected diabetic male albino Wistar rats	Antioxidant activity	JSE in nanoparticle form was more effective than JSE at reducing the oxidative burst induced by diabetes and/or <i>Candida</i> infection in rats	Bitencour et al. [2017]
Keshav Shristi Bhayandar,	Fraction of ethanol extract	Human cancer cell lines: breast adenocarcinoma (MCF7), ovarian adenocarcinoma (A2780), prostate carcinoma (PC-3), non-small- -cell lung carcinoma (H460)	Anticancer activity	The highest inhibition of cell proliferation by JSE was reported for A2780 cell line (IC $_{50}$ – 49 $\mu g/mL$ )	Yadav et al. [2011]
Mumbai, India		Agar cup-plate assay.	Antibacterial activity	JSE showed antibacterial activity against <i>E. coli, P. aeruginosa, S. aureus, B. subrilis</i> with zone of inhibition of 20, 11, 17, 15 mm, respectively with 20 and 11 mm, respectively	
Chenai, India	Methanol extract	HepG2 cells, MTT assay	Anticancer activity	JSE, induced apoptosis in HepG2 cells through decrease in MMP and downregulation of HFN-1 $\alpha$	Prakash & Devaraj [2019]
Botanical gardens in Egypt	Methanol extract	Human breast cancer (MCF-7 cell line and MDA-231 cell line), colon cancer (HCT-116 cell line), MTT assay	Anticancer activity	Strong JSE activity against HCT-116 cells, with IC $_{\rm 50}$ of 1.24 $\mu \rm g/mL$	Elhawary <i>et al.</i> [2020]

TABLE 2 – continued

Origin of jamun seeds	Type of extract/Class of compounds	Methods	Bioactivity	Mode of action/Key finding	References
Viçosa, Minas Gerais, Brazil	Mixture of ethanol, methanol and acetone (1:1:1, v/v/v) extract	Agar diffusion assay	Antibacterial activity	JSE was active against A. hydrophila, C. violaceum, E. coli, P. aeruginosa, S. enterica serovar Typhimurium, S. marcescens, L. monocytogenes, and S. aureus	Santos et al. [2020]
Santa Maria, RS, Brazil	Aqueous extract	Lymphocytes, and ADA, DPP-4, and acetylcholinesterase activities, CD26 expression	Immunomodulatory properties	JSE exhibits immunomodulatory properties probably via the pathway of DPP-4-ADA complex	Bellé <i>et al.</i> [2013]
India	Methanol extract	Rat heart-derived H9C2 cardiomyoblast cells	Anti-inflammatory activity	JSE decreased glucose-induced cardiac stress, suppressed gelatinase activity in H9C2 cells, gelatinase-B expression and NF-κB nuclear translocation in these cells	Atale <i>et al.</i> [2021]
Gujarat, India	70% (v/v) Ethanol extract	Hydrogen peroxide induced cytotoxicity in H9C2 cells	Cardioprotective properties	JSE is capable of cardioprotective activity due to lowering intracellular oxidative stress, preventing depletion of cellular antioxidants and improving cell viability	Devkar <i>et al.</i> [2012]
Uttar Pradesh, India	Methanol extract	H9C2 cardiomyoblast cells	Cardioprotective properties	Exposure of glucose-stressed H9C2 cells to JSE showed decline in the activity of catalase and superoxide dismutase and collagen content	Atale <i>et al.</i> [2013]
Chittagong, Bangladesh	Methanol extract	Alloxan-induced diabetic Wistar albino rats	Cardio- and hepatoprotective properties	JSE at dose of 200 mg/kg reversed cardiac and liver damage caused by alloxan in rats	Nahid <i>et al.</i> [2017]
India	Aqueous extract	High fat diet- streptozotocin induced type 2 diabetic rats	Antihyperglycemic and antidyslipidemic activity	JSE at doses of 200 and 400 mg/kg decreased rat serum total cholesterol (by 39.9 and 44.2%, respectively), triglycerides (by 43.1 and 46.7%, respectively), LDL-cholesterol (by 28.3 and 32.9%, respectively) compared to control group	Sharma <i>et al</i> . [2017]
India	Ethanol extract	Streptozotocin induced Alzheimer's disease Wistar rats	Neuroprotective properties	JSE at doses of 200 and 400 mg/kg decreased amyloid load, tau phosphorylation and levels of tumor necrosis factor $\alpha$ (TNF- $\alpha$ ) and interleukin-1 $\beta$ (IL-1 $\beta$ ) in the hippocampus of JSE treated rats compared to negative control group	Kosaraju <i>et al.</i> [2014]
Local market, Warangal, India	Methanol extract	Scopolamine induced spatial memory impairments in male albino Wistar rats	Antiamnesic activity	JSE at doses of 200 and 400 mg/kg decreased lipid peroxidation and acetylcholinesterase activity, increased activity of superoxide dismutase and catalase in brain of treated animals, and positively affected short term or working memory compared to control group	Alikatte <i>et al.</i> [2012]

ABTS = 2,2'-azinobis-(3-ethylbenzthiazolin-6-sulfonic acid); ADA – adenosine deaminase; DNS – 3,5-dinitrosalicylic acid; DPP-4 – dipeptidyl peptidase 4; DPPH – 2,2-diphenyl-1-picrylhydrazyl; FRAP – ferric-reducing antioxidant power; GAE – gallic acid equivalents; HFN-1α – hepatocyte nuclear factor-1α; IC<sub>30</sub> – concentration of the compound/extract causing 50% inhibition; JSA – jamun seed extract; MMP – mitochondrial membrane potential; ORAC – oxygen radical absorbance capacity; PTP1B – protein tyrosine phosphatase 1B; ROS – reactive oxygen species; SC<sub>30</sub> – concentration of the antioxidant causing 50% radical scavenging; TE – Trolox equivalents.

and 44% of the mentioned reduction after oral administration of the extract. For the aqueous extract, the ability for blood glucose reduction was lower - 26% and 27% after 1 and 2 h, respectively. In the experiment with streptozotocin-diabetic rats (15 days, addition of 500 and 1000 mg of powdered jamun seeds per kg body weight to the rat diet) caused positive changes in diabetes markers. Fasting blood glucose was reduced by 75 and 122 mg/dL (in diabetic control it increased by 34 mg/dL). The value of post-treatment fasting and peak blood glucose 38 and 36 mg/dL was much lower than that in diabetic control (78 mg/dL). The positive changes in liver glycogen were reported; involving a decrease by 50 and 52 mg/g of liver in experimental group, and 90 mg/g of liver in normal control [Sridhar et al., 2005]. The decreased levels of blood glucose and increased glucose tolerance were found due to administration of jamun seed kernels (100 mg/kg body weight) to streptozotocin-induced diabetic rats [Ravi et al., 2004b]. In the same experiment, a decrease in the liver glycogen content was observed. It is worth emphasizing that no hypoglycemic effect was shown when powdered seed coat was used as a dietary ingredient. Ravi et al. [2003] reported that the activities of important enzymes for carbohydrate metabolism were returned almost to the normal levels due to administration of jamun seed kernels to diabetic rats. In the study of Raza et al. [2017], an aqueous ethanolic extract of jamun seeds caused glucose reduction by 14.36% and increased blood insulin level by 7.24% in hyperglycemic rats. Findings of Sharma et al. [2011b] also showed positive properties of jamun seeds including their significant effect on decreasing blood glucose level. The fraction isolated from the crude extract using Sephadex LH-20 column chromatography possessed potent antihyperglycemic activity in experiments with alloxan-induced diabetic rabbits. Phytochemicals present in jamun seeds have a beneficial effect on hypoglycaemic activity by stimulating the glucose uptake (GLUT 4) by skeletal muscle cells [Syama et al., 2018].

A long-run human study conducted for 1 year on 99 patients with type 2 diabetes mellitus who poorly controlled blood sugar level and were administered *S. cumini* seed powder at a dose of 10 g/day showed decrease in fasting plasma glucose and postprandial blood sugar, thus indicating the beneficial role of jamun seed powder in controlling type 2 diabetes mellitus [Sidana *et al.*, 2017]. The study also confirmed the pharmaceutical value of *S. cumini* as a regional, traditional medicine for diabetes management.

# Antihyperlipidemic and antihypercholesterolemic activity

The presence of several bioactive compounds in jamun seeds helps to regulate the blood lipid profile. Oral infusion of an alcoholic jamun seed extract (100 mg/kg body weight) in diabetic rats resulted in a significant reduction in serum lipids [Prince et al., 2004]. The jamun seed extract also decreased the total serum cholesterol to high-density lipoprotein (HDL) cholesterol ratio, serum low-density lipoprotein (LDL) cholesterol level and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity in alloxan-induced diabetic rabbits and streptozotocin-induced diabetic rats [Sharma et al., 2003; 2011a,b; Sridhar et al., 2005]. The plasma lipoprotein cholesterol (HDL-, LDL-, and VLDL-C) and fatty

acid composition were altered in streptozotocin-induced diabetic rats when administered the ethanolic jamun seed extract [Ravi et al., 2005]. In the experiment of Ulla et al [2017], the supplementation of the rats high-carbohydrate and highfat diet with jamun seed powder for 56 days (2.5%, w/w, of diet) reduced white adipose tissue (WAT) weights, and plasma lipids, such as total cholesterol, triglyceride, LDL and HDL cholesterol concentration. In experiments of Sharma et al. [2017], diabetic rats were treated with a water jamun seed extract (200 and 400 mg/(kg×day)). The authors observed decreased serum levels of total cholesterol (by 39.9 and 44.2%, respectively), triglycerides (by 43.1 and 46.7%, respectively), and LDL-cholesterol (by 28.3 and 32.9%, respectively) compared with diabetic control group. Due to addition of extracts to rat diet, the concentration of HDL-cholesterol increased by 14.6 and 20.2%, respectively.

Parveen *et al.* [2020] demonstrated antihyperlipidemic effect of jamun seeds in a human study. The supplementation of the diet of patients diagnosed with prediabetes with jamun seed capsulated powder (4.5 g/day) significantly improved the level of total cholesterol and LDL-cholesterol from 266 to 216 mg/dL and from 189 to 139 mg/dL, respectively.

## **Anticancer activity**

Jamun seed extract exhibited protection in albino mice against peroxidative damage contributing to skin cancer [Parmar *et al.*, 2010]. The oral intake of extracts (125 mg/kg body weight) reduced tumor burden, number of papilloma cells and their size. In experiments of Arun *et al.* [2011], the jamun seed extract administered orally (500–1500 mg/kg body weight) to mice before the exposure to genotoxic carcinogens (7,12-dimethylbenz( $\alpha$ )anthracene and urethane) prevented the breakage of pBR322 DNA, significantly reduced the chromosomal aberrations in metaphase, and reduced the formation of micronuclei in polychromatic erythrocytes.

Among in vitro studies, Yadav et al. [2011] examined the cytotoxic activity of the jamun seed extract by MTS assay on various cancer cell lines. The results were expressed as IC<sub>50</sub> values (the concentration of the extract inhibiting cell proliferation up to 50% of the negative control). With  $IC_{50}$  of 49  $\mu$ g/mL, A2780 (ovarian cancer) cell line was found to be most sensitive while non-small-cell lung carcinoma (H460) proved to be the least sensitive (IC<sub>50</sub> 165  $\mu$ g/mL). A very low IC<sub>50</sub> value (0.06–0.08  $\mu$ g/mL) was shown by flavopiridol (positive control) on all the cell lines. The induction of apoptosis in human hepatoma cells (HepG2) by the jamun seed extract was reported by Prakash & Devaraj [2019]. In this study, the use of different extract concentrations (10, 20, and 40  $\mu$ g/mL) decreased the mitochondrial potential as well as down-regulated a hepatocyte nuclear factor-1 a (HFN-1 $\alpha$ ). It was confirmed by western blotting. In turn, Aqil et al. [2012] used an MMT assay to evaluate the effect of jamun seed extracts (crude and hydrolyzed) on cancer cell viability. Both extracts exhibited strong antiproliferative activity against human non-small-cell lung cancer A549. The activity of the crude and hydrolyzed extract, expressed as  $IC_{50}$ , reached the value of 64 and 38  $\mu$ g/mL, respectively. The methanolic extract of jamun seeds exhibited cytotoxic activity against colon cancer cell line (HCT-116), with IC<sub>50</sub> value of 1.24  $\mu$ g/mL [Elhawary *et al.*, 2022]. According to molecular docking study, myricetin 3-glucoside, myricitrin, reynoutrin, and quercitrin present in the extract were most potential ligands within a protein active site (FIH-1).

### Cardio- and hepatoprotective properties

The methanolic jamun seed extract administered to mice at the dose of 200 mg/kg body weight revealed the protective and recovery ability on cardiac tissue due to its capability to decrease myocardial necrosis biomarkers such as aspartate aminotransferase (AST), alanine transaminase (ALT), uric acid, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) [Nahid et al., 2017]. Atale et al. [2013] reported reduction in size of myocyte, lower generation of reactive oxygen species (ROS), and lower accumulation of collagen in response to the administration of the jamun seed extract. According to the study of Devkar et al [2012], jamun seeds are potential cardioprotective agents due to a higher content of phenolic compounds, can reduce intracellular oxidative stress, preventing depletion of cellular antioxidants and improving cell viability. The mentioned research investigated hydrogen peroxide-induced cytotoxicity in H9C2 cells.

Hepatoprotective effect of the methanolic seed extract was reported when administered at doses of 100, 200 and 400 mg/kg to Wistar albino rats treated with carbon tetrachloride dosages. The extract significantly reversed the elevated marker enzymes (glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (ALP), acid phosphatase (ACP) and bilirubin), which were comparable even with those of the Liv.52®-treated group. The dose of 400 mg/kg body weight was highly effective against the hepatotoxicity caused by carbon tetrachloride [Sisodia & Bhatnakar, 2009]. Likewise, the methanolic jamun seed extract when administered at a dose of 200 mg/kg body weight to diabetic rats, exhibited hepatoprotective effect by significantly increasing the protein concentration, ALT, AST, ALP and bilirubin levels, and reducing enhanced liver enzymes even more than in the rats treated with the gliclazide (25 mg/kg) [Nahid et al., 2017].

## **Neuroprotective properties**

The therapeutic potential of dipeptidyl peptidase-4 (DPP-4) inhibitors in the treatment of Alzheimer's disease (AD) was confirmed in experimental studies [Holscher, 2010]. Because phenolic compounds are known as DPP-4 inhibitors, Kosaraju *et al.* [2017] tested the neuroprotective effect of the jamun seed extract against the streptozotocin-induced AD in a rat model. The administration of jamun seed extract at doses of 200 and 400 mg/kg decreased amyloid load, tau phosphorylation and inflammation in the brain. Levels of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) in the hippocampus of rats from group treated with jamun seed extract was reduced when compared with a negative control group.

The antiamnestic effect of the jamun seed methanolic extract was evaluated in a rat model by Alikatte *et al.* [2012]. The extract administration (200 and 400 mg/kg) exerted positive effects on short-term or working memory and reversed cognitive impairments in rats. In brains of rats treated with extracts, the level of lipid peroxidation was lower

and the activities of superoxide dismutase and catalase higher than in the control group. The authors reported also suppression of acetylcholinesterase activity in experimental groups.

### **Anti-inflammatory activity**

Due to the occurrence of several bioactive compounds, jamun seed powder or its extract can act as an anti-inflammatory agent, decreasing both acute and chronic inflammation. It was confirmed by several *in vivo* studies. Bioactive compounds of ethyl acetate and methanol extracts of jamun seeds orally administered to Wistar rats with carrageenan-induced paw edema (200 and 400 mg/kg body weight) elicited anti-inflammatory effect [Kumar *et al.*, 2008]. Chaudhuri *et al.* [1990] used the chloroform fraction of jamun seed in a lower dose (100 mg/kg body weight) and also reported the inhibition of carrageenan-induced paw edema in rats. The inhibition of migration of leucocytes into the pleural fluid was noted. In addition, the authors observed the reduction of the weight of cotton pellet-induced granuloma.

The study of Atale *et al.* [2021] demonstrated the anti-inflammatory effect of the jamun seed extract in rats with high-glucose-induced heart-derived H9C2 cardiomyoblasts. The bioactive compounds present in the extract prevented glucose-induced cardiac stress, gelatinase activity in H9C2 cardiomyocytes, gelatinase-B expression and NF-κB nuclear translocation in these cells. The docking studies confirmed a strong interaction between jamun seed phenolic compounds and gelatinase-B.

The results of a study by Bellé *et al.* [2013] indicated that the jamun seed extract can act as an inhibitor of the DPP-4 and adenosine deaminase (ADA) in human lymphocytes. Probably, the bioactive compounds present in extract may interact with DPP-ADA complex and modify the purinergic signaling.

## **Antioxidant activity**

The antioxidant potential of jamun seeds was analyzed by several *in vitro* methods, using various techniques for the extraction of bioactive compounds. The phenolics (gallic acid, ellagic acid, ferulic acid, (+)-catechin, and quercetin) of seeds originated from underutilized indigenous black jamun landraces found in the Gir forest region of India showed significant antiradical activity against DPPH [Gajera et al., 2017]. The DPPH scavenging activity of extracts of jamun kernel powder obtained using an ultrasonic-assisted aqueous extraction, regular water extraction, and a three-phase partitioning extraction was determined by Mahindrakar & Rathod [2020a,b; 2021]. The concentration of the antioxidant causing 50% radical scavenging (SC<sub>50</sub>) was 10.59, 12.97, and 12.15  $\mu$ g/mL, respectively. Much higher SC<sub>50</sub> values of 105.3, 153.8, and 501.6 µg/mL were found for ABTS\*+, DPPH\* and hydroxyl radical, respectively, by Abdin et al. [2019] who determined radical scavenging activity of the chromatographically (D101 resin) purified jamun seed aqueous ethanol extract. In turn, Shrikanta *et al.* [2015] reported a very low SC<sub>50</sub> value of 0.40 mg/mL for DPPH\* scavenging activity of 80% (v/v) ethanol extract. The extract was also tested in the assay based on the reduction of Mo(VI) to Mo(V) and its total antioxidant capacity was determined at 3.33 mmol GAE/g extract. Phenolic compounds isolated from jamun seeds with the highest

DPPH• scavenging activity were ellagitannins and ellagic acid derivatives (SC<sub>50</sub> values in the range of 25.0–87.2  $\mu$ M) [Liu *et al.*, 2018]. The same compounds also strongly inhibited ROS generation in the RAW264.7 macrophages.

Aqil *et al.* [2012] investigated antioxidant activity of the crude and hydrolyzed extracts of jamun seeds as ferric-reducing antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), and using antiradical assays (DPPH and ABTS). In the DPPH assay, the crude and hydrolyzed extracts exhibited  $SC_{50}$  of 16.3 and 19.8  $\mu g/mL$ , respectively. For both extracts, results of the ABTS assay were the same –  $SC_{50}$  of 4.6  $\mu g/mL$ . Results of FRAP were expressed by the concentration inducing 50% reduction of the ferric iron, which amounted to 23.6  $\mu g/mL$  (crude extract) and 24.7  $\mu g/mL$  (hydrolyzed extract). Both extracts were characterized by the same ORAC value – 3.379 mmol Trolox equivalents/g.

The *in vivo* experiment carried out by Bitencourt *et al.* [2017] demonstrated the antioxidant potential of the jamun seed extract. *Candida albicans*-infected diabetic rats were treated for three weeks with an aqueous seed extract and the same extract in the form of nanoparticles with a daily dose of 100 mg/kg. The crude extract and its nanoparticle form were able to decrease levels of thiobarbituric acid reactive substances (TBARS) in serum, kidney, liver, and pancreas of the treated groups when compared to control animals.

### **Antimicrobial activity**

According to Bag et al. [2012], the extract of jamun seeds exhibited the antibacterial potential against multidrug-resistant human bacterial pathogens. The possibility of applying the jamun seed extract as a novel antimicrobial agent was confirmed by means of the agar well diffusion and microbroth dilution assays. Jasmine et al. [2010] found that the crude extracts of jamun seeds could act against isolated β-lactamase--producing drug-resistant bacteria. The zone of inhibition was in the range of 14–21 mm and a minimum inhibitory concentration (MIC) was in the range of  $31.75-62.5 \mu g/mL$ . According to the authors, saponins present in the extract were the active phytochemicals. Eight sesquiterpenoids isolated from jamun seeds were active (100  $\mu$ g/disk) against *S. aureus*. However, the same compounds at the same concentration caused no effect against E. coli and C. albicans [Liu et al., 2017a]. According to Santos *et al.* [2020], phenolic extracts of jamun seeds were activite against Aeromonas hydrophila, Chromobacterium violaceum, E. coli, Pseudomonas aeruginosa, Salmonella enterica serovar Typhimurium, Serratia marcescens, Listeria monocytogenes, and S. aureus. The strongest antimicrobial activity was reported in the case of S. aureus. The extract used inhibited also violacein production by C. violaceum. Inhibition of E. coli, S. aureus, and P. aeruginosa growth by a fraction isolated from the ethanol extract of jamun seed was also reported by Yadav et al. [2011]. The zones of inhibition in agar cup-plate assay were 20, 17 and 11 mm, respectively. Yadav et al. [2017], using an agar well diffusion assay, demonstrated the antimicrobial activity of the jamun seed extract against Bacillus subtilis. The minimum inhibitory concentration of the methanolic extract was 0.3 mg/mL. The results of flow cytometry showed that antimicrobial activity of compounds present in the extract was related to the induction of membrane permeability in bacterial cells. According to docking analysis, among bioactive compounds of the jamun seed extract, lupeol showed the highest binding energy with DD-carboxypeptidase and LD-carboxypeptidase from B. subtilis, and stigmasterol and betasitosterol showed the highest binding energy for class D  $\beta$ -lactamase and  $\beta$ -lactamase.

The research conducted by Chandrasekaran & Venkatesa-lu [2004] showed antifungal activity of bioactive compounds extracted from jamun seeds using water and methanol. Extracts were active against such dermatophytic fungi as Candida albicans, Tricophyton rubrum, T. mentagrophytes, Microsporum gypseum, and Aspergillus niger.

# APPLICATION OF JAMUN SEEDS AND THEIR EXTRACT IN THE FOOD INDUSTRY

Jamun seed powder and its infusion are traditionally used in the treatment of diabetes and ulcers. Currently, the application of these seeds to prepare herbal formulations is gaining popularity worldwide. Raza et al. [2017] recommended the jamun seed powder as a health-promoting additive to foods due to its antihyperglycemic properties. However, its use in the production of bread, pasta or cookies still requires researches of product safety and quality, and processes conditions optimization. In the case of infusions/extracts, their low storage stability is disadvantageous. Modern techniques, such as ultrafiltration and nanofiltration, show promise in solving this problem [Balyan & Sarkar, 2018]. The cited study estimated parameters of the first-order kinetic model to fit the changes of total phenolic contents and total flavonoid contents of UF and NF fractions of the jamun seed aqueous extract during storage. These parameters can be useful for designing appropriate storage conditions for industrial scale-up of the process. Another possibility of increasing the stability of the jamun seed extract was proposed by Peixoto & Freitas [2013]. The authors spray-dried the aqueous extract using silicon dioxide and cassava starch as carriers. The obtained powder had low hygroscopicity at 43% relative humidity and was characterized by adequate flowability and compactability. Moreover, the antihyperglycemic and antioxidant properties of the spray-dried extract were comparable to those of the lyophilized one.

Whole jamun-based functional confection (WJFC) containing 2% of the jamun seed powder was produced and investigated by Sehwag & Das [2016] and Sehwag  $et\ al.$  [2018]. WJFC was characterized by a high content of dietary fiber and a low calorific value. It could be applied as a natural prebiotic, antioxidant or antidiabetic preparation. WJFC as an inhibitor of  $\alpha$ -amylase activity helped in maintaining a low blood glucose level.

The study of VenuGopal & Anu-Appaiah [2017] investigated effects of, the addition of jamun seeds during production of wines from jamun fruits. The seeds added to wine increased the content of phenolic compounds at the beginning of fermentation. However, the content of phenolics reduced throughout aging. The presence of phenolic compounds and polysaccharides originating from seeds influenced wine browning. In turn, Singh & Kocher [2020] used response surface methodology to optimize the parameters

of the fermentation of *S. cumini* fruits with seed power supplementation. Phenolics (specially tannins) of seeds were responsible for stabilizing sensory attributes and antioxidant potential of stored wines.

Abdin *et al.* [2022] used the jamun seed extract as a component of the edible sodium alginate/gum Arabic films. Such a product, featuring appropriate physicochemical properties, can serve as a good source of antioxidant compounds and can be used in modern food packaging.

# **CONCLUSION AND FUTURE PROSPECTIVE DIRECTIONS**

According to the review, the seed of the jamun fruit has a richly-varied composition of bioactive compounds, including terpenoids, phenolic compounds and saponins with high contents of gallic acid, ellagic acid and hydrolysable tannins. These compounds are responsible for the extensive biological activities of jamun seeds and their extracts. Jamun seeds appear to be a low-cost source of a natural antidiabetic agent, although their antioxidant, anti-inflammatory antimicrobial potential is becoming more and more appreciated. As modern techniques for the extraction, separation and purification of jamun seeds bioactives are developed, it seems that powder, extracts and fractions may soon be harnessed in the production of functional foods and nutraceuticals intended for people at risk of diabetes, cancer, cardiovascular, hepatic and neurodegenerative diseases, and bacterial and microbial infections. Nevertheless, more research is needed to elucidate the molecular mechanisms of the of health-beneficial activities of jamun seed compounds. The biological activity of saponins and lignans from jamun seeds, and the bioavailability of bioactive compounds are still poorly understood. In addition, the nutritional value of jamun seeds seems to be still little known, especially in terms of proteins, their amino acid composition and biological value. Clinical trials of jamun seed-based goods on humans, taking into account all safety concerns, will increase the value of jamun seeds for use in the food and non-food industries.

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### **CONFLICT OF INTERESTS**

Authors declare no conflict of interest.

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