

Recent advances in pharmacological potential of *Syzygium cumini*: A review

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ABSTRACT

Syzygium cumini (Linn.) Skeels. (Myrtaceae) (Synonym. *Eugenia jambolana*), commonly known as Jamun or Black Plum is indigenous to India. The plant has traditionally been used for its rich nutrition and medicinal value. The current review focuses on the recent research investigations involving the studies on diverse pharmacological actions of Jamun. The electronic database search was performed in order to achieve this aim. Jamun plant has been reported to be enriched with an array of phytoconstituents like ellagic acid, glucoside, anthocyanins, kaempferol, isoquercetin, myrecetin and so on. The seeds which are mostly utilized for their medicinal value are said to contain an alkaloid- jambosine and glycoside-jambolin or antimellin which inhibit the conversion of starch to sugar. Different plant parts have been claimed to contain different constituents, due to which they possess an assorted pharmacological prospective. Jamun has been used for the treatment of diabetes since ages. Apart from this it has also shown its beneficial potential as anti-allergic, antibacterial, anticancer, anticlastogenic, anti-diarrhoeal, anti-fertility, anti-fungal, anti-hyperlipidemic, anti-hypertensive, anti-inflammatory, anti-lieshmanial, anti-nociceptive, anti-oxidant, anti-viral, ascaricidal, cardioprotective, chemoprotective, diuretic, gastroprotective, hepatoprotective, hypothermic, neuropsychopharmacological and radioprotective agent. These actions and the lacunas in the specific areas have been discussed in this article. This will provide a platform for the future researchers especially in the less explored areas.

Keywords: *Syzygium cumini*, Pharmacological activity, Anti-diabetic

INTRODUCTION

Syzygium cumini (S. cumini) (L.) Skeels (family: Myrtaceae), synonyms- *Syzygium jambolana* DC., *Eugenia cumini* (Linn.) Druce., *Syzygium jambolanum* (Lam.) DC., *Myrtus cumini* Linn., *Eugenia djouant* Perr., *Eugenia caryophyllifolia* Lam., *Calyptanthes jambolana* Willd., commonly known as Black Plum in English, Jamun in Hindi, Jambu in Sanskrit and Jaman in Urdu is a large evergreen tree indigenous to India, though *Syzygium cumini* (SC) trees are found throughout the Asian subcontinent, South America, Eastern Africa, Madagascar and so on [1]. Different plant parts have been reported to contain a variety of components. The fruit pulp contains Vitamin A & C, nicotinic acid, riboflavin, folic acid, maleic acid, choline, sugar, amino acid, K, Ca, Na, P, Fe, Mn, Zn. Gallic acid is said to be responsible for the sourness of the fruit while anthocyanins for the colour. The leaves are enriched with acylated flavonol glycosides, myricetin, myricitin, quercetin, galloyl carboxylase, esterase and tannins. The flowers are rich in quercetin, kaempferol, myricetin, oleanolic acid, quercetin-3-D-galactoside, eugenol-triterpenoid A & B. The roots contain flavonoid glycosides and isorhamnetin 3-O-rutinoside. The stem bark has betulinic acid, β -sitosterol, quercetin, kaempferol, ellagic acid, gallic acid, myrecetin etc. The seeds contain glycoside jambolin, gallic acid, essential oils and so on [2]. The various parts of the tree have been used traditionally for the treatment of various human ailments. SC find its place in numerous traditional systems of medicine like Ayurveda, Siddha, Unani and Homeopathic systems of medicine. It was one of the best remedy for diabetes before the discovery of insulin [3]. As per Ayurveda, the barks of SC possess astringent, acrid, digestive and wound healing properties. They are beneficial for the treatment of biliousness, dysentery, sore throat, bronchitis, thirst, asthma and ulcers. According to Siddha system of medicine, it supposed to be semen promoting, haematinic and hypothermic. Unani System of medicine characterizes it to be a tonic for liver, to enrich blood, reinforce teeth and gums [4].

PHARMACOLOGICAL ACTIONS OF SYZYGIUM CUMINI

1. Anti-allergic

Allergy is an abnormal reaction of the body to the allergen introduced by ingestion, injection, inhalation or skin contact. A novel, safe and effective remedy is required for this ailment. In an investigation, the aqueous extract of SC leaves (25-100mg/kg, p.o.) inhibited the rat paw edema induced by 48/80 (allergenic compound), histamine and 5-HT. However, the extract could not produce any beneficial effects against the platelet aggregating factor-induced paw edema [5].

2. Antibacterial

Now a days, people have started using antibiotics as OTC (Over The Counter) drugs which has led to antibiotic resistance, thus safer novel antibacterial agents are required. In case of SC, its stem, leaf and fruit extracts were found to be effective against all the bacterial strains used in the study. Best results were observed against *Roultella plantikola* (zone of inhibition-25 mm) [6].

Microbroth dilution and Agar well diffusion assays were utilized to study the antibacterial effects of SC seeds against multidrug-resistant human bacterial pathogens and it was found that the ethyl acetate fraction from the ethanol extract was most effective. Then, the ethyl acetate fraction was subjected to phytochemical analysis and TLC-bioautography which exhibited the phenolics to be the main component responsible for the activity [7].

Ethyl acetate, petroleum ether and methanolic extracts of the SC leaf were found to be effective against *Salmonella typhimurium*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterobacter aerogenes* [8].

Acetone, aqueous and ethanolic bark extracts were evaluated for their antibacterial effects against twelve strains of *Vibrio cholera*, of which the ethanolic extract was found to be most effective [9].

Aqueous leaf extract of SC has shown beneficial effects against *Klebsiella sp.*, *Salmonella paratyphi A & B*, *Citrobacter sp.*, *Proteus mirabilis*, *Escherichia coli*, *Staphylococcus aureus*, *Shigella sonnei*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Shigella boydii*, *Streptococcus faecalis*, *Shigella flexneri* and *Salmonella typhi* [10].

3. Anti-cancer

Various treatment strategies for cancer involve surgery, hormonal therapy, chemotherapy, radiation therapy and targeted therapy (e.g. monoclonal antibody therapy and immunotherapy). Apart from killing cancerous cells, some normal, healthy cells may be destroyed and may affect many vital organs such as kidney, heart, lungs, nervous system etc. Many herbal anti-cancer drugs are being used to avoid the unwanted side effects.

Ellagitannins isolated from SC have shown to inhibit Wnt signaling in a transfected human 293T cell line [11].

A few of the current investigations have proved the selective cytotoxic activity of jamun fruit extract after studying its pro-apoptotic and antiproliferative effects on estrogen independent (MDA-MB-231) breast cancer cells, estrogen dependent/aromatase positive (MCF-7aro) and normal/nontumorigenic (MCF-10A) breast cell line [12] [1].

Anti-cancer effects of 40% SC extract have been studied on human cervical cancer cells (11.8% growth inhibition observed in SiHa (HPV-16 positive) cells and 14.4% in HeLa (HPV-18 positive) cells) [13].

4. Anticlastogenic

Anticlastogenic agent is one which protects the disruption or breakages of chromosomes. SC extract has exhibited its utility in mutagenesis prevention and carcinogenesis initiation. The alcoholic seed extract decreased the hydroxyl radical induced strand breaks in pBR322 DNA in vitro and the aqueous extract was found to reduce the chromosomal aberrations in mice (induced by DBMA and urethane) [14].

5. Anti-diabetic

Various preclinical and clinical studies have been performed to evaluate the anti-diabetic potential of SC [15].

Numerous investigations performed in the past have indicated that SC seeds [16] [17] [18] [19] [20] [21], fruit pulp [22] [23] [24], whole fruit [25] [26], bark [27] [28], leaves [29] and flowers [30] possess anti-diabetic activity.

Mycaminose (50 mg/kg) - a compound isolated from SC seeds and ethyl acetate & methanol fraction at the doses of 200 and 400 mg/kg showed a significant ($p < 0.05$) decrease in blood glucose level when evaluated for the anti-diabetic activity in streptozotocin (STZ)-induced diabetes in rats [31].

The aqueous and alcoholic SC extracts were evaluated for their anti-diabetic potential in alloxan induced diabetic rabbits. It was found that the aqueous extract was more effective in improving blood glucose in glucose tolerance test and in decreasing fasting blood glucose [24].

Numerous studies have been performed to show the beneficial effects of SC extract in normalizing the elevated lipid profiles of diabetic rats [16] [22] [32], elevating the serum insulin [16] [32] and increasing SOD and GPx activities [16]. The SC seeds possess protective effect against diabetes related complications like neuropathy [33], gastropathy [33], nephropathy [33], diabetic cataract [34] and also reduced peptic ulceration [35].

SC possesses the potential to inhibit the carbohydrate hydrolyzing enzymes [36]. A polyherbal formulation (ADJ6) containing SC and some other antidiabetic herbs have shown a significant inhibitory action against α -glucosidase and α -amylase [37]. SC seeds have shown the pancreatic islet cells regeneration potential in streptozotocin [38] and alloxan [39] diabetic rats.

Various clinical studies have been performed to validate the use of SC in diabetes [40] [26]. In a recent open labeled randomized parallel designed controlled study, Type II diabetic individuals were administered the standardized SC seed powder which exhibited a reduction in fasting blood sugar, insulin resistance and elevation in HDL cholesterol at the end of 3rd month [41].

6. Anti-diarrheal

Natural products are a drug of choice for diseases like diarrhea. SC ethanolic extract (400 mg/kg) administered orally has exhibited a reduction in gastrointestinal activity in PGE2 induced enteropooling and castor oil induced diarrhea in rats [42].

7. Anti-fertility

A review has stated that oleanolic acid – a phytoconstituent isolated from the flowers of SC has the potential to arrest spermatogenesis, thus exhibiting the anti-fertility action in the male albino rats [4].

8. Antifungal

The indiscriminate utilization of medicines has led to resistance against some fungal species, thus there is a requirement of a safer remedy.

The methanolic fruit extract of SC has shown excellent antifungal action against the targeted pathogenic fungi - *Fusarium oxysporium*, *Rhizoctonia solani* and *Sclerotium rolfsii* [43].

A research investigation utilized different concentrations of n-hexane, alcohol and aqueous extracts of different plant parts of SC (barks of stem and roots, fruits and leaves) to study their antifungal potential against *Ascochyta rabiei*-the causative agent for blight disease of *Cicer*

arietinum. All the aqueous extracts, n-hexane extract of stem-bark and alcoholic extracts of both the barks exhibited significant antifungal activity [44].

The aqueous, benzene, chloroform, ethanol, methanol and petroleum ether extracts of SC leaf were evaluated against various species of *Aspergillus* i.e., *A. tamari*, *A. niger*, *A. ochraceus*, *A. flavus*, *A. columnaris*, *A. fumigates*, *A. candidus* and *A. flavipes*. The results revealed that the methanolic extract was most potent [10].

9. Anti-hyperlipidemic

Of the various lipid-lowering drugs available in the market, the herbal drugs are found to be more safe and efficacious. The anti-hyperlipidemic potential of SC fruit pulp was evaluated in diet induced hyperlipidaemic rats. The results revealed that the fruit pulp was as potent as simvastatin in reducing serum LDL cholesterol, triglycerides & total cholesterol and elevating HDL cholesterol [45].

Flavonoids isolated from the seeds have exhibited hypolipidemic effects in diabetic rats [21] [20].

The ethanoilc extract of SC kernels (100 mg/kg b.w.) was evaluated for its hypolipidemic potential for the levels of triglycerides, cholesterol, phospholipids, free fatty acids in the plasma, kidney and liver tissues of STZ (55 mg/kg b.w.) induced diabetic rats. The results showed that the extract was able to restore all the parameters to their normal range [46].

10. Anti-inflammatory

The anti-inflammatory drugs are those which help to overcome a localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection.

Ethyl-acetate and methanolic extracts of SC leaves and seeds (both at the doses of 200 and 400 mg/kg p.o.) showed a significant anti-inflammatory activity in carrageenan induced paw oedema in wistar rats [47] [48].

11. Antileishmanial

Antileishmanial agents are those that destroy protozoa of the genus *Leishmania*. The essential oil of SC and its main component α -pinene was evaluated for its antileishmanial action against *Leishmania amazonensis*. α -pinene showed its efficacy with IC₅₀ of 19.7 mg/ml. Immunomodulatory action was considered as the most probable mechanism of action [49].

12. Antinociceptive

Antinociceptive activity is a process of blocking the detection of a painful or injurious stimulus by sensory neurons. With SC, the hydro-alcoholic leaf extract was evaluated for its analgesic potential in rats. To assess the cutaneous nociception, hot plate and formalin tests were used while for muscular nociception, forelimb grip force was measured. The extract at the dose of 100–300 mg/kg i.p. exhibited a significant decrease in the pain scores in all the phases of the formalin test but extract even at the dose of 300 mg/kg was not able to modify the grip force in

intact rats. Therefore, the extract exhibited an excellent analgesic activity (on cutaneous and deep muscle pain) [50].

The methanolic extract of SC fruits exhibited a significant central analgesic activity which was investigated using the Eddy's Hot Plate method [43].

13. Antioxidant

Generation of free radicals initiates/aggravates various diseases like cancer, AIDS, arthritis, Alzheimer and diabetic complications. Thus, there is a requirement of safer drugs that have property of scavenging the free radicals.

With regard to SC fruit, polyphenols have shown outstanding antioxidant capacity when compared to the standard polyphenols [51].

The methanolic extract of leaves, bark and seeds of SC were fractionated in different solvents: n-hexane, chloroform, ethyl acetate, butanol and water. These fractions were studied for their antioxidant and free radical scavenging activities. Of all the fractions, the polar ones i.e., ethyl acetate and water fractions showed excellent results [52].

The leaf and seed extract of SC exhibited a significant antioxidant activity when they were assessed by various in vitro methods such as Ferric reducing antioxidant power (FRAP) assay, 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay, Nitric oxide radical scavenging, ABTS Assay, Total Reducing antioxidant potential, Total antioxidant activity, Reducing power and Hydroxyl radical scavenging activity[53].

RSC (Radical Scavenger Capacity) of SC was determined by using DPPH (2, 2-diphenyl-1-picrylhydrazyl radical) assay. The second order rate constants- k_2 was evaluated to determine RSC and then these were compared to natural and synthetic antioxidants. The k_2 value of SC was determined to be 15.60 L/mol g s in methanol at 25°C proving that it has a excellent antioxidant potential [54].

14. Antiviral

With the changing environment, new viral diseases are being identified, so there is a demand for a safer, non-toxic remedy. The cold and hot aqueous extracts of leaves and barks of SC were evaluated for their antiviral potential against H5N1 (avian influenza virus which causes a highly contagious disease of poultry) using CPE reduction assay to establish virucidal, pre-exposure and post-exposure potential of these extracts. With hot and cold aqueous bark extracts and hot aqueous leaf extracts, 100% inhibition of the virus was observed in virus yield reduction assay and in egg based in ovo assay. CC50/EC50 (selective index) for cold aqueous extract (43.5) and hot aqueous extract (248) of bark exhibited their potency against H5N1 virus [55]. The aqueous extract of leaves was also found to inhibit the goatpox virus [56] and the buffalopox virus [57].

15. Ascariocidal

Different SC extracts were used to study their ascariocidal action against *Tetranychus urticae* Koch. The results showed the inhibition rate of 98.5%, 94% and 90% respectively for ethanolic, hexane and ethyl acetate extracts [58].

16. Cardioprotective

In case of SC, the hydroalcoholic extract of leaves was evaluated in spontaneously hypertensive and normotensive wistar rats. The findings of the research investigation revealed that the extract decreased the blood pressure as well as the heart rate. Extracellular calcium influx and inhibition of arterial tone were suggested as the most probable mechanism of action [59]. The hydroalcoholic extract of SC was evaluated for its antihypertensive, and vasorelaxant effect. Polyethylene catheters were inserted into the inferior vena cava and lower abdominal aorta in the anaesthetized rats for dosing and measuring blood pressure. The extract at the doses of 0.5; 1; 5; 10; 20 and 30 mg/kg, i.v. was able to induce hypotension (due to reduction in endothelium mediated peripheral resistance) and bradycardia (due to meandering cardiac muscarinic activation) [60].

The elevated serum levels of alanine transaminase (ALT), serum creatine phosphokinase (CPK), aspartate transaminase (AST), lactate dehydrogenase (LDH), HDL-cholesterol due to Doxorubicin(1.5 mg / kg/b.w., 15 days) induced cardiotoxicity were brought to normal range after the administration of aqueous suspension of SC seed extract (100 mg/kg/b.w. for 15 days) [61].

The oral administration of the methanolic extract of SC at the doses of 250 mg/kg and 500 mg/kg consecutively for 30 days reversed and retained the activity of AST, ALT, LDH and CPK to normal levels against the isoproterenol- induced myocardial infarction [62].

17. Chemoprotective

Various herbal drugs have proved their beneficial effect in protecting healthy tissues from the toxic effects of anti-cancer drugs. The aqueous and ethanolic SC seed extracts have shown chemoprotective action in the *in vivo* oxidative stress and genomic damage [63].

It has been reported that SC extract in the doses of 125 and 250 mg/kg/b.w./animal/day exhibited the cancer chemopreventive properties in the DMBA-induced croton oil promoted two stage skin carcinogenesis in Swiss albino mice. It was found that the extract was able to decline the tumor incidence, cumulative number of papillomas and elevate the average latency time as compared to the control group [64] [65].

The tumor burden, tumor incidence and cumulative number of gastric carcinomas induced by benzo-a-pyrene were found to decrease after the treatment with 25 mg/kg b.w./day of the SC extract exhibiting its broad spectrum chemoprotective effects [66].

The genotoxic effects caused by of the carcinogens urethane and DMBA in mice were also found to decline after the administration of SC seed extract [14].

18. Diuretic

The Diuretics are used for the treatment of various human ailments such as heart failure, high blood pressure, liver disease, some types of kidney disease and also in cases overdose or poisoning. Now day's herbs are a better option as diuretics.

Petroleum ether, chloroform, methanolic and aqueous extracts of SC bark were evaluated for their diuretic activity in Wistar albino rats at the dose of 500mg/kg body weight. The methanolic and aqueous extracts were found to be active as diuretic as depicted by an elevation in total urine output and in the excretion of electrolyte concentration of sodium and potassium ions [67].

19. Gastroprotective

Natural products provide a safer remedy to protect the gastric mucosa of aggressive or irritating agents.

Seed kernel extract of SC (200 mg/kg) was evaluated for its antiulcer activity. First, the diabetes was induced using low dose streptozotocin (35mg/kg) in combination with high fat diet. Then, the gastric ulceration was produced in diabetic rat's ethanol and indomethacin models. It was observed that there was a significant decrease in the gastric ulcer index after the administration SC extract alone and as well as in combination with Acarbose (5mg/kg) [68].

In another research investigation, the hard liquor (48% ethanol- 1ml/150gm b.w.) and aspirin (200 mg/kg, orally) were used to induce gastric ulcer in rats. The aqueous extract of SC leaves at the doses of 200 and 400 mg/kg produced ulcer inhibition (%) of 32.17% and 61.09% respectively in hard liquor model and 23.01% and 70.33% respectively in aspirin model [69].

SC fruit extract at the dose of 200mg/kg b.w. was administered orally for 10 days to streptozotocin induced diabetic and to rats exposed to ulcerogens (like aspirin, 95% ethanol, cold-resistant stress and pylorus-ligation). The observations of the study revealed that there was a decrease in acid-pepsin secretion, cell shedding and LPO while an increase in the GSH (in gastric mucosa), mucosal glycoprotein and mucin [35] [70] [71].

20. Hepatoprotective

Hepatoprotective agents are those that provide protection to the liver (which performs important functions like metabolism, secretion, storage, and detoxification of endogenous and exogenous substances).

The alcoholic extract of the pulp of SC (100 and 200mg/kg/day) exhibited a significant hepatoprotective action on paracetamol (PCM)-induced hepatotoxicity in albino rats. The elevated serum levels of ALT, AST, AP were decreased and histopathological studies depicted a reduction in fibrosis and necrosis [72].

The anthocyanins rich SC pulp extract (50 to 500 ppm) has shown its beneficial effects in preventing the CCl₄ induced liver damage by declining the lipid peroxidation, suppressing the CCl₄-induced release of LDH, and elevating the GPx (antioxidant enzyme) activity [73].

Aqueous leaf extract [74] and methanolic seed extract [75] have also shown hepatoprotective effects through biochemical estimations and histopathological studies.

21. Hypothermic

In an research investigation, after insertion of a mister probe into the rectum of rats, the basal body temperature was recorded and then pyrexia was induced by Brewer's yeast (*Sacchromyces*

cerevisiae) (10mL/kg of 20% suspension, subcutaneous). After 18 hours, the rectal temperature of the rats was again recorded and the test group was treated with SC methanolic fruit extract (100 mg/kg, orally). The standard group was administered oral dose of 33mg/kg of paracetamol and control group was given 0.2 ml normal saline. Upto 3 hours, temperature was recorded hourly and % reduction in temperature was recorded. The extract exhibited a significant antipyretic activity as compared to standard [43]. The chloroform and methanolic extracts of SC have also shown antipyretic activity [76].

22. Inhibits lipid peroxidation

Some enzymatic and non-enzymatic reactions lead to lipid peroxidation associated with mutagenesis and cellular damage. The fruit pulp, seed coat and kernel extracts were evaluated for their lipid peroxidation inhibition activity and was seen that the seed and coat and the pulp extracts were less active than the kernel [77].

An research investigation utilized the pulp extract (enriched with anthocyanins) to study its potential to inhibit the iron (FeSO₄)-induced lipid peroxidation in different organs of rat (Liver, liver mitochondria, brain, testes etc.) *in vitro*. A concentration of 5ppm was found to show beneficial results with highest lipid peroxidation inhibition in liver mitochondria (86%), followed by liver (83%), testes(72%) and brain(68.3%) [78].

SC seed extract when administered orally for 15 days to alloxan treated rats, exhibited an elevated antioxidant the enzyme level and declined lipid peroxidation activity [79].

23. Neuropsychopharmacological

Neuropsychopharmacological agents include the studies of anxiety disorders, affective disorders, psychotic disorders, degenerative disorders, eating behavior, and sleep behavior. The methanolic SC extract has exhibited the anti-amnesic activity against scopolamine induced spatial impairments in rats [80]. The methanolic and ethyl acetate SC seed extracts at the doses of 200 mg/kg and 400 mg/kg were evaluated for their CNS activity utilizing rota rod and actophotometer. A significant CNS activity was observed for both the extracts [81].

24. Radioprotective

Radioprotective agents are those that reduce the effect of radiation on tissues. SC leaf extract provided protection against radiation induced intestinal mucosal damage due to exposure of different doses of gamma radiations [82].

Dichloromethane extract of SC leaf and Hydroalcoholic seed extract when administered intraperitoneally exhibited radioprotective effects [83] [84]. SC leaf extract in various concentrations (0.0, 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml) was found to reduce the radiation induced DNA damage in the cultured human peripheral blood lymphocytes [85].

CONCLUSION

The present article has focused on the recent research investigations carried out on the diverse pharmacological actions of Jamun. Various parts of the plant and their extracts have been used for anti-diabetic action, but very less study has been performed on its isolated phytoconstituents

and very few clinical trials have been carried out. Apart from its utility in diabetes, it is a very useful drug as anti-bacterial, anti-fungal, anti-viral, anti-cancer, anti-hyperlipidemic, hepatoprotective, cardioprotective, gastroprotective and so on. Its potential as anti-fertility agent needs to be explored in order to establish its safety on long term use. Thus, further studies need to be performed with respect to pharmacological action of its isolated constituents, its mechanism of action and clinical studies.

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Conflicts of interest

There are no conflicts of interest.

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