Phytochemical constituents and pharmacological activities of *Lagenaria siceraria*: A comprehensive review

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INTRODUCTION

The ancient system of Indian medicine has been well explored for their role played in treating various diseases. The ancient literature has shown that there are abundant information that are available in Ayurveda, Siddha, Unani, and other traditional systems of medicines in curing various important lifestyle diseases such as diabetes mellitus, cardiovascular diseases, and hypertension among others. In recent times, the search for herbal drugs has gained great importance as they are considered much safer than the synthetic drugs. Notably, the traditional systems of medicines were considered as the best remedy for treating ailments such as dengue and jaundice where the allopathic system of medicines has failed to do so or rather ineffective in treating the ailments.

Since Vedic period, the Ayurvedic text mentions the use of more than 2000 herbs as medicines for curing different types of diseases. The ancient Indian folks have used these household spices and herbs for treating different diseases. It is known that several communities of people living in developing countries follow only traditional systems of medicines to treat their primary ailments. Due to these facts, several scientists and research laboratories across the world are engaged in exploring the active ingredients in these medicinal plants for treating life-threatening diseases.[3] As a result, the therapeutic importance of medicinal plants has gained momentum in the recent past in standardizing and conserving these herbal plants. Among them, cucurbitaceous plants have shown remarkable pharmacological activities. In this present review, we have chosen *Lagenaria siceraria* (LS) (bottle gourd), which is an important medicinal plant in the Cucurbitaceae family.

LS

Several important vegetables such as cucumber, pumpkin, and bottle gourd belong to the Cucurbitaceae family. Among this, the extracts of lagena (bottle gourd) find application as an antioxidant, laxative, cardioprotective, diuretic, hepatoprotective, central nervous system (CNS) stimulant, anthelmintic, antihypertensive, immunosuppressive, and analgesic.

PHYTOCHEMICAL CONSTITUENTS

Fruit contains Vitamin B complex and choline along with vitamin and beta-carotene cucurbitacins, fibers, and polyphenols is also seen. Sterols such as campesterol and sitosterol have been identified. The fruit is found to have antihapetotoxic activity, high-performance liquid
chromatography (HPLC) analysis of methanol from plant shows the presence of flavones C glycoside. LS fruits are a good source of ascorbic acid, fibers, proteins, cucurbitacins, saponins, and fucosterols.

Extract of its leaves showed the presence of sterols, polyphenolics, flavonoids, saponin, protein, and carbohydrates. A novel protein, lagnin, has also been isolated from its seeds, and it possesses antitumor, immunoprotective, and antiproliferative properties.

The fruit is rich in several essential amino acids and vitamins. A water-soluble polysaccharide is also isolated from fruit contains methyl alpha-d-galacturonate, 3-o-acetyl methyl alpha-d-galacturonate in ratio 1:1 which shows cytotoxic activity in vitro human breast adenocarcinoma cell line (MCF-7). Mono- and di-caffeoylquinic acid was seen. Triterpenoids such as 22-deoxiscucurbitacin D and 22-deoxiscucurbetanis were isolated; oleanolic acid, beta-sitosterol, etc., are other important compounds that found in the plant.[2]

**ACTIVITIES IN LS**

**Immunomodulatory**

The fresh juice of LS, the methanolic extract of LS fruit, showed significant reactions in rat with increase in white cells and lymphocyte. HPLC analysis showed the presence of lagnin (a ribosome-inactivating protein) which is responsible for the activity.

**Analgesic Activity**

The analgesic activity of LS was evaluated by Tail immersion method to determine the pain threshold capacity of rats using analgesiometer. It was found that the methanolic extract of LS fruit showed moderate activity at 180 min (3.97 ± 0.01) and the aqueous extract showed significant activity at 180 min (5.81 ± 0.006).[3]

**Antioxidant Activity**

The fruit juice showed antiradical activity; on dilution, no activity was seen. The extract was found to be effective in carbon tetrachloride (CCL4)-induced liver damage fresh fruits also showed the same activity HPLC analysis of methanol extract is found to have lagnin (a ribosome-inactivating protein) which is responsible for the activity. Acetone extract of fruit epicarp of LS fruit showed maximum antioxidant activity against in vitro model using 1, 1-diphenyl-

Using various in vitro assays such as reducing power assay, radial scavenging assay, superoxide scavenging assay, 3-(4,5-dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium bromide) (MTT) reducing assay, and lipid peroxidation inhibition assay, it was found that the ethyl acetate extract of bottle gourd fruit contains potent antioxidant activity.[4]

It is clear that the ethyl acetate extract of LS is found to have maximum antioxidant property in different in vitro including reducing power assay, radical scavenging assay, superperoxide scavenging assay, MIT reduction, and lipid peroxidation inhibitor assay. DPPH assay was performed by this method. Half-maximal inhibitory concentration (IC50) value was calculated, and change in absorbance with respect to control was calculated. New phenolic glycoside (E)-4-hydroxymethyl phenyl-6-o-caffeoyl-β-D-glucopyranoside was isolated.[5]

The methanolic extract of LS leaves is a potential source of natural antioxidant, and it plays an important role as therapeutic agent by preventing and slowing the progress of ROS and associated stress-related degenerative disease.[6]

The acetone extract of LS fruit epicarp shows maximum antioxidant activity. It was found that the presence of ellagitannins in the acetone extract of LS fruit is responsible for this radical scavenging activity.[7] Isoquercitrin was the major constituent which is responsible for the antioxidant property in LS. Polyphenolic compounds were isolated from extracts of LS. Flavones C glycosides such as isovitexin, isoorientin, saponarin, and saponarin 4-o-glucosidase were obtained in the methanol and water extracts of LS. Flavanoids such as isouqueretin and kaempferol were isolated from the ethyl acetate and n-butanol extracts of dried fruit sample. Phenolic acid such as gallic acid was also isolated. Ultra performance liquid chromatography studies were carried out (at 280 nm) by Mohan et al. method and were found that peak “7” is similar to that of derivative of caffeic acid. The levels of these compounds were found to be maximum in fruit extracts. Catechol moiety of isoquercetin was found to have the maximum antioxidant activity. From this study, it is found to be that gallic acid is in low content in LS. Isoquercetin present in LS can be used as α-glucosidase inhibitor.[8] Between the fresh and dried fruit extracts (such as ethyl acetate and n-butanol extracts) of LS, there is a minor difference in antioxidant properties and chemical profiles. Hence, both types of fruits either fresh or dried contain similar antioxidant property.[9]

It has been proven that the epicarp is the best source of antioxidant than the mesocarp, and it was found that
the ethyl acetate fractions of both epicarp and mesocarp have higher content of antioxidant. The total flavonoid content of the fruit was found to be 17.9 mg/g, which was measured by Sharma et al. method.\[10\]

Free radical scavenging method was studied which shown that the ethanolic extract of the Lagenaria seeds has maximum scavenging activity (75.19%) by DPPH free radical scavenging method.\[10\] The antioxidant activity of the fruit juice was studied using pyrogallol-induced oxidative stress. It was found that stimulation of humoral and cellular response was observed in immunosuppressed patients and thus showed a significant protection against the oxidative stress.\[11\]

**Antihyperglycemic Activity**

Hyperglycemia results in the generation of free radicals, which can exhaust antioxidant defenses, thus lead to disruption of cellular functions, oxidative damage to membranes, and enhanced susceptibility to lipid peroxidation, as reflected by the increased level of lipid peroxide in the liver. The beneficial effects of several flavonol glycosides, rutin, quercetin, anthocyanins, and various flavonoid-rich extracts, and various plants are already known to have antidiabetic activity, especially against type 2 diabetes mellitus. The oral glucose tolerance test showed that the globulins of the seeds of all species except *Cucumeropsis mannii* caused a significant drop in blood sugar. The results of electrophoresis showed that all species possess acidic and neutrals albumins and globulins, with molecular weight of protein subunits ranging from 6.36 to 44.11 kDa for albumins, 6.5 to 173.86 kDa for globulins, and 6.5 to 49.66 kDa for glutelins.

The extract of aerial parts in fruit showed activity in diabetes. The antihyperglycemic activity is due to the presence of good flavonoid content in fruit. Hyperglycemia was induced by streptozotocin (50 mg/kg, i.p.) in rats. Treatment was done by MELS at doses of 200 and 400 mg/kg, p.o. for 14 days. Glibenclamide (500 μg/kg) was used as a reference drug. Antihyperglycemic potential was assessed by fasting blood glucose measurement (on days 0, 4, 8 and 15), biochemical tests (serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total cholesterol (TC), and triglycerides (TGs)), antioxidant assay (lipid peroxide, catalase, and glutathione), and histologic study of the liver, kidney, and pancreas tissue.

Administration of phytosterols at a dose of 30 mg/kg has significantly decreased the blood glucose level and also has a significant increase in the oral glucose tolerance test animals in glucose tolerance.\[12\]

**Diuretic Activity**

The methanolic extract showed diuretic potential.\[13\] It was assayed by different parameters such as urine concentration, sodium, potassium, and chloride concentration.

**Cardioprotective Activity**

The LS fruit juice when given in rats with isoproterenol-induced myocardial infarction and there is cardioprotective effect.

Mali et al. evaluated the LS fruit powder against isoprenaline-induced cardiotoxicity in rats for cardioprotective activity. It was found that the pretreatment of LS powder (500 mg/kg) for 51 days protects the heart of rats against isoprenaline-induced cardiotoxicity. Hence, it has cardioprotective activity that was confirmed.\[14\]

The ethanolic extract of LS fruit (EELSF) shows cardioprotective activity based on lipid profile in isoprenaline-induced myocardial infarction in albino rat model. It was reported that the EELSF contains cardioprotective property and it is useful in the treatment of various cardiovascular diseases.\[15\]

**Immunosuppressive Activity**

The aqueous extract of LS fruit shows preferential suppression on cell-mediated immunity and shows no effect on humoral immunity. It was found that the extract could suppress the non-specific immune system.\[16\]

**Antigiardial Activity**

Earlier, the petroleum ether and methanolic extracts of certain cucurbitaceous vegetables were tested against *Giardia lamblia*. It was found that the petroleum ether extract of *C. maxima* seeds shows highest activity against *G. lamblia*.\[13\]

**Hepatoprotective Activity**

The ethanolic extract of LS fruit contains hepatoprotective and antioxidant activity against antitubercular drugs induced hepatotoxicity\[17\] and CCl$_4$-induced hepatotoxicity. Fucosterol and campesterol were the two sterols in petroleum ether fraction of LS which might be responsible for this activity.\[18\]

**Cytotoxic Activity**

Cancer is the leading cause of mortality. Cucurbitaceae family showed antitumor activity. It has been proved that the activity is due to cytotoxic and antioxidant property.

For the study, healthy mice were selected and Ehrlich’s ascites carcinoma (EAC) was inoculated, and it is treated with MELS (200 and 400 mg k) and standard drug 5-Flourouracil (20 mg/k) for about 9 days. Parameters such as hematological parameter, biochemical estimations, and antioxidant assay of liver
tissue were estimated. Experimental results revealed that anticancer activity was due to cytotoxicity and antioxidant properties. Antitumor activity of MELS against EAC tumor mice was known by studying parameters such as tumor volume, packed cell volume, viable and non-viable cell count, and median survival time. In this study, viable cell count was increased (2.20–31.99%) in treated groups, the mean survival time was increased up to 61.54% and this revealed the antitumor property of extract MELS. The level of lipid peroxide in liver was elevated in EAC-treated mice.\textsuperscript{[19]}

Triterpenoids present in fruit show cytotoxic activity. Compounds such as 3-o-coumaroyl-D:C-friedoleana-7, 9(11)-dien-29-oic acid and 20-epibryonolic acid showed cytotoxic activity against SK-Hep-1 cell line with IC50. The cytotoxicity of compounds 1-9 was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium bromide (MTT) colorimetric method-based procedure. Compounds 3b-O(E)-coumaroyl-D:C-friedoleana-7, 9(11)-dien-29-oic acids and 20-epibryonolic acid showed significant cytotoxic activity against the SK-Hep-1 cell line with IC50 values of 4.8 and 2.1mg/ml, respectively.

A water-soluble polysaccharide, isolated from fruiting bodies of LS, is composed of methyl-alpha-d-galacturonate, 3-O-acetyl methyl-alpha-d-galacturonate, and beta-d-galactose in a ratio of nearly 1:1:1. Compositional analysis, methylation analysis, periodate oxidation, and nuclear magnetic resonance (NMR) studies ((1) H, (13) C, 2D-COSY, TOCSY, NOESY, HMQC, and HMBC) revealed the presence of the following repeating unit in the polysaccharide. This polysaccharide showed cytotoxic activity \textit{in vitro} against MCF-7.

Four new D:C-friedoleanan-type triterpenes, 3 beta-O-(E)-fenoloyl-D:C-friedoleana-7,9(11)-dien-29-ol (1), 3 beta-O-(E)-coumaroyl-D:C-friedoleana-7,9(11)-dien-29-ol (2), 3 beta-O(E)-coumaroyl-D:C-friedoleana-7,9(11)-dien-29-oic acid (3), and methyl 2 beta,3 beta-dihydroxy-D:C-friedoleana-8-en-29-olate (6), together with five known triterpenes with the same skeleton, 3-epikarounidiol (4), 3-oxo-D:C-friedoleana-7,9(11)-dien-29-oic acid (5), bryonolol (7), bryonic acid (8), and 20-epibryonolic acid (9), were isolated from the methanol extract of the stems of LS. The structures of those compounds were elucidated using spectroscopic methods. Compounds 3 and 9 showed significant cytotoxic activity against the SK-Hep-1 cell line with IC50 values of 4.8 and 2.1 µg/ml, respectively.

**Hypolipidemic and Hyperlipidemic Activity**

Oral administration of the extract reduced TGs, cholesterol, and decreased low-density lipoprotein (LDL) and increased in high-density lipoprotein. The dietary fiber present in the fruit that lowers the cholesterol level. Saponins present in this fruit increase the lipoprotein activity and fast removal of fatty acids in the blood.

The white sterol crystals or phytosterols from the methanol extract were isolated for the 1st time and identified as a mixture of four sterols including fucosterol (1), racemosol (2), stigmasterol (3), and stigmasta-7,22-dien-3β,4β-diol (4). These compounds were identified by spectroscopic evidence including Fourier transform infrared, (1) H-NMR, mass spectra, and gas chromatography. The white sterol crystals, which are the mixture of four sterols, were evaluated for antihyperlipidemic activity in Wistar rats.

These sterol crystals (30 mg/kg) showed significant reductions in lipid profiles which included cholesterol, TGs, LDL, and VLDL. In addition, a significant increase in high-density lipoproteins (HDL) cholesterol observed, which is a good cholesterol that protects heart from coronary artery diseases. These sterol crystals or phytosterols can be used as an antihyperlipidemic agent to treat the hyperlipidemic.

The absence of necrosis, inflammation in the heart, and significant reduction in serum cholesterol in LS and L-arginine-treated rats indicated cardioprotective activity. Antioxidant activity of orientin and isoorientin appears to reduce the N-s-nitro-L-arginine methyl ester (L-NAME)-induced damage. It is concluded that LS fruit possesses antihypertensive and cardioprotective activity.

The studies revealed that plant LS showed a positive, Liebemann–Burchard test for sterols. White “sterol crystal” was extracted and it is identified as mixture of sterols (fucosterol, stigmasterol, racemosol, and stigmasta-7,22-dien-3β,4β-diol). These sterol crystals showed reduction in cholesterol level, TGs, LDL, very LDL (VLDL) levels, and HDL cholesterol which is good cholesterol that protects heart from coronary artery disease is also significantly increased by the “white sterols” in LS. Thus, they can be used as antihyperlipidemic agent to treat hyperlipidemia. Antihyperlipidemic activity was observed at a dose of 30 mg/kg.\textsuperscript{[20]} The methanolic extracts of LS fruits possess antihyperlipidemic activity. It was confirmed by performing test against experimentally induced hyperlipidemia in rats. It is cleared at the end of the 30th day, the lipid levels were much reduced and there is a significant increase in the excretion of bile acids.\textsuperscript{[21]} It shows positive test for sterols, i.e., phytosterol. Phytosterol is the mixture of four sterols (racemosol, stigmasterol, stigmasta-7,22-dien-3β,4β-diol, and fucosterol). It was found that the presence of phytosterol in bottle guard fruit having antihyperlipidemic property which helps to treat...
hyperlipidemia. Thus, it reduces the lipid level (TC, LDL cholesterol, and TG level in the serum), and it increases the HDL cholesterol level. It is also helpful for the treatment of coronary artery diseases in India.

The ethanolic extract of LS fruit contains antiatherosclerotic potential. Thus, it reduces the risk of atherosclerosis. It also reduces the cholesterol, TGs, LDL, and VLDL levels in serum and increases the HDL level. The extract induces lipoprotein lipase activity, and by reducing HMG COA reductase activity in hypercholesterolemic rats, it decreases the cholesterogenesis in liver.

The aqueous extract of LS leaves also shows good antihyperlipidemic activity. It reduces the TC, TG, LDL-C, VLDL, and AIS levels in serum and increases HDL level. Thus, it possesses antihyperlipidemic activity.

**CNS Activity**

The activity was performed with petroleum ether, methanol, and chloroform. Petroleum ether showed maximum analgesic activity and CNS depressant activity is due to the presence of chemical compounds.

**Anthelmintic/Antimicrobial Activity**

The extract of LS leaves showed significant dose-dependent anthelmintic activity against earthworm and tapeworm. The methanolic extract of LS caused paralysis of 9 min and time of death of 17 min while benzene extract revealed paralysis of 12 min and death of 22 min against the earthworm *Pheretima posthuma*. The crude extracts of LS not only demonstrated paralysis but also caused death of worms, especially at higher concentration of 100 mg/ml in shorter time as compared to reference drug Piperazine citrate. This study confirmed the crude extracts of seeds of LS has anthelmintic property.

The isolation of low molecular mass peptide-like compounds (678.9 dalton) from LS seeds has antimicrobial and trypsin inhibitory activity. On testing, these compounds show antimicrobial activity against *E. coli*, and at a molar ratio of 1:2, it shows trypsin inhibitory activity.

**Anti-uriclastic Activity**

Fruit powder against sodium oxalate-induced urolithiasis in rats showed antiuriclastic activity.

**Antianorectic Activity**

Anorexia nervosa is the third common illness among adolescent females. The fruit extract showed antianorectic activity.

The ethanolic extract of LS fruit shows antianorectic effect against physical stress and LPS induces anorexia.

**NUTRACEUTICALS**

Results showed improved TG, HDL, and VLDL levels with the decrease in risk of heart disease. LSFE levels acts as nutraceuticals for disease prevention.

**Fibrinolytic Activity**

Kaempferol-a-flavonoid isolated from the fruit showed fibrinolytic activity.

**Antidepressant Activity**

This activity is due to flavonoids, saponins, and sterols. Prajapati et al. suggested that the methanolic extract of LS Standley fruits (MESF) has antidepressant activity due to the presence of flavonoids, saponins, and sterols in it. The chemical constituents present in the MESF are flavonoids, saponins, phytosterols, carbohydrates, tannins, protein, and amino acids.

**Anti-stress Activity**

Stress-induced elevated blood cell count of white blood cell (lymphocytes, neutrophils, and basophils) has significantly reduced. Lowering on stress-induced hyperglycemia is an indication of antistress and adaptogenic activity of plant. There is an increased cortisol level; this extract significantly decreased stress-induced level of cortisol.

LS is capable of increasing the capacity to tolerate non-specific stress. It is also used in the adverse changes associated with stressors that alter and impair the normal functioning of microorganism.

**Antihypertensive Activity**

Mali et al. evaluated the LS fruit in L-NAME-induced hypertension in rats for its antihypertensive and cardioprotective activity. It was found that the LS fruit possesses both these activities.

In this study, the LS fruit powder possesses antihypertensive activity against dexamethasone-induced hypertension in rats. It was found that the dexamethasone-induced hypertension in rats was partially reversed by the long-term treatment of LS (500 mg/kg).

**Anti-obesity Activity**

The ethnomedicinal reputes of the plant for its fat-lowering effect. The methanolic extract and its ether, ethyl acetate, n-butanolic, and aqueous fractions showed dose-dependent lipase inhibitory activities with IC50 (mg/mL) 293.4, 231.7, 189.6, 370.0, 252.2, and 261.9, respectively. For comparison, the IC50 of the standard drug Orlistat was 145.7 mg/mL. As the results indicate, the chloroform fraction was most potent and ethyl acetate fraction least potent.
The LS fruit has a good ability to inhibit the pancreatic lipase activity. It suppresses the lipid digestion. Thereby, it prevents the entry of lipid into the body. Regular intake of LS fruit aqueous decoction helps to treat obesity.[31]

**Antibacterial Activity**

Minimum bactericidal concentration (MBC): The MBC was determined by samples from all wells showing no growth as well as sample from the lowest concentration showing growth in the MIC assay, was subculture on freshly prepared nutrient agar. Plates were incubated for 24 h at 37°C. The highest dilution that yielded no single bacterial colony on a solid medium was taken as MBC 20.[25]

**CONCLUSION**

The present review brings in the various phytochemical constituents and various pharmacological activities of the fruit LS. The review provides, in addition, the importance of phytochemical constituents and its role in the different pharmacological properties.

**REFERENCES**