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Sparsh Bhat

Suresh Joghee

Meenakshi S. Iyer

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REVIEW

The Therapeutic Potential of *Nelumbo Nucifera*: A Comprehensive Review of Its Phytochemistry and Medicinal Properties

Sparsh Bhat ^a, Suresh Joghee ^{a,*}, Meenakshi S. Iyer ^b

^a Department of Pharmacognosy, JSS College of Pharmacy, Mysuru, Karnataka, 570015, India

^b Department of Prosthodontics, JSS Dental College and Hospital, Mysuru, Karnataka, 570015, India

Abstract

Nelumbo nucifera generally known as 'sacred lotus' is a plant with high medicinal value in traditional medicine system especially in Chinese medicine system which is having a wide distribution worldwide in Asian, Western European, American and Australian continent. All the parts of the plant have different medicinal value, as their extract contains various valuable chemical constituents which yield desired remedial effects against many diseases. The plant is used traditionally more compared to its commercial usage. It has also been used for dental and skin care products in many herbal formulations. In this review, data about its general description, its distribution, chemical constituents and therapeutic effects has been provided. The plant has various uses against many diseases and the review focus on anti-epileptic, anti-viral, anti-cancer, antimicrobial, anti-inflammatory, anti-hyperlipidemic, anthelmintic, anxiolytic & anti-depressant, anti-cariogenic, analgesic, hepatoprotective, vasorelaxant, anti-coagulant, anti-obesity, anti-neurodegenerative, anti-aging, anti-oxidant, and immunomodulatory properties of the plant.

Keywords: *Nelumbo nucifera*, Lotus, Nelumbonaceae, Anticancer, Antiaging

1. Introduction

Officially Nelumbonaceae family consists of two plants i.e. *Nelumbo nucifera* and *Nelumbo lutea* (see Table 1). In this review we will discuss about *Nelumbo nucifera* which is an aquatic perennial herbal plant having a growth of about 1.5 m and a maximum horizontal stretch of 3 m. The diameter of its leaves may reach up to 60 cm that floats on top of the water surface whilst its roots are still linked to the mucky bottom of the water bodies. The flowers are found on stalks that rise above the leaves and can be up to 20 cm in diameter [1].

This plant has been valued for ages as a sacred symbol by many cultures, including Hindus, Buddhists, and Egyptians. Most Asian nations, including Japan, China, Nepal, India, Sri Lanka, and Thailand, are home to this species and it's also the national

flower of Vietnam and India. *Nelumbo nucifera* was long ago introduced to America and Western Europe, and it is also found in Russia and Australia [3]. It has varied colloquial names such as Chinese water lily, lotus, etc. [4] In India it's commonly called as 'kamala', but it still has different vernacular names in various regions of India as well as in different parts of the world:

Sanskrit: Sitopala, Abja, Kalhira, Pankaja, Padma,
English: Lotus.

Hindi: Kamal, Kanwal

Oriya: Padma.

Kannada: Kamal, Naidile, Tavare, Tavaregedd,

Punjabi: Pamposh, Kanwal,

Tamil: Aravindan, Tamarai, Paduman, Sarojam [5].

There are various botanical names used in different sites and literatures for Lotus such as

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* Corresponding author at: JSS College of Pharmacy, Mysuru, Karnataka, 570015, India.
E-mail addresses: sparsh.mahanoori@gmail.com (S. Bhat), jsuresh@jssuni.edu.in (S. Joghee), dr.meenakshis@jssuni.edu.in (M.S. Iyer).

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Table 1. Taxonomic classification [2].

Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Order	Nelumbonales
Family	Nelumbonaceae
Genus	<i>Nelumbo</i>
Species	<i>nucifera</i>

Nymphaea nelumbo, *Nelumbium nelumbo* or *Nelumbium speciosum*, even these are correct as they were the old names referring the plant, but *Nelumbo nucifera* is the latest official name given [4]. Lotus has 0.5–2.5 cm in dia. cylindrical shaped rhizomes that are yellowish-white to yellowish-brown in colour having longitudinal brown patch marks with different nodes and internodes [6]. In a study conducted by Maharana S. et al., 2022 it was observed that the seeds have blackish brown colour with oval to globular shape and the fruit size ranges from 0.5 to 2 cm. In microscopic analysis it was observed that the fruit pericarp is unbreakable and extremely hard, the fruit wall surface had minute pores and in order to facilitate gas exchange, these pores are bordered with hexagonal cells. Other than the epidermal pores the fruit also displayed rosette scleride and double-layered palisade tissue. Alkaloids, flavonoids, steroids, saponins, terpenoids, phenols and tannins were the phytochemicals found in the methanolic seed extract. The starch grains' morphology was discovered to be basic, elliptical to polygonal, and oval in shape. By using acetic acid, water, and butanol (1:1:4 v/v/v) as the solvent system, the HPTLC fingerprint of the hot and cold extract revealed the presence of 9 bands on the plate, R_f ranging from 0.05 to 0.94 [7]. In another study by Ruvanthika et al., 2017 glycosides were present in aqueous, acetone and ethanol extract of the seeds [8].

1.1. Chemical constituents

Flower Petals:

The *Nelumbo nucifera* flower petals' ethanolic extract contains eight distinct compounds:

- A. myricetin-3-O-D-glucopyranoside,
- B. quercetin-3-O-D-glucuronide,
- C. astragalin,
- D. quercetin,
- E. 3,4-dihydroxybenzoic acid,
- F. kaempferol,
- G. p-hydroxybenzoic acid,
- H. β -sitosterol.

Compounds A, B, D, E, F, G, and H were among those isolated from *Nelumbo nucifera* petals for the first time. Compounds A and E were initially discovered in the genus *Nelumbo* [9].

Rhizomes: By using chemical and spectroscopic techniques, the rhizomes of *Nelumbo nucifera* yielded maslinic acid, hyptatic acid-A, 2 α ,24-diacetoxy-3 β -hydroxyolean-12-en-28-oic acid (new triterpenoid), betulin, and lupeol [10].

Seed Embryos: Four familiar chemical compounds, liensinine, neferine, anisic acid and isoliensinine, —as well as three bisbenzylisoquinoline alkaloids, nelumborines A and B, and nelumboferine —were identified from the embryos of *Nelumbo nucifera* seeds [11].

Seeds: 1-Heptadecanol; 1-Monolinoleoylglycerol trimethylsilyl ether; 3-hydroxy-7-isopropenyl-1,4a-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl ester; 4,22-Stigmastadiene-3-one; 9,12-Octadecadienoic acid; Di-n-octyl phthalate; 11-Hexadecenoic acid; Acetic acid; Ergost-25-ene-3,5,6,12-tetrol, (3.beta., 5.alpha., 6.beta., 12.beta.); Hexadecanoic acid; n-tetradecanoic acid; Vitamin A aldehyde; and Essential oil [8].

Seed pods: 3.alpha.-(Trimethylsiloxy) cholest-5-ene; 9-Octadecenoic acid ethyl ester; 11, 14-Eicosadienoic acid; 13-Tetradecenal; Hexadecanoic acid; Docosanoic acid; Linoleic acid ethyl ester; and Tetradecanoic acid [8].

Medicinal Activity:

1. Anti-epileptic:

Rajput et al., 2017 [12] researched in a strychnine-induced seizure model, the anti-epileptic activity using oral dosage of ethanolic *Nelumbo nucifera* fruit extract was assessed in rats of 5 groups (7 rats per group) everyday for a period of 15 days. In comparison to the control group, it was discovered that fruit's ethanolic extract at a certain dose significantly delayed the seizures' onset. However, the duration and intensity of the seizures increased and decreased, respectively, thereby improving the survival rate of the rats by 42.85% in comparison to the outcome of diazepam-reference drug. The results showed that this extract has beneficial anti-epileptic action, but to validate these outcomes further innovative research, in a large number of animals is required.

2. Anti-viral:

W.-K Cho et al., 2022 [13] conducted a study on RAW 264.7-TIB-71 Macrophage cell line and tested the 100 mg/ml concentration of *Nelumbo nucifera*

water extract of leaf. The neuraminidase and hemagglutinin activities of Influenza A Virus (IAV) were both significantly suppressed by *Nelumbo nucifera* leaf water extract, which also boosted viability of cell by averting the cytopathogenic effects of H3N2 & H1N1 IAV infection. The outcomes implied that IAV infection was significantly inhibited by *Nelumbo nucifera* water extract of leaf and this extract might be formulated as a natural anti-viral drug that can prevent influenza viral infection.

3. Anti-cancer:

Wu et al., 2017 [14] conducted a study in which it was discovered that MDA-MB-231 & 4T-1 breast cancer cells had much less migration when exposed to (NLE) *Nelumbo nucifera* extract of leaf and (NLPE) *Nelumbo nucifera* polyphenol extract of leaf. RhoA, Rac1, and Cdc42 expression was reduced in the presence of NLE and NLPE, it also inhibited p38 MAPK and ERK activation. Furthermore, NLPE and NLE treatment dramatically decreased in vivo lung metastasis of breast cancer and protein kinase C α activation. Overall results displayed the affect of NLPE and NLE on migration of breast cancer cell, indicating its future usage as chemo-preventive medicines to stop the spread of the disease.

Another study [15] displayed that the results, in comparison to the control group, rats given NLE had significantly lower levels of serum aspartate amino transferase, alanine amino transferase, and albumin, all of which are signs of hepatocellular injury. NLE reduced DEN-induced oxidative stress, accompanied by a dip in lipid peroxides and a rise in the activity of catalase, glutathione peroxidase, glutathione transferase, and superoxide dismutase in liver tissues. In NLE-administered rats, the non-enzymatic antioxidants' status, such as reduced glutathione, was discovered to be elevated as well. In addition, when compared to the DEN-only group, NLE reduced tumour growth, hepatic GST π , PKCa, and Rac1 expressions. NLE supplementation therefore lessened the harmful effects of liver cancer. The above mentioned results displayed that NLE prevents carcinogenic effects on liver brought on by DEN therapy by inhibiting hepatic cell oxidative stress, lipid peroxidation, and boosting the anti-oxidant defence mechanism.

Chen et al., 2014 [16] assessed the antiradical scavenging, ferric reducing power assays and metal chelating to determine the anti-oxidation activity of chemicals isolated from *Nelumbo nucifera* leaves. The outcomes demonstrated the antioxidative action of these substances. Additionally, the study looked at how well the extracted phytochemicals repressed

the growth of human melanoma, gastric, and prostate cancer cells and according to the results, melanoma, stomach, and prostate cancer cells were significantly prevented from proliferating by 7-hydroxydehydronuciferine. All of these results point to the *Nelumbo nucifera* leaves as a reliable source of physiologically active compounds with anti-oxidant characteristics.

4. Anti-microbial:

According to Kumar et al., 2011 [17] research results, *Nelumbo nucifera*'s methanolic extract exhibited comparable anti-bacterial activity against reference standards at 150 mcg/ml concentration on *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Micrococcus luteus*, *Bacillus aureus*, *Escherichia coli*, *Klebsiella pneumonia*. This extract concentration might be employed in alternative medicine to avert the progression of numerous diseases. Additionally, based on the needs of the treatment, these data may help in creating appropriate dosage forms like lotion, ointment, and cream.

5. Anti-inflammatory:

According to Rajput et al., 2021 [18], when comparing control to the *Nelumbo nucifera* ethanolic fruit extract, the extract significantly reduced paw inflammation and edema level in Wistar rats given carrageenan at all doses (third to the fifth hour). This makes it a valuable treatment option for people with chronic inflammatory diseases. However, to substantiate these findings, additional preclinical and clinical testing is needed.

According to Cho et al., 2012 [19], by preventing NO generation in RAW 264.7 cells that have been triggered by lipopolysaccharide (LPS), extracts from *Nelumbo nucifera* leaves displayed anti-inflammatory properties. The expression of the induced nitric oxide synthase protein was inhibited in order to achieve this suppression of NO generation. Furthermore, interleukin-6 (IL-6), a cytokine linked to an inflammatory response, was shown to be inhibited by *Nelumbo nucifera* leaf extracts which suggests that addition of leaves extract of *Nelumbo nucifera* in oral formulations will work well to avoid periodontal disorders or treating the same.

6. Anti-hyperlipidemic:

According to the study conducted by S. Liu et al., 2013 [20], *Nelumbo nucifera* leaf flavonoids (NLF) effectively inhibits -glucosidase, -amylase, and PPL. Furthermore, NLF have high lipid-lowering effect, which was proven by the reported therapeutic

effects of NLF against experimentally induced hyperlipidemia in rats. These results authenticated traditional knowledge that implied that these flavonoids may provide a supplementary strategy for the management and treatment of hyperlipidemia.

A study conducted in recent years [21] revealed an additional proof that lotus stamen could be utilised as an alternate therapy for dyslipidemia. 30 patients with hyperlipidemia were placed into two groups for a 4-week randomised, controlled interventional study: the oral lotus stamen tea group, and the control group. The study chose to provide the intervention for 4 weeks while monitoring the subject at the 2nd and 4th weeks. However, this paper presented early study findings that indicated lotus stamen tea could lower both LDL and total cholesterol levels in blood following a 2-week intervention. Blood triglyceride and HDL cholesterol levels did not change, and there were no adverse effects or abnormal renal or liver function as a result of this intervention. Additionally, blood liver enzyme levels and blood renal function did not change.

7. Anthelmintic:

Yen et al., 2014 [22] study was the first to identify *Nelumbo nucifera*'s anthelmintic properties against *Hymenolepis nana*. Thus, we discovered that aporphines and oxoaporphines, respectively, had radical scavenging action against peroxy radical in addition to their cestocidal activity for *H. nana*. Therefore, while having radical scavenging properties, those compounds nevertheless had cestocidal action against *H. nana*. These findings may prove helpful in the research for naturally occurring anthelmintics that are more effective.

8. Anxiolytic & Anti-depressant:

Khan et al., 2017 [23] study displayed that the *Nelumbo nucifera* fruit has anxiolytic and anti-depressive properties, and it's possible that this is because both the seed pods and the seeds are abundant in important phytochemical components including alkaloids and flavonoids. Furthermore, the anti-depressant and anxiolytic effects of *Nelumbo nucifera* fruit were substantially comparable to those of Imipramine and Diazepam. Further research is required in this area due to *Nelumbo nucifera* fruit's significant potential for aiding in the treatment of CNS diseases like anxiety and depression.

9. Anti-cariogenic:

Lee et al., 2019 [24] study examined the anti-cariogenic effect of *Nelumbo nucifera* leaf extract (NLE)

against nine different kinds of oral-disease causing bacteria. The anti-cariogenic activity of NLE in all nine species of bacteria, including *S. mutans*, the activation of GTase was suppressed by at least 50%. The leaf extract was found to have 85% GTase activity inhibitory impact on *S. anginosus*. According to the study results, a concentration of NLE exhibited potent growth, GTase activation, and acid generation inhibitory effects. The study results displayed that NLE has anti-cariogenic properties against the oral bacteria causing dental caries. After conducting additional research in the near future, NLE can thus be used as an anti-cariogenic product.

10. Analgesic:

Rajput et al., 2019 [25] assessed *Nelumbo nucifera* fruit (NNF) extract's central analgesic activity in mice by both the acetic acid-induced writhing test & the tail-flick test, which showed that NNF extract had excellent analgesic effect that was comparable to aspirin. This suggests that both the seeds and the pods, which make up the two segments of NNF, seem to be rich in saponins, flavonoids, and tannins. NNF extract thus appears to have a considerable potential in the treatment of conditions linked to pain, and requires additional experimental research in this area.

11. Vasorelaxant:

Gong et al., 2020 [26] with the use of porcine coronary arteries, examined the vasorelaxant effects of *Nelumbo nucifera* extract along with its underlying mechanisms. The vasorelaxant properties of extracts from four different *Nelumbo nucifera* sections i.e. sporiocarpium, seed, leaf and flower extracts were examined. Of them, *Nelumbo nucifera* sporiocarpium (NNS) extracts demonstrated the most potent endothelium-dependent vasorelaxation. The vasorelaxation action of NNS was greatly decreased by inhibitors of endothelial nitric oxide synthase (eNOS), phosphoinositide 3 kinase (PI3K), and soluble guanylyl cyclase (sGC), but was unaltered by inhibitors of cyclooxygenase and EDHF. In endothelial cells, NNS caused concentration-dependent phosphorylation of eNOS. Overall, the research showed that NNS is an effective endothelium-dependent vasodilator that works through the PI3K-eNOS-sGC pathway. This research revealed NNS as a promising herbal option for the treatment of CVD linked to atherosclerosis and endothelial dysfunction.

12. Anti-coagulant:

Ramya et al., 2017 [27] studied that in comparison to other concentrations of 0.25 g/ml, 0.125 g/ml, and

0.062 g/ml, the leaf extract concentration of 0.5 g/ml had the greatest effect with respect to all of the tested extracts. As a result, *Nelumbo nucifera* leaf extract in various concentrations of methanol, ethanol, and ethyl acetate prevents clot formation and raises prothrombin time in a dose-dependent manner, which may be due to the existence of steroids, flavonoids, and tannins in it. *Nelumbo nucifera* leaf extract has pharmacologically active anti-coagulant components, according to the results of in vitro studies on the topic, which may be useful in preventing blood clotting disorders. As a result, *Nelumbo nucifera* leaf may be employed as an alternative source of natural anti-coagulant in the future after more research regarding the same is conducted.

Rajput et al., 2019 [28] performed a study in which 35 male Wistar rats were divided evenly into 5 groups for the anti-coagulant assessment. The results indicated that *Nelumbo nucifera* fruit (NNF) extract 200 mg/kg greatly increased prothrombin time and thrombin time while dramatically lowering fibrinogen levels in comparison to control. Without influencing the other coagulation parameters, such as the activated partial thromboplastin time, prothrombin time, or thrombin time, NNF 100 mg/kg also dramatically decreased the fibrinogen level when compared to the control. NNF displayed potent anti-coagulant activity, and can possibly be explained by its effect of inhibition on thromboxane A₂ production and the activation, adhesion, and aggregation of platelets. Neferine, an alkaloid, along with various flavonoids present in the extract may be the cause of its anti-coagulant effect which may be useful in doctoring different atherosclerotic and thrombotic conditions, however further studies are required to establish these results.

13. Hepatoprotective:

Wang et al., 2019 [29] study outcomes showed that the recently advanced technique was successfully used to evaluate the defensive function of lotus leaf, also exploring the prospective lotus leaf hepatoprotective mechanisms. According to the data, lotus leaf actively defended the liver from damage brought on by Genkwa Flos by controlling the metabolism of various amino acids, sphingosine, and LPC. In addition, lotus leaf's anti-oxidant, anti-inflammatory, and lipid-regulating properties were closely linked to its hepatoprotective effects. This study may help to disclose the lotus leaf's defence mechanism and find several clinical applications for it with further studies.

14. Anti-obesity:

Ono et al., 2006 [30] researched the pharmacological basis of *Nelumbo nucifera* leaf extract's (NNE) anti-obesity activity. Using mice that had been given a high-fat diet and NNE treatment for five weeks, the efficacy of NNE on the activity of digestive enzymes, lipid metabolism, and thermogenesis was observed, along with efficacy in preventing obesity. Mice with high-fat diet induced obesity were given NNE, which stopped the liver triacylglycerol levels, parametrial adipose tissue weight, and body weight from rising. When mice were given NNE and exercised, skeletal muscle UCP3 mRNA expression tended to be higher. As a result, NNE hampered digestion, increased energy expenditure, sped up the metabolism of lipids, and prevented the absorption of carbohydrates and lipids. NNE is therefore advantageous for the prevention of obesity.

Ahn et al., 2013 [31] investigated on anti-obesity activity concentrated on two distinct pathways, i.e. fat absorption and fat storage. As the best method of treating obesity, a combination of these processes is preferred. The varied components of *Nelumbo nucifera* leaves allow for a variety of actions. The results showed that the benzoisoquinoline alkaloids prevented the absorption and storage of fat. While flavonoids were better at preventing fat storage, other alkaloids and meta-stigmanes were better at preventing fat absorption. As a result, *Nelumbo nucifera* leaves may have synergistic effects in the management of obesity by jointly limiting fat absorption and fat formation and they may be used to treat obesity since they prevent pancreatic lipase and adipocyte differentiation.

15. Anti-neurodegenerative:

Jung et al., 2015 [32] studied BACE1 and ChEs inhibition through bioactivity-guided fractionation and isolation study of *Nelumbo nucifera* embryos which revealed that the major compounds vitexin, liensinine, and neferine, along with the minor compounds northalifoline and quercetin-3-O-glucoside, imparted significant BACE1 and ChEs inhibitory effects, and ONOO⁻ scavenging effects, proposing their prospective role in treating Alzheimer's Disease. For the first time, the extracted compounds' AChE and BACE1 inhibitory actions were compared. The results of this investigation showed that by reducing oxidative stress, these substances may have therapeutic or preventative effects on Alzheimer's Disease.

16. Anti-aging:

Kim et al., 2011 [33] investigated the water extracts of flower, seed, leaf, stem, and root from *Nelumbo nucifera* for their functional cosmetic effects. All of the *Nelumbo nucifera* extracts met the requirements for cosmetic use. The seed and flower extracts from *Nelumbo nucifera* displayed such strong anti-oxidant properties that the concentration for each extract was 5 µg/ml to show 50% inhibition. The seed, flower, and leaf extracts of *Nelumbo nucifera* displayed DOPA-oxidase inhibitory effect of 57%, 59%, and 50%, respectively, compared to arbutin's 44%. At 200 µg/ml, The seed, flower, and leaf extracts of *Nelumbo nucifera* demonstrated 54%, 56%, and 49% elastase inhibition, respectively, whereas adenosine displayed 26% inhibition. Also, no skin irritation was observed in the volunteers who were tested for skin irritation with water cream containing *Nelumbo nucifera*'s 1% leaf, stem, flower, and root extract and 4% combined extracts. It was concluded that the seed and flower extracts of *Nelumbo nucifera* have significant anti-wrinkle potential for cosmetic products.

Kim and Moon, 2015 [34] studied lotus seed tea's skin protective property against UVB irradiation on hairless mouse model divided into two groups i.e. control group and lotus seed tea group for six months. Both groups received UVB exposure for an additional three months after the initial six months of treatment. The skin moisture content and biopsy-based morphological and histological investigations were done both during and after the administration. There was no discernible change between the skin moisture content of the control group and the lotus seed tea group before UVB irradiation ($P < 0.05$). However, following the UVB treatment, significant modifications were seen. When compared to the control group, the lotus seed tea group clearly demonstrated skin protection. The consumption of the lotus seed tea boosted UVB exposure protection, as evidenced by various tests in the study. As a result, drinking lotus seed tea regularly has the impact of stopping the skin moisture loss, reducing the aberrant keratinocytes' development, and assisting in the inhibition of protein oxidation.

17. Anti-oxidant:

Chunyun Zhang et al., 2017 [35] did a study *Nelumbo nucifera* seed embryo and observed that the seed embryos had less overall flavonoid content than lotus leaves. Compared to lotus leaves' flavonoid O-glycosides, lotus seed embryos' flavonoid C-glycosides displayed stronger anti-oxidant effects

suggesting that lotus seed embryos may become a potential source for antioxidants.

18. Immuomodulatory:

D. Mukherjee et al., 2010 [36] studied the total leukocyte count, differential leukocyte count, the neutrophil adhesion test, the phagocytic response, the delayed type hypersensitivity reaction and the nitroblue-tetrazolium reduction test on swiss albino mice to assess the immunomodulatory activity of the plant's seed and rhizome extracts and it was observed that both the extracts modulated various immunological parameters, thereby stimulating the defense system.

2. Toxicity Studies

P. Kunanusorn et al., 2011 performed a research to evaluate the safety of *Nelumbo nucifera* stamens extract an acute and subchronic oral toxicity studies were performed on Sprague–Dawley rats for 90 days. *Nelumbo nucifera* stamens extract's oral fatal dose for female and male rats was found to be greater than 5000 mg/kg, while the extract's no-observed-adverse-effect level for rats' both sexes was thought to be 200 mg/kg/day [37].

3. Conclusion

The review focuses on geographical distribution, phytoconstituents, pharmacological activities, and toxicology of the *Nelumbo nucifera*. There are varied Pharmacological applications of the herb like anti-epileptic, anti-viral, anti-cancer, antimicrobial, anti-inflammatory, anthelmintic, anxiolytic & anti-depressant, anti-cariogenic, analgesic, anti-coagulant, anti-neurodegenerative, anti-aging, and immunomodulatory, etc. It also exhibits muscle relaxant, anti-aging & anti-wrinkle applications due to the plant having vasorelaxant & anti-oxidant properties and can be utilized in some tonics or serum and facial creams. Other than the plant being a source for treatment for various diseases, it is also cooked as a curry and side dish with meals in Asian countries. The plant *Nelumbo nucifera* needs more in-depth research for its use on scientific lines.

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None.

Conflicts of interest

None.

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