Review Article

Recent Advances of Whole Plant *Nelumbo nucifera* – A Review

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ABSTRACT

The lotus (*Nelumbo nucifera*) is a perennial basal aquatic plant belonging to the small Nelumbaceae family, which contains only one genus with two species *Nelumbo nucifera Gaertn* (Nymphaeaceae), also known as the sacred lotus, is a well-known medicinal plant. Lotus seeds are edible and have been used for centuries as a traditional medicine to treat various ailments. The plant has several therapeutic properties for which different parts are used. The longevity of lotus seeds is unique. Studies have shown that they have hepatoprotective, hypoglycemic, immunomodulatory, anti-analgesic, anti-Parkinsonian, anti-reproductive, anti-dermatophyte and psychopharmacological properties. This article reviews the traditional uses, phytochemistry and therapeutic reports on the different parts of *N.nucifera*, namely seeds, rhizomes, leaves and flowers. This report also describes the different compounds isolated from different parts of this plant and the therapeutic effects obtained from these plant constituents. The high content of fiber, starch, vitamins and minerals suggests that there may be good opportunities for future upgrading and application as functional additives and ingredients in the food industry. There is a need to study the properties of the lotus plant for incorporation as a functional ingredient in the food industry such as flour in the bakery industry, as an antioxidant, in baby foods, extruded products, beverages, etc., especially the properties of the lotus plant from the rhizome part.

Keywords: *Nelumbo nucifera*, phytochemicals, traditional medicine, pharmacological activities.

INTRODUCTION

Lotus is an aquatic perennial plant. It is a member of the tiny Nelumbonaceae family, which consists of just one genus, Nelumbo, and two species, *Nelumbo lutea* Pear and *Nelumbo nucifera* Gaertn., also known as Asian and American lotus, respectively. The Asian lotus tree is considered sacred in Buddhism and Hinduism, thus its other name, the sacred lotus[1]. Scientists are becoming more and more interested in the holy lotus due to its significance in gardening, medicine, and plant phylogeny. An overview would surely improve lotus breeding and application to have sufficient basic understanding about this plant as well as its traditional usage, chemical composition, physicochemical characteristics, phytoconstituents, also their numerous physiological, psychological, and therapeutic information currently accessible on the subject[2]. There are several therapeutic applications for every portion of N. nucifera. Pharyngopathy, pectoralgia, spermatorrhoea, leucoderma, smallpox, dysentery, cough, haematemesis, epistaxis, haemoptysis, haematuria, metrorrhagia, hyperlipidaemia, fever, cholera, hepatopathy, and hyperdipsia are among the traditional ailments treated with the leaf, rhizome, seed, and flower[3]. This plant is also used in Ayurveda to cure strangury, vomiting, leprosy, skin conditions, and nervous weariness. It is also used as an anthelmintic and diuretic[4]. It is used as an antidote to poisons and to treat skin conditions, cancer, leprosy, and tissue inflammation[5].

1. Physical Characteristics and Morphology

Large aquatic rhizomatous plant *Nelumbo nucifera* has long, thin creeping stems with nodal roots. Perennial Lotus plants have orbicular leaves that are both airborne and floating[6]. While floating leaves have a flat appearance, aerial leaves are cup-shaped[7]. Its petioles have noticeable prickles and are rather lengthy and tough. Flowers are solitary, hermaphrodite, and range in colour from white to rose. They also have a very fragrant aroma. Flowers are ovoid, glabrous, and have an average diameter of 10–25 cm[8]. Fruit with seeds is firm, ovoid, and black in colour. The seeds are organised in whorls within the fruit, and as the pod bends down towards the water, the seeds mature and release[9]. Eight inches long and two inches in diameter make up tuberous roots. The lotus root's smooth, green exterior layer belies its numerous large air pockets inside, which let the tuber float in the aquatic system. These pockets span the length of the tube[10]. Figure 1 represent the various parts of *Nelumbo nucifera* a) Flower b) leaf c) seed d) root.

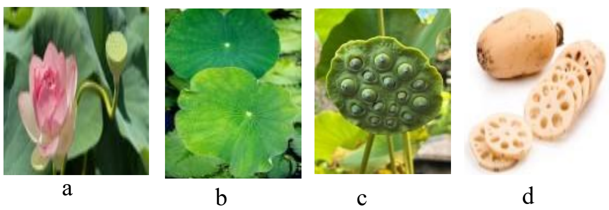

Figure 1: Various parts of *Nelumbo nucifera* a) Flower b) leaf c) seed d) root

1.1 Leaves

Both varieties of huge leaves are aerial and floating, ranging in size from 20 to 90 cm. The leaves are leathery when they are fresh, but after drying, they become nearly membranous and brittle. The lower surface has some brownish red blotching, and the petioles of the aerial leaves are erect and stout white, while those of the floating leaves are not strong enough[11]. The diameter is abruptly acute to form a short tip, and they are petiolate, entire glaucous, non-wettable, strong cupped in the case of aerial leaves and flat in the case of floating ones, radiantly nerved. For airborne leaves, the typical length is from 24 to 33 cm, while for floating leaves, it is 23 to 30 cm. Petioles are smooth, green or greenish brown in colour with tiny brown spots; they can also be rough with very minute but definite pinches; the fragrance is pronounced; and the fracture is fibrous[12]. The petiole of the leaf stalk usually exhibits four distinct, big holes in the center and minor cavities on the perimeter when transversely sliced[13].

1.2 Fruit and seed

Fruit is a collection of immature nutlets. Ripe nutlets have a firm, smooth, brownish or greyish black pericarp that is pedunculated, one-seeded, and somewhat longitudinally striated[14]. They are ovoid, roundish, or oblongish, up to 1.0 cm long and 1.5 cm broad. The ripe carpel is filled with seeds[15]. The fruit of N. nucifera possesses an amazing ability to remain dormant, and its seeds have been shown to last longer than those of any other flowering plant species. After 150 years of captivity in a glass-topped box, Robert Brown, the first botanist at the British Museum, tested with Nelumbo fruits at different periods between 1843 and 1845 and found that they still had the ability to germinate[16].

1.3 Flowers

Sepals, petals, and stamens are spirally arranged and gradually pass one into another. Solitary, large, 10–25 cm in diameter, white pink or pinkish white fragrant peduncles arising from the nodes of the rhizomes, sheathing at the base, 1-2 cm long, green or blackish green, hard and stout, smooth or rough due to the presence of numerous small scattered prickles[17].

1.4 Root

The epidermal root consists of two cell layers with the thickness of 97.50 - 124.09 µm on average and accounts for 5.91 - 8.29% the root radius. The parenchymal cells have a spongy cortex root, covering the pericycle. The parenchyma cells are arranged into many inter cellular air spaces, allowing the roots to transport air and to breathe easily in the anaerobic environment[18]. The innermost part of the cortex is the shell with thick and round cells allocated in consecutive rings to help improving the resistance ability of the root. The roots of lotus plant are very important as 70% of them are used in the form of fresh food[19]. Twenty percent are used to produce different products like vinegar, root powder, juices, etc. Different scientists have extracted polysaccharides from lotus roots as well as lotus root residues[20].

2. History of medical and other uses

Along the banks of the Nile River, lotus and the closely related species known as "sacred blue lotus" (*Nymphaea* caerulea) have long been prevalent. The lotus flower, fruits, and sepals were sacred to the Pharaohs of Egypt and were frequently portrayed as architectural elements. It travelled from Egypt to Assyria and was extensively dispersed across Persia, India, and China[21]. Under *Sir Joseph Banks'* assistance, it was initially introduced to Western European horticulture in 1787 as a stove house water lily[19]. These days, it's nearly universal in collections of contemporary botanical gardens. In Australia, China, India, Iran, and Japan, it is a common plant. It was brought to Japan from China and has been grown there for over a millennium. It is an industrial crop farmed on more than 40,000 hectares in China. It is common across India and has been discovered as high as 1400 meters in the Himalayan lakes[22].

Historically, *N. nucifera* has been used medicinally in all sections of the plant[23]. In addition to being helpful for chronic dyspepsia, diarrhoea, and haemorrhoids, rhizomes also contain cholagogue, diuretic, and nutritional properties[24]. In native Ayurvedic medicine, the stem is used to cure strangury, vomiting, leprosy, skin conditions, and nervous weariness[25]. The leaves also used as an anthelmintic, diuretic, Haematemesis, epistaxis, haemoptysis, haematuria, metrorrhagia, and hyperlipidaemia. The flowers can be used to cure fever, cholera, diarrhoea, and stomach ulcers[19].

3. Phytochemicals

Flavonoids and Alkaloids are minor amount of alkaloids, which are intestinal antispasmodics and relieve diarrhoea, are present in the embryos. The alkaloid isoquinoline, found in lotus seeds, has calming, antispasmodic, and heart-beneficial properties. It eliminates pathogenic heat from the heart and heat-induced spontaneous haemorrhage. Alkaloids (e.g., dauricine, lotusine, nuciferine, pronuciferine, liensinine, isoliensinine, roemerine, nelumbine, neferine) are the main phytochemicals found in lotus seeds. The transmembrane currents of Na^+, K^+, and Ca^{2+} in heart cells are blocked by dauricine and neferine [19].

4. Traditional uses

Asia uses the seeds and fruits as a health food and to treat a wide range of conditions, such as enteritis, chronic diarrhoea, palpitations, sleeplessness, spermatatorrhoea, leucorrhoea, dermatopathy, halitosis, menorrhagia, leprosy, tissue inflammation, cancer, fever, and heart problems. They are also used as an antiemetic, diuretic, refrigerant, and poisoning antidote. Lotus seedpods are occasionally used in traditional medicine to support the function of the heart. Cough can be effectively treated with a mixture of seed powder and honey. In traditional

Chinese medicine, lotus seed embryos are used to treat neurological problems, sleeplessness, high fevers accompanied by restlessness, and cardiovascular ailments (such as arrhythmia and hypertension)[26, 27, 28].

5. Pharmacologically active-constituents

From the leaf, rhizome, seed, and flower, a number of pharmacologically active components that are responsible for the therapeutic properties have been identified. It has been possible to separate distinct classes of phytoconstituents from different *N. nucifera* sections. Alkaloids, steroids, triterpenoids, flavonoids, glycosides, and polyphenols are among the most significant classes[29,30]. Numerous pharmacological properties of *N. nucifera* have been demonstrated by studies on its various components. Anti-ischaemia[31], gastero-intestinal activity, anti-inflammatory[32], antioxidant, antiviral, antidiabetic, immunomodulatory, anti-neurodegenerative, antiobesity and hypolipidemic, anti-Parkinsonian, antidermatophytic and antidiarrheal, psychopharmacologic, antitumor and anti-cancer, antihepatotoxic, anticholestatic, neuromodulatory, anti-haemolytic, anti-angiogenesis, anti-fatigue, anti-aging, and diuretic[13] properties have all been demonstrated by extracts from various sections.

6. Pharmacological Benefits

6.1 Anti-ischaemic

In the isolated rat heart, the N. nucifera seed has strong anti-ischaemic properties. By assessing cardiac output, the effective dosage of seed extract against ischaemia produced in the isolated rat heart was determined. Doses ranging from 0.1 to 30 mg/ml were evaluated. Although cardiac output was equal following treatment with 3 or 10 mg/ml dosages (63.5 ± 3.2 and 65.8 ± 4.0 ml/min, respectively), maximum recovery was observed with a dose of 10 mg/ml. The ideal dose for the rat's anti-ischaemic actions was therefore found to be 3 mg/ml[31].

6.2 Gastro intestinal tract

Carbohydrate-based oligosaccharides and polysaccharides are garnering attention as a way to control the growth of gut bacteria. Prebiotics are non-digestible carbohydrates that are gaining popularity since they are safe, affordable, and have a higher resistance to the digestive system while also increasing the number of good microorganisms in the gastrointestinal tract. Prebiotics such as galacto-oligosaccharides, fructo-oligosaccharides, and isomalto-oligosaccharides might delay the growth of pathogenic microorganisms and encourage the growth of Lactobacillus and Bifidobacterium, two types of gut bacteria[33]. Lotus seeds have been utilised as a functional meal to support gastrointestinal health in humans for many years. Resistant starch, or resistant starch type 3 (RS3), can be found in good amounts in lotus seeds. Furthermore, RS controls the intestinal tract by controlling the absorption of minerals from the intestines, reducing the effects of blood lipids, and preventing colorectal cancer, mostly through the action of short-chain fatty acids[34]. Numerous investigations have indicated that LSO averts constipation by promoting the formation of advantageous bacteria within the digestive system. Digestive enzymes and Bifidobacterium adolescentis produce more acetic, butyric, and propionic acids when exposed to LSO. These acids can operate directly on the colon's smooth muscles or by activating vagus nerve and mucosal layer receptors to influence intestinal motility. Probiotics are a rapidly expanding component of the food industry because they increase the amount of beneficial microorganisms in the digestive system[35]. Processed lotus seeds to produce resistant starch (RS) and documented the lotus seed starch's prebiotic properties. According to the scientists, resistant starch increased the number of advantageous bacteria and enhanced the level of short chain fatty acids (SCFAs), particularly butyric acid, which is good for the body[36]. Lotus seed RS may be added to a variety of dishes as a probiotic. *Zeng et al.,* (2018) used 20% and 30% concentrations of ethanol to fractionate resistant starch. The outcomes showed that both fractions had prebiotic effects in Lactobacillus acidophilus and B. adolescentis. Probiotic activity of lotus seed RS with 20% ethanol were found to be greater than those with 30% ethanol[37].

6.3 Anti-inflammation

Through the stimulation of healing processes, the body's innate immune cells shield the afflicted tissues from external stimuli like germs and viruses throughout the process of inflammation. Numerous immune cells linked to an inflammatory response, such as neutrophils, macrophages, and phagocytes, secrete inflammatory mediators such as TNF-α, nitric oxide (NO), and interleukins, as well as inflammatory proteins like cyclooxygenase (COX)-2 and nitric oxide synthase (NOS), in response to exogenous impulse stimulation. Atherosclerosis, diabetes, tumour formation, immune system disorders, and other inflammation-related illnesses were caused by the excessive release of inflammatory mediators as a result of the inflammatory reactions. When inflammatory mediators are overindulged, lotus seed extracts function as an anti-inflammatory agent. After fat and polyphenols were removed, lotus seed protein was extracted using alkaline solubilisation, yielding an extraction percentage of 18.40%. SDS-PAGE analysis revealed the existence of main 4 protein, which has a molecular weight of 18, 19, 21, and 22 kDa[38]. Atherosclerosis, diabetes, tumour formation, immune system disorders, and other inflammation-related illnesses were caused by the excessive release of inflammatory mediators as a result of the inflammatory reactions. When inflammatory mediators are overindulged, lotus seed extracts function as an anti-inflammatory agent. After fat and polyphenols were removed, lotus seed protein was extracted using alkaline solubilisation, yielding an extraction percentage of 18.40%. SDS-PAGE analysis revealed the existence of main 4 protein, which has a molecular weight of 18, 19, 21, and 22 kDa. *Moon et al.* (2019) investigated the mRNA expressions of iNOS and

COX-2 by real-time PCR. They came to the conclusion that, at doses of 1000 µg/mL, lotus seed protein isolates strongly suppressed the expressions of the COX-2 and iNOS genes. Neferine, liensinine, and iso-liensinine from lotus seed embryos are examples of bisbenzylisoquinoline alkaloids that are thought to lower NO generation in lipopolysaccharide-activated RAW264.7 macrophages[39,40]. They came to the conclusion that lotus seed embryo alkaloids might reduce the production of IL-1β, IL-6, and TNF-α as well as the expression of iNOS that is produced by lipopolysaccharide by inhibiting the phosphorylation and degradation of IκBα, as well as by lowering the amount of cytosolic Ca2+ and calmodulin (CaM). Furthermore, by inhibiting the COX-2 enzyme in Sprague-Dawley rats, many in vivo investigations investigated the anti-inflammatory efficacy of red and white lotus seed extract at 400 and 600 mg/kg, respectively[41]. An innovative polymer weighing 391 kDa was extracted from lotus seed plumules, incubated with splenocytes derived from BALB/c mice and non-obese diabetes (NOD), and assessed for its anti-inflammatory properties. Plumule polysaccharides increased TNF-α, interleukin (IL)-10, and IL-6 outputs through splenocytes from both NOD and BALB/c mice at ages of 15, 22, and 26 weeks, respectively, at a dosage of 1000 µg/mL of lotus seeds. Nevertheless, treatment of lotus seed plumule polysaccharides markedly increased the splenocytes' production ratios of pro- and anti-inflammatory (IL-10/IL-6) cytokines [42].

6.4 Anti-oxidant

Free radicals, such as the hydroxyl radical (OH•), superoxide anion (O_2•), and hydrogen peroxide (H_2O_2), have been implicated in the pathogenesis of several illnesses and diseases. Oxidative stress caused by free radicals is linked to a number of illnesses, such as diabetes, cancer, heart disease, respiratory conditions, dementia, and many more. The exterior layer of lotus seeds contains a substantial quantity of unsaturated fatty acids, which contributes to their endurance. Ascorbic acid, glutathione, and other physiologically active compounds with antioxidant potential are also abundant in seeds[43, 44, 45].

6.5 Anti-viral

Herpes simplex virus-1 (HSV-1) multiplication was markedly inhibited by an ethanol extract of the seed (100 mg/ml), with an IC_{50} of 50 mg/ml. Moreover, *N. nucifera* (NNFR) possesses a sub-fraction that inhibits HSV-1. At 50 mg/ml, NNFR reduced aciclovir-resistant HSV-1 propagation by up to 85.9% by inhibiting HSV-1 replication in HeLa cells. NNFR dramatically inhibited HSV-1 proliferation in HeLa cells in a fractionation method guided by a bioassay, all while appearing to be non-cytotoxic. In HeLa cells treated with NNFR, there was a reduction in the synthesis and mRNA transcription of the infected cell protein. Therefore, it is believed that NNFR's antiviral effects are achieved by first inhibiting immediate early transcripts, such as infected cell protein (ICP) 0 and ICP4 mRNA, and then preventing the accumulation of all viral products downstream[15, 25].

6.6 Anti-diabetic

Diabetes is one of the endocrine illnesses that interferes with proper glucose metabolism. The most prevalent genetic condition caused by decreased insulin production and insufficient insulin is diabetes mellitus. *Nelumbo nucifera* Gaertn., an aquatic Indian plant, produced hypoglycaemia and an improvement of glucose tolerance in normal rabbits. Further investigations were undertaken. Chronic administration of plant extracts (test drugs) to normal rats did not produce a sustained fall of fasting blood sugar levels although daily doses caused hypoglycaemia as an acute effect; concurrent glucose tolerance studies showed beneficial effects. In vitro studies with rat hemidiaphragms revealed that test drug treatment of donor animals significantly enhanced the effect of insulin. The improvement of glucose tolerance therefore may also be due to increased peripheral glucose utilization caused by increased sensitivity of skeletal muscles to endogenous insulin. Comparative studies were also carried out in moderately diabetic rabbits using test drugs (equivalent to 1000 mg/kg of crude material) and standard drugs phenformin and tolbutamide (100 mg/kg each). The test drugs showed acute and chronic effects in suppressing hyperglycaemia, but were less potent than standard drugs. However, test drugs significantly improved glucose tolerance in these animals. With severely diabetic rabbits, these drugs proved to be ineffective even at four-fold higher doses[45,46].

6.7 Immunomodulatory

Treating infectious disorders by immune system activation is a sensible and safe strategy. Lotus seeds exhibit a wider variety of biological activities that may increase the population of lymphocytes and total leucocyte count, demonstrating the immunological activity of the seeds[47, 48].

6.8 Anti-neurodegenerative

Alzheimer's disease (AD) is a neurodegenerative condition that affects people and is characterised by loss and dystrophy of neurones, neurofibrillary tangles, and amyloid-bearing plaques[49,50]. The brains of AD patients appear to have too low acetylcholine concentrations, according to several study findings. Pain-Relieving Action *Vikrama Chakravarthy P et al.* (2009) investigated the analgesic impact of red and white lotus seeds on albino rats for their research. Six groups of 48 adult Sprague Dawly rats were created. Group II received conventional treatment with Diclofenac, whereas Group I was treated as the control group. After feeding Groups III, IV, and V, respectively, methanolic extracts of N. nucifera seeds of the red and white kinds at 400 mg/kg and 600 mg/kg for seven days, it was shown that both lotus seed extracts had a significant analgesic effect. Among all the extracts, the higher dose group of white lotus seed (600mg/kg) exhibited more pronounce activity[51].

6.9 Anti-obesity and hypolipidemic

Impact research has indicated that in rats given a high-fat diet, the ethanolic extract of N. nucifera has a positive impact on lowering adipose tissue weights, improving blood lipid profiles, and adjusting serum leptin levels. It also has an inhibitory effect on adipogenesis[52, 53, 54].

6.10 Anti-Parkinsonian

M.Vishnu Vardhan Reddy et al., (2014) measured a variety of behavioural and biochemical parameters in order to examine the antioxidant and anticataleptic properties of *Nelumbo nucifera's* methanolic seed extract, which was partitioned with chloroform and used in the rat model of haloperidol-induced catalepsy. Male albino rats were given a dose of haloperidol (1 mg/kg, i.p.) to induce catalepsy. When compared to the haloperidol-treated group, all drug-treated groups showed a substantial decrease in cataleptic ratings; the group that received *Nelumbo nucifera* (200 and 400 mg/kg body weight) saw the largest decrease. The brain's biochemical characteristics, such as catalase, superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS), were measured. The study found that in rats with haloperidol-induced catalepsy, *Nelumbo nucifera* therapy restored the levels of TBARS, Catalase, and SOD [55, 56].

6.11 Anti-dermatophytic and Antidiarrheal

Using the disc diffusion method, the antidiarrheal activity of N. nucleifera seed oil was assessed. It was shown to strongly inhibit the strains of Salmonella, Shigella, Klebsiella, Escherichia coli, Pseudomonas, and Staphylococcus aureus. The Nucifera seed's inhibitory action Mice and rats were used to test for the neuropharmacological effects of the ethanolic extract of *Nelumbo nucifera* Gaertner seeds. Anxiolytic activity (increased zero maze, light-dark model transition in mice), motor coordination activity, locomotor activity, and cerebral activator activity (nootropic) were assessed in relation to the extracts' effects on phenobarbitone sodium-induced sleep delay and sleeping time. *Nelumbo nucifera* (50, 100, and 200 mg/kg p.o.) ethanolic extract exhibits a dose-dependent anxiolytic effect in addition to a substantial ($p<0.05$) depression in general behavioural tests and potentiation of phenobarbitone-induced sleep duration. *Nelumbo nucifera* gaertner's ethanolic extract has nootropic action on the conditional avoidance response. Thus, it may be said that plants have the potential to add significant value to the current toolkit of nootropic agents with antistress properties[57].

6.12 Psychopharmacologic

Neferine derived from lotus seed embryos has anti-immobility effects in mice during forced swimming, suggesting that it may have antidepressant properties. Neferine is a direct agonist of the 5hydroxytryptamine (1A) receptor, which means that it can prevent the reuptake of 5-HT or activate 5-HT metabolism. The antidepressant effect was similar to imipramine and maprotiline. The acetylcholinesterase activity and acetyltransferase expression in rats with scopolamine-induced dementia were ameliorated by sacred lotus seed extract [34, 58].

6.13 Antitumor and anti-cancer

Tyrosinase activity and melanin concentration in B16 melanoma cells were significantly reduced by the volatile-rich petroleum ether fraction (linolenic acid, α-linolenic acid, and linolenic acid ethyl ester) from NLEs through induction of death. Nuciferine treatment, on the other hand, was found to have a positive antitumor effect, as demonstrated by the notable suppression of tumour size and melanoma cell growth[59]. Potential mechanisms for this effect included downregulating TLR-4 targeting, inactivating NF-KB signalling, and inhibiting p65 phosphorylation. Nuciferine has been shown to be effective against neuroblastoma and colorectal cancer using a network-based study of traditional Chinese medicine (TCM) [28]. One potential molecular mechanism of action for nuciferine may entail blocking the PI3K-AKT signalling pathways and IL-1 level. Research using glioblastoma cells showed that nuciferine might disrupt SRY-box 2 (SOX2)-AKT/signal transducer and activator of transcription 3 (STAT3)-Slug signalling, hence preventing proliferation, motility, stemness, angiogenesis, and epithelial-to-mesenchymal transition[60]. Furthermore, research using MCF-7 human breast cancer cells in a xenograft nude mice model examined the effects of supplementing with flavonoid-enriched extracts from NLEs (mostly gallic acid, rutin, and quercetin) on breast cancer [61]. NLEs were found to have anti-carcinogenesis effects by phosphorylating p^{53} at Ser15, promoting G1 phase cell cycle arrest, inhibiting FAS induction by inactivating HER 2 and suppressing SREBP-1 expression, and lowering ER-α phosphorylation by inhibiting the PI3K/Akt pathway. Likewise, NLEs' antimetastatic effects on MDA-MB-231 breast cancer cells might be explained by their suppression of matrix metalloproteinase (MMP)-2 and PI3K/AKT/MEK/ERK pathways, which in turn inhibits the production of connective tissue growth factor (CTGF). Furthermore, it was believed that the TGF-β_1/SMAD3 and TGF-β_1/$ERK_{1/2}$ signalling pathways were crucial in preventing NLEs from affecting cell migration and metastasis in ER breast cancer. Lotus leaves offer a promising treatment approach for breast cancer, according to these several lines of strong evidence. Additionally, NLE supplementation alleviated liver preneoplastic lesions by decreasing the size of the tumour and correcting the raised levels of glutathione Stransferase pi (GSTπ), PKCα, and small GTPase 1 (Rac_1) in the liver. Additionally, nuciferine therapy was found to significantly reduce the growth of NSCLC (human lung adenocarcinoma epithelial cell line) by boosting axin stabilisation, inhibiting Wnt/β-catenin signalling, and causing apoptosis[62].

6.14 Anti-hepatotoxic

The remission of chronic liver illnesses is seldom impacted by conventional medications or treatments. Notably, an increasing amount of research has shown that NLEs have remarkable pharmacological effects against liver toxicity and illness, including antisteatosic, anticholestatic, and antifibrogenic qualities. The well-known poison carbon tetrachloride (CCl_4) produces steatosis, central lobular necrosis, oxidative stress, and even lipid peroxidation. An increasing body of in vivo research demonstrates the critical functions of NLEs in preventing liver damage brought on by CCl_4. The modulation of glutathione metabolism, phenylalanine metabolism, tryptophan metabolism, sphingolipid metabolism, and phospholipid metabolism may be linked to the hepatoprotective mechanism of NLEs. Alcohol use, obesity, diabetes, or drug use can cause an abnormal buildup of triglycerides and the consequent production of lipid droplets in the cytoplasm of hepatocytes, a condition known as steatosis or fatty liver. The hepatic steatosis and necroinflammation caused by a high-fat diet were dramatically reduced by nuciferine (10 and 15 mg/kg per BW) therapy, according to the histological grading of liver sections. According to this discovery, nuciferine (20 mg/kg bw) reduced liver steatosis, hepatocyte ballooning, and blood lipid levels (TG, TC, and LDL-C) in rats with HFD-induced non-alcoholic fatty liver disease (NAFLD). This effect is associated with the drug's ability to restore the dysfunction of glycerophospholipid, linoleic acid, alpha-linolenic acid, arginine, and proline metabolism[63].

6.15 Anti-cholestatic

Essential trace elements such as zinc (Zn), copper (Cu), mercury (Hg), and magnesium (Mn) have a role in liver cirrhosis, causing damage to liver tissue, inflammation, and fibrosis in the process (*García-Nino & Zazueta* 2015). Heavy metal levels and indicators of liver impairment have been used to measure the anticholestatic effects of NLEs. After Nile tilapia were exposed to a combination of lead (Pb), cadmium (Cd), mercury (Hg), and zinc (Zn), there were increased ALT and AST activity as well as several histological lesions. These reactions were avianised by NLE powder. NLEs were also successful in eliminating heavy metal residues from fish muscular tissues, which decreased hepatic metallothionein and oxidative stress (MDA, CAT, SOD, and GPX)[60].

6.16 Neuro modulatory

The ability of polyphenols and alkaloids to penetrate the blood-brain barrier and disperse throughout the brain after dietary consumption might potentially dictate their effectiveness in treating disorders of the central nervous system. It has been shown that NLEs have an anxiolytic effect and lessen aversion to fear; its primary bioactive components, flavonoids and alkaloids, may work on certain brain mediators to reduce anxiety. Alkaloids from NLEs (20 mg/kg) did, in fact, have a sedative-hypnotic effect by altering neurotransmitters in the brain, including boosting γ-aminobutyric acid and preventing the release of picrotoxin and bicuculline. Furthermore, alkaloid-rich NLEs exhibited elevated levels of dopamine, 5-hydroxyindoleacetic acid, and serotonin, which suggested anxiolytic-like effects. NLEs extracts (2.72 and 39.09 mg/g TPC) from leaf stalks and old leaves, respectively, may be able to reduce the activity of many important enzymes (acetylcholinesterase, butyrylcholinesterase, and beta-secretase) associated with Alzheimer's disease. Lotus leaf benefits include these, which raise the possibility that lotus leaves might be useful as a possible treatment for neurological disorders[64].

6.17 Anti-haemolytic

Based on an APPH test, a recent study on $HepG_2$ cells showed that the extract from NLEs displayed antihaemolytic activities in a concentration-dependent manner. Its primary phenolic constituents could be very important. The breakdown of lotus leaf-derived flavonoids and alkaloids is likely the cause of NLEs-resistant haemolysis [29].

6.18 Anti-angiogenesis

In both cell and animal models, the strong angiogenesis-inhibiting potential of NLEs was studied. In vivo VEGF-induced proliferation, tube formation, and CAM angiogenesis were all inhibited by NLEs. NLEs extracts (10–100 μg/ml) demonstrated significant dose-dependent suppression of VEGF-induced angiogenesis, proliferation, and tube formation in human umbilical vein endothelial cells (HUVECs). In line with these discoveries, NLE treatment of HUVECs in a Matrigel angiogenesis model might prevent the creation of vascular-like structures [66].

6.19 Anti-fatigue

The swimming test was utilised to assess the anti-fatigue activity of NLEs. The findings of *Xu and Wang* (2014), who demonstrated that flavonoids from NLEs (50, 100, and 150 mg/kg) treated mice for 28 days significantly prolonged the exhaustive swimming time of mice, are consistent with the results of this study, which suggested that NLEs flavonoids had significant antifatigue activity by increasing their swimming time. When taken as a whole, NLEs can help avoid weariness, however it's yet unknown how they work[66].

6.20 Anti-aging

An antiaging ingredient found in sacred lotus (*Nelumbo nucifera*) seed extract helps to lessen signs of ageing such as elasticity loss, acne, pores, wrinkles, fine lines, blemishes, and so on. A good vehicle contains compounds with strong anti-aging properties. It encourages skin that seems younger. Using a noninvasive device called the Visioscan VC, software for evaluating the surface of living skin, and a noninvasive photometric device called the Sebumeter for measuring the amount of sebum secretions on both sides of the face, *Mahmood and Akhtar* (2013) investigate the effectiveness of green tea and lotus extract cosmetic formulations for the treatment of facial wrinkles in healthy Asians. The findings indicated that the combination of green tea and lotus in various emulsions had a synergistic antiaging effect. The active ingredients in both herbal plants that exhibit antioxidant activity may have a positive impact on the skin's surface, suggesting that both plants will likely be used in new antiaging treatments in the future[67].

6.21 Diuretic

Mukherjee and associates observed that the rhizome of *N. nucifera* has diuretic properties. At dosages of 300, 400, and 500 mg/kg, the rhizome's methanol extract significantly reduced the amount of water in the rats bodies. Urine volume increased in a dose-dependent manner, and there was a notable excretion of K^+ along with the elimination of Na^+ and Cl^-. Urine production increased less than it did with the conventional diuretic furosemide (20 mg/kg) [23,58].

7. Application of lotus seed in foods

Numerous significant components found in lotus seeds can be further processed for use in food product formulations and other uses. Investigating novel sources for functional ingredients that can improve the nutritional and functional qualities of food items that are being developed with value added. Two essential elements in the food business are flour and starch. Flours and starches with certain qualities must impart functionally useful traits in order to manufacture novel goods. Wheat flour serves as the primary raw ingredient for baked goods. However, current research suggests substituting alternative, nutrient-rich, and health-promoting flours for wheat flour, either completely or in part[69].

CONCLUSIONS

Nelumbo nucifera, a perennial aquatic herb in the Nymphaeaceae family, is becoming more well-known due to its historical and nutritional significance. According to the conventional medical system, it was used to treat tissue inflammation, cancer, diabetes, skin conditions, bleeding problems, and cardiovascular ailments. These days, it is important to conduct and record evidence-based study to identify a potential mechanism of action for such impacts. Furthermore, if it can be made into a functional food, it will be valuable economically.

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