



Therapeutic Versatility of *Nelumbo nucifera*: From Traditional Medicine to Modern Pharmacology

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Abstract

Introduction: Medicinal plants remain central to global healthcare, with increasing interest in safer, cost-effective alternatives to synthetic drugs. *Nelumbo nucifera* has a long history in traditional medicine and demonstrates diverse pharmacological potential. This review aims to critically evaluate its therapeutic versatility by integrating traditional knowledge with modern scientific evidence. **Methods:** A comprehensive literature-based analysis was conducted, synthesising data from ethnomedicinal records, phytochemical studies, and preclinical and clinical investigations. Evidence from in vitro, in vivo, and limited human studies was systematically assessed to determine pharmacological efficacy and mechanisms of action. **Results and Discussion:** *Nelumbo nucifera* contains over 50 bioactive compounds, including alkaloids, flavonoids, and phenolics, contributing to multi-target pharmacological activities. Experimental studies demonstrate strong antioxidant (65-92% scavenging), anti-inflammatory (30-65% cytokine reduction), antimicrobial, antidiabetic (25-50% glucose reduction), cardioprotective, neuroprotective, and anticancer effects. Mechanistically, these effects involve modulation of NF- κ B, MAPK, and oxidative stress pathways. Clinical studies, though limited, indicate improvements in lipid profiles, glycemic control, and oxidative stress markers with favourable safety profiles. However, variability in phytochemical composition, lack of standardisation, and insufficient large-scale trials remain major limitations. **Conclusion:** *Nelumbo nucifera* exhibits significant therapeutic promise across multiple disease conditions. Future research should prioritise standardised formulations, advanced analytical approaches, and large-scale clinical trials to validate its clinical utility and facilitate integration into evidence-based medicine.

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1. Introduction

Medicinal plants continue to play a vital role in healthcare systems worldwide, with approximately 80% of the global population relying on traditional

medicine for primary health care, particularly in low- and middle-income countries [1]. Chronic diseases are becoming increasingly common, but the incidence of

adverse drug reactions, the fourth leading cause of death in non-institutionalised adults, occurs in 10-20% of hospitalised patients using synthetic drugs, and antimicrobial resistance is on the rise during this same time period, as well as treatment costs; thus, there is always an endeavour to find safer, cost-effective & sustainable therapeutic alternatives[2]. Drugs that have an origin from nature make up about 25-30% of drugs that are currently approved and remain a rich source of structural diversity, along with usage across wide classes of pharmacological activities [3].

Nelumbo nucifera has received considerable attention with proven traditional use and numerous accredited therapeutic benefits. This aquatic perennial plant has been employed in traditional systems such as Ayurveda and Traditional Chinese Medicine for over 2,000-3,000 years[4]. Plant parts used to treat inflammatory disorders are from various edible herbs, including leaves, flowers, seeds and rhizomes. The health benefits of *N. nucifera* are due to the interactions between over 50 known bioactive elements, including alkaloids (nuciferine and neferine), flavonoids, tannins and phenolic acids [5].

The global herbal medicine sector has recently been valued at an estimated USD 180 billion worldwide as of 2023, with an expected compound annual growth rate (CAGR) of between 6 and also 8 %. Improved analytical tools, including high-performance liquid chromatography (HPLC), liquid chromatography-mass spectrometry (LC-MS), and molecular pharmacology methods, have allowed for the systematic evaluation of traditional medicinal claims [6]. Various experimental studies have revealed the powerful antioxidant activity of *N. nucifera*, as reflected in free radical scavenging capacities of 70% to 85% in in vitro assays, and also significant anti-inflammatory, antidiabetic, hepatoprotective and neuroprotective actions [7].

Unlike previous reviews that primarily focus on either ethnomedicinal uses or isolated pharmacological aspects of *Nelumbo nucifera*, the present review provides an updated and integrated perspective by correlating traditional knowledge with recent experimental and emerging clinical evidence. It compiles available quantitative pharmacological data, outlines key mechanistic pathways, and discusses translational challenges and research gaps, thereby offering a comprehensive framework for future research and evidence-based application.

2. Methodology

This narrative review evaluated the therapeutic versatility of *Nelumbo nucifera* by integrating

traditional medicinal knowledge with contemporary pharmacological evidence. Relevant literature was identified through PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar using combinations of keywords including “*Nelumbo nucifera*,” “sacred lotus,” “phytochemicals,” “bioactive compounds,” “traditional uses,” “pharmacological activities,” “therapeutic potential,” and “clinical studies,” with Boolean operators AND and OR [8].

Studies investigating *N. nucifera* or its plant parts, phytochemical composition, traditional uses, pharmacological activities, mechanisms, preclinical efficacy, clinical outcomes, and safety were considered. In vitro, in vivo, human studies, and relevant reviews were consulted. Duplicate, unrelated, insufficient, and non-relevant publications were excluded. Retrieved records were screened by title and abstract, followed by full-text assessment. Data on plant parts, phytoconstituents, experimental models, pharmacological activities, mechanisms, and major findings were extracted. Evidence was qualitatively synthesized according to therapeutic activities, clinical evidence, safety, research gaps, and future research priorities [9].

3. Botanical Description

N. nucifera is an aquatic perennial herb with different morphological adaptations to a freshwater environment. The plant has large, circular, peltate leaves 30–90 cm in diameter with a hydrophobic surface (lotus effect), which is coated with wax, allowing the water to be repelled more easily. The flowers, which are more or less solitary, fragrant and large, 10-25 cm in diameter, have many pink or white petals arranged spirally around a central receptacle [4]. Thermoregulation is also exhibited by the plant, with floral temperatures showing maintenance between 30-35 °C during anthesis. Seeds are hard-shelled and ovoid, about 1-2 cm in length, and surprisingly long-lived; their germination rate can be well over 1,000 years. Their rhizomes are cylindrical and spongy, ranging from 10-30 cm in length and 2-5 cm wide, acting as an organ for storage due to their starch content and allowing vegetative propagation [10].

It is distributed all around warm and subtropical areas like India, China, Japan, Korea and Southeast Asia. Though it originated in a small area of north eastern bdromossa has been introduced from there into other parts of Australia and North America [11]. It grows in warm locations, optimum growth temperatures lie between 20 °C and 35 °C, shallow stagnant water bodies from 0.5-2.5 m deep are suitable for its growth, the plant should preferably grow in nutrient-rich soils with a pH range of slightly acid to neutral (6.5-7.5),

shallow clayey or loamy soils and the effect of soil properties on heavy metal bioavailability to aquatic plants. Cultivation is generally done from segments of rhizome or seeds, with a quicker return to crop yields being one of the primary advantages of using rhizome propagation. The plant is highly regarded as it grows from seed to maturation and harvest in a time frame of only 4-5 months under best agronomic conditions, giving the high-value crop a large economic significance by providing an important source of medicine [12].

3.1 Phytochemical Profiling of *Nelumbo nucifera*

The pharmacological potential of *Nelumbo nucifera* is closely associated with the distribution of its bioactive compounds across different plant parts. Leaves are predominantly rich in alkaloids such as nuciferine and neferine, along with flavonoids like quercetin and kaempferol, contributing to anti-obesity, antioxidant, and anti-inflammatory activities. Seeds contain

bisbenzylisoquinoline alkaloids (neferine, liensinine, isoliensinine) associated with cardioprotective, sedative, and antiarrhythmic effects. Flowers are abundant in flavonoids and glycosides, which are primarily responsible for antioxidant and anti-inflammatory properties, while rhizomes contain phenolic compounds and polysaccharides contributing to digestive and antioxidant functions. This correlation highlights the importance of plant-part-specific phytochemistry in determining therapeutic efficacy [13].

The variability in phytochemical distribution among different plant parts underscores the importance of targeted extraction and standardisation strategies. A comprehensive profiling of these constituents is essential to understand their therapeutic potential and to support the development of evidence-based herbal formulations. The detailed classification of these phytoconstituents along with their biological activities is summarised in Table 1 [12].

Table 1: Phytochemical composition of *N. nucifera* across different plant parts.

S. No.	Plant Part	Phytoconstituent Class	Major Compounds Identified	Reported Biological Activities	References
1.	Leaves	Alkaloids	Nuciferine, Neferine, Roemerine, Anonaine	Anti-obesity, Antidiabetic, CNS modulation	[14, 15]
		Flavonoids	Quercetin, Kaempferol, Rutin, Isoquercitrin	Antioxidant, Anti-inflammatory	
		Phenolics	Gallic acid, Catechin	Free radical scavenging	
2.	Seeds	Alkaloids	Neferine, Liensinine, Isolienisnine	Antiarrhythmic, Sedative, Cardioprotective	[16, 17]
		Proteins & Amino acids	Essential amino acids	Nutritional support	
		Flavonoids	Kaempferol, Myricetin	Antioxidant	
3.	Flowers	Flavonoids	Kaempferol, Quercetin, Anthocyanins	Anti-inflammatory, Antioxidant	[18, 19]
		Glycosides	Flavonoid glycosides	Hepatoprotective	
		Volatile compounds	Linalool, Eugenol	Aromatic, Antimicrobial	
4.	Rhizomes (Roots)	Starch & Polysaccharides	Amylose, Amylopectin	Energy source, Digestive aid	[20, 21]
		Phenolics	Catechol, Gallic acid	Antioxidant	
		Vitamins	Vitamin C, B-complex	Nutritional	
5.	Embryo	Bisbenzylisoquinoline Alkaloids	Neferine, Liensinine, Isolienisnine	Antiarrhythmic, Neuroprotective	[13]
		Flavonoids	Flavone derivatives	Antioxidant	
6.	Stamens	Flavonoids	Kaempferol derivatives	Antioxidant, Anti-aging	[22]
		Alkaloids	Nuciferine	CNS effects	

3.2 Ethnomedicinal and Traditional Uses

The traditional uses of *Nelumbo nucifera* described in this section are primarily based on ethnomedicinal knowledge and historical practices. It is important to distinguish these claims from pharmacological activities supported by experimental evidence. While several traditional applications have been validated through in vitro and in vivo studies, others remain

insufficiently investigated. Therefore, ethnomedicinal uses should be interpreted cautiously unless supported by well-defined experimental or clinical data [23].

This wide-scale (a) therapeutic importance of *N. nucifera* as a medicinal plant has been traced back to more than 2,000 years, especially through the

traditional medicinal systems such as Ayurveda, Unani and Traditional Chinese Medicine (TCM). It is described as “Sheetala” (cooling) in Ayurveda and is used to reduce Pitta and Kapha doshas, or to balance the excess of pitta [24]. In TCM, it regulates energy flow, organ function, etc. Leaves, flowers, seeds, stamens and rhizomes are all therapeutically active parts of the plant. Preparations include decoctions (1 mL/g) and powders or extracts of dried seed (3-6 g/day), orally for digestive and reproductive health. Leaf (50-100 mL) decoction is taken for bleeding disorders/metabolic diseases. Milled dry and powdered rhizome form fresh juice formulation or freshly prepared juices, etc [25].

Therapeutically, *N. nucifera* is commonly indicated for gastrointestinal disorders such as diarrhoea, dysentery and indigestion due to its astringent and anti-inflammatory properties. For the plant's cardiovascular conditions, especially in hypertension and hyperlipidemia, it has lipid-lowering and vasorelaxant effects confirmed by traditional use of leaf and seed extracts. Owing to the antimicrobial and antioxidant activities of flower and leaf extracts, these are widely used in topical formulations for treating skin problems (inflammation, infections, and pigmentation) [26]. Also, with respect to nervous system disorders [anxiety, insomnia and cognitive dysfunction], seeds are traditionally used with the calming effect of extracts produced from them (e.g., fractions containing high levels of alkaloids such as nuciferine) or neuroprotective activity. This diversity

of uses further highlights its ethnopharmacological relevance and modern therapeutic potential [12].

4. Pharmacological Activities of *Nelumbo nucifera*

The pharmacological activities of *N. nucifera* are very showy, which can be ascribed to the diverse phytoconstituents such as alkaloids (nuciferine, neferine), flavonoids (quercetin, kaempferol), phenolic acids and tannins. These compounds exert multi-target interactions and exhibit profound bioactivity on different physiological systems. The mechanisms through which its biological activities are mediated include antioxidant, anti-inflammatory, and enzyme-modulating pathways that have been confirmed in both experimental (in vitro) and whole organism (in vivo) investigations [27].

To ensure accurate interpretation of pharmacological evidence, the reported activities of *Nelumbo nucifera* have been carefully categorized based on the type of experimental model. Findings derived from in vitro studies (cell-based assays), in vivo studies (animal models), and clinical investigations (human studies) are clearly distinguished throughout this section. It is important to note that while in vitro and animal studies provide valuable mechanistic insights and preliminary efficacy data, these findings may not directly translate to clinical outcomes. Therefore, conclusions regarding therapeutic efficacy are drawn cautiously, with greater emphasis placed on evidence supported by human studies (Figure 1) [28].

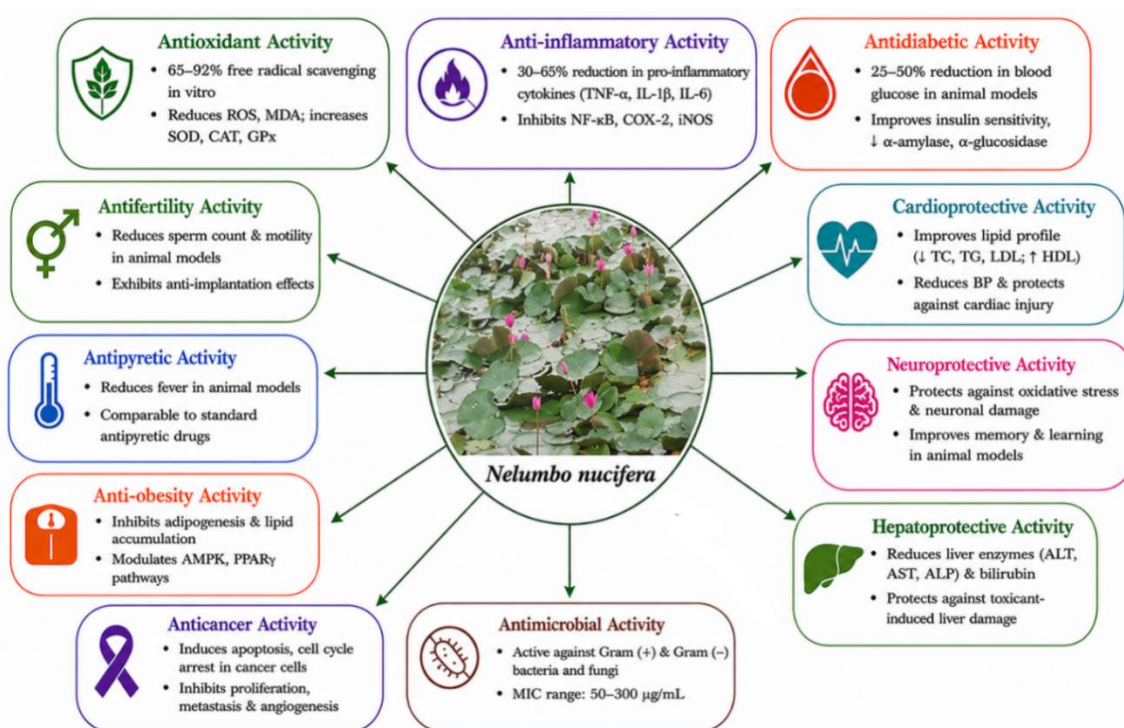


Figure 1: Pharmacological activities of *N. nucifera*, highlighting diverse therapeutic effects.

4.1 Antioxidant Activity

Oxidative stress is one of the main etiology for chronic diseases, and *N. nucifera* showed a strong antioxidant profile. In vitro assays, including DPPH and ABTS radical scavenging methods, demonstrated 65–92% free radical inhibition at concentrations ranging from 50–250 µg/mL, indicating significant antioxidant potential [29]. This effect is mainly exerted by the high total phenolic (80–180 mg GAE/g extract) and flavonoid content (40–95 mg QE/g). Furthermore, both in vitro and in vivo studies have reported suppresses lipid peroxidation in a range of 40–75% with normal action and protects cellular membranes from oxidative damage. Increased activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and catalase has also been reported, highlighting a double mechanism conferring direct scavenging and enzymatic protection [30].

4.2 Anti-inflammatory Activity

Chronic inflammation is the key to many diseases, and *N. nucifera* displays strong anti-inflammatory activity. In in vivo experimental studies (animal models), plant extracts have been reported to decrease pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 by 30–65%. At administered doses ranging from 100–400 mg/kg, inhibition of inflammatory enzymes (about 40–55% cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS)) was also observed. These effects are mediated through the suppression of central inflammatory signalling pathways such as NF- κ B and MAPK, consistently associated with reduced output of pro-inflammatory mediators and enhanced integrity of damaged tissue [31].

4.3 Antimicrobial Activity

In vitro studies have demonstrated that, methanolic and aqueous extracts of *N. nucifera* exhibit inhibitory effects against both Gram-positive and Gram-negative bacterial species with minimum inhibitory concentration (MIC) values between 50 and 300 µg/mL. In particular, there has been considerable activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*. Similarly, in vitro antifungal assays have shown 45–80% against fungi, especially *Candida albicans*. The antimicrobial action is considered to be due to disruption of microbial cell membranes, inhibition of enzyme systems, and interference with nucleic acid synthesis under controlled experimental conditions [32, 33].

4.4 Antidiabetic Activity

In in vivo studies using diabetic rat models, *Nelumbo nucifera* extracts have demonstrated significant antidiabetic effects. Administration of extracts at doses ranging from 200–400 mg/kg resulted in a 25–

50% decrease in fasting blood glucose at doses between 200 and 400 mg/kg. Enzyme inhibition studies exhibiting α -glucosidase and α -amylase inhibition of 55–85% in controlling post-prandial hyperglycemia. Second, the improvement in insulin sensitivity and enhanced hepatic glucose uptake by peripheral tissues has also been reported. Flavonoids and alkaloids were found to protect pancreatic β -cells and modulate glucose metabolic pathways [34, 35].

4.5 Cardioprotective Activity

Another important pharmacological activity of *N. nucifera* is its cardiovascular protection. An in vivo research shows decreases of total cholesterol and triglycerides of 20–45%, at the same time increasing high-density lipoprotein (HDL) levels by 10–30%. Their lipid-modulating effects contribute to reduced atherosclerosis risk. Also, antihypertensive activity has been reported with reductions in systolic blood pressure of 10–25 mmHg as a possible result of vasodilation and improvement in endothelial function. It also prevents lipid peroxidation in cardiac tissues, protecting against oxidative damage [36, 37].

4.6 Neuroprotective Activity

Alkaloids are the main bioactive components of *N. nucifera*, and they have been reported to exert mainly neuroprotective effects through their representative alkaloid constituents, namely, nuciferine and neferin. In animal models, these compounds are found to enhance cognitive function by 30–55%, and oxidative neuronal damage is reduced by an additional 35–50%. It regulates neurotransmitters such as dopamine and serotonin and inhibits acetylcholinesterase activity to enhance memory and learning functions of the brain. Furthermore, its antioxidant and anti-inflammatory properties help protect against neurodegenerative diseases, including Alzheimer's disease [38].

4.7 Anticancer Activity

In in vitro cytotoxicity studies using cancer cell lines, *Nelumbo nucifera* has demonstrated notable antiproliferative potential. Extracts exhibited IC₅₀ values of approximately 100 µg/mL, indicating moderate to strong cytotoxic activity. At tested concentrations in cell-based assays, the plant showed 40–70% inhibition of cancer cell growth, primarily through induction of apoptosis and cell cycle arrest at the G₀/G₁ or G₂/M phases. Mechanistically, it modulates important molecular pathways such as p53 activation; it regulates caspase-dependent apoptosis and inhibits angiogenesis. These pathways are essentially regulated by the action of flavonoids and alkaloids [39].

4.8 Hepatoprotective Activity

In in vivo studies using hepatic injury models, *Nelumbo nucifera* has demonstrated significant hepatoprotective potential. Plant extract treatments lead to up to 30-60% decreased liver enzymes ALT, AST and ALP, suggesting that the liver function is improved. Moreover, antioxidant enzymes like SOD and catalase are increased by 25-45%, which lowers oxidative stress in hepatic tissues. Histopathological studies corroborate a distinct mitigation in hepatic necrosis alongside improved cellular architecture, validating its efficacy as an organ-protective agent against liver injury [40].

4.9 Anti-obesity Activity

N. nucifera has demonstrated potential to treat obesity by altering lipid metabolism, inhibiting digestion-related enzymes and adipogenesis. Various experimental studies show that 50-75% inhibition of pancreatic lipase activity at a concentration range of 100-300 µg/mL using α-amylase- and lipid-pooled extracts from both leaves and seeds can reduce fatty absorption from the intestine. Oral administration of extracts in HFD-induced obesity models at doses of 200-400 mg/kg for 6-8 weeks has resulted in a reduction by near 15-30% body weight gain compared to untreated controls. In parallel, total fat mass declines by 20-35% [41].

4.10 Anti-ulcer Activity

The anti-ulcer activity of *Nelumbo nucifera* has been supported by in vivo experimental studies using ethanol- and NSAID-induced gastric ulcer models. Administration of plant extracts at doses ranging from 250-500 mg/kg significantly reduced the gastric ulcer index by 40-65%, indicating protective effects on the gastric mucosa. Additionally, the plant increased gastric mucus production by 30-50%, forming a protective barrier against acid and pepsin. Concurrently, a 20-40% reduction in gastric acid secretion was observed, contributing to decreased mucosal irritation under experimental conditions. These effects are attributed to its cytoprotective, antioxidant, and antisecretory properties [42].

4.11 Antithrombotic Activity

The in vitro studies also show that 30-55% inhibition of platelet aggregation with 50-150 µg/mL concentration (ADP, collagen as agonists). It exerts this effect by way of suppressing thromboxane A₂ synthesis, an important stimulator of platelet aggregation and vasoconstriction. It also regulates intracellular calcium signalling and decreases the activation and aggregation of platelets. Other studies also find an increase in the time of clotting and a decrease in fibrin formation imply anticoagulant activities. Together, these effects promote blood flow and decrease myocardial and thrombotic risk factors,

leading to cardiovascular protection, so the presence of flavonoids and alkaloids modulates these hemostatic pathways [43].

4.12 Immunomodulatory Activity

Plant extracts (100-300mg/kg) improve phagocytic activity in macrophages, as evidenced by a 25-50% increase in clearance of yeast pathogens and an indication of strengthening innate immune function. Also, this plant modifies the production of cytokines by increasing the anti-inflammatory cytokines such as IL-10 and lowering the pro-inflammatory measures, including TNF-alpha and IL-6 [44]. In addition, they found that lymphocyte proliferation was increased by 20-40%, indicating stimulation of adaptive immunity. These effects are mediated through the modulation of signalling pathways, including NF-κB and MAPK, resulting in regulated immune responses. *N. nucifera* exhibits immunoregulatory activity, indicating that it has potential therapeutic applications for treating immune-related disorders such as infections, inflammation, and autoimmune diseases [45].

4.13 Anti-aging Activity

Nelumbo nucifera is associated with anti-aging effects primarily due to its antioxidant and cytoprotective properties. In in vivo and in vitro experimental studies, plant extracts have demonstrated significant reduction in oxidative stress markers, including a 35-60% decrease in malondialdehyde (MDA), a key indicator of lipid peroxidation. At the same time, this increases the activity of internal antioxidant enzymes like superoxide dismutase (SOD) and catalase by 25-45% to strengthen cellular defences. Such impacts safeguard biomolecules (DNA, proteins, and lipids) from oxidative degradation [46]. The plant also has benefits in stopping advanced glycation end products (AGEs) and supporting mitochondrial activity, two major players in slowing cellular senescence-related symptoms. An in vitro and preclinical studies suggest protective effect against skin damage and improves elasticity, helping reduce wrinkles, while flavonoids and phenolics are important in protection against UV-induced scotogenesis, emphasizing its large role in anti-aging therapeutics [47].

4.15 Anti-anxiety and Sedative Activity

N. nucifera has been known to possess significant anxiolytic and sedative effects, mainly attributed to its alkaloids (e.g., a major constituent, nucleifines). Animal model behavioural studies show a 20-40% decrease in anxiety behaviour in tests such as the elevated plus maze and open field test [48]. Also, the plant increased time spent asleep by 25-35% and reduced sleep latency, showing strong sedative effects. Such effects are mediated via modulation of certain central neurotransmitter systems, with increased

GABAergic activity promoting inhibitory neurotransmission and relaxation. It also acts upon dopaminergic and serotonergic pathways to stabilise mood and reduce stress. These go along with very few side effects noted from *N. nucifera* as opposed to synthetic anxiolytics, making it an attractive option for the management of anxiety disorder and insomnia and adjunct therapies for other neurological disorders [49].

4.14 Anti-atherosclerotic Activity

It is precisely characterised by synergistic modulation of lipid metabolism, oxidative stress and vascular inflammation that *N. nucifera* shows marked anti-atherosclerotic effects. In animal models of diet-induced hyperlipidemic models, leaf and seed extracts given at doses ranging from 200-400 mg/kg were shown to reduce atherosclerotic plaque formation by 25-45%. Inhibition of low-density lipoprotein (LDL) oxidation by 30-50% is one of the main mechanisms by which hedgehog proteins act to inhibit both foam cell formation and initial plaque development[50]. The plant also improves nitric oxide (NO) bioavailability and vasodilation, thus facilitating endothelial function. One of the anti-inflammatory actions is that TACs are capable of downregulating adhesion molecules such as VCAM-1 and ICAM-1 and suppressing pro-inflammatory cytokines, leading to a decreased infiltration of monocytes into vascular walls. Flavonoids and alkaloids can both stabilise plaques and prevent their rupture, which suggests their role in the prevention of other cardiovascular complications like myocardial infarction and stroke [51].

4.16 Anti-fertility Activity

Various extracts of *N. nucifera* were found to have reversible anti-fertility effects mainly in male reproductive animals. In in vivo studies using male animal models, varying doses of 200-300 mg/kg plant extracts administered to animals for several weeks caused a decrease in 30-50% sperm motility and a sharp reduction in sperm count; These effects are linked to disruption of spermatogenesis, possibly through changes in testicular enzyme activity and oxidative stress in reproductive organs[52]. Hormonal modulation has also been noted such as decreased testosterone levels and further disruption of the hypothalamic-pituitary-gonadal (HPG) axis. Moreover, these antifertility functions are reported to be reversible after stopping treatment, likely extremely promising in the development of plant-based contraceptive agents. However, safety, efficacy and mechanism need to be confirmed in human modelling [53].

4.17 Anti-viral Activity

Results from preliminary investigations suggest that *N. nucifera* may have antiviral activity against a range of viral pathogens. In vitro assays described 40-70% inhibition of viral replication for concentrations between 50 and 200 mg/mL, depending on the viral strain and type of extract. The antiviral mode of action is thought to occur at several points in the viral lifecycle, including (but not limited to) inhibition of entry into host cells, which is followed by interference with viral RNA or DNA replication and modulation of protein synthesis related to the expression characteristics necessary for replication & spread[54]. Flavonoids and phenolic compounds contribute to these effects, as they have the ability to bind with viral enzymes and proteins. The antioxidant and immunomodulatory effects of the plant also encourage a stronger host defence against viral infections. These results, though very promising, are mostly still preclinical and require validation before transitioning to in vivo and clinical studies [55].

4.18 Anti-osteoporotic Activity

N. nucifera has potent anti-osteoporotic activity by promoting bone formation and suppressing bone resorption. Using in vitro assays, phytochemicals from plant extracts promote osteoblast differentiation, which correlates with a 20-40% increase in alkaline phosphatase (ALP) activity, used as a marker of bone formation. Moreover, up to 25-35% more mineralised nodules formed (higher deposition of calcium-rich extracellular matrix). For the most part, in vivo studies using ovariectomized models, an animal model for postmenopausal osteoporosis, demonstrated an increase of 15-25% in bone mineral density (BMD) and improved trabecular microarchitecture following the administration of extracts at doses from 200-400 mg/kg[56]. At the same time, it suppresses osteoclastogenesis by 30-50% via inhibition of the RANKL/RANK signalling pathway to inhibit bone resorption in *N. nucifera*. Simultaneous anabolic and anti-resorptive actions together with the ability to promote calcium retention through inhibition of renal tubular transporters, and antioxidant protection of bone tissue, provide evidence that 12-step can be a natural agent for osteoporosis treatment [57].

4.20 Anti-melanogenic/Skin whitening activity

N. nucifera exerts anti-melanogenic activity mainly associated with the regulation of melanin biosynthesis pathways. In in vitro studies using melanocyte cultures, at concentrations of 50-200 µg/mL, the extracts inhibited tyrosinase activity by 30-60% and reduced melanin production in melanocyte cultures by 25-50%. The inhibition of that process is necessary because tyrosinase catalyses the rate-limiting steps in melanin synthesis. The plant also downregulates main melanogenic proteins, including microphthalmia

associated transcription factor (MITF) and tyrosinase-related protein-1 (TRP-1), resulting in reduced pigmentation. The mechanisms underlying this effect are hypothesised to include interference with oxidative reactions involved in melanogenesis from the presence of flavonoids and phenolic compounds. The characteristics of these properties justify their use to treat hyperpigmentation disorders, such as melasma and in the development of cosmeceutical formulations for skin-whitening and skin tone improvement [58, 59].

4.19 Anti-photoaging Activity

N. nucifera provides effective photoprotection against ultraviolet (UV)-induced skin damage that is related to antioxidant and matrix-preventing effects. In in vitro and preclinical studies, demonstrated that, long-term exposure to ultraviolet (UV) radiation induces matrix metalloproteinases (MMPs), specifically, MMP-1; MMP-1 is a collagenase. Studies indicate that *N. nucifera* inhibits MMP-1 expression by 35-55% away from collagen degradation[60]. At the same time, collagen production is increased by 20-40%, contributing to an uplift in skin elasticity and structural integrity. The plant also decreases the production of UV-induced ROS generation by 40-65%, preventing oxidative injury in lipids and proteins and DNA skin cells. It also depresses inflammatory mediators and promotes repair processes, leading to decreased wrinkle formation and the retardation of skin aging. Thus, these findings denounce possible applications of *N. nucifera* as a natural agent in dermatology and anti-aging [61].

4.20 Anti-asthmatic Activity

The mechanism of the anti-asthmatic effects shown by *N. nucifera* is related to bronchodilatory effect, anti-inflammatory and immunomodulatory properties. In in vivo studies using experimental respiratory models in mouse, administration of plant extracts in experimental respiratory models at doses equal to 100–300 mg/kg regulates the airway inflammation that includes a decrease by 25-45% of markers such as eosinophil infiltration and production of pro-inflammatory cytokines, for instance IL-4 and IL-5[62]. Increased pulmonary function is characterised by a 20-30% reduction in airway resistance and improved airflow. The plant acts as a leukotriene inhibitor, as well as a histamine release-inhibiting and bronchoconstricting agent. These effects are mediated through inhibition of inflammatory signalling pathways, including NF- κ B and immune response modulation. This dual bronchodilatory and anti-inflammatory action suggests that *N. nucifera* can be useful in the treatment of asthma and other respiratory disorders [63].

21 Anti-allergic Activity

N. nucifera also shows very good anti-allergic activity by mast cell stabilising and antiallergic mediator releasing inhibitory activity. In vitro, inhibition of histamine release was reported between 30% and 50%, with around 25%-45% reduction in mast cell degranulation at concentrations ranging from 50 to 150 μ g/mL. These effects are especially important in protecting against hypersensitivity reactions linked to allergic diseases. The plant diminishes immunoglobulin E (IgE) and pro-inflammatory cytokines levels, thus alleviating allergic inflammation[64]. Flavonoids in the plant have both immune-modulating properties and the ability to inhibit allergen-triggered signalling pathways. These results provide a rationale for its traditional use in the treatment of allergic disorders, including rhinitis, dermatitis, and asthma [65].

4.22 Nephroprotective Activity

N. nucifera demonstrated a prominent renal protective activity against chemically induced nephrotoxic injury by mechanisms involved in antioxidant, anti-inflammatory, and cellular protection activities. In nephrotoxicity experimental models (for example, in cisplatin or gentamicin-induced injury), administration of plant extracts at doses of 200-400 mg/kg reduces serum creatinine and blood urea levels by 20-35%, reflecting improved renal filtration function[66]. In addition, the levels of oxidative stress markers such as malondialdehyde (MDA) are decreased by 30-50%, whereas those of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and catalase, produced by colon cells were significantly increased by 25-40%. Shronk and co-workers identified two major alterations that attenuate oxidative damage to renal tissues. Histopathological studies show less tubular necrosis, decreased glomerular congestion, and normalisation of kidney architecture. The nephroprotective effect is mostly due to flavonoids and phenolic compounds, which stabilise cell membranes and inhibit free radical-mediated injury [67].

4.23 Anti-mutagenic/Genoprotective Activity

The lotus flower, *N. nucifera*, is a sacred set of healing herbs that can protect genetic material from oxidative and chemical damage. In in vitro studies using cell-based models, 25-45% decrease in DNA damage and mutagenesis has been found in cells treated with plant extracts, as indicated by their capacity to prevent or reduce the induction of DNA strand breaks. Its preferential protective effect is mainly associated with its antioxidant activity to scavenge reactive oxygen species (ROS), which are responsible for DNA damage. In addition, the plant improves DNA repair processes and stabilises genomic integrity. A reduction

of both chromosomal aberrations and micronucleus formation has also been observed, thereby strengthening its contribution towards the prevention of mutagenesis. These properties are especially related to the decreasing risk of carcinogenesis and other genetic diseases [68, 69].

5. Clinical Evidence on *Nelumbo nucifera*

Although the number of clinical investigations conducted on *N. nucifera* is still limited, available studies provide preliminary evidence regarding its safety and potential efficacy in humans. Existing trials are mainly small-scale, pilot clinical studies assessing its effects on metabolic, cardiovascular and neurological outcomes. In human studies involving subjects with mild hyperlipidemia, randomized or controlled study designs (where reported), with sample sizes typically ranging from 20–60 participants and intervention durations of 6–8 weeks administration of *N. nucifera* extracts (usually taken at 500–1000 mg/day for periods of 6–8 weeks) is associated with reductions in total cholesterol and LDL levels by 15–25% and elevation in HDL cholesterol levels by about 10–20%. In the same way, trials of glycaemic control (mostly short-term intervention studies of 8–12 weeks duration) describe a 10–20% reduction in fasting blood glucose levels and small but statistically significant improvements in insulin sensitivity after supplementation for 8–12 weeks [24, 25].

N. nucifera is generally well tolerated in short-term studies, with minimal adverse effects reported at commonly used doses. However, long-term safety remains insufficiently evaluated due to the limited duration of available clinical investigations. In addition, safety outcomes may vary depending on the plant part used (leaves, seeds, rhizomes), type of extract, and differences in phytochemical composition. Therefore, caution is warranted when extrapolating

safety data, and further long-term, standardized studies are required to establish a comprehensive safety profile [70].

Safety-wise, *N. nucifera* is highly tolerated without any severe adverse effects observed in short-term studies with doses below 1000–1500 mg/day. Reported adverse effects are minimal, with mild gastrointestinal discomfort observed in a small proportion of participants (>5%). Moreover, it has been confirmed reductions in oxidative stress markers (15–30%) following supplementation, although study conditions and measurement parameters vary [71, 72]. While these results are promising, several challenges exist for clinical translation. Most studies are characterised by small sample sizes (20–60 subjects) and short duration, limiting statistical power and long-term safety evaluation. Moreover, there is also considerable variability in extract standardisation, dosage form and phytochemical composition, which complicates the comparison of studies. In addition, due to the absence of large-scale RCTs and a deficiency of adequate pharmacokinetic data, it is still difficult to draw firm conclusions about efficacy and mechanism of action. Hence, carefully controlled multicenter clinical trials with a standardised formulation are necessary to confirm the therapeutic efficacy of *N. nucifera* in clinical practice as well as to help incorporation into evidence-based medicine (Figure 2) [5, 73].

Nelumbo nucifera, the available clinical evidence remains limited. Most findings are derived from small-scale studies with short durations and lack standardized formulations or dosing regimens. Therefore, conclusions regarding clinical efficacy should be interpreted with caution. Further well-designed, large-scale clinical trials are required to establish safety, efficacy, and optimal therapeutic use in humans [74].

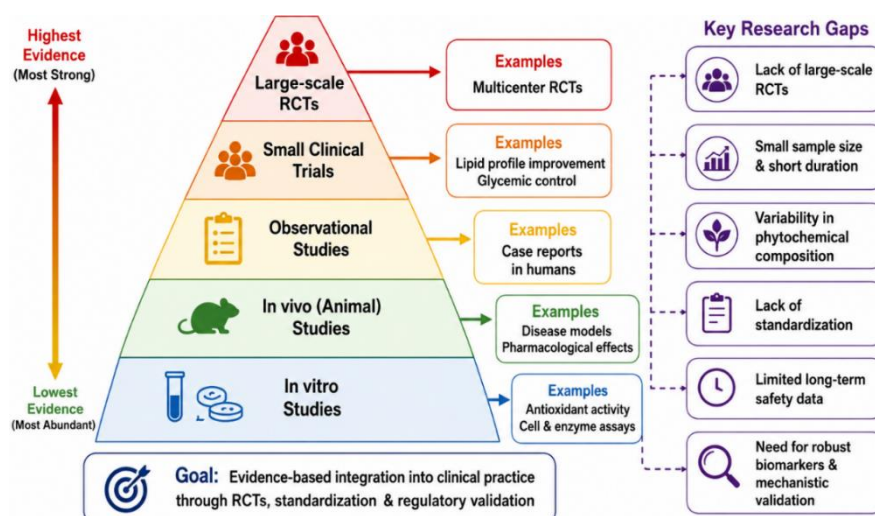


Figure 2: Translational Evidence Hierarchy and Research Gaps in *Nelumbo nucifera* Studies

6. Challenges and Limitations

Phytochemical variability due to geographical and environmental factors, lack of extract standardization, inconsistent dosing regimens, and limited reproducibility across studies remain major challenges. These issues lead to variability in biological outcomes and hinder comparison between studies. Addressing these limitations through standardized methodologies and well-designed experimental protocols is essential for improving reliability and facilitating clinical translation of *N. Nucifera* [75].

Although *N. nucifera* has a broad pharmacological profile, its clinical translation is hampered by multiple challenges. Inequitable variability in phytochemical composition, based on geographical location, seasonal variation and part of the plant used, is a main issue. Studies show that variation of total phenolic and flavonoid content (of 20-40%) can lead to differences in biological activity. Moreover, extraction methods and dosage forms are not uniform, which leads to a deviation of 15-35% concentration level for bioactive compounds from one study to another, making reproducibility difficult [76].

An additional key limitation is the restriction of clinical validation. Human studies on this topic are scarce compared to the countless preclinical studies, often with small sample sizes ($n = 30-100$) and relatively short durations of treatment (4-12 weeks). As a result, long-term efficacy and safety data are lacking. In addition, *N. nucifera*-based therapies are held back by regulatory hurdles. There are usually no clear regulatory pathways for herbal products, so the approval process can be delayed by different guidelines across regions. Troubles of quality control, standardisation, and validation of energetic constituents additionally make regulatory acceptance more complicated [77, 78].

7. Future Perspectives

Future studies regarding *N. nucifera* should address these limitations through proper clinical trials. Further systematic investigations, including double-blind, placebo-controlled randomized controlled trials (RCTs), are required to establish efficacy and safety, rather than assuming predefined sample sizes or durations. To ensure consistency, standardised extracts with known phytochemical markers should be developed [79].

There is great potential for integration with modern drug discovery methods. More advanced techniques such as metabolomics, molecular docking and nanotechnology-based delivery systems can be used to boost bioavailability and target specificity. However,

claims regarding quantitative improvements in therapeutic efficacy should be interpreted cautiously and require robust experimental validation [80]. Similarly, it shows potential in personalised and precision medicine. Its multi-target pharmacological effects may be adaptable to individual genetic and metabolic profiles; however, current evidence remains preliminary and requires further validation. In the advancement of pharmacogenomics and systems biology, this plant can be combined into personalised therapeutic regimens [27, 81].

8. Conclusion

Nelumbo nucifera is a medicinal plant with diverse pharmacological potential supported by traditional knowledge and preclinical evidence. Its bioactive constituents exhibit multi-target actions against oxidative stress, inflammation, metabolic disorders, and neurological conditions. However, despite promising in vitro and in vivo findings, clinical validation remains limited and inconclusive. Significant challenges, including variability in phytochemical composition, lack of extract standardization, and heterogeneity in experimental designs, hinder reproducibility and translational applicability. Current clinical studies are generally small-scale and short-term, restricting definitive conclusions regarding efficacy and long-term safety. Therefore, future research should prioritize well-designed, large-scale randomized controlled trials, standardized formulations, and detailed pharmacokinetic and safety evaluations. Integration of advanced approaches such as omics technologies and novel drug delivery systems may further enhance therapeutic potential. A critical and evidence-based approach is essential to establish *N. nucifera* as a reliable component of modern healthcare.

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Authors contribution

AKP: Study Conception and Design; **DK:** Data Collection; **AK:** Draft Manuscript; **AK, AKP:** Reviewing and Editing; **DK, LPS:** All authors reviewed the results and approved the final version of the manuscript.

Conflict of Interest

The authors have no conflict of interest to declare.

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Artificial Intelligence Declaration

The authors declare that no artificial intelligence (AI)

tools were used in the generation of scientific content, data analysis, or interpretation in this manuscript. AI tools were used only for language refinement and formatting assistance, where applicable.

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