Scientific Basis for the Therapeutic Uses of Nelumbo nucifera Gaertn (Kamal): A Systematic Review.

Dr. Sonali Takawale Kesari[1], Dr. Jayshree Changade[2]*

[1]PG scholar, Department of Dravyaguna Vigyana, Dr. D. Y. Patil College of Ayurved and Research Centre, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune-411018, Maharashtra, India.[1]
Email: drsonalikesari@gmail.com
[2]Professor & HOD, Department of Dravyaguna Vigyana, Dr. D. Y. Patil College of Ayurved and Research Centre, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pimpri, Pune-411018, Maharashtra, India.[2]
Email: jayshreeulemale28@gmail.com

Abstract
The present review highlights the chemical qualities, therapeutic benefits, toxicity profile of *Nelumbo nucifera Gaertn*.(Kamal) which is a commonly used plant in Ayurvedic medicine. While there has been some scientific research conducted on the potential therapeutic effects of the plant, more studies are needed to confirm its effectiveness and safety. Due to the generally different approaches taken by each examination, no factual pooling of results or assessment of the nature of the investigations was carried out. Some studies have found that compounds found in *Nelumbo nucifera Gaertn.*, such as Nuciferine, have anti-inflammatory, antioxidant and anticancerproperties. However, further research is needed to understand the full range of therapeutic uses and potential side effects of the plant. *Nelumbo nucifera Gaertn*.(Kamal) is widely used plant in Ayurvedic medicine, with numerous reported therapeutic benefits. This review provides an overview of the plant's chemical composition,therapeutic effects, and toxicity profile. While some scientific studies have investigated its potential therapeutic effects, further research is necessary to validate its efficacy and safety. Due to the heterogeneity of the studies reviewed, no meta-analysis was conducted. Further research is required to fully elucidate its therapeutic uses and potential side effects. Preliminary research suggests that *Kamal* may have beneficial effects on the Renal System, circulatory system, and digestive system, with low toxicity. These findings are promising and support the potential use of Kamal as a therapeutic agent.

Introduction:

Lotus (*Nelumbo nucifera*) is an aquatic monocotyledonous plant known by several common names, including Indian lotus, Chinese water lily, and sacred lotus, and has been described under various synonyms such as *Nelumbium nelumbo*, *N. speciosa*, *N. speciosum*, and *Nymphaea nelumbo*[1].The plant comprises multiple usable parts seedpods, rhizomes, seeds, Asia, particularly in China, Japan, India, and other Southeast Asian regions, as well as in parts of the Americas and Oceania[2].Cultivation areas are estimated to exceed 330,000 hectares in China and approximately 4,000 hectares in Japan[3].In India, lotus grows widely in lakes and other aquatic environments across diverse altitudes, ranging from high-altitude regions such as Kashmir (around 1,400 m) to low-lying southern areas like Kanyakumari (approximately 0.3 m)[4]. *Nelumbo nucifera* is naturally distributed across parts of Asia and is also found in regions such as Australia and Russia; it was introduced to Western Europe and the Americas in earlier historical periods[5]. The species is widely appreciated for the striking aesthetic appeal of its large, ornamental flowers and has long held profound spiritual significance in several ancient cultures, including Buddhist, Hindu, and Egyptian traditions. In Hinduism, the flower itself is regarded as sacred, while in Buddhism the sanctity extends to the entire plant. Owing to its cultural and visual prominence, the lotus is recognized as the national flower of both India and Vietnam[6].At present, *Nelumbo nucifera* has gained considerable scientific interest due to its rich content of bioactive secondary metabolites distributed across different plant parts. The flowers are abundant in flavonols and anthocyanins[7], while the plumule contains alkaloids, flavonoids, steroids, and polysaccharides[8]. In addition, the rhizome (commonly referred to as lotus root) and seeds are rich in polyphenols, fatty acids, procyanidins, and polysaccharides Collectively[9], these phytoconstituents contribute to a wide range of health-promoting biological activities[10]. The principal edible components of lotus are the rhizome and seeds. In contrast, He-Ye (lotus leaves), despite an annual production exceeding 800,000 tons, are frequently discarded as by-products of the lotus processing industry, leading to substantial biomass waste[11]. In China alone, the yearly yield of *Nelumbo nucifera* leaves (NLEs) is estimated at 7,000–10,000 tons, of which only about 1% is utilized in the tea and food service sectors[12]. However, lotus leaves possess several additional functional applications. Structurally, their surface is characterized by microscale mound-like projections and nanoscale hair-like features that enable enhanced light absorption, efficient water transport, and rapid vapor release. These properties have facilitated the development of simple and versatile devices based on lotus leaves for improved solar-driven water evaporation[13]. Furthermore, natural lotus leaves have been utilized as a superhydrophobic platform for the fabrication of sensitive and reproducible sensors capable of detecting paraquat, owing to their strong hydrophobic concentrating effect[14]. This systematic review synthesizes the current evidence from clinically relevant investigations while seeking to establish a scientific rationale for the therapeutic potential of *Nelumbo nucifera* Gaertn. The primary objective is to provide a comprehensive overview of the medicinal

applications of this species, with focused consideration of its pharmacological relevance, thereby facilitating the identification of prospective directions for future research.

Material and Methods

The protocol for this investigation was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

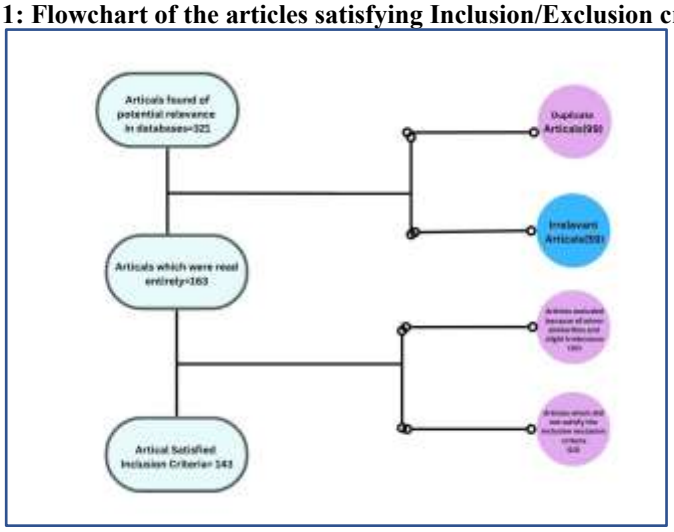
Data Sources :

The literature search was conducted using MEDLINE (via PubMed), Cochrane, and PubChem databases, covering the period from January 2008 to January 2026. The search strategy employed relevant descriptors associated with *Nelumbo nucifera* Gaertn., including "Nelumbo nucifera," "sacred lotus," "Indian lotus," "Padma," "Kamala," "Kamal," "lotus," "neferine," and "nuciferine." In addition, a manual search of the reference lists of eligible articles was performed to identify further relevant studies as a secondary search approach. Unpublished data and conference proceedings were also considered and included where available.

Study Selection:

The included articles addressed biological activities, traditional applications, and the isolation and identification of chemical constituents of *Nelumbo nucifera* Gaertn. Studies were excluded if they met any of the following criteria: (1) titles or abstracts did not contain the specified search terms; (2) the publication was a review or systematic review; or (3) biologically active constituents were not isolated during the study and were instead obtained from commercial sources. Articles presenting contradictory or inconsistent findings were also excluded from the analysis.

Figure 1: Flowchart of the articles satisfying Inclusion/Exclusion criteria:



Study selection adhered to the PRISMA methodology: initially, all records were screened based on titles and abstracts; subsequently, articles identified as potentially eligible were subjected to full text evaluation in accordance with predefined inclusion criteria; and finally, studies fulfilling all criteria were included for data extraction. Records that generated ambiguity at the screening stage were retained and advanced to the eligibility phase for detailed assessment. The complete text of each selected article was carefully reviewed. Information on biological activities, extraction methods, isolation and identification of chemical constituents, along with primary outcome measures, was extracted by the first author and independently verified by the second author.

Data Extraction:

The variables of interest extracted from each study included the journal source, site of plant collection, traditional uses of *Nelumbo nucifera* Gaertn, isolated chemical constituents, and reported biological activities. Any discrepancies arising during data extraction were resolved through discussion among the reviewers.

Result

Figure 1 illustrates the schematic workflow of the study selection process. An initial database search identified 321 potentially relevant articles. Of these, 99 duplicates were removed, and 59 records were excluded based on irrelevant titles or abstracts. The remaining 163 articles were advanced to the next stage of screening,as the other 10 exhibited minor overlap or limited relevance. Following full-text evaluation,10 articles did not meet the predefined inclusion criteria and were therefore excluded. Consequently, a total of 143 studies were included in the final analysis. Manual searching of reference lists did not yield any additional eligible articles.

Botanical Description:

Nelumbo nucifera is a big water plant with long, thin stems that creep along the ground and have nodal roots. The leaves of perennial lotus plants are round and can be found in the air and on the ground[15]. While floating leaves have a flat appearance, aerial leaves are cup-shaped[16]. 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[17]. 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[18]. The tuberous root, approximately 8 inches long and 2 inches wide, has a smooth green outer surface and numerous internal air cavities that aid buoyancy in water. Figure 1 illustrates the main parts of the plant: flower, leaf, seed, and root[19].

Leaves:

The plant produces large aerial and floating leaves measuring about 20–90 cm. Fresh leaves are leathery but become thin and brittle on drying, often showing brownish-red patches beneath. Aerial leaves have erect, sturdy whitish petioles, while floating leaves possess weaker ones. The blades are entire, glaucous, non-wettable, and radiately veined—cup-shaped in aerial leaves and flat in floating leaves. Petioles are green to greenish-brown, slightly rough with fine spots, fibrous in fracture, and contain four large central air cavities with smaller peripheral spaces in cross-section[20]

Fruits & Seed:

The fruit consists of a group of immature nutlets that become firm, smooth, and brownish- to greyish-black on ripening. Each nutlet is pedunculated, single-seeded, slightly longitudinally striated, and varies from ovoid to oblong in shape, measuring about 1 cm in length and 1.5 cm in width. The mature carpel encloses a fully developed seed. Notably, the seeds show exceptional longevity and can remain viable for many years; historical observations even recorded successful germination after prolonged storage of more than a century[21].

Flowers:

The flowers are solitary, large, and fragrant, measuring about 10–25 cm in diameter, with colours ranging from white to pink or pinkish white. Sepals, petals, and stamens are arranged spirally and gradually merge into one another. The stout peduncle arises from the rhizome node, is 1–2 cm long at the sheathing base, green to blackish green in colour, and may appear smooth or slightly rough due to the presence of small scattered prickles[22].

Root:

The lotus root has a two layered epidermis, forming a small portion of the root's radius. Beneath it lies a spongy cortex made of parenchyma cells with large intercellular air spaces, which help the plant survive in low-oxygen (anaerobic) conditions. The inner cortex contains thick, rounded cells arranged in rings, providing structural strength. Lotus roots are widely consumed about 70% are eaten fresh, while the rest are processed into products like vinegar, powder, and juice. Researchers have also isolated polysaccharides from both the roots and their residues[23].

Table 1: Overview of different lotus species and their distinctive attributes.[24]

Common name	Scientific name	Origin	Characteristics	Habitat
Sacred Lotus	*Nelumbo nucifera*	Asia and Australia	Large, fragrant pink or white flowers; broad, round leaves	Ponds, lakes, and water gardens
American Lotus	*Nelumbo lutea*	North America	Yellow flowers; large, round leaves with a distinctive notch	Slow-moving rivers and lakes
Egyptian White Water-lily	*Nymphaea lotus*	Egypt	White flowers with a yellow center; night-blooming	Still or slow-moving water bodies
Pygmy Water-lily	*Nymphaea tetragona*	Eurasia	Small white or pink flowers; small, round leaves	Cold, still freshwater bodies
Blue Lotus	*Nymphaea caerulea*	Ancient Egypt	Vibrant blue flowers; used in traditional medicine and for ornamental purposes	Freshwater habitats; ornamental ponds

Screening of Early-Flowering Cultivars and Their Influence on Flowering Duration in Nelumbo nucifera

Flowering time is a key trait influencing the breeding and commercial value of ornamental plants. In Nelumbo nucifera, the natural flowering season is largely confined to June to August. As this period coincides with hot weather and reduced tourist activity, many lotus scenic sites face operational challenges. Consequently, there is growing demand for cultivars that bloom earlier.

In the Study conducted by Huiyan Jiang et al, in 2019-2020, 30 highly ornamental lotus cultivars were evaluated over two consecutive years (2019–2020) to document their phenological stages. Using K-means clustering, several cultivars with stable and early flowering potential were identified, including 'Fenyanzi', 'Chengshanqiuyue', 'Xianghumingyue', and 'Wuzhilian'. The association between accumulated temperature and

flowering time was further examined in 19 cultivars across different growth stages. Results indicated that early-flowering cultivars adapt effectively to early-season temperature fluctuations and are less sensitive to low temperatures.
Additionally, analysis of key traits, such as rhizome weight and phenological duration in three representative cultivars showed that rhizome nutrient reserves and early plant morphology significantly influence flowering time. Overall, these findings contribute to developing a systematic breeding strategy for early flowering lotus cultivars and support the establishment of improved flowering regulation techniques, ultimately enhancing ornamental value and promoting industry growth[25].

Traditional Uses:
Nelumbo nucifera Gaertn. commonly known as "Sacred lotus" and locally referred to as "Kamal" or " “sacred lotus, Indian lotus, Water lily and Chinese water lily.” and it holds significant value in traditional medicine .*N. nucifera* (lotus) has a long history of medicinal use across multiple traditional healthcare systems, including those of China, India, Japan, Thailand, and Korea, where different parts of the plant have been employed for a wide range of therapeutic applications.Across centuries of practice, virtually all parts of this aquatic species including the stamens, leaves, petioles, flowers, seeds, and rhizomes have been incorporated into traditional Chinese medical formulations for over a millennium. In contemporary times, this long-standing therapeutic relevance is reflected in large scale cultivation, with the annual production of *N. nucifera* leaves for traditional medicinal use and pharmaceutical applications in China exceeding 800,000 tonnes Traditionally, *N. nucifera* has been valued for its role in maintaining physiological balance, particularly through its beneficial influence on the circulatory system. In Chinese medicine, the leaves are commonly prescribed for managing conditions such as hyperlipidemia, hematemesis, and metrorrhagia, for reducing fever, and for alleviating inflammatory skin disorders . Beyond medicinal preparations, dried lotus leaves are widely consumed as herbal teas in several Asian regions, especially in China and Taiwan, where they are traditionally used for weight management and reduction of body fat index . In Thailand, lotus stamens are an essential component of traditional medicinal formulations. Herbal infusions prepared from the stamens are customarily consumed to support cardiovascular health, regulate blood glucose and lipid levels, and mitigate oxidative stress within the body. Traditional medical systems report that plant derived phytochemicals play an important role in managing a wide range of diseases, including leukoderma, smallpox, dysentery, haematemesis, cough, haemorrhage, metrorrhagia, haematuria, fever, hyperlipidaemia, cholera, liver disorders, and excessive thirst. To examine these traditional claims, several researchers have carried out scientific studies using both *in vivo* and *in vitro* experimental models. The findings from these investigations suggest that the plant possesses multiple pharmacological properties, such as anticancer, hepatoprotective, antioxidant, antiviral, hypolipidemic, anti-obesity, antipyretic, hypoglycaemic, antifungal, anti-inflammatory, and antibacterial activities[5].

Phytochemical Investigation
The therapeutic application of *Nelumbo nucifera Gaertn* has yet to receive formal scientific validation, leading to skepticism regarding its efficacy in various diseases. In Ayurveda, *Kamal* is classified as aquatic perinnial herb. The phytochemistry of *Nelumbo nucifera Gaertn* has been extensively*o*studied, with over thirty bioactive compounds identified, isolated, and characterised. Key constituents
include the chemical compositions like phenol, alkaloids, glycoside, terpenoids and steroids . The plant contains various nutritional values like lipids, proteins, amino acids, minerals, carbohydrates, and fatty acids.[5]
A study of 18 natural populations of Nelumbo nucifera across different floristic regions of Thailand revealed marked variation in phenolic and polyphenolic content in the perianth and stamen. Flavonoids were identified as the predominant phytochemicals, with higher levels found in the stamen compared to the perianth. The study also reported, for the first time, a significant correlation between the phytochemical profiles of these two floral parts[6].

Pharmacological Activities of Flavonoids Isolated from *Nelumbo nucifera Gaertn.*
A wide range of pharmacologically active constituents responsible for the therapeutic effects of *N. nucifera* have been identified from its leaves, rhizomes, seeds, and flowers. Distinct groups of phytochemicals have been isolated from different parts of the plant, with alkaloids, steroids, triterpenoids, flavonoids, glycosides, and polyphenols being the most prominent classes. Studies on these constituents have confirmed diverse pharmacological activities, including anti-ischaemic, gastrointestinal, anti-inflammatory, antioxidant, antiviral, antidiabetic, and immunomodulatory effects. In addition, extracts from various plant parts have shown anti-neurodegenerative, anti-obesity and hypolipidemic, anti-Parkinsonian, antidermatophytic, antidiarrheal, psychopharmacological, antitumor and anticancer, antihepatotoxic, anticholestatic, neuromodulatory, anti-haemolytic, anti-angiogenic, anti-fatigue, anti-aging, and diuretic properties[7].From a chemical perspective, flavonoids belong to the phenylpropanoid class and are characterized by a C6–C3–C6 carbon framework, comprising two aromatic rings. In plants, flavonoids predominantly occur in glycosylated forms. Glycosylation alters their solubility, stability, and potential toxicity, while also influencing cellular localization and biological activity[8].Naturally occurring flavonoids exist mainly as O- and C-glycosides, which differ in their functional roles in both plant physiology and human health[9]. O-glycosylation, leading to the formation of flavonoid O-glycosides (FOGs), is widespread in plants and has been extensively characterized[10]. In contrast, the biosynthesis of flavonoid C-glycosides (FCGs) has received comparatively limited attention, and the C-glycosyltransferases involved are far less studied than O-glycosyltransferases [11].

Unlike O-glycosylation, which involves the attachment of sugar moieties to hydroxyl oxygen atoms, C-glycosylation results in the formation of a stable carbon–carbon bond between the sugar and the flavonoid backbone. This relatively rare glycosidic linkage is highly resistant to acid- or enzyme-mediated hydrolysis and is therefore associated with marked differences in the biological functions and activities of FCGs compared with FOGs. From a pharmacological perspective, C-glycosylation significantly influences flavonoid bioavailability, pharmacokinetics, and biological effects, including antioxidant, anti-inflammatory, hepatoprotective, antiviral, and anticancer activities[12].

Nelumbo nucifera is among the richest natural sources of flavonoids, primarily accumulating them as FOGs and FCGs. The major flavonoid glycosides identified in lotus tissues are summarized in Figure 3. Notably, Zhu et al reported higher antioxidant activity of FCG-rich lotus extracts compared with FOG-dominant extracts, highlighting the potential impact of C-glycosylation on flavonoid bioactivity. Interestingly, lotus exhibits distinct tissue-specific flavonoid accumulation, with flavonoid C-glycosides (FCGs) predominantly concentrated in the embryo, where they account for over 70% of total flavonoids. While leaves accumulate high flavonoid levels almost exclusively as flavonoid O-glycosides (FOGs)[13],[14]. Except embryo FOGs deriving from Quer 19 (hyperoside O6, isoquercitrin O7 and Quer-3-Gln O9), Kae (astragalin O12) and Iso (Iso-3-Glc O14) were detected in all analyzed tissue. A pronounced tissue specific pattern is evident in the accumulation of flavonoid O-glycosides (FOGs) between vegetative and reproductive organs. In leaves, FOGs originate from six major aglycones namely quercetin (Quer), kaempferol (Kae), isorhamnetin (Iso), luteolin (Lut), diosmetin (Dio), and syringetin (Syr), listed in decreasing order of abundance , with quercetin derivatives such as rutin, hyperoside, and isoquercitrin constituting the principal components . Vegetative tissues, particularly young and mature leaves, leaf pulp, and veins, exhibit high FOG levels, where hyperoside, isoquercitrin, and quercetin-3-glucuronide together account for over 70% of total flavonoids. In contrast, floral tissues such as petals and stamens show a dominance of kaempferol-derived FOGs, representing more than 60% of total flavonoids, despite these tissues having overall lower flavonoid content. Additionally, FOGs derived from myricetin, kaempferol, isorhamnetin, and syringetin were detected exclusively in reproductive tissues and were absent from vegetative organs, highlighting marked differences in flavonoid biosynthesis and accumulation between these tissue types. Quantitatively, with the exception of the seed coat, reproductive tissues accumulate substantially lower levels of flavonoid O-glycosides (FOGs) than vegetative organs. FOGs are particularly c in the embryo and are nearly undetectable in seed kernels, whereas the embryo exhibits a marked enrichment of flavonoid C-glycosides (FCGs) [25,27,35]. The predominant embryonic FCGs are derived mainly from apigenin and, to a lesser extent, luteolin, with apigenin-6-C-glucosyl-8-C-arabinoside (schaftoside) alone contributing over 35% of the total flavonoid content . This distinctive FCG profile of the embryo may hold taxonomic relevance and could serve as a basis for authentication using these compounds as potential chemotaxonomic markers. Flavonoid compounds, synthesised via the biosynthetic pathway which starts with the condensation of one *p*-coumaroyl-coA together with 3 malonyl-coA moieties catalyzed by chalcone synthase (CHS) leading to the synthesis of chalcone, the first committed flavonoid Glucose .Following the initial condensation reaction, successive hydroxylation, methylation, and acetylation steps generate a diverse array of flavonoid derivatives. These modifications result in the accumulation of flavonols and flavones in lotus tissues, including apigenin (Api), diosmetin (Dio), isorhamnetin (Iso), kaempferol (Kae), luteolin (Lut), myricetin (Myr), quercetin (Quer), and syringetin (Syr). The resulting aglycones may subsequently undergo glycosylation at multiple positions through the action of a broad spectrum of glycosyltransferases, leading to the formation of structurally diverse flavonoid O-glycosides (FOGs) and flavonoid C-glycosides (FCGs) observed in different lotus tissues.

In *Nelumbo nucifera*, two distinct classes of glycosyltransferases exhibit markedly different tissue-specific distribution patterns. The predominance of FOGs in leaves suggests high activity and widespread expression of O-flavonoid glycosyltransferases, whereas C-flavonoid glycosyltransferases appear to be more restricted, with activity largely confined to the embryo. This tissue specificity is consistent with the pronounced accumulation of FCGs in embryonic tissues. Consequently, lotus leaves and embryos represent promising biological sources for the isolation and functional characterization of these distinct glycosyltransferase classes. From a structural perspective, embryo localized FCGs are primarily derived from apigenin, with a lesser contribution from luteolin, whereas leaf-associated FOGs predominantly originate from quercetin, followed by kaempferol, isorhamnetin, luteolin, diosmetin, and syringetin. The differential flavonoid profiles between leaves and embryos therefore provide a valuable framework for elucidating regulatory mechanisms governing flavonoid biosynthesis at both molecular and biochemical levels. Future investigations employing isotopically labeled precursors to trace biosynthetic pathways, along with transcriptomic approaches such as RNA sequencing, are likely to offer deeper insights into the biosynthesis and regulation of flavonoid diversity in lotus and facilitate the optimized utilization of these bioactive compounds[15].

Pharmacological effects of *Nelumbo nucifera* Gaertn extracts and isolated compounds:

1. Antioxidant Activity-

excessive intracellular accumulation of reactive oxygen species (ROS), reactive nitrogen species (RNS) and other free radical species leads to Oxidative stress, which contributes to onset and progression of various diseases, like diabetes, obesity, diabetic nephropathy, and Alzheimer's disease (AD), neurological diseases, such as , amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). Oxidative stress is also linked to cancer and cardiovascular disease[16].Phenolic extracts of lotus leaves shows Antioxidant activity.Lotus leaves mainly contains compounds like rutin, catechin, sinapic acid, chlorogenic acid, syringic acid, and quercetin. These

compounds efficiently neutralize free radicals, such as DPPH and ABTS, and help protect cells from oxidative damage[17]. According to Lin al. etisolated several flavonoids from *N. nucifera* leaf extracts, including catechin, quercetin, isoquercitrin, quercetin-3-glucuronide, hyperoside, astragalin, and myricetin-3-glucoside. The first four compounds effectively inhibited LDL oxidation, while myricetin-3-glucoside showed the strongest DPPH scavenging activity, indicating that the antioxidant potential of lotus leaves depends on both flavonoid content and composition[18].Zhu et al.identified 14 flavonoids, including four novel compounds-Quer-3-O-Ara, Quer-3-O-Rha-(1→2)-Glc, Dio-7-Hex O17, and Iso-3-O-Ara-(1→2)-Glc, from *N. nucifera* leaf extracts. These extracts demonstrated strong antioxidant activity, highlighting the contribution of both known and newly characterized flavonoids.[19]

The hydroalcoholic extract of *Nelumbo nucifera* seeds (HANN) was evaluated using both in vitro and in vivo models, it shows antioxidant potential.The extract showed a total phenolic content of 7.61 ± 0.04% (w/w), and its characteristic HPTLC fingerprint was established using different solvent systems. HANN demonstrated potent free-radical-scavenging activity, reflected by low IC_{50} values in the DPPH (6.12 ± 0.41 µg/mL) and nitric oxide (84.86 ± 3.56 µg/mL) assays[20].Chen et al. evaluated the antioxidant potential of the flavonoid-rich seed epicarp of *N. nucifera*, a commonly discarded byproduct. The extract exhibited strong in vitro antioxidant activity, as demonstrated by ABTS, DPPH, and FRAP assays[21]. Accordingly, the seed epicarp may serve as a promising raw material for future functional food applications. Liu et al.further reported that antioxidant activity of *N. nucifera* seed epicarp varied across ripening stages in China, with catechin, epicatechin, hyperoside, and isoquercitrin identified as major constituents. DPPH and ABTS assays showed strong radical-scavenging activity, which declined progressively with maturation[22]

Zhu et al. identified eight flavonoid C-glycosides and eight O-glycosides in *N. nucifera* seed embryos, with FCGs being the dominant flavonoid class, and reported Kae-7-Glc and luteolin-7-O-neohesperidoside for the first time in this tissue. Comparative analysis showed that embryo extracts exhibited antioxidant activity comparable to or exceeding that of leaf extracts, despite a lower total flavonoid content. Notably, FCGs from embryos demonstrated stronger antioxidant potential than FOGs from leaves[23].Jiang et al. identified four novel flavonoid C-glycosides (nelumbosides A–D) from *N. nucifera* embryos and assessed their antioxidant activity using ABTS and DPPH assays. Among them, nelumboside B showed the strongest radical-scavenging potential.[24] The seeds are rich in ascorbic acid, glutathione, and several other biologically active constituents that exhibit notable antioxidant activity.ethyl acetate (EA) and ethyl alcohol (ET) lotus petal extracts shows, high free radiacal scavenging capacity interpreting its high antioxidant capacity[25].Methanolic extract of Stamen of N.nucifera plant collected from korea shows strong antioxidant potential. Kaempferol (Kae) was identified as the primary contributor to the antioxidant activity of the extracts. This was demonstrated using both in vitro DPPH assays and an in vivo Wistar rat model, where reduced ROS generation in kidney homogenates was confirmed using the DCHF-DA probe[26].

Feng et al. identified twenty flavonoids in *N. nucifera* plumule extracts, fourteen of which were flavonoid C-glycosides, and assessed antioxidant activity across 38 lotus cultivars using DPPH and FRAP assays in vitro study. A strong positive correlation was observed between total polyphenol content and antioxidant capacity. Taikonglian, Yinqiu, Jinqi, and Hongtailian showed the highest antioxidant potential, supporting their suitability for healthcare applications [27].

2.Antiinflammatory Activity

Lotus petal extracts shows antiinflammatory activity by assessing proinflammatory cytokine TNF-α secretion levels of human macrophages. Lipopolysaccharide (LPS) was used to induce an inflammatory response in macrophages which mimic bacteria induced inflammation, and the levels of the pro-inflammatory cytokine TNF-α in the culture supernatant were measured using ELISA.The Experiemental results showed that EA and ET lotus petal extracts were rich in three major phytocompounds: chlorogenic acid, ferulic acid, and coumarin. Kim et al. reported that Kae, a flavonoid from *N. nucifera*, reduced ROS levels, enhanced GSH, and significantly lowered iNOS and TNF-α expression in an age-related in vivo model in a dose-dependent manner. Their findings suggest that Kae exerts strong anti-inflammatory effects by modulating glutathione, NF-κB, and MAPK signaling pathways[28]. Li et al demonstrated that Quer-3-Gln O9 isolated from *N. nucifera* leaves exhibited anti-inflammatory activity by suppressing LPS-induced nitric oxide production in RAW264.7 macrophages[29].During inflammation, innate immune cells protect injured tissues by releasing mediators such as TNF-α, NO, interleukins, COX-2, and iNOS; however, their excessive production contributes to chronic inflammatory disorders. Lotus seed–derived constituents have been shown to counteract this response by suppressing inflammatory mediator overexpression. Lotus seed protein isolates significantly downregulated COX-2 and iNOS gene expression, while bisbenzylisoquinoline alkaloids from seed embryos reduced NO, IL-1β, IL-6, and TNF-α production by inhibiting NF-κB signaling, decreasing intracellular Ca^{2+} levels, and limiting CaM activity.[30-32]

In vivo studies further demonstrated that red and white lotus seed extracts inhibit COX-2 activity in experimental models41. Additionally, polysaccharides isolated from lotus seed plumules modulated immune balance by regulating pro- and anti-inflammatory cytokine ratios, indicating an immunoregulatory mechanism[33].

3.Immunomodulatory Effect

Enhancing immune responses to manage infectious diseases is considered a safe and rational approach. Lotus seeds have demonstrated immunomodulatory activity by increasing lymphocyte populations and total leukocyte counts[34],[35]

EA and ET lotus petal extracts which contains chlorogenic acid, ferulic acid, and coumarin,

showed immunomodulatory activity by reducing TNF-α production through inhibition of the NF-κB–mediated inflammatory pathway. Overall, lotus petal extracts demonstrate promising potential for development as dietary supplements to support weakened immune function[36].

4.Anti-Diabetic and Anti-Obesity Activities

Diabetes mellitus is a common endocrine disorder characterized by impaired glucose metabolism due to inadequate insulin production or action. Studies on *Nelumbo nucifera* Gaertn. have shown that its extracts induce hypoglycaemia and improve glucose tolerance in normal rabbits. Although chronic administration in normal rats did not sustain fasting blood glucose reduction, acute dosing produced hypoglycaemic effects and enhanced glucose tolerance. In vitro experiments using rat hemidiaphragms indicated that the extracts increased insulin sensitivity, suggesting improved peripheral glucose utilization. In moderately diabetic rabbits, the extracts reduced hyperglycaemia and significantly improved glucose tolerance, though their efficacy was lower than standard antidiabetic drugs, while no benefit was observed in severely diabetic models even at higher doses. [37],[38]

Studies have demonstrated notable anti-diabetic and anti-obesity effects of *Nelumbo nucifera*, largely attributed to its flavonoid-rich extracts. Flavonoids from stamens effectively inhibited aldose reductase, a key enzyme in the polyol pathway linked to type 2 diabetes, while leaf flavonoids regulated insulin secretion and reduced blood glucose levels through Ca^{2+}-dependent PKC–ERK1/2 signaling, with catechin identified as a major active compound. Both in vitro and in vivo models confirmed the ability of leaf extracts and catechin to improve postprandial hyperglycemia and reverse glucose intolerance in diet-induced diabetic animals. In addition, flavonoids from leaves, rhizomes, and seeds exhibited anti-obesity activity by inhibiting pancreatic lipase, α-amylase, and α-glucosidase, suppressing adipocyte differentiation, and improving lipid metabolism. These findings collectively highlight *N. nucifera* as a promising natural source for managing hyperglycemia, insulin dysfunction, and obesity-associated metabolic disorders.Research findings show that ethanolic extracts of *N. nucifera* reduce adipose tissue mass, improve lipid profiles, regulate serum leptin levels, and inhibit adipogenesis in rats fed a high-fat diet.[39],[40],[41].

The oral hypoglycaemic activity of Nelumbo nucifera has been demonstrated using an ethanolic extract of its rhizome. In experimental studies, the extract significantly lowered blood glucose levels in normal rats, glucose-loaded hyperglycaemic rats, and streptozotocin-induced diabetic rats when compared to control groups. It also improved glucose tolerance and enhanced the effect of externally administered insulin in normal animals. The glucose-lowering effect of the extract was found to be nearly comparable to tolbutamide, showing about 73% activity in normal rats and 67% in diabetic ratsFurther investigation identified tryptophan as one of the active anti-diabetic constituents from the lotus rhizome nodes. In glucose-fed mice, both the methanolic extract of the nodes (400 mg/kg) and isolated tryptophan (100 mg/kg) produced significant blood glucose-lowering effects, supporting its potential role in diabetes management[42].

5.Antiangiogenesis and Anticancer activity.

Inhibition of angiogenesis is a key strategy in cancer therapy. *Nelumbo nucifera* leaf extracts were first reported to suppress VEGF-induced angiogenesis in both in vitro and in vivo models.[43].Flavonoid-rich leaf extracts, particularly flavonoid O-glycosides, demonstrated significant anti-proliferative effects against breast cancer in human MCF-7 cells and xenograft mouse models.[44].Further studies showed that these extracts reduced breast cancer metastasis induced by using MDA-MB-231 and 4T-1 breast cancer cells, by targeting PKCα and by downregulating connective tissue growth factor through the PI3K/AKT/ERK signaling pathway.[45]Collectively, these findings highlight the chemopreventive potential of *N. nucifera* leaf flavonoids, while also indicating the need for more cancer-specific investigations due to the complex and multifactorial nature of cancer.

The angiogenesis inhibitory potential of *N. nucifera* leaf extracts (NLEs) has been demonstrated in both cellular and animal models. NLEs significantly suppressed VEGF-induced endothelial cell proliferation, tube formation, and CAM angiogenesis in vivo. In human umbilical vein endothelial cells, NLEs (10–100 μg/mL) produced a clear dose-dependent inhibition of VEGF-mediated angiogenic responses. Consistently, treatment with NLEs in a Matrigel model prevented the formation of vascular-like structures by HUVECs66.[46]

Extracts of *Nelumbo nucifera* demonstrate significant anticancer potential across multiple experimental models. The volatile-rich petroleum ether fraction of leaf extracts reduces tyrosinase activity and melanin production in B16 melanoma cells by inducing cell death, while nuciferine suppresses tumour growth and melanoma cell proliferation through inhibition of TLR-4/NF-κB signalling and p65 phosphorylation. Network-based and cellular studies further indicate activity against neuroblastoma, colorectal cancer, and glioblastoma via modulation of PI3K–AKT, IL-1, and SOX2–AKT/STAT3–Slug pathways, leading to reduced proliferation, migration, stemness, angiogenesis, and epithelial–mesenchymal transition. Flavonoid-rich leaf extracts also exert anti-carcinogenic and antimetastatic effects in breast cancer by promoting p53-mediated G1 arrest, inhibiting HER2/SREBP-1 and ER-α signalling, suppressing MMP-2 and PI3K/AKT/MEK/ERK pathways, and modulating TGF-β-dependent signalling. Additional evidence shows reduced liver preneoplastic lesions and inhibition of non-small-cell lung cancer growth through axin stabilization, Wnt/β-catenin suppression, and apoptosis induction[47],[48],[49].

In vitro studies:

Breast cancer:

Flavonoid-rich leaf extract of *Nelumbo nucifera* showed antiproliferative activity against MCF-7 breast cancer cell line at 0.5–5 mg/mL[50]. The extract inhibited cell proliferation through cell-cycle arrest at G0/G1 phase by

modulating Cyclin-D1/CDK complexes and apoptosis pathways[51]. Aqueous leaf extract inhibited proliferation, angiogenesis, migration, and invasion in MDA-MB-231 breast cancer cell line at 0.5–5 mg/mL.The effect involved modulation of MMP-2, TIMP, VEGF and PI3K-AKT/ERK signaling pathways. [52]. Aqueous and methanol leaf extracts reduced cell viability and migration in 4T1 mouse mammary carcinoma cell line and MDA-MB-231 breast cancer cell line (2–4 mg/mL, 24 h). The cytotoxic effect was associated with apoptosis induction and RhoA/Rac signaling pathways[53]. Methanol and acetone extracts of leaves and rhizomes inhibited proliferation of MCF-7 breast cancer cell line at 6.25–100 µg/mL. The extracts significantly reduced cancer cell viability, although detailed molecular mechanisms were not reported.[54]. Methanolic flower receptacle extract showed cytotoxic activity against MCF-7 breast cancer cell line at 200–600 µg/mL. The activity was mainly attributed to strong antioxidant potential and induction of cytotoxic stress[55]. Alkaloids liensinine, isoliensinine, and neferine induced cell death in breast cancer cells including MCF-10A breast epithelial cell line. The mechanism involved oxidative stress-mediated apoptosis via MAPK signaling pathways.[56]. Neferine significantly inhibited proliferation of MCF-7 breast cancer cell line. It promoted apoptosis by regulating Bax/Bcl-2 expression and caspase-dependent pathways[57]. Neferine demonstrated cytotoxic activity against MCF-7 breast cancer cell line (0.099–100 µM, 72 h). The compound enhanced drug uptake by modulating P-glycoprotein (P-gp) transport mechanisms.[58]. Neferine induced autophagy and apoptosis in MCF-7 breast cancer cell line. The effect involved AMPK-mTOR signaling, cytosolic Ca^{2+} regulation, and PERK-mediated stress pathways[59]. Neferine exerted strong anticancer activity in breast cancer cells through autophagy induction and mitochondrial-mediated apoptosis, highlighting its potential as a natural anticancer compound. The alkaloid neferine from Nelumbo nucifera reduced proliferation of MDA-MB-231 breast cancer cell line at 2–10 µM (24 h). The anticancer effect was mediated through apoptosis and regulation of miR-374a with inhibition of PI3K/Akt and MEK/ERK signaling pathways.[60]. The alkaloids liensinine and nuciferine inhibited proliferation of MCF-7 breast cancer cell line and MDA-MB-231 breast cancer cell line at 10–60 µM (24 h). The mechanism involved apoptosis induction via Bax/Bcl-2 regulation and activation of caspase-3[61]. Liensinine significantly reduced viability of MCF-7 breast cancer cell line and MDA-MB-231 breast cancer cell line at 20 µM (24 h). The compound induced autophagy through autophagosome-lysosome fusion, RAB7A recruitment, and mitochondrial fission via DNM1L activation.[62]. Seco-neferine F, a derivative of neferine, showed cytotoxic activity against MDA-MB-231 breast cancer cell line with IC_{50} of 39 µM (48 h). The compound induced significant anticancer effects, although the precise molecular mechanism was not reported.[63].

Cervical Cancer:

(−)-Lirinidine, isolated from the ethanolic petal extract, exhibited potent antiausterity activity against HeLa (human cervical cancer) cells (PC_{50}: 2–11 µM, 24 h) by inducing apoptosis through increased caspase-3 expression and decreased Bcl-2, p-Akt, and p-mTOR levels[64]. Isoliensinine inhibited proliferation and colony formation in Caski, C33A, HeLa, and SiHa cervical cancer cells (5–25 µM, 24–48 h) by inducing apoptosis and G0/G1 cell-cycle arrest through upregulation of p21 and caspase-9 and downregulation of Mcl-1, CDK2, cyclin E, p-Akt, and GSK3α[65]. Neferine (5–50 µM, 48 h) suppressed viability, induced cytotoxicity, and reduced migration of HeLa and SiHa cervical cancer cells by promoting apoptosis, autophagy, ROS generation, and G0/G1 cell-cycle arrest, with increased Bax, cytochrome c, cleaved caspase-3/9, PARP cleavage, and autophagy-related proteins, alongside decreased Bcl-2, procaspase-3/9, and TCTP [66].

Colon Cancer:

Ethanolic stamen extract (100–400 µg/mL, 24 h) exhibited cytotoxic activity against HCT-116 human colon cancer cells by inducing apoptosis and suppressing invasion-related pathways through activation of Fas/FasL/TRAIL signaling, caspases, and Bax, while downregulating Bcl-2, Bcl-xL, MMP-2, MMP-9, iNOS, COX-2, and NF-κB [67]. Neferine (0.039–100 µM, 72 h) reduced the viability of HCT-8 human colon cancer cells and enhanced intracellular drug accumulation by increasing rhodamine-123 uptake and inhibiting P-glycoprotein (P-gp) activity [58].Neferine and isoliensinine (2–12 µM, 24 h) exhibited cytotoxic effects against HCT-15 human colon cancer cells by inducing ROS-mediated apoptosis through activation of p38/MAPK signaling, increased Bax, caspase-9, caspase-3, and PARP cleavage, along with reduced Bcl-2 expression, loss of mitochondrial membrane potential (ΔΨM), and elevated intracellular Ca^{2+} levels[68.]Nuciferine (0.05–1.0 mg/mL, 24 h) reduced cell viability and inhibited invasion in CT26 murine colon carcinoma, HT29, and HCT116 human colon cancer cells, primarily through suppression of the PI3K/Akt signaling pathway and downregulation of IL1B expression [69].

Liensinine (5–20 µM, 24–48 h) suppressed proliferation of HT29 and DLD-1 human colorectal cancer cells by inducing apoptosis and G2/M cell-cycle arrest, characterized by increased cleaved caspase-3, PARP, Bax, p-CDK1, cyclin A2, and p-JNK, along with decreased Bcl-2 and Bcl-xL expression[70].

Hyperoxide and rutin (100–200 µM, 24 h) exhibited cytotoxic and antiproliferative effects against HT29 human colorectal cancer cells by inducing apoptosis through increased Bax/Bcl-2 ratio and activation of caspase-3, caspase-8, and caspase-9 [71].

Invitro studies in esophageal Cancer:

Neferine (5–30 µM, 24–48 h) suppressed proliferation and colony formation of KYSE30, KYSE150, and KYSE510 human esophageal squamous cell carcinoma cells by inducing ROS-mediated apoptosis and G2/M cell-

cycle arrest, with increased p21, cleaved PARP, caspase-3/9, and p-JNK, and decreased cyclin B1, Bcl-2, and Nrf2 expression[72].

Invitro Studies in Eye Cancer:
Neferine (0.1–200 μM, 24 h) inhibited proliferation, migration, and viability of WERI-Rb-1 human retinoblastoma cells by inducing apoptosis and oxidative stress, evidenced by increased Bax, cleaved caspase-3/9, and MDA levels, along with decreased Bcl-2, c-Myc, Ki-67, Survivin, VEGF, SOD, and GSH expression [73].

Invitro Studies in Gallbladder Cancer:
Liensinine (40–120 μM, 24–48 h) inhibited proliferation and colony formation of GBC-SD and NOZ human gallbladder carcinoma cells by inducing apoptosis and G2/M cell-cycle arrest, accompanied by activation of caspase-3/9 and PARP, increased Bax, and suppression of Bcl-2, cyclin B1, CDK1, CDC25C, PI3K, ZFX, and p-Akt signaling[74].

Invitro Studies in Gastric Cancer:
Water-soluble seed polysaccharides (50–200 μg/mL, 48 h) exhibited growth-inhibitory activity against MFC gastric cancer cells, although the underlying mechanism was not reported [75].Neferine (2.5–40 μg/mL, 24 h) exerted cytotoxic effects and reversed multidrug resistance in adriamycin-resistant SGC7901/ADM human gastric cancer cells by downregulating P-glycoprotein (P-gp) expression and MDR1 mRNA levels[76]. .Neferine (1–10 μM, 24 h) inhibited viability, proliferation, and migration of GIST-1 human gastrointestinal stromal tumor cells by inducing apoptosis and cell-cycle arrest, associated with increased p15, p16, p21, Bax, cleaved caspase-3/9, and miR-449a expression, and suppression of Bcl-2, cyclin D1, MMP-2/9, PI3K/Akt, and Notch signaling pathways[77].
7-Hydroxydehydronuciferine (IC_{50} = 62.9 μM) inhibited proliferation of AGS human gastric cancer cells, an effect associated with its antioxidant activity[78]. Liensinine (40–80 μM, 48 h) inhibited proliferation of BGC823 and SGC7901 human gastric cancer cells by inducing ROS-mediated apoptosis and G0/G1 cell-cycle arrest, characterized by increased Bax, cleaved caspase-3/9, and PARP, along with decreased Bcl-2, p-Akt, cyclin D1, and CDK4 expression[79].
8-
In vitro Studies in Head and Neck Cancer:
Neferine (7.5–30 μM, 24 h) reduced viability and inhibited colony formation in HN6, CAL27, and HN30 head and neck squamous cell carcinoma cells by inducing ROS-mediated apoptosis, G1 cell-cycle arrest, and autophagy through activation of the ASK1/JNK pathway, with increased Bax, LC3, p62, p-ASK1, and p-JNK and decreased Bcl-2 expression[80].

Invitro Studies in Haematological Disorders:
Kaempferol from the methanolic stamen extract (3.5–35 μM, 24 h) did not exhibit cytotoxicity against KU812F chronic myelocytic leukemia cells, but suppressed FcεRI signaling by downregulating FcεRI α- and γ-chains, reducing intracellular Ca^{2+} levels, and inhibiting histamine release [81]. Neferine (4–64 μM, 48 h) reduced the survival of imatinib-resistant K562/G01 human myelogenous leukemia cells and reversed multidrug resistance by downregulating P-glycoprotein (P-gp) expression and MDR1 mRNA levels[82].

Invitro Studies in Laryngeal cancer
Nuciferine AMC-HN-8, TU-212 (Laryngeal squamous cell carcinoma) 25–100 μM (24 h) Inhibited cell survival ↓TRIM44; ↓TLR4; ↓Akt signaling[83].

Invitro Studies in Liver Cancer:
Water-soluble seed polysaccharides (50–200 μg/mL, 48 h) inhibited the proliferation of HuH-7 human liver cancer cells and H22 mouse hepatocarcinoma cells, although the underlying mechanism was not reported[75] . Polyphenolic seed extract (6.25–50 μg/mL, 24–48 h) exhibited cytotoxic effects against HepG2 human liver cancer cells, which were associated with its antioxidant activity[84]. Procyanidins from seedpod extract (12.5–400 μg/mL, 6–96 h) reduced viability and inhibited proliferation of HepG2 human liver cancer cells by inducing ROS-mediated autophagy and S-phase cell-cycle arrest, accompanied by increased LC3 and GFP-LC3 expression[85]. Neferine (10–40 μM, 24 h) reversed thermotolerance in HepG2 human hepatocarcinoma cells by promoting apoptosis and downregulating Bcl-2 expression[86]. Neferine (5–30 μM, 24 h) inhibited growth and reduced viability of Hep3B and Sk-hep-1 liver cancer cells by inducing apoptosis through upregulation of pro-apoptotic proteins (Bim, Bid, Bax, Bak, Puma), activation of caspases and PARP cleavage, and downregulation of c-Myc, cyclin D1/D3, CDK4, and E2F1[87].Neferine (2–25 μM, 48 h) reduced the viability of HepG2 human liver cancer cells by inducing ROS-mediated apoptosis through activation of p53/PTEN, TNF-α, p38, and ERK1/2 pathways, with increased Bax, Bad, caspase-3/9, and PARP cleavage and decreased Bcl-2 and p-Akt expression[88]. Neferine (2.5–100 μM, 24–48 h) exhibited cytotoxic, anti-migratory, and anti-invasive effects against HepG2 human liver cancer cells by inducing apoptosis and inhibiting epithelial–mesenchymal transition (EMT), as evidenced by increased E-cadherin and decreased vimentin, Snail, and N-cadherin expression[89]. Neferine (1–5 μM, 2 weeks) induced cytotoxicity in HepG2 and Hep3B human liver cancer cells by promoting autophagy through activation of RyR-mediated Ca^{2+} signaling and the ULK1–PERK and AMPK–mTOR pathways[59]. Isoliensinine (3–10

μg/mL, 24–48 h) inhibited proliferation of HepG2, Huh-7, and H22 liver cancer cells by inducing apoptosis and sub-G1 cell-cycle arrest, accompanied by increased caspase-3 activation and suppression of Bcl-2, Bcl-xL, MMP-9, NF-κB activity, and p65 phosphorylation, while enhancing p65–PP2A binding [90],[91].

Invitro Studies in Lung Cancer:
Ethanolic seed pod extract (10–80 μM, 24–48 h) inhibited proliferation and colony formation of A549 and H460 human non-small cell lung cancer cells by inducing apoptosis and DNA damage, as evidenced by increased cleaved PARP and γ-H2AX levels and suppression of Axl expression[92]. Neferine (1–30 μM, 12–72 h) inhibited proliferation of A549 human lung carcinoma cells by inducing ROS-mediated autophagy and suppressing the PI3K/Akt/mTOR signaling pathway, accompanied by decreased glutathione (GSH) levels[93]. Neferine (1–30 μM, 48 h) reduced viability of A549, H520, H661, and H446 human lung carcinoma cells by inducing ROS-mediated apoptosis and G1 cell-cycle arrest, characterized by increased Bax, Bad, cytochrome c, caspase-3/9 activation, p53, p27, PTEN, and MAPK signaling, along with decreased Bcl-2, cyclin D1, NF-κB, antioxidant enzymes, and mitochondrial membrane potential[94]. Neferine (0.039–100 μM, 72 h) reduced the viability of A549 human lung carcinoma cells and enhanced intracellular drug accumulation by increasing rhodamine-123 uptake and inhibiting P-glycoprotein (P-gp) activity[58]. Neferine (10 μM, 4 h) suppressed the growth of A549, H1299, and LLC-1 lung cancer cells by inducing autophagy, as evidenced by increased LC3-II expression[59].Neferine, alone or in combination with cisplatin (10 μM, 48 h), induced cytotoxicity in A549 human lung cancer cells by promoting ROS-mediated autophagy, characterized by increased LC3-II expression and suppression of the PI3K/Akt/mTOR signaling pathway, along with reduced glutathione (GSH) levels.[95]. Neferine, alone or combined with cisplatin (10 μM, 12–72 h), inhibited proliferation and reduced viability of A549 human lung cancer cells by inducing ROS-mediated apoptosis and sub-G1 cell-cycle arrest, accompanied by increased Bax, Bad, cytochrome c, caspase-3/9 activation, PARP cleavage, p53, LDH leakage, and NO release, along with decreased Bcl-2, FAK, VEGF, and MMP-2 expression [96]. Nuciferine (10–50 μM, 24 h) exhibited antiproliferative, anti-invasive, and anti-migratory effects against A549 human lung adenocarcinoma cells by inducing apoptosis and suppressing Wnt/β-catenin signaling, with increased Bax and Axin expression and decreased Bcl-2, c-Myc, cyclin D, and VEGF-A levels[97]. Nuciferine (0.05–1.0 mg/mL, 24 h) reduced cell viability and inhibited invasion in A549 and NCI-H1650 human lung adenocarcinoma cells, although the underlying mechanism was not reported [69].

Invitro studies in Nasopharyngeal Cancer:
Seed-derived alkaloids (50–200 μg/mL, 24 h) inhibited proliferation of CNE-1 human nasopharyngeal carcinoma cells by inducing apoptosis through activation of Fas/FasL signaling, caspase-3/8/9, and Bax, while suppressing Bcl-2, Bcl-xL, and NF-κB and increasing IκB-α expression [98].

Invitro Studies in Neural Cancer:
Neferine (1–30 μM, 24 h) suppressed proliferation and migration of IMR32 human neuroblastoma cells by inducing apoptosis, autophagy, and G2/M cell-cycle arrest, accompanied by caspase-3 and PARP cleavage, increased LC3-II and Beclin-1 expression, and reduced p-FAK and p-S6K1 signaling[99]. Nuciferine (0.05–1.0 mg/mL, 24 h) reduced viability and suppressed invasion of SY5Y human neuroblastoma cells by inhibiting PI3K/Akt signaling and downregulating IL1B expression [69]. Nuciferine (20–180 μM, 24–72 h) inhibited proliferation, colony formation, migration, invasion, and epithelial–mesenchymal transition in U87MG and U251 human glioblastoma cells by inducing apoptosis and G2 cell-cycle arrest, while suppressing HIF1A/VEGFA, Akt/STAT3 signaling, stemness markers, and EMT-related proteins [100].

Invitro Studies in Ovarian Cancer:
Neferine (1–10 μM, 24–72 h) exhibited cytotoxic and growth-inhibitory effects against A2780, HO8910, and SKOV3 human ovarian cancer cells by inducing apoptosis, autophagy, and G1 cell-cycle arrest, associated with increased p21, p27, LC3-II, Atg7, p38 MAPK, and JNK activation, and decreased cyclin D, p-p70S6K, and p-4EBP1 expression[101].

Invitro Studies in Prostate Cancer:
Polyphenolic seed extract (6.25–50 μg/mL, 24–48 h) exhibited antiproliferative effects against LNCaP human prostate adenocarcinoma cells, which were associated with its antioxidant activity[84]. Nuciferine, 7-hydroxydihydronuciferine, caaverine, liriodenine, and anonaine exhibited cytotoxic activity against DU-145 human prostate cancer cells (IC_{50} = 80.8–218.4 μM, 24 h), although the underlying mechanism was not reported[78]. Neferine (3.12–100 μM, 24–72 h) reduced proliferation and inhibited migration of PC3, LNCaP, and $CD44^+$ PC3 cancer stem cells in human prostate cancer by inducing apoptosis and G1 cell-cycle arrest, with upregulation of p21, p27, p53, caspase-3, and cleaved PARP, and downregulation of Bcl-2, CDK4, MMP-9, Slug, Snail, and antioxidant enzymes[102]. Neferine (5–20 μM, 18 h) reduced cell viability in DU145 and LNCaP human prostate cancer cells by inducing apoptosis and autophagy, characterized by increased LC3B-II, autophagosome formation, and p-JNK activation, along with decreased p62 expression[103]. Neferine, liensinine, and isoliensinine (1–100 μM, 24–48 h) induced cytotoxicity and reduced migration in LNCaP, PC3, and DU-145 human prostate cancer cells, particularly in PC3 and DU145 cells, by promoting apoptosis and autophagy, with increased Bax, LC3B-II, cleaved caspase-9, and PARP cleavage, and decreased Bcl-2 and PARP, along with modulation of AR signaling, PSA, and 5-α reductase expression[104].

Invitro Studies in Renal Cancer:
Neferine (5–25 μM, 24 h) inhibited proliferation of Caki-1 human renal cancer cells by inducing apoptosis, characterized by increased Bax and decreased Bcl-2 and XIAP expression, along with suppression of NF-κB/p65 signaling and an increased sub-G1 cell population [105].
Invitro Studies in Sarcoma:
Neferine (1–20 μM, 24–72 h) inhibited proliferation of U2OS and Saos-2 human osteosarcoma cells by inducing G1 cell-cycle arrest, associated with increased p21 expression and activation of p38 MAPK and JNK signaling pathways, along with decreased cyclin E levels[106].
Invitro Studies in Skin Cancer:
Aqueous rhizome extract (1–1000 μg/mL, 24 h) inhibited proliferation and migration of A431 human epidermoid carcinoma cells by downregulating MMP-2 and MMP-9 expression [50]. Methanolic extracts from flower bud and leaves (3–30 μM, 72 h) inhibited melanogenesis in B16 melanoma 4A5 murine melanoma cells by downregulating tyrosinase, TRP-1, and TRP-2 expression[107]. Procyanidin extract from seedpod (25–100 μg/mL, 1–5 days) exhibited cytotoxicity and inhibited proliferation of B16 murine melanoma cells by inducing apoptosis and S-phase cell-cycle arrest, along with increased intracellular calcium levels[108]. Leaf extract and gallic acid (0.1–0.5 mg/mL and 60–100 μM, 24–72 h) reduced melanogenesis in B16F1 murine melanoma cells by downregulating tyrosinase, MITF, TRP-1, melanin production, and suppressing the PKA/CREB signaling pathway[109]. 7-Hydroxydehydronuciferine (10–100 μM, 24 h) inhibited proliferation and exhibited cytotoxic effects in A375.S2 human melanoma cells by inducing apoptosis[78].
7-Hydroxydehydronuciferine (10–100 μM, 24 h) induced cytotoxicity and reduced migration in A375.S2, A375, and A2058 human melanoma cells by promoting apoptosis, autophagy, and G2/M cell-cycle arrest, accompanied by increased ATG-5, ATG-12, ATG-16, and acidic vesicular organelle (AVO) formation[110].
7.Anti-Ischaemic
In an isolated rat heart model, *N. nucifera* seed extract demonstrated pronounced anti-ischaemic activity. The effective dose was identified by evaluating cardiac output following induced ischaemia. Extract concentrations between 0.1 and 30 mg/ml were tested. While cardiac output was comparable at 3 and 10 mg/ml (63.5 ± 3.2 and 65.8 ± 4.0 ml/min, respectively), the highest degree of functional recovery was achieved at 10 mg/ml. Based on these findings, 3 mg/ml was considered the optimal dose for mediating the anti-ischaemic effect in rats[111].
8.Anti Viral
An ethanol extract of *N. nucifera* seed significantly suppressed herpes simplex virus-1 (HSV-1) replication at a concentration of 100 mg/ml, with an IC_{50} value of 50 mg/ml. In addition, a specific subfraction of *N. nucifera* (NNFR) exhibited potent anti-HSV-1 activity. At 50 mg/ml, NNFR reduced the propagation of aciclovir-resistant HSV-1 by up to 85.9% through inhibition of viral replication in HeLa cells. Bioassay-guided fractionation confirmed that NNFR markedly limited HSV-1 proliferation without showing cytotoxic effects. Treatment of HeLa cells with NNFR resulted in decreased synthesis and mRNA expression of viral proteins in infected cells. These findings suggest that the antiviral action of NNFR involves early suppression of immediate-early transcripts, particularly infected cell protein (ICP) 0 and ICP4 mRNA, thereby blocking subsequent viral protein production and replication.(15,24 R.A)[112].
9.Diuretic
Mukherjee et.al reported that the rhizome of *N. nucifera* exhibits notable diuretic activity. Administration of the methanolic rhizome extract at doses of 300, 400, and 500 mg/kg significantly decreased body water content in rats. Urine output increased in a dose-dependent manner, accompanied by enhanced excretion of potassium as well as sodium and chloride ions. However, the diuretic effect was less pronounced than that produced by the standard drug furosemide (20 mg/kg)[113].
10.Anti aging
Sacred lotus (*Nelumbo nucifera*) seed extract contains bioactive constituents with anti-ageing potential, helping to reduce visible signs of skin ageing such as loss of elasticity, wrinkles, fine lines, enlarged pores, acne, and blemishes. Effective cosmetic formulations rely on suitable vehicles that deliver compounds with strong anti ageing activity and promote a youthful skin appearance. Mahmood and Akhtar (2013) evaluated the efficacy of cosmetic formulations containing green tea and lotus extracts for managing facial wrinkles in healthy Asian subjects, using non-invasive tools such as the Visioscan VC to assess skin surface characteristics and a Sebumeter to measure facial sebum levels. Their results demonstrated a synergistic anti ageing effect when green tea and lotus extracts were combined in different emulsions. The antioxidant rich active constituents of both plants appear to positively influence skin surface parameters, suggesting their promising potential for inclusion in future anti ageing therapies[114].
11.Anti Fatigue
The swimming endurance test was employed to evaluate the anti-fatigue potential of NLEs. The results align with the findings of Xu and Wang (2014), who reported that mice treated with flavonoids from NLEs at doses of 50, 100, and 150 mg/kg for 28 days showed a significant increase in exhaustive swimming time. These observations indicate that NLE-derived flavonoids possess notable anti-fatigue activity, as reflected by prolonged swimming endurance. Overall, NLEs appear to help reduce fatigue, although the precise mechanisms underlying this effect remain unclear.[115]
12.Analgesic Activity
Vikrama Chakravarthy P. et al. (2009) evaluated the pain-relieving effects of red and white *N. nucifera* seed extracts in albino rats. Forty-eight adult Sprague Dawley rats were divided into six groups, with Group I serving

as the control and Group II receiving the standard drug diclofenac. Groups III, IV, and V,VI were administered methanolic extracts of red and white lotus seeds at doses of 400 and 600 mg/kg for seven days. Both extracts produced significant analgesic effects, with the white lotus seed extract at 600 mg/kg showing the most pronounced activity among all treatments[116].

13.Anti Haemolytic

Pangjit et al., 2016 in their study using HepG2 cells reported that *N. nucifera* leaf extract (NLEs) possesses clear anti-haemolytic activity, as demonstrated by an APPH assay, with the effect increasing in a concentration-dependent manner). This protective action is largely attributed to the presence of phenolic compounds. The IC_{50} values for haemolysis inhibition were 114.66 µg/ml for the aqueous extract (total phenolic content, TPC: 485.77 mg/g), 45.37 µg/ml for the 50% ethanol extract (TPC: 43 mg/g), and 69.45 µg/ml for the 95% ethanol extract (TPC: 652.77 mg/g) (Semaming et al., 2018). The resistance to haemolysis offered by NLEs is thought to arise from the protective effects of flavonoids and alkaloids present in lotus leaves[117].

14.Antiparkinsonism

M. Vishnu Vardhan Reddy et al. (2014) evaluated the antioxidant and anticataleptic effects of a methanolic *Nelumbo nucifera* seed extract, fractionated with chloroform, using a rat model of haloperidol-induced catalepsy. Catalepsy was induced in male albino rats by intraperitoneal administration of haloperidol (1 mg/kg). Compared with the haloperidol-only group, all treated groups showed a significant reduction in cataleptic scores, with the most pronounced improvement observed in rats receiving *N. nucifera* at doses of 200 and 400 mg/kg body weight. Biochemical analysis of brain tissue revealed that treatment with *N. nucifera* normalized oxidative stress markers, including catalase, superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS), indicating restoration of antioxidant status in haloperidol-induced cataleptic rats[118].

15. Hepatoprotective

Antihepatotoxic-Carbon tetrachloride (CCl_4) is a well-known hepatotoxic agent that triggers oxidative stress, leading to acute liver injury, steatosis, centrilobular necrosis, and enhanced lipid peroxidation. Increasing in-vivo evidence indicates that *N. nucifera* leaf extracts (NLEs) play a significant protective role against CCl_4-induced hepatic damage. This hepatoprotective activity appears to involve modulation of key metabolic pathways, including glutathione, phenylalanine, tryptophan, sphingolipid, and phospholipid metabolism.Studies in rats exposed to 2-acetylaminofluorene have shown that NLEs rich in phenolic and flavonoid constituents—such as gallic acid, catechin, peltatoside, rutin, isoquercitrin, miquelianin, and astragalin—can improve biochemical markers associated with liver fibrosis and hepatocarcinogenesis. These improvements are reflected by reductions in serum alpha-fetoprotein (AFP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (γGT). Furthermore, NLE supplementation mitigates lipid peroxidation by enhancing nuclear factor erythroid-2 related factor-2 (Nrf2) signaling and upregulating its downstream antioxidant enzymes, including catalase, glutathione peroxidase (GPx), and superoxide dismutase-1 (SOD-1), in experimental models induced by acetylaminofluorene or diethylnitrosamine.[119]A study by Hui-Hsuan Lin ,et al investigated the protective effect of lotus (Nelumbo nucifera Gaertn.) seedpod extract (LSE), which is rich in polyphenols and has strong antioxidant activity, against acetaminophen (APAP)-induced liver toxicity in HepG2 cells. Co-treatment with LSE improved cell survival, reduced ROS production, decreased apoptosis, and suppressed inflammatory markers such as COX-2, NF-κB, and iNOS.Mechanistically, LSE helped restore mitochondrial integrity and inhibited multiple apoptosis pathways, suggesting its potential as a supportive therapeutic option in APAP overdose–induced hepatotoxicity.These findings suggest that LSE may have potential as a supportive treatment in cases of APAP overdose[119].Antisteatosic properties-Hepatic steatosis, commonly termed fatty liver, is characterized by excessive triglyceride accumulation and lipid droplet formation within hepatocytes, often associated with alcohol intake, obesity, diabetes, or drug exposure. Experimental evidence demonstrates that nuciferine administration (10 and 15 mg/kg body weight) markedly reduces high-fat diet (HFD)–induced hepatic steatosis and necroinflammatory changes on histological examination (Guo et al., 2013). Consistently, treatment with nuciferine (20 mg/kg bw) lowers circulating lipid parameters—triglycerides, total cholesterol, and LDL-cholesterol—while improving hepatic steatosis and hepatocellular ballooning in HFD-induced NAFLD models. These protective effects appear to be associated with restoration of disturbed metabolic pathways, including glycerophospholipid, linoleic acid, α-linolenic acid, arginine, and proline metabolism (Cui et al., 2020).[119]3.Anticholestatic properties- Zinc (Zn), copper (Cu), mercury (Hg), and manganese (Mn) are important trace elements whose imbalance in liver cirrhosis contributes to hepatic injury, inflammation, and fibrosis (García-Niño & Zazueta, 2015). The anticholestatic potential of *N. nucifera* leaf extracts (NLEs) has been evaluated through liver injury biomarkers and heavy-metal burden. In Nile tilapia exposed to a mixture of lead (Pb), cadmium (Cd), Hg, and Zn, NLE powder mitigated elevations in ALT and AST activities and reduced histopathological damage. Additionally, NLEs facilitated the clearance of heavy-metal residues from muscle tissue, accompanied by decreased oxidative stress markers and modulation of hepatic metallothionein levels (Abdel Rahman et al., 2019).[119]

16.Neuromodulatory properties

Dietary polyphenols and alkaloids are capable of crossing the blood–brain barrier and accumulating in neural tissue, which may underlie their therapeutic relevance in central nervous system disorders[120]. *N. nucifera* leaf extracts (NLEs) have been shown to reduce fear-related aversion and exert anxiolytic effects, likely through the action of their principal alkaloid and flavonoid constituents on neurochemical mediators [121].

Alkaloid fractions (20 mg/kg) produce sedative–hypnotic activity by modulating neurotransmission, including enhancement of γ-aminobutyric acid signaling and antagonism of picrotoxin- and bicuculline-induced effects.

These alkaloid-rich extracts also demonstrate anxiolytic-like responses associated with elevated serotonin, 5-hydroxyindoleacetic acid, and dopamine levels[122]. Furthermore, NLEs derived from leaf stalks and mature leaves inhibit enzymes implicated in Alzheimer's disease- acetylcholinesterase, butyrylcholinesterase, and β-secretase-supporting their potential relevance in neuroprotection[123]. Collectively, these findings suggest that lotus leaves may hold therapeutic promise for neurological disorders.

17.Anti-fatigue activity

The anti-fatigue potential of *N. nucifera* leaf extracts (NLEs) has been assessed using swimming endurance models. Flavonoid rich fractions significantly prolonged swimming duration, indicating enhanced resistance to physical fatigue[124]. Similar findings were reported by Xu and Wang (2014), where repeated administration of NLE flavonoids (50, 100, and 150 mg/kg) for 28 days markedly increased exhaustive swimming time in mice. Overall, these observations suggest a preventive role of NLEs against fatigue, although the precise underlying mechanisms remain to be fully elucidated[125].

17. Probiotic properties

1.Antimicrobial and antiviral activities (in vitro)

In vitro evidence indicates that *N. nucifera* leaf extracts (NLEs) exhibit broad antimicrobial activity against numerous oral pathogens including *Streptococcus* spp., *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces* spp, as well as the fungus *Candida albicans* [126]. These antimicrobial properties are largely attributed to alkaloids and flavonoids, particularly benzylisoquinoline alkaloids, which show antiviral activity against herpes simplex virus type-1 by binding to viral particles and inhibiting host cell infection in cytopathic assays[127]. Additionally, the intrinsic micro-/nanostructured, water-repellent surface of lotus leaves may further contribute to antibacterial interactions Collectively, these findings highlight lotus leaves as a promising natural source of antimicrobial and antiviral agents[128].2.Beneficial modulation of gut microbiota-In vivo studies indicate that *N. nucifera* leaf extracts (NLEs) enhance gut microbial diversity, increasing Clostridiaceae and Bacteroidales S24-7 while reducing Peptostreptococcaceae [129]. Nuciferine treatment in high-fat diet–fed rats lowers the Firmicutes/Bacteroidetes ratio, suppresses lipopolysaccharide-producing *Desulfovibrio*, and promotes *Akkermansia muciniphila* and short-chain fatty acid–producing bacteria[130].Metabolomic analyses further associate these microbial shifts with changes in metabolites such as pyruvate, glycine, succinate, uric acid, and indoxyl sulfate, with selected metabolites proposed as biomarkers of nuciferine's effect on hyperuricaemia [131].Collectively, lotus leaves may serve as potential prebiotic agents that support gut immunity and probiotic growth.

19.Anti-osteoporotic and anti-muscle atrophy properties

Polysaccharides derived from *N. nucifera* leaf extracts (NLEs) dose-dependently inhibit osteoclast differentiation by suppressing NFATc1, c-Fos, and osteoclast-related genes (ATP6V0D2, DC-STAMP, and CTSK), leading to significant attenuation of trabecular bone loss after four weeks of oral administration (Hwang et al., 2020)[132]. Nuciferine further exhibits bone-protective effects through inhibition of osteoclastogenesis and bone resorption, potentially via downregulation of MAPK and NF-κB signaling and enhancement of PDGF-BB production [133].

Given the association between osteoporosis and muscle fiber atrophy, NLEs containing quercetin-3-O-β-glucuronide have been shown to improve calf muscle volume, area, and density and reduce dexamethasone-induced muscle damage. These effects are linked to activation of AMPK and AKT–mTOR pathways and suppression of muscle atrophy–related genes (Park et al., 2020)[134]. Collectively, lotus leaves demonstrate potential in preventing osteoporosis and muscle atrophy.

20.Anti-dermatophytic and antidiarrheal activity:

The antidiarrheal potential of *Nelumbo nucifera* seed oil was evaluated using the disc diffusion method and demonstrated strong inhibitory effects against *Salmonella*, *Shigella*, *Klebsiella*, *Escherichia coli*, *Pseudomonas*, and *Staphylococcus aureus*. Neuropharmacological evaluation of the ethanolic seed extract in mice and rats revealed anxiolytic activity in the elevated zero maze and light–dark transition models, along with effects on motor coordination, locomotion, and cognitive function. Oral administration of the extract (50, 100, and 200 mg/kg) produced dose-dependent anxiolytic responses, significant suppression of general behavioral activity ($p < 0.05$), and prolonged phenobarbitone-induced sleep duration. Additionally, the extract improved conditional avoidance response, indicating nootropic potential. These findings suggest that *N. nucifera* seeds may serve as a valuable natural source of nootropic and antistress agents[135].

21.Anti-neurodegenerative and analgesic activity:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by neuronal loss and degeneration, neurofibrillary tangles, amyloid plaque deposition, and reduced acetylcholine levels in the brain. Experimental evaluation of the analgesic potential of red and white *Nelumbo nucifera* seeds was conducted in adult Sprague–Dawley rats divided into six groups, including control and diclofenac-treated standard groups. Oral administration of methanolic seed extracts at doses of 400 and 600 mg/kg for seven days produced significant analgesic effects in both varieties, with the higher dose of white lotus seed (600 mg/kg) showing the most pronounced activity[136].

22.Usefulness in Pulmonary Fibrosis:

Isoliensinine isolated from lotus seeds has been shown to lessen bleomycin-induced pulmonary fibrosis in experimental mice, partly by suppressing inflammatory mediators. Similarly, a study by Niu and colleagues (2013) reported that neferine reduced amiodarone-induced lung fibrosis, mainly due to its anti-inflammatory action.[137].

23. Nelumbo nucifera & Reproductive Health:

Nelumbo nucifera has been studied for its influence on reproductive health, mainly through its effects on hormones like estrogen and progesterone. Since estrogen plays a key role in puberty, menstrual balance, and menopause, changes in its levels can affect conditions such as menorrhagia, where excess estrogen may lead to heavy or prolonged bleeding. Experimental studies in rats show that lotus seed extract can reduce steroid hormone production and exhibit antiestrogenic effects, including lowering reproductive organ weight and altering the estrous cycle without disturbing general health. It has also been reported to suppress certain reproductive hormones, suggesting possible antifertility effects in animal models. However, well-designed clinical trials in humans are still lacking, highlighting the need for further research to establish safe and effective doses[138].

Dietary use of Nelumbo nucifera:

Nelumbo nucifera is widely used as a food plant in many Asian countries. Almost every part rhizome, seeds, leaves, stem, and flowers has dietary value. The rhizome is commonly eaten as a vegetable and also prepared as pickles, fritters, or cutlets, especially in India and China. In Vietnam, the stem is used in salads, while in Japan and China the leaves are traditionally used during summer and in weight-management remedies. Seeds are eaten raw, popped, roasted, or ground into flour for bread; roasted seeds are even used as a coffee substitute. Petals serve as garnish, and stamens are added to tea for flavor.

Nutritionally, the rhizome provides carbohydrates with modest protein and very little fat, while the seeds are energy-dense and rich in protein and carbohydrates. Lotus seeds are also good sources of minerals such as calcium, potassium, magnesium, iron, zinc, and selenium, along with beneficial fatty acids like linoleic and oleic acid. Although all parts are used in traditional medicine, the rhizome and seeds are most studied for their nutritional and health benefits. Experimental studies in animals have also suggested potential benefits in supporting female reproductive health.

Lotus seeds contain several valuable components that can be utilized in developing nutritious food products. Exploring such novel functional ingredients helps enhance both the nutritional value and functional properties of foods. Since flour and starch are key ingredients in the food industry, their specific characteristics play an important role in product development. Although wheat flour is widely used in baking, there is growing interest in partially or fully replacing it with nutrient-rich, health-promoting alternatives.[139].

The nutritional significance of Nelumbo nucifera mainly comes from its rhizomes (lotus root) and seeds, both offering distinct dietary benefits.The rhizome is rich in dietary fiber, which supports digestion and maintains gut health[140]. It is also a good source of vitamin C, helping reduce oxidative stress while supporting immunity and skin health[141].In addition, its nutrient profile contributes to anti-inflammatory effects, which are valued in traditional medicine Lotus seeds provide complex carbohydrates that release energy slowly, helping maintain metabolic balance.They are considered a complete plant protein because they contain all essential amino acids . The seeds mainly contain unsaturated fats, which are beneficial for heart health . They also supply B-complex vitamins and key minerals such as magnesium, phosphorus, and potassium, which support nerve function and overall metabolism .In cooking, the rhizome is highly versatile and is used in dishes ranging from stir-fries to snacks. Lotus seeds, once mainly used in traditional and ceremonial recipes, are now commonly added to soups, desserts, and savory dishes. Their mild, nutty taste and nutritional benefits make them popular in modern diets .

The rhizomes of Nelumbo nucifera are commonly eaten as a vegetable in many Asian countries and are valued as a nutritious health food due to their rich mineral content.The tissue is packed with starch granules, and fresh rhizome contains a high amount of starch, which is tasteless and odourless. Studies comparing lotus starch with maize and potato starch have shown that lotus starch has better binding and disintegration properties, making it useful as a tablet excipient. Around 50% (v/v) alcohol has been reported to be ideal for extracting its active constituents.Phytochemical studies of the methanolic extract have identified a steroidal triterpenoid, betulinic acid. Fresh rhizome is composed mainly of water, along with small amounts of fat, sugars, protein, fibre, and ash. It also provides vitamins such as thiamine, riboflavin, niacin, and vitamin C, along with an asparagine-like amino acid. The rhizome contains measurable levels of oxalates and essential minerals including calcium, iron, magnesium, potassium, sodium, zinc, copper, and trace amounts of barium.Various parts of Nelumbo nucifera Gaertn., particularly the leaves, are used as food and not only as natural wrappers . The young leaves and petioles of the North American lotus (Nelumbo nucifera subsp. lutea) are traditionally consumed by Native Indians (Council, 1966).Across Asia, tender lotus leaves are also eaten as vegetables .Due to these dietary uses and associated bioactivities, lotus leaves and their active constituents show strong potential for applications in the food industry, they are used in Meat products, Bakery products, Beverages, Fruit preservation, Food packaging membrane, Health products.[142]

Safety:

Although Nelumbo nucifera leaves have been traditionally used in medicine for many years, detailed safety evaluations are still limited. The Chinese Pharmacopoeia recommends a daily dose of 3–10 g of dried lotus leaf (approximately 0.56–1.85 g/day of extract).Acute toxicity studies in rats and mice have shown that oral doses up to 5000 mg/kg and 2400 mg/kg, respectively, did not produce toxic effects. These findings suggest that lotus leaf is generally safe at the tested doses.However, precise clinical dosing in humans remains unclear because data on LD_{50} values and minimum effective doses are still limited. More well-designed human studies are needed to confirm its safety and optimal therapeutic range.[143]

Discussion

Nelumbo nucifera Gaertn. (Sacred Lotus) is one of the most revered aquatic medicinal plants in Asia and has been extensively used in traditional healthcare systems for centuries. The findings compiled in this review demonstrate

that the therapeutic importance attributed to lotus in traditional medicine is increasingly being supported by modern scientific evidence. The plant contains a diverse range of phytochemicals and exhibits multiple biological activities, making it a promising candidate for future drug discovery and development.

A notable observation from the reviewed literature is the remarkable phytochemical diversity present in different parts of the plant. Leaves, flowers, stamens, seeds, embryos, rhizomes, and seed pods each possess distinct chemical profiles, suggesting that various plant parts may contribute differently to therapeutic outcomes. Among the identified constituents, flavonoids appear to be the most abundant and pharmacologically significant compounds. Interestingly, lotus tissues show a unique pattern of flavonoid distribution, with leaves being particularly rich in flavonoid O-glycosides, while embryos predominantly accumulate flavonoid C-glycosides. Such tissue-specific accumulation reflects the complex biosynthetic machinery of the plant and may account for the differences observed in biological activities among various plant organs.

Oxidative stress is recognized as a major factor contributing to the development of numerous chronic diseases, including diabetes, cardiovascular disorders, neurodegenerative diseases, obesity, and cancer. The studies reviewed consistently demonstrate that extracts from lotus leaves, petals, stamens, embryos, and seeds possess substantial antioxidant activity. This activity is largely attributed to flavonoids such as quercetin, rutin, hyperoside, isoquercitrin, catechin, and kaempferol derivatives. These compounds effectively neutralize free radicals and reduce oxidative damage within biological systems. Interestingly, embryo extracts rich in flavonoid C-glycosides often exhibited antioxidant activities comparable to or even greater than leaf extracts, despite containing lower overall flavonoid levels. This finding highlights the importance of flavonoid structure in determining biological activity and suggests that the medicinal value of lotus extends beyond simply the quantity of phytochemicals present.

The anti-inflammatory potential of *N. nucifera* represents another important aspect of its pharmacological profile. Chronic inflammation is now recognized as a central factor in the progression of many non-communicable diseases. Several studies have shown that lotus extracts and isolated compounds can suppress inflammatory mediators such as TNF-α, nitric oxide, COX-2, and various pro-inflammatory cytokines. These effects are largely mediated through the regulation of signaling pathways such as NF-κB and MAPK. Such findings provide scientific support for the traditional use of lotus in conditions associated with inflammation and indicate its potential as a natural source of anti-inflammatory agents with fewer adverse effects than synthetic drugs.

In addition to its anti-inflammatory activity, lotus has demonstrated promising immunomodulatory properties. Various extracts have been shown to influence immune cell function and cytokine production, thereby helping maintain immune balance. Rather than simply stimulating or suppressing immunity, lotus appears to exert a regulatory effect that supports normal immune function. This characteristic may be particularly valuable in conditions involving immune dysregulation and chronic inflammatory responses.

The growing global burden of obesity and diabetes has intensified the search for safe and effective natural therapies. In this regard, *N. nucifera* has attracted considerable attention due to its demonstrated effects on glucose and lipid metabolism. Experimental studies suggest that lotus extracts improve glucose tolerance, enhance insulin sensitivity, reduce postprandial hyperglycemia, and inhibit enzymes involved in carbohydrate digestion. Furthermore, several investigations have reported reductions in adipose tissue accumulation, improvements in lipid profiles, and inhibition of adipocyte differentiation following administration of lotus extracts. These observations indicate that lotus may provide a multifaceted approach to the management of metabolic disorders by simultaneously targeting multiple pathological mechanisms.

Among the various pharmacological activities reviewed, the anticancer potential of *N. nucifera* is perhaps the most extensively investigated. Numerous studies have demonstrated the ability of lotus extracts and isolated compounds to inhibit the growth of cancer cells derived from breast, cervical, colon, liver, lung, ovarian, prostate, gastric, and several other cancers. Alkaloids such as neferine, nuciferine, liensinine, and isoliensinine have emerged as particularly promising bioactive compounds.

The anticancer effects reported in the literature involve multiple mechanisms, including induction of apoptosis, arrest of the cell cycle, inhibition of angiogenesis, suppression of metastasis, and modulation of various intracellular signaling pathways. Such multitarget activity is particularly important because cancer is a highly complex disease involving numerous molecular abnormalities. Neferine, in particular, has attracted significant attention due to its ability to induce programmed cell death, regulate autophagy, and overcome multidrug resistance in certain cancer models. These findings suggest that lotus-derived compounds may have potential not only as standalone therapeutic agents but also as adjuncts to existing cancer treatments.

The antiangiogenic activity of lotus further strengthens its potential role in cancer management. Since tumour growth and metastasis depend heavily on the formation of new blood vessels, inhibition of angiogenesis represents an important therapeutic strategy. Several studies have demonstrated that lotus leaf extracts suppress VEGF-mediated angiogenic processes, thereby limiting vascular development required for tumour progression. Such findings highlight another important mechanism through which lotus may contribute to cancer prevention and treatment.

Despite the encouraging findings, certain limitations must be acknowledged. A large proportion of the available evidence originates from in vitro experiments and animal studies. Although these studies provide valuable mechanistic insights, they do not always accurately predict clinical outcomes in humans. In addition, differences in plant sources, geographical origin, cultivation conditions, extraction methods, and analytical techniques can result in significant variations in phytochemical composition and biological activity. These factors complicate direct comparison among studies and emphasize the need for standardized preparations.

Another important challenge is the limited availability of clinical data. While laboratory studies provide strong evidence of biological activity, human trials remain relatively scarce. Further research is therefore required to establish optimal dosages, safety profiles, pharmacokinetic characteristics, and long-term efficacy. Such studies will be essential for translating the promising experimental findings into evidence-based clinical applications.
Taken together, the available evidence suggests that *Nelumbo nucifera* is far more than a traditional medicinal plant. Its rich phytochemical composition and broad range of pharmacological activities make it a valuable natural resource with significant potential for future pharmaceutical, nutraceutical, and functional food applications. Continued interdisciplinary research integrating phytochemistry, molecular pharmacology, toxicology, and clinical science will be crucial for fully realizing the therapeutic potential of this remarkable plant.

Conclusion

The present review highlights the immense medicinal value of *Nelumbo nucifera* Gaertn. and provides comprehensive evidence supporting many of its traditional therapeutic applications. The plant is rich in diverse bioactive compounds, particularly flavonoids, alkaloids, polyphenols, glycosides, and polysaccharides, which collectively contribute to its wide range of pharmacological activities.
Scientific studies conducted over the past decades have demonstrated significant antioxidant, anti-inflammatory, immunomodulatory, antidiabetic, anti-obesity, antiangiogenic, and anticancer properties of various lotus extracts and isolated constituents. Among these, flavonoids and bisbenzylisoquinoline alkaloids such as neferine, nuciferine, liensinine, and isoliensinine appear to be the major contributors to the observed biological activities. Their ability to regulate multiple molecular pathways associated with oxidative stress, inflammation, metabolism, and tumour progression highlights the therapeutic versatility of this species.
Particularly encouraging is the growing body of evidence supporting the anticancer potential of lotus-derived compounds. Experimental studies have consistently shown their ability to inhibit cancer cell growth, induce apoptosis, suppress angiogenesis, and reduce metastatic potential through diverse molecular mechanisms. These findings suggest that *N. nucifera* may serve as an important source of lead molecules for future anticancer drug development.
However, despite the wealth of preclinical evidence, clinical validation remains limited. Further studies focusing on standardization, pharmacokinetics, toxicity evaluation, and well-designed clinical trials are required before lotus-based preparations can be widely incorporated into evidence-based therapeutic practice.
Overall, the available literature strongly supports the view that *Nelumbo nucifera* is a pharmacologically rich and therapeutically promising medicinal plant. The integration of traditional knowledge with modern scientific research continues to reveal new dimensions of its medicinal potential, positioning lotus as a valuable candidate for future pharmaceutical and nutraceutical development. Future investigations aimed at bridging the gap between laboratory findings and clinical applications will further enhance our understanding and utilization of this important medicinal species.

Table No 2: Nelumbo nucifera Gaertn, Different parts and Phytochemicals within it.

SR.NO	Nelumbo nucifera Gaertn Parts	Phytochemicals
1.	Embryo	Liensinine, Isoliensinine, Neferine, Nuciferine, Lotusine, Pronuciferine, Rutin, Hyperin, Demethylcoclaurine
2.	Stamen	N-methylisococlaurine, N-norarmepavine, Roemerin, Kaempferol, Kaempferol-3-O-β- D-glucoronopyranoside, Kaempferol-3-O-β- D-glucopyranoside,
3.	Flower	Quercetin, Luteolin, Luteolin glucoside, Kaempferol, Kaempferol-3-*O*-glucoside, Isoquercitrin, Roemerine, Nuciferine, Nornuciferine Armepavine, Pronuciferine, N-nornuciferine, Anonaine, Liriodenine Quercetin, Tartaric acid, Gluconic acid, Acetic acid, Malic acid, Ginnol, Nonadecane, Succinic.
4.	Leaf	Quercetin-glucuronide-3-O-β-D, Rutin, Isoquercitrin, Hyperin,
5.	Seeds	Dauricine, Nuciferine, Roemerine, Lotusine, Armepavine, Liensinine Isoliensinine, Neferine,

Funding: The authors received no funding for this work.

Data Availability Statement:
All information obtained and reviewed for this research is entirely documented in the manuscript, with complete tables and figures provided. Generated data is compiled through original analysis by authors.

Conflicts of Interest:
The authors declare that they have no conflicts of interest related to this work. There are no financial interests (such as funding, employment, consultancies, stock ownership, or patent rights) or non-financial interests (including personal, academic, political, or religious affiliations) that could have influenced the design, execution, or interpretation of the research presented in this manuscript.

Ethics approval and consent to participate: Not applicable.

Consent for publication: Both the participants have provided their consent for the publication of this work.

Acknowledgements: Dr.D.Y.Patil College of Ayurved & Research Centre, Pimpri,Pune-411018.

Referances

1. Liao, Y., Chen, J., Zhang, D., Wang, X., Yuan, B., Deng, P., et al. (2019). Lotus leaf as solar water evaporation devices. *Materials Letters, 240*, 92–95.
2. Sheikh, S. (2014). Ethno-medicinal uses and pharmacological activities of lotus (Nelumbo nucifera). *Journal of Medicinal Plants Studies, 2*, 42–46.
3. Kurashita, H., Kuroda, K., Narihiro, T., Takagi, M., Goto, M., Ikeda, S., et al. (2021). Accurate evaluation of blackening disease in lotus (Nelumbo nucifera Gaertn.) using a quantitative PCR-based assay for Hirschmanniella diversa Sher and H. imamuri Sher. *Crop Protection, 139*, Article 105380.
4. Hussain, S., Shah, F., Hameed, O., Naik, H. R., & Reshi, M. (2016). Functional behavior of Lotus rhizome harvested from high altitude dal lake of Kashmir. *Indian Journal of Ecology, 43*, 835–837.
5. Paudel, K.R.; Panth, N. Phytochemical profile and biological activity of *Nelumbo nucifera*. *Evid.-Based Complement. Altern. Med.* **2015**, *2015*.
6. Sheikh, S.A. Ethno-medicinal uses and pharmacological activities of lotus (*Nelumbo nucifera*). *J. Med. Plants Stud.* **2014**, *2*, 42–46.
7. Deng, J., Chen, S., Yin, X., Wang, K., Liu, Y., Li, S., et al. (2013). Systematic qualitative and quantitative assessment of anthocyanins, flavones and flavonols in the petals of 108 lotus (Nelumbo nucifera) cultivars. *Food Chemistry, 139*, 307–312.
8. Chen, S., Li, X., Wu, J., Li, J., Xiao, M., Yang, Y., et al. (2021). Plumula Nelumbinis:A review of traditional uses, phytochemistry, pharmacology, pharmacokinetics and safety. *Journal of Ethnopharmacology, 266*, Article 113429.
9. Chen, G., Zhu, M., & Guo, M. (2019). Research advances in traditional and modern use of Nelumbo nucifera: Phytochemicals, health promoting activities and beyond. *Critical Reviews in Food Science and Nutrition, 59*, S189–S209.
10. Limwachiranon, J., Huang, H., Shi, Z., Li, L., & Luo, Z. (2018). Lotus flavonoids and phenolic acids: Health promotion and safe consumption dosages. *Comprehensive Reviews in Food Science and Food Safety, 17*, 458–471.
11. Huang, B., Ban, X., He, J., Tong, J., Tian, J., & Wang, Y. (2010b). Hepatoprotective and antioxidant activity of ethanolic extracts of edible lotus (Nelumbo nucifera Gaertn.) leaves. *Food Chemistry, 120*, 873–878.
12. Liu, G., Qiu, L., Deng, H., Wang, J., Yao, L., & Deng, L. (2020). Ultrahigh surface area carbon nanosheets derived from lotus leaf with super capacities for capacitive deionization and dye adsorption. *Applied Surface Science, 524*, Article 146485.
13. Liao, Y., Chen, J., Zhang, D., Wang, X., Yuan, B., Deng, P., et al. (2019). Lotus leaf as solar water evaporation devices. *Materials Letters, 240*, 92–95.
14. Yao, L., Dai, P., Ouyang, L., & Zhu, L. (2021). A sensitive and reproducible SERS sensor based on natural lotus leaf for paraquat detection. *Microchemical Journal, 160*, Article 105728.
15. Win S. Study on Lotus Fiber Production in Sunn Ye Inn, Sintgaing Township. Banmaw University Research Journal. 2020;11(1):344-50.
16. Dandin VS, Sebastian JK, Dalavi JV, Nagella P, Madhav NA, Khot VV. Bioactive Compounds and Biological Activities of Lotus (Nelumbo nucifera Gaertn.). InBioactive Compounds in the Storage Organs of Plants 2023 Oct 25 (pp. 1-46). Cham: Springer Nature Switzerland.Anton, J. (2023). Sexus Botanicus: The Love Lives of Plants. MIT Press. https://doi.org/10.1007/978-3-031-29006-0_26-1
17. Tu Y, Yan S, Li J. Impact of harvesting time on the chemical composition and quality of fresh lotus seeds. Horticulture, Environment, and Biotechnology. 2020 Aug;61:735-44. https://doi.org/10.1007/s13580-020-00233
18. Sharan M, Haldar S. Development of Union Fabrics from Lotus Petiole Waste. InSustainable Approaches in Textiles and Fashion: Fibres, Raw Materials and Product Development 2022 May 12 (pp. 101-121). Singapore: Springer Nature Singapore. https://doi.org/10.1007/978- 981-19-0878-1_5
19. Wang L. A critical review on robust self-cleaning properties of lotus leaf. Soft Matter. 2023;19(6):1058-75. https://doi.org/10.1039/D2SM01521H
20. Dube US, Goyanar G, Venkatesh US, Thelly MT. In depth review on Phytochemicals, taxonomy, botanical description and Physiological Significance of Nelumbo nucifera.
21. Rathod P, Salvi R, Salunke R, Rohondia A, Rathod R, Misal K, Indulkar A, Gorde N, MK K, Juvatkar PV, Gokhale S. NELUMBO NUCIFERA: A PLANT WITH MULTIPLE PHARMACOLOGICAL ACTIVITIES. Foldscope & its Applications. 2022:116.

22. Trang NT, Thao TT, Hong HT. Study on the anatomical morphology of lotus varieties (Nelumbo nucifera gaertn.) in Vietnam. Plant cell biotechnology and molecular biology. 2019 Apr 25;20:95-105.
23. Kandeler R, Ullrich WR. Symbolism of plants: Examples from European-Mediterranean culture presented with biology and history of art: JULY: Lotus. Journal of experimental botany. 2009 Jul 1;60(9):2461-4
24. Yang H, He S, Feng Q, Liu Z, Xia S, Zhou Q, Wu Z, Zhang Y. Lotus (Nelumbo nucifera): a multidisciplinary review of its cultural, ecological, and nutraceutical significance. Bioresources and bioprocessing. 2024 Jan 27;11(1):18.
25. Jiang H, Chen J, Liu G, Zhou P, Jin Q, Wang Y, Guo H, Qian P, Xu Y. Screening of early flowering lotus (Nelumbo nucifera Gaertn.) cultivars and effects of different cultivars on flowering period. Plants. 2023 Apr 17;12(8):1683.
26. Jung, H.A.; Kim, J.E.; Chung, H.Y.; Choi, J.S. Antioxidant principles of *Nelumbo nucifera* stamens. *Arch. Pharm. Res.* **2003**, *26*, 279–285.
27. Feng, C.Y.; Li, S.S.; Yin, D.D.; Zhang, H.J.; Tian, D.K.; Wu, Q.; Wang, L.J.; Su, S.; Wang, L.S. Rapid determination of flavonoids in plumules of sacred lotus cultivars and assessment of their antioxidant activities. *Ind. Crops Prod.* **2016**, *87*, 96–104.
28. Kim HK, Park HR, Lee JS, Chung TS, Chung HY, Chung J. Down-regulation of iNOS and TNF-alpha expression by kaempferol via NF-kappaB inactivation in aged rat gingival tissues. *Biogerontology*. 2007;8(4):399-408. doi:10.1007/s10522-007-9083-9.
29. Li, F.; Sun, X.Y.; Li, X.W.; Yang, T.; Qi, L.W. Enrichment and separation of quercetin-3-O-β-D-glucuronide from lotus leaves (*nelumbo nucifera* gaertn.) and evaluation of its anti-inflammatory effect. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2017**, *1040*, 186–191
30. Kwon, K., Kwon, O.Y. and Kang, K.H., 2011, February. Antiinflammatory effects of Nelumbo nucifera leaves extracts on the lipopolysaccharide-activated Raw 264.7 cells. In International Conference on Technology Systems and Management (pp. 97-104). Berlin, Heidelberg: Springer Berlin Heidelberg.
31. Meng XL, Chen ML, Chen CL, Gao CC, Li C, Wang D, Liu HS, Xu CB. Bisbenzylisoquinoline alkaloids of lotus (Nelumbo nucifera Gaertn.) seed embryo inhibit lipopolysaccharide-induced macrophage activation via suppression of Ca2+-CaM/CaMKII pathway. Food and Agricultural Immunology. 2019 Jan 1;30(1):878-96. https://doi.org/10.1080/09540105.2019.1638889
32. Xu X, Wang L, Zhang K, Zhang Y, Fan G. Managing metabolic diseases: The roles and therapeutic prospects of herb-derived polysaccharides. Biomedicine & Pharmacotherapy. 2023 May 1;161:114538. https://doi.org/10.1016/j.biopha.2023.114538)
33. Rai S, Wahile A, Mukherjee K, Saha BP, Mukherjee PK. Antioxidant activity of Nelumbo nucifera (sacred lotus) seeds. Journal of ethnopharmacology. 2006 Apr 6;104(3):322-7.)
34. Hu W, Jiang Y, Xue Q, Sun F, Zhang J, Zhou J, Niu Z, Li Q, Li F, Shen T. Structural characterisation and immunomodulatory activity of a polysaccharide isolated from lotus (Nelumbo nucifera Gaertn.) root residues. Journal of Functional Foods. 2019 Sep 1;60:103457. https://doi.org/10.1016/j.jff.2019.103457
35. Temviriyanukul P, Sritalahareuthai V, Promyos N, Thangsiri S, Pruesapan K, Srinuanchai W, Nuchuchua O, Siriwan D, On-Nom N, Suttisansanee U. The effect of sacred lotus (Nelumbo nucifera) and its mixtures on phenolic profiles, antioxidant activities, and inhibitions of the key enzymes relevant to Alzheimer's disease. Molecules. 2020 Aug 14;25(16):3713. https://doi.org/10.3390/molecules25163713
36. Phytochemicals and Immunomodulatory Effect of *Nelumbo nucifera* Flower Extracts on Human Macrophages Rungnapa Pankla Sranujit 1,*, Chanai Noysang 1 , Patcharaporn Tippayawat 2 , Nateelak Kooltheat 3 , Thitiya Luetragoon 4 and Kanchana Usuwanthim
37. Huralikuppi JC, Christopher AB, Stephen PM. Anti-diabetic effect of Nelumbo nucifera (Gaertn): Part I preliminary studies in rabbits. Phytotherapy Research. 1991 Apr;5(2):54-8. https://doi.org/10.1002/ptr.2650050203.
38. Lee MW, Kim JS, Cho SM, Kim JH, Lee JS. Antidiabetic constituent from the node of lotus rhizome (Nelumbo nucifera Gaertn). Natural Product Sciences. 2001;7(4):107-9. https://koreascience.kr/article/JAKO200103041135582. 46. Mukherjee D, Khatua TN, Venkatesh P, Saha BP, Mukherjee PK. Immunomodulatory potential of rhizome and seed extracts of Nelumbo nucifera Gaertn. Journal of ethnopharmacology. 2010 Mar 24;128(2):490-4. doi:10.1016/j.jep.2010.01.015)
39. Song J, Kim J, Park HJ, Kim H. Anti-obesity effects of a prunus persica and nelumbo nucifera mixture in mice fed a high-fat diet. Nutrients. 2020 Nov 4;12(11):3392. https://doi.org/10.3390/nu12113392. 53.
40. Liu S, Li D, Huang B, Chen Y, Lu X, Wang Y. Inhibition of pancreatic lipase, α-glucosidase, α-amylase, and hypolipidemic effects of the total flavonoids from Nelumbo nucifera leaves. Journal of ethnopharmacology. 2013 Aug 26;149(1):263-9. https://doi.org/10.1016/j.jep.2013.06.034 54.
41. Arooj M, Imran S, Inam-ur-Raheem M, Rajoka MS, Sameen A, Siddique R, Sahar A, Tariq S, Riaz A, Hussain A, Siddeeg A. Lotus seeds (Nelumbinis semen) as an emerging therapeutic seed: A comprehensive review. Food Science & Nutrition. 2021 Jul;9(7):3971- 87. https://doi.org/10.1002/fsn3.2313)
42. Journal of Pharmacy and Pharmacology 2009; 61: 407–422
43. Lee, J.S.; Shukla, S.; Kim, J.A.; Kim, M. Anti-angiogenic effect of *nelumbo nucifera* leaf extracts in human umbilical vein endothelial cells with antioxidant potential. *PLoS ONE* **2015**, *10*.)
44. Yang, M.Y.; Chang, Y.C.; Chan, K.C.; Lee, Y.J.; Wang, C.J. Flavonoid-enriched extracts from *Nelumbo nucifera* leaves inhibits proliferation of breast cancer in vitro and in vivo. *Eur. J. Integr. Med.* **2011**, *3*.

45. Wu, C.H.; Yang, M.Y.; Lee, Y.J.; Wang, C.J. *Nelumbo nucifera* leaf polyphenol extract inhibits breast cancer cells metastasis in vitro and in vivo through PKCα targeting. *J. Funct. Foods* **2017**, *37*, 480–490.
46. Tungmunnithum, D., Drouet, S., & Hano, C. (2022). Validation of a high-performance liquid chromatography with photodiode array detection method for the separation and quantification of antioxidant and skin anti-aging flavonoids from Nelumbo nucifera Gaertn. stamen extract. Molecules, 27(3), 1102. https://doi.org/10.3390/molecules27031102**).**
47. Bishayee A, Patel PA, Sharma P, Thoutireddy S, Das N. Lotus (Nelumbo nucifera Gaertn.) and its bioactive phytocompounds: A tribute to cancer prevention and intervention. Cancers. 2022 Jan 21;14(3):529. https://doi.org/10.3390/cancers14030529)
48. Yang MY, Chang YC, Chan KC, Lee YJ, Wang CJ. Flavonoid-enriched extracts from Nelumbo nucifera leaves inhibits proliferation of breast cancer in vitro and in vivo. European Journal of Integrative Medicine. 2011 Sep 1;3(3):e15363.https://doi.org/10.1016/j.eujim.2011.08.008.
49. Krubha A, Vasan PT. Phytochemical analysis and anticancer activity of Nelumbo nucifera floral receptacle extracts in MCF-7 Cell Line. J. Acad. Ind. Res. 2016 May;4:251-6.)
50. Karki R, Rhyu DY, Kim DW. Effect of *Nelumbo nucifera* on proliferation, migration and expression of MMP-2 and MMP-9 in cancer cells. Korean J Plant Res. 2008;21:96-102.
51. Yang MY, Chang YC, Chan KC, Lee YJ, Wang CJ. Flavonoid-enriched extracts from *Nelumbo nucifera* leaves inhibit breast cancer proliferation in vitro and in vivo. Eur J Integr Med. 2011;3:e153-e163.
52. Chang CH, Ou TT, Yang MY, Huang CC, Wang CJ. *Nelumbo nucifera* leaf extract inhibits angiogenesis and metastasis of breast cancer cells via CTGF-mediated PI3K/Akt/ERK signaling. J Ethnopharmacol. 2016;188:111-122.
53. Wu CH, Yang MY, Lee YJ, Wang CJ. *Nelumbo nucifera* leaf polyphenol extract inhibits breast cancer metastasis through PKCα targeting. J Funct Foods. 2017;37:480-490.
54. Arjun P, Priya S, Krishnamoorthy M, Balasubramanian K. Phytochemical analysis and anticancer activity of *Nelumbo nucifera* extracts against MCF-7 cells. J Acad Ind Res. 2012;1:8185.
55. Krubha A, Vasan PT. Phytochemical analysis and anticancer activity of *Nelumbo nucifera* floral receptacle extracts in MCF-7 cell line. J Acad Ind Res. 2016;4:251-256.
56. Zhang X, Wang X, Wu T, Li B, Liu T, Wang R, et al. Isoliensinine induces apoptosis in triple-negative breast cancer cells through ROS generation and p38 MAPK/JNK activation. Sci Rep. 2015;5:12579.
57. Yang D, Zou X, Yi R, Liu W, Peng D, Zhao X. Neferine increases the anticancer effect of dehydroepiandrosterone in MCF-7 human breast cancer cells. Appl Biol Chem. 2016;59:585-596.
58. Kadioglu O, Law BYK, Mok SWF, Xu SW, Efferth T, Wong VKW. Mode-of-action analysis of neferine against multidrug-resistant tumor cells. Front Pharmacol. 2017;8:238.
59. Law BYK, Michelangeli F, Qu YQ, Xu SW, Han Y, Mok SWF, et al. Neferine induces autophagy-dependent cell death in apoptosis-resistant cancers via RyR-mediated calcium signaling. Sci Rep. 2019;9:20034.
60. Liu Z, Zhang S, Wang T, Shao H, Gao J, Wang Y, et al. Neferine inhibits breast cancer cell growth and metastasis through regulation of miR-374a/FGFR2 signaling. Chem Biol Interact. 2019;309:108716.
61. Kang EJ, Lee SK, Park KK, Son SH, Kim KR, Chung WY. Liensinine and nuciferine inhibit breast cancer growth and associated bone loss. Evid Based Complement Alternat Med. 2017;2017:1583185.
62. Zhou J, Li G, Zheng Y, Shen HM, Hu X, Ming QL, et al. Liensinine sensitizes breast cancer cells to chemotherapy through DNM1L-mediated mitochondrial fission. Autophagy. 2015;11(8):1259-1279.
63. Huang Z, Xu H, Chen H, Sun B, Huang H, Fan H, Zheng J. Seco-neferine A-F, benzyltetrahydroisoquinoline alkaloid derivatives from Plumula Nelumbinis and their biological activities. Fitoterapia. 2021;153:104994.
64. Maneenet J, Omar AM, Sun S, Kim MJ, Daodee S, Monthakantirat O, et al. Benzylisoquinoline alkaloids from *Nelumbo nucifera* petals with antiausterity activity against HeLa cells. Z Naturforsch C J Biosci. 2021;76(11-12):401-406.
65. Li HL, Cheng Y, Zhou ZW, Long HZ, Luo HY, Wen DD, et al. Isoliensinine induces cell-cycle arrest and apoptosis in cervical cancer cells through AKT/GSK3α signaling inhibition. Oncol Lett. 2022;23:8.
66. Dasari S, Bakthavachalam V, Chinnapaka S, Venkatesan R, Samy ALPA, Munirathinam G. Neferine targets HeLa and SiHa cervical cancer cells through a pro-oxidant mechanism. Phytother Res. 2020;34:2366-2384.
67. Zhao X, Feng X, Wang C, Peng D, Zhu K, Song JL. Anticancer activity of *Nelumbo nucifera* stamen extract in HCT-116 human colon cancer cells. Oncol Lett. 2017;13:1470-1478.
68. Prasath M, Narasimha MB, Huang CY, Viswanadha VP. Neferine and isoliensinine induce ROS-mediated apoptosis in colorectal cancer HCT-15 cells. Afr J Pharm Pharmacol. 2019;13:90-99.
69. Qi Q, Li R, Li HY, Cao YB, Bai M, Fan XJ, et al. Identification of antitumor activity and mechanisms of nuciferine using network pharmacology and experimental validation. Acta Pharmacol Sin. 2016;37:963-972.
70. Wang, Y.; Li, Y.-J.; Huang, X.-H.; Zheng, C.-C.; Yin, X.-F.; Li, B.; He, Q.-Y. Liensinine perchlorate inhibits colorectal cancer tumorigenesis by inducing mitochondrial dysfunction and apoptosis. *Food Funct.* **2018**, *9*, 5536–5546.
71. Guon, T.E.; Chung, H.S. Hyperoside and rutin of *Nelumbo nucifera* induce mitochondrial apoptosis through a caspase-dependent mechanism in HT-29 human colon cancer cells. *Oncol. Lett.* **2016**, *11*, 2463–2470.
72. An, K.; Zhang, Y.; Liu, Y.; Yan, S.; Hou, Z.; Cao, M.; Liu, G.; Dong, C.; Gao, J.; Liu, G. Neferine induces apoptosis by modulating the ROS-mediated JNK pathway in esophageal squamous cell carcinoma. *Oncol. Rep.* **2020**, *44*, 1116–1126.

73. Wang S, Wang Y, Zhao J, Wang H, Liang Y. Neferine suppresses proliferation and migration of retinoblastoma cells through apoptosis induction. Cell Mol Biol Lett. 2020;25:15.
74. Shen, Y.; Bian, R.; Li, Y.; Gao, Y.; Liu, Y.; Xu, Y.; Song, X.; Zhang, Y. Liensinine induces gallbladder cancer apoptosis and G2/M arrest by inhibiting ZFX-induced PI3K/AKT pathway. *Acta Biochim. Biophys. Sin.* **2019**, *51*, 607–614.
75. Zheng, Y.; Wang, Q.; Zhuang, W.; Lu, X.; Miron, A.; Chai, T.-T.; Zheng, B.; Xiao, J. Cytotoxic, Antitumor and Immunomodulatory Effects of the Water-Soluble Polysaccharides from Lotus (*Nelumbo nucifera* Gaertn.) Seeds. *Molecules* **2016**, *21*, 1465.
76. Huang, C.; Li, Y.; Cao, P.; Xie, Z.; Qin, Z. Synergistic effect of hyperthermia and neferine on reverse multidrug resistance in adriamycin-resistant SGC7901/ADM gastric cancer cells. *J. Huazhong Univ. Sci. Technol.* **2011**, *31*, 488–496.
77. Xue, F.; Liu, Z.; Xu, J.; Xu, X.; Chen, X.; Tian, F. Neferine inhibits growth and migration of gastrointestinal stromal tumor cell line GIST-T1 by up-regulation of miR-449a. *Biomed. Pharmacother.* **2019**, *109*, 1951–1959.
78. Liu, C.-M.; Kao, C.-L.; Wu, H.-M.; Li, W.-J.; Huang, C.-T.; Li, H.-T.; Chen, C.-Y. Antioxidant and Anticancer Aporphine Alkaloids from the Leaves of *Nelumbo nucifera* Gaertn. cv. Rosa-plena. *Molecules* **2014**, *19*, 17829–17838.
79. Yang, J.-H.; Yu, K.; Si, X.-K.; Li, S.; Cao, Y.-J.; Li, W.; Zhang, J.-X. Liensinine inhibited gastric cancer cell growth through ROS generation and the PI3K/AKT pathway. *J. Cancer* **2019**, *10*, 6431–6438.
80. Zhu, F.; Li, X.; Tang, X.; Jiang, J.; Han, Y.; Li, Y.; Ma, C.; Liu, Z.; He, Y. Neferine promotes the apoptosis of HNSCC through the accumulation of p62/SQSTM1 caused by autophagic flux inhibition. *Int. J. Mol. Med.* **2021**, *48*, 124.
81. Byun, D.-S. Kaempferol Isolated from *Nelumbo nucifera* Stamens Negatively Regulates FcεRI Expression in Human Basophilic KU812F Cells. *J. Microbiol. Biotechnol.* **2009**, *19*, 155–160.
82. Qin, Q.; Chen, X.-P.; Yang, Z.-S.; Xiao, Y.-H.; Min, H.; Li, Y.-J. Neferine increases STI571 chemosensitivity via inhibition of P-gp expression in STI571-resistant K562 cells. *Leuk. Lymphoma* **2011**, *52*, 694–700.
83. Li, Q.-H.; Sui, L.-P.; Zhao, Y.-H.; Chen, B.-G.; Li, J.; Ma, Z.-H.; Hu, Z.-H.; Tang, Y.-L.; Guo, Y.-X. Tripartite Motif-Containing 44 is Involved in the Tumorigenesis of Laryngeal Squamous Cell Carcinoma, and its Expression is Downregulated by Nuciferine. *Tohoku J. Exp. Med.* **2021**, *254*, 17–23.
84. Shen, Y.; Guan, Y.; Song, X.; He, J.; Xie, Z.; Zhang, Y.; Zhang, H.; Tang, D. Polyphenols extract from lotus seedpod (*Nelumbo nucifera* Gaertn.): Phenolic compositions, antioxidant, and antiproliferative activities. *Food Sci. Nutr.* **2019**, *7*, 3062–3070.
85. Duan, Y.; Xu, H.; Luo, X.; Zhang, H.; He, Y.; Sun, G.; Sun, X. Procyanidins from *Nelumbo nucifera* Gaertn. Seedpod induce autophagy mediated by reactive oxygen species generation in human hepatoma G2 cells. *Biomed. Pharmacother.* **2016**, *79*, 135–152.
86. Xiao-Hong, A.; Xiao-Qing, T.; Yan-Ping, L.; Hua-Qing, L.; Lin, D. Effect of Neferine on Adriamycin-resistance of Thermotolerant Hepatocarcinoma Cell Line HepG2/thermotolerance. *Chin. J Cancer* **2007**, *26*, 357–360.
87. Yoon, J.-S.; Kim, H.-M.; Yadunandam, A.K.; Kim, N.-H.; Jung, H.-A.; Choi, J.-S.; Kim, C.-Y.; Kim, G.-D. Neferine isolated from *Nelumbo nucifera* enhances anti-cancer activities in Hep3B cells: Molecular mechanisms of cell cycle arrest, ER stress induced apoptosis and anti-angiogenic response. *Phytomedicine* **2013**, *20*, 1013–1022.
88. Poornima, P.; Quency, R.S.; Padma, V.V. Neferine induces reactive oxygen species mediated intrinsic pathway of apoptosis in HepG2 cells. *Food Chem.* **2013**, *136*, 659–667.
89. Deng, G.; Zeng, S.; Ma, J.; Zhang, Y.; Qu, Y.; Han, Y.; Yin, L.; Cai, C.; Guo, C.; Shen, H. The anti-tumor activities of Neferine on cell invasion and oxaliplatin sensitivity regulated by EMT via Snail signaling in hepatocellular carcinoma. *Sci. Rep.* **2017**, *7*, 41616.
90. Shu, G.; Yue, L.; Zhao, W.; Xu, C.; Yang, J.; Wang, S.; Yang, X. Isoliensinine, a Bioactive Alkaloid Derived from Embryos of *Nelumbo nucifera*, Induces Hepatocellular Carcinoma Cell Apoptosis through Suppression of NF-κB Signaling. *J. Agric. Food Chem.* **2015**, *63*, 8793–8803.
91. Shu, G.; Zhang, L.; Jiang, S.; Cheng, Z.; Wang, G.; Huang, X.; Yang, X. Isoliensinine induces dephosphorylation of NF-κB p65 subunit at Ser536 via a PP2A-dependent mechanism in hepatocellular carcinoma cells: Roles of impairing PP2A/I2PP2A interaction. *Oncotarget* **2016**, *7*, 40285–40296.
92. Kim, N.; Yang, I.; Kim, S.; Lee, C. Lotus (*Nelumbo nucifera*) seedpod extract inhibits cell proliferation and induces apoptosis in non-small cell lung cancer cells via downregulation of Axl. *J. Food Biochem.* **2021**, *45*, e13601.
93. Poornima, P.; Weng, C.F.; Padma, V.V. Neferine from *Nelumbo nucifera* induces autophagy through the inhibition of PI3K/Akt/mTOR pathway and ROS hyper generation in A549 cells. *Food Chem.* **2013**, *141*, 3598–3605.
94. Poornima, P.; Weng, C.F.; Padma, V.V. Neferine, an alkaloid from lotus seed embryo, inhibits human lung cancer cell growth by MAPK activation and cell cycle arrest. *BioFactors* **2014**, *40*, 121–131.
95. Selvi, S.K.; Vinoth, A.; Varadharajan, T.; Weng, C.F.; Padma, V.V. Neferine augments therapeutic efficacy of cisplatin through ROS mediated non-canonical autophagy in human lung adenocarcinoma (A549 cells). *Food Chem. Toxicol.* **2017**, *103*, 28–40.
96. Sivalingam, K.S.; Paramasivan, P.; Weng, C.F.; Viswanadha, V.P. Neferine Potentiates the Antitumor Effect of Cisplatin in Human Lung Adenocarcinoma Cells via a Mitochondria-Mediated Apoptosis Pathway. *J. Cell. Biochem.* **2017**, *118*, 2865–2876. [

97. Liu, W.; Yi, D.-D.; Guo, J.-L.; Xiang, Z.-X.; Deng, L.-F.; He, L. Nuciferine, extracted from *Nelumbo nucifera* Gaertn, inhibits tumor-promoting effect of nicotine involving Wnt/β-catenin signaling in non-small cell lung cancer. *J. Ethnopharmacol.* **2015**, *165*, 83–93.
98. Zhao, X.; Feng, X.; Peng, D.; Liu, W.; Sun, P.; Li, G.; Gu, L.; Song, J.-L. Anticancer activities of alkaloids extracted from the Ba lotus seed in human nasopharyngeal carcinoma CNE-1 cells. *Exp. Ther. Med.* **2016**, *12*, 3113–3120.
99. Pham, D.-C.; Chang, Y.-C.; Lin, S.-R.; Fuh, Y.-M.; Tsai, M.-J.; Weng, C.-F. FAK and S6K1 Inhibitor, Neferine, Dually Induces Autophagy and Apoptosis in Human Neuroblastoma Cells. *Molecules* **2018**, *23*, 3110.
100. Li, Z.; Chen, Y.; An, T.; Liu, P.; Zhu, J.; Yang, H.; Zhang, W.; Dong, T.; Jiang, J.; Zhang, Y.; et al. Nuciferine inhibits the progression of glioblastoma by suppressing the SOX2-AKT/STAT3-Slug signaling pathway. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 139.
101. Xu, L.; Zhang, X.; Li, Y.; Lu, S.; Lu, S.; Li, J.; Wang, Y.; Tian, X.; Wei, J.-J.; Shao, C.; et al. Neferine induces autophagy of human ovarian cancer cells via p38 MAPK/JNK activation. *Tumor Biol.* **2016**, *37*, 8721–8729.
102. Erdogan, S.; Turkekul, K. Neferine inhibits proliferation and migration of human prostate cancer stem cells through p38 MAPK/JNK activation. *J. Food Biochem.* **2020**, *44*, e13253.
103. Nazim, U.M.; Yin, H.; Park, S. Neferine treatment enhances the TRAIL-induced apoptosis of human prostate cancer cells via autophagic flux and the JNK pathway. *Int. J. Oncol.* **2020**, *56*, 1152–1161.
104. Liu, C.M.; Wu, Z.; Pan, B.; An, L.; Zhu, C.; Zhou, J.; Jiang, Y. The antiandrogenic effect of neferine, liensinine and isoliensinine by inhibiting 5-α-reductase and androgen receptor expression via PI3K/AKT signaling pathway in prostate cancer. *Pharmazie* **2021**, *76*, 225–231.
105. Kim, E.; Sung, E.-G.; Song, I.-H.; Kim, J.-Y.; Sung, H.-J.; Sohn, H.-Y.; Park, J.-Y.; Lee, T.-J. Neferine-induced apoptosis is dependent on the suppression of Bcl-2 expression via downregulation of p65 in renal cancer cells. *Acta Biochim. Biophys. Sin.* **2019**, *51*, 734–742.
106. Zhang, X.; Liu, Z.; Xu, B.; Sun, Z.; Gong, Y.; Shao, C. Neferine, an alkaloid ingredient in lotus seed embryo, inhibits proliferation of human osteosarcoma cells by promoting p38 MAPK-mediated p21 stabilization. *Eur. J. Pharmacol.* **2012**, *677*, 47–54.
107. Nakamura, S.; Nakashima, S.; Tanabe, G.; Oda, Y.; Yokota, N.; Fujimoto, K.; Matsumoto, T.; Sakuma, R.; Ohta, T.; Ogawa, K.; et al. Alkaloid constituents from flower buds and leaves of sacred lotus (*Nelumbo nucifera*, Nymphaeaceae) with melanogenesis inhibitory activity in B16 melanoma cells. *Bioorg. Med. Chem.* **2013**, *21*, 779–787
108. Duan, Y.; Zhang, H.; Xu, F.; Xie, B.; Yang, X.; Wang, Y.; Yan, Y. Inhibition effect of procyanidins from lotus seedpod on mouse B16 melanoma invivo and in vitro. *Food Chem.* **2010**, *122*, 84–91.
109. Lai, P.-J.; Kao, E.-S.; Chen, S.-R.; Huang, Y.-T.; Wang, C.-J.; Huang, H.-P. *Nelumbo nucifera* Leaf Extracts Inhibit Melanogenesis in B16 Melanoma Cells and Guinea Pigs through Downregulation of CREB/MITF Activation. *J. Food Nutr. Res.* **2020**, *8*, 459–465.
110. Wu, P.-F.; Chiu, C.-C.; Chen, C.-Y.; Wang, H.-M.D. 7-Hydroxydehydronuciferine induces human melanoma death via triggering autophagy and apoptosis. *Exp. Dermatol.* **2015**, *24*, 930–935.
111. Kim JH, Kang M, Cho C, et al. Effects of Nelumbinis Semen on contractile dysfunction in ischemic and reperfused rat heart. *Arch Pharm Res*. 2006;29(9):777-785. doi:10.1007/BF02974079.
112. Rathod P, Salvi R, Salunke R, Rohondia A, Rathod R, Misal K, Indulkar A, Gorde N, MK K, Juvatkar PV, Gokhale S. NELUMBO NUCIFERA: A PLANT WITH MULTIPLE PHARMACOLOGICAL ACTIVITIES. Foldscope & its Applications. 2022:116.
113. Mukherjee, P.K., Pal, M., Saha, K., Saha, B.P. and Das, J. (1996), Diuretic Activity of Extract of the Rhizomes of Nelumbo nucifera Gaertn. (Fam. Nymphaeaceae). Phytother. Res., 10: 424-425.
114. https://doi.org/10.1002/(SICI)1099-1573(199608)10:5<424::AID-PTR857>3.0.CO;2-3
115. Tungmunnithum, D., Drouet, S., & Hano, C. (2022). Validation of a high-performance liquid chromatography with photodiode array detection method for the separation and quantification of antioxidant and skin anti-aging flavonoids from Nelumbo nucifera Gaertn. stamen extract. Molecules, 27(3), 1102.
116. https://doi.org/10.3390/molecules27031102
117. Zhang L, Shan Y, Tang K, Putheti R. Ultrasound-assisted extraction flavonoids from Lotus (Nelumbo nuficera Gaertn) leaf and evaluation of its anti-fatigue activity. Int. J. Phys. Sci. 2009 Aug 1;4(8):418-22.
118. Chakravarthi PV, Gopakumar N. Evaluation of Analgesic Activity of Lotus seeds (Nelumbo nucifera) in Albino Rats. Veterinary World. 2009 Sep 1;2(9):55-62.
119. Semaming Y, Chunpricha S, Suriya A. Antioxidant activity and protective effect against oxidative stress induced-hemolysis of Nymphaea lotus L. extracts. Asia Pac J Sci Technol. 2018;23(4):9.)
120. Reddy MV, Manmohan Singhal MS. Evaluation of anti-Parkinsonian activity of seed extract of Nelumbo nucifera.
121. Lin HH, Hsu JY, Tseng CY, Huang XY, Tseng HC, Chen JH. Hepatoprotective Activity of *Nelumbo nucifera* Gaertn. Seedpod Extract Attenuated Acetaminophen-Induced Hepatotoxicity. *Molecules*. 2022;27(13):4030. Published 2022 Jun23.doi:10.3390/molecules27134030.
122. .Figueira, I., Garcia, G., Pimp˜ ao, R. C., Terrasso, A. P., Costa, I., Almeida, A. F., et al. (2017). Polyphenols journey through blood-brain barrier towards neuronal protection. *Scientific Reports, 7*, 11456.
123. Prasad, D. K., & Sriharsha, S. N. (2015). Evaluation of anxiolytic activity of leaf extracts of Nelumbo nucifera in laboratory rodents. *International Journal of Pharmacy and Biological Sciences, 5*, 24–30.

124. Yan, M.-Z., Chang, Q., Zhong, Y., Xiao, B.-X., Feng, L., Cao, F.-R., et al. (2015). Lotus leaf alkaloid extract displays sedative–hypnotic and anxiolytic effects through GABAA receptor. *Journal of Agricultural and Food Chemistry, 63*, 9277–9285.
125. Temviriyanukul, P., Sritalahareuthai, V., Promyos, N., Thangsiri, S., Pruesapan, K., Srinuanchai, W., et al. (2020). The effect of sacred Lotus (Nelumbo nucifera) and its mixtures on phenolic profiles, antioxidant activities, and inhibitions of the key enzymes relevant to Alzheimer's disease. *Molecules, 25*, 3713.
126. Zhang L, Shan Y, Tang K, Putheti R. Ultrasound-assisted extraction flavonoids from Lotus (Nelumbo nuficera Gaertn) leaf and evaluation of its anti-fatigue activity. Int. J. Phys. Sci. 2009 Aug 1;4(8):418-22.
127. Xu, H. C., & Wang, M. Y. (2014). Effect of flavonoids from Lotus (Nelumbo nuficera Gaertn) leaf on biochemical parameters related to oxidative stress induced by exhaustive swimming exercise of mice. *Biomedical Research, 25*, 1–5.
128. Agnihotri et al., 2008; Lee et al., 2019; Li & Xu, 2008; Mehta et al., 2014). Extracts obtained from lotus leaves collected in Mansbal Lake (Jammu & Kashmir, India) also demonstrate antibacterial effects against fish pathogens such as *Staphylococcus aureus*, *Aeromonas hydrophila*, and *Pseudomonas fluorescens* .
129. Kashiwada, Y., Aoshima, A., Ikeshiro, Y., Chen, Y.-P., Furukawa, H., Itoigawa, M., et al. (2005). Anti-HIV benzylisoquinoline alkaloids and flavonoids from the leaves of Nelumbo nucifera, and structure–activity correlations with related alkaloids. *Bioorganic & Medicinal Chemistry, 13*, 443–448.
130. Li, S., Chen, A., Chen, Y., Yang, Y., Zhang, Q., Luo, S., et al. (2020). Lotus leaf inspired antiadhesive and antibacterial gauze for enhanced infected dermal wound regeneration. *Chemical Engineering Journal, 402*, Article 126202.
131. Cheng, L., Zhang, W., Jin, Q., Zhu, Y., Chen, R., Tian, Q., et al. (2020). Immunology, Health and Disease the effects of dietary supplementation with lotus leaf extract on the immune response, and intestinal microbiota composition of broiler chickens. *Poultry Science, 100*, Article 100925.
132. Wang, Y., Yao, W., Li, B., Qian, S., Wei, B., Gong, S., et al. (2020b). Nuciferine modulates the gut microbiota and prevents obesity in high-fat diet-fed rats. *Experimental & Molecular Medicine, 52*, 1959–1975.
133. Wang, L.-M., Wang, P., Teka, T., Zhang, Y.-C., Yang, W.-Z., Zhang, Y., et al. (2020a). 1H NMR and UHPLC/Q-Orbitrap-MS-Based metabolomics combined with 16S rRNA gut microbiota analysis revealed the potential regulation mechanism of nuciferine in hyperuricemia rats. *Journal of Agricultural and Food Chemistry, 68*, 14059–14070.
132. Hwang, Y.-H., Jang, S.-A., Lee, A., Cho, C.-W., Song, Y.-R., Hong, H.-D., et al. (2020). Polysaccharides isolated from lotus leaves (LLEP) exert anti-osteoporotic effects by inhibiting osteoclastogenesis. *International Journal of Biological Macromolecules, 161*, 449–456.
133. Song, C., Cao, J., Lei, Y., Chi, H., Kong, P., Chen, G., et al. (2020). Nuciferine prevents bone loss by disrupting multinucleated osteoclast formation and promoting type H vessel formation. *The FASEB Journal, 34*, 4798–4811.
134.Park, S. H., Oh, J., Jo, M., Kim, J. K., Kim, D. S., Kim, H. G., et al. (2020). Water extract of Lotus leaf alleviates dexamethasone-induced muscle atrophy via regulating protein metabolism-related pathways in mice. *Molecules, 25*, 4592.
135.Mukherjee PK, Goswami D, Das B, Banerjee S. Nelumbo nucifera: Pharmacological Profile, Metabolite Profiling and Therapeutic Uses. In Natural Medicines 2019 Jul 18 (pp. 139-164). CRC Press. eBook ISBN9781315187853.
136.Chakravarthi PV, Gopakumar N. Evaluation of Analgesic Activity of Lotus seeds (Nelumbo nucifera) in Albino Rats. Veterinary World. 2009 Sep 1;2(9):55-62.
137.Niu CH, Wang Y, Liu JD, Wang JL, Xiao JH. Protective effects of neferine on amiodarone-induced pulmonary fibrosis in mice. European journal of pharmacology. 2013 Aug 15;714(1-3):112-9.)
138.Balkrishna A, Joshi RA, Prajapati UB, Srivastava A, Shankar R. Nelumbo nucifera Gaertn.(Lotus): Importance in reproductive healthcare. Journal of Drug Research in Ayurvedic Sciences. 2025 Mar 1;10(2):130-6.
139.Bangar SP, Dunno K, Kumar M, Mostafa H, Maqsood S. A comprehensive review on lotus seeds (Nelumbo nucifera Gaertn.): Nutritional composition, health-related bioactive properties, and industrial applications. Journal of Functional Foods. 2022 Feb 1;89:104937. https://doi.org/10.1016/j.jff.2022.104937
140.Chen H, Li J, Yao R, Yan S, Wang Q (2020) Mechanism of lipid metabolism regulation by soluble dietary fibre from micronized and non-micronized powders of lotus root nodes as revealed by their adsorption and activity inhibition of pancreatic lipase. Food Chem 305:125435
141.Qiu ZZ, Chin KB (2022a) Evaluation of antioxidant activities of lotus rhizome root powder prepared by different drying conditions and its application to raw and cooked pork patties. Food Packag Shelf 33:100917
142.Yang H, He S, Feng Q, et al. Correction: Lotus (Nelumbo nucifera): a multidisciplinary review of its cultural, ecological, and nutraceutical significance. *Bioresour Bioprocess*. 2024;11(1):112. Published 2024 Dec 20. doi:10.1186/s40643-024-00829-6.