

FROM PHYTOCHEMISTRY TO CUTANEOUS REPAIR: MOLECULAR INSIGHTS INTO THE DERMATOLOGICAL APPLICATIONS OF NELUMBO NUCIFERA

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ABSTRACT

The Indian lotus, *Nelumbo nucifera* Gaertn, is a valuable medicinal plant that has been used in Asian medicine to treat infections, inflammation and other issues. Because *Nelumbo nucifera* includes a variety of substances, including alkaloids, flavonoids, phenolic acids, tannins, terpenoids, glycosides, polysaccharides and volatile compounds many scientists are currently studying it. This review discusses the compounds found in *Nelumbo nucifera* and their potential use for skin health, including wound healing, infection treatment and skin protection. Through processes involving Nrf2 and HO-1, flavonoids and phenolic substances such as quercetin, kaempferol, rutin, catechin, and phenolic acids boost the body's defense against radicals. *N. nucifera* also shows anti-inflammatory effects by reducing the activity of the inflammation pathway and reducing signals such as TNF- α , IL-1 β , IL-6, NO and PGE2. Experiments suggest that *N. nucifera* can protect skin cells called fibroblasts, help build collagen, speed up skin regeneration and stop microbes from growing. Studies with wounds and other animal models show that compounds from *N. nucifera* may help tissue repair, although some proposed mechanisms like growth signals involving TGF- β /Smad and VEGF need more proof. The review also talks about uses for chronic wounds. Diabetic ulcers and acne, along with ways to make products and safety points. Even though early studies are encouraging, there is still evidence from clinical trials, differences in extracts and a lack of standard rules. Future work should aim at making preparations, better ways to apply the product to skin and well-planned human studies to prove safety and effectiveness.

Keywords: *Nelumbo nucifera*, Wound healing, Skin regeneration, Antioxidant, Inflammation

INTRODUCTION

Nelumbo nucifera which is known as the Indian lotus or sacred lotus is a very old aquatic medical plants that belongs to the Nelumbonaceae family. It can be found throughout Asia. In countries such as Japan, China, India and Sri Lanka it has served as a source of food and as a traditional medicine as well as a part of culture for many centuries^[1,2]. All parts of the plant including seeds, stamens, flowers, leaves, rhizomes and seed pods are used in different types of traditional medicine including Ayurveda and Traditional Chinese Medicine (TCM) for the treatment of many health problems like cardiovascular diseases, diabetes, inflammatory disorders and skin diseases. There has been a lot of research that supports the claims made by traditional medicine practitioners and has made *Nelumbo nucifera* a significant plant for further pharmacological studies ^[1,3].

The high therapeutic effectiveness of *Nelumbo nucifera* is due to its diverse composition of phytochemicals. The plant contains various bioactive chemicals including alkaloids (Nuciferine, Neferine, Liensinine and Isoliensinine), phenolic acids, tannins, flavonoids, glycosides and essential oils. These have been separated from various parts of the plant^[4]. The compounds have impressive biological properties such as antioxidant, antimicrobial, anti-inflammatory, antidiabetic, anti-obesity, hepatoprotective, cardioprotective, neuroprotective, anticancer and wound healing activities. The enhancement of phytochemical profiling techniques and analytical methods helps in discovering new metabolites as well as their mechanisms of action^[5].

Different plant parts have been studied in detail regarding their various characteristics and efficacy but among them the lotus flower has attracted scientific interest due its high concentration of flavonoids and phenolic compounds that possess strong antioxidant and antimicrobial properties. Oxidative damage and microbial infection are still among the main causes of delayed wound healing and the development of resistance to antibiotics^[6]. Therefore, finding natural products that can minimize oxidative damage while stopping infection and stimulating tissue recovery has become important within the pharmaceutical research area. Studies have shown that lotus flower extracts can inhibit the growth of some pathogenic bacteria and fungi while improving antioxidant properties of cells which makes them effective for wound treatment and infection control^[7].

In the past few years, network pharmacology has developed into a robust systems biology approach to explore the complex interactions among phytochemicals, molecular targets, biological pathways and diseases. In contrast to the traditional notion of "one drug – one target" network pharmacology imparts pertinent information regarding the multi-component and multi-target

character of herbal medications^[1]. By combining network pharmacology with molecular docking and bioinformatics and subsequent experimental validation one can forecast active pharmacological agents determine key signal transduction pathways and establish therapeutic mechanisms of agents. The goal of this review is to give an organized overview of the current understanding of the chemical constituents, traditional medical uses and the pharmacological activities of the flower of *Nelumbo nucifera*^[2]. In particular the advances of network pharmacology will be covered along with the available experimental data highlighting the antibacterial and antifungal properties of the flower of *Nelumbo nucifera*. Combining traditional knowledge and modern pharmacological research this review aims to provide a scientific basis for further development of the medicaments derived from *Nelumbo nucifera* in the treatment of infectious diseases and other similar disorders^[4]

2. Taxonomy Classification

KINGDOM	PLANTAE
Clade	Eudicots
Order	Proteals
Family	Nelumbonaceae
Genus	Nelumbo
Species	Nelumbo nucifera Gaertn

Table 1. Taxonomic classification of *Nelumbo nucifera* Gaertn. Adapted from Kew Plants of the World Online

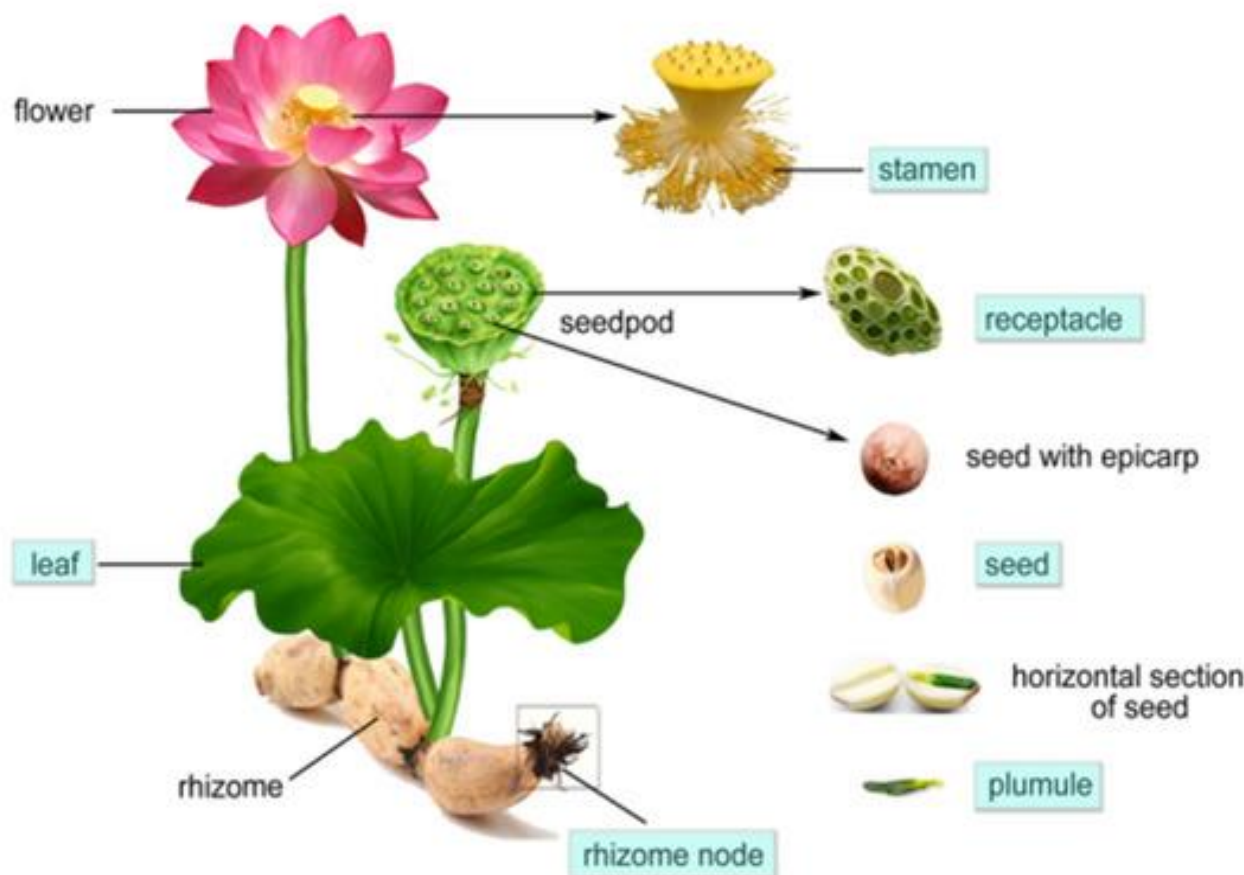
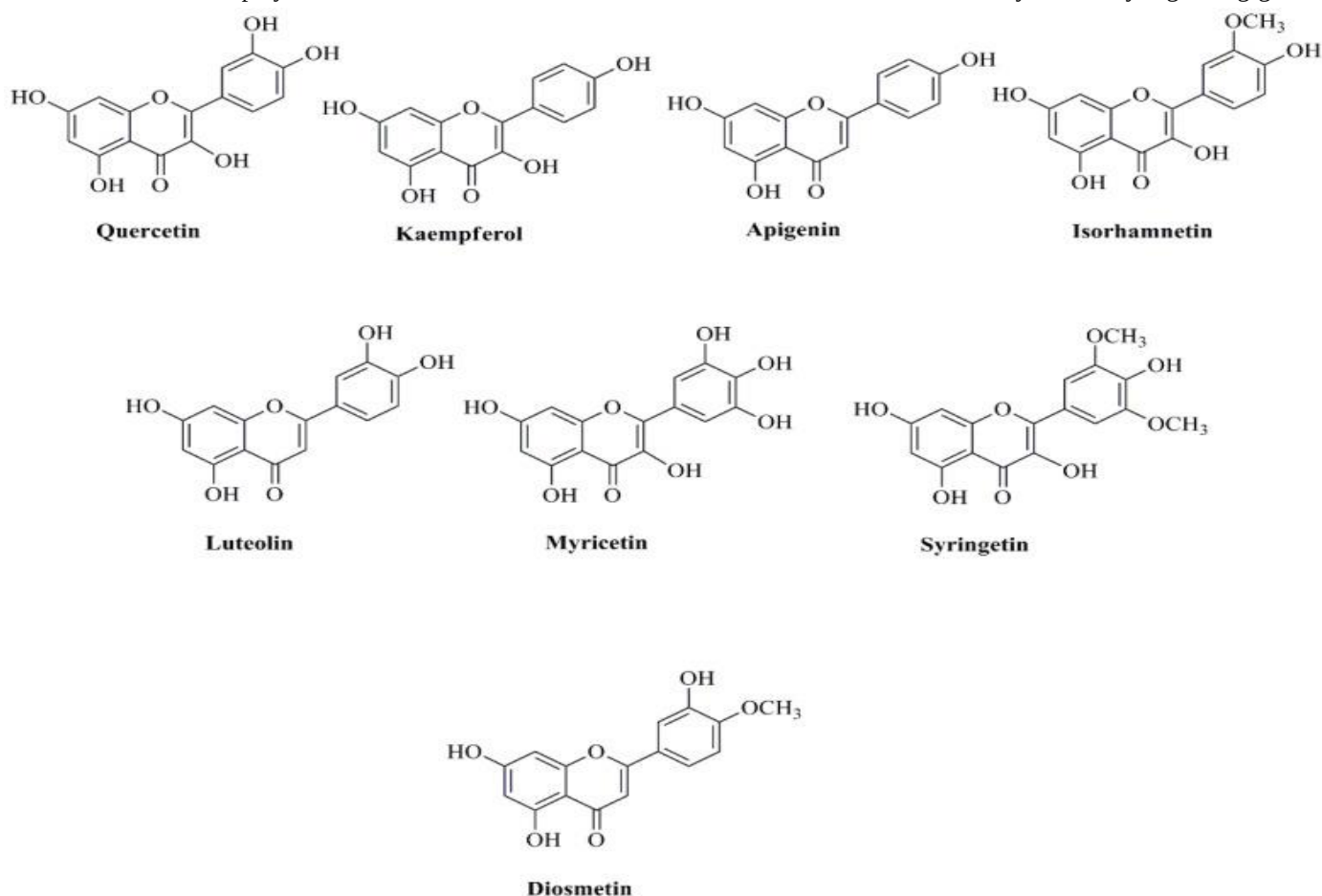


Figure 1. Schematic representation of the major morphological parts of *Nelumbo nucifera* Gaertn. Adapted from Pei *et al*^[8]

3. Phytochemical Constituents

Nelumbo nucifera has a wide range of pharmacological actions due to its abundance of structurally varied phytochemicals^[1-4]. Numerous secondary metabolites found in various plant parts such as flowers, leaves, seeds, rhizomes, stamens and seed embryos have been discovered by extensive phytochemical research^[1,2]. Alkaloids, flavonoids, phenolic acids, tannins, terpenoids, glycosides, steroids, polysaccharides and volatile oils are the principal types of these bioactive substances. The plant part, geographic origin, growing circumstances and extraction technique all affect the qualitative and quantitative makeup of these components^[4,5].

Benzylisoquinoline alkaloids are thought to be the distinctive phytochemicals of *N. nucifera* among these substances^[9,10]. The leaves, embryos and seeds are the main sources from which major alkaloids such as nuciferine, neferine, liensinine, isoliensinine, roemerine, pronuciferine and anonaine have been identified. Antioxidant, anti-inflammatory, antihyperlipidemic, antihypertensive, antiarrhythmic, neuroprotective, anticancer and cardioprotective properties are only a few of the several pharmacological activities that these alkaloids display. Nuciferine has also been shown to have anti-diabetic and anti-obesity effects by regulating glucose



homeostasis and lipid metabolism^[11,12]

Another significant class of bioactive components is flavonoids which are especially prevalent in flowers, leaves and stamens. Quercetin, kaempferol, myricetin, rutin, isoquercitrin, hyperoside, catechin, epicatechin and their glycosides are significant flavonoids^[9].

By scavenging reactive oxygen species (ROS) lowering lipid peroxidation and boosting endogenous antioxidant enzymes these substances have potent antioxidant qualities^[5].

Additionally, flavonoids support *Nelumbo nucifera*'s wound healing, hepatoprotective, antibacterial, anti-inflammatory and cardioprotective properties

Gallic acid, chlorogenic acid, caffeic acid, ferulic acid, p-coumaric acid, protocatechuic acid, and syringic acid are among the phenolic chemicals that are abundant in this plant. The antioxidant potential of lotus extracts is greatly enhanced by phenolic acids which are essential for shielding cells from oxidative damage. Furthermore, the antibacterial and astringent qualities of tannins found in flowers and leaves support the traditional usage of lotus for gastrointestinal issues and wound healing^[9].

Figure 2. Major phytochemical constituents of *Nelumbo nucifera* Gaertn. Adapted from Bishayee et al^[8].

Triterpenoids, phytosterols (stigmsterol, β -sitosterol), polysaccharides, amino acids, proteins, vitamins, minerals and volatile components are other significant phytochemicals. Lotus polysaccharides have immunomodulatory, antioxidant and antidiabetic properties and have garnered significant interest^[13].

In addition to having antibacterial and antioxidant qualities, volatile oils found in flowers contribute to their distinctive scent. These phytochemicals work in concert to provide the various therapeutic effects linked to *Nelumbo nucifera*^[9].

The identification and qualification of phytochemicals in various parts of *Nelumbo nucifera* have been made easier by recent developments in chromatographic and spectrometric techniques such as high-performance liquid chromatography (HPLC), Ultra-performance liquid chromatography (UPLC), liquid chromatography-mass spectrometry (LC-MS/MS), gas chromatography-mass spectrometry (GC-MS), high-performance thin-layer chromatography (HPTLC), nuclear magnetic resonance (NMR) and Fourier-transform infrared spectroscopy (FTIR)^[2]. The development of lotus-derived nutraceuticals and phytopharmaceuticals has been aided by these analytical techniques which have greatly enhanced phytochemical standardization and quality control.

4. Molecular Mechanisms Underlying Skin Protection and Repair by *Nelumbo nucifera*

Haemostasis, inflammation, proliferation, re-epithelialization, angiogenesis, extracellular matrix deposition and tissue remodelling are all involved in the coordinated biological process of cutaneous wound healing^[1,14]. Prolonged inflammation, microbial infection and excessive oxidative stress can disrupt this cycle and postpone tissue regeneration. *Nelumbo nucifera* contains phytochemicals with antioxidant, anti-inflammatory, antibacterial and cytoprotective qualities, including flavonoids, phenolic compounds and alkaloids which may help protect and repair the skin^[2]. Lotus flower extracts have been proven to exhibit anti-inflammatory and antioxidant properties in skin-related cellular models and certain lotus ingredients such as nuciferine have been shown to protect human dermal fibroblasts^[3,15].

4.1 Antioxidant mechanism

One of the primary causes of skin aging and impaired wound healing is oxidative stress. Overproduction of reactive oxygen species (ROS) can harm keratinocytes and fibroblasts as well as cellular proteins, lipids and DNA^[16]. Flavonoids and phenolic substances found in *Nelumbo nucifera* can scavenge free radicals and lessen oxidative damage. Myricetin and quercetin derivatives were the main flavonoid component of *Nelumbo nucifera* extract which demonstrated high antioxidant activity in DPPH, ABTS and ferric-reducing tests^[9].

The cytoprotective properties of lotus phytochemicals are especially related to the Nrf2/HO-1 antioxidant pathway. Nrf2 activation releases cellular resistance to oxidative stress by promoting the transcription of cytoprotective and antioxidant genes such as HO-1, SOD, CAT and GPx. The role of Nrf2-mediated antioxidant defence has been supported by using *Nelumbo nucifera* leaf extracts which have shown increased Nrf2 nuclear accumulation along with elevated HO-1, SOD-1 and catalase expression.

4.2 Anti-inflammatory Mechanism

Persistent inflammation can prevent tissue regeneration and increase tissue damage even though it is a necessary stage of wound healing^[5,11,19]. Extracts from *Nelumbo nucifera* have been shown to suppress inflammatory mediators and signaling pathways. *Nelumbo nucifera* leaf extracts decreased the expression and production of TNF- α , IL-1 β , IL-6 inducible nitric oxide synthase (iNOS), nitric oxide (NO) and prostaglandin E2 (PGE2) in LPS-stimulated macrophages. Significantly, these effects were linked to decreased NF-KB activity, indicating that NF-KB is a key molecular target of anti-inflammatory activity generated from lotus^[17].

More recently, a floral extract from *Nelumbo nucifera* showed anti-inflammatory properties in human HaCaT keratinocytes and macrophages. Without showing any signs of cytotoxicity. The extract lowered TNF- α -induced IL-6 and IL-8 expression in keratinocytes as well as NO and PGE2 production in activated macrophages^[20,21]. Because excessive levels of cytokines can lead to chronic inflammation and delayed tissue healing these findings are especially important to skin protection^[16].

4.3 Antimicrobial Protection

Inflammation can be prolonged and wound closure might be hampered by microbial colonization of injured skin. Therefore, *Nelumbo nucifera*'s antibacterial ability is important to its prospective use in wound care and skin protection^[13]. Flavonoids, phenolics, tannins and alkaloids are among the groups of chemicals found in lotuses that may have antibacterial properties. Methicillin-resistant *Staphylococcus aureus* (MRSA) and other harmful microbes are susceptible to the antibacterial action of materials obtained from *Nelumbo nucifera* in experimental studies^[22]. The exact molecular processes underlying the antibacterial action of entire *Nelumbo nucifera* extracts however, are still not well understood. Therefore, rather than being definitively established mechanisms for *Nelumbo nucifera*, membrane rupture, interference with microbial enzymes, oxidative imbalance and inhibition of microbial growth should currently be provided as suggested mechanisms^[23].

4.4 Protection of Dermal Fibroblasts

Because dermal fibroblasts create extracellular matrix components, especially collagen, they are crucial for wound healing and skin homeostasis^[24,25]. Fibroblast senescence can be brought on by oxidative and environmental stress which inhibits tissue regeneration.

Nuciferine a significant alkaloid obtained from *Nelumbo nucifera* has been studied in a model of human dermal fibroblast senescence induced by hydrogen peroxide^[23].

The senescent phenotype and the expression of secretory phenotypic markers linked to inflammatory senescence including CXCL1, CXCL2, IL-8 were both diminished by nuciferine therapy. According to these results nuciferine may help maintain skin homeostasis by shielding dermal fibroblasts from cellular senescence brought on by oxidative stress^[26,27].

4.5 Fibroblast proliferation and collagen deposition

During the proliferative stage of wound healing, fibroblast migration, proliferation and extracellular matrix deposition are crucial processes. One of the main mechanisms controlling fibroblast activity and collagen synthesis during tissue repair is TGF- β /Smad signalling. Modulation of TGF- β signalling can affect granulation tissue formation, re-epithelialization, collagen deposition and scar formation according to research on wound healing^[30].

There is currently little direct evidence that an isolated lotus phytochemical activates the TGF- β /Smad pathway in a skin wound model. Production this pathway should be characterized as a possible mechanistic target requiring additional experimental confirmation^[31].

4.6 Angiogenesis and Tissue Regeneration

Because newly formed blood vessels provide oxygen and nutrients to repairing tissues, angiogenesis is essential during wound repair. Growth factors like FGF and VEGF control the migration, proliferation and creation of new blood vessels by endothelial cells. By affecting this pathway, natural products can aid in the healing of wounds^[32,33]. Although *Nelumbo nucifera*'s general pharmacological profile points to possible tissue-regenerative action there is still little concrete proof that *Nelumbo nucifera* flower phytochemicals selectively activate VEGF/FGF in cutaneous wound models^[34,35]. Therefore, additional research utilizing wound models and an angiogenesis assay is necessary to definitively confirm this mechanism^[4,6].

5. In Vitro antioxidant experimental evidence of *Nelumbo nucifera*

5.1 Lotus seed embryo flavonoids:

Methanolic extracts made from the seeds of six different lotus species were studied by Nguyen Thi Quynh and associates. Twenty-seven phytochemical components were discovered by gas chromatography analysis the most common of which was methyl- α -D-galactopyranoside. The DPPH radical scavenging test was used to measure antioxidant, ascorbic acid all lotus cultivars showed significant free radical scavenging activity. These results suggest that lotus seeds have a strong antioxidant potential and could be used as natural antioxidants in functional foods^[1].

5.2 Lotus Stamen Flavonoids :

Dichloromethane, ethyl acetate and n-butanol were used by Jung et al. To fractionate methanolic preparations of lotus stamen. From the ethyl acetate fraction seven flavonoids and one sterol glucopyranoside were separated. DPPH, reactive oxygen species (ROS) and peroxynitrite (ONOO⁻) scavenging assays were used to assess their properties. In every paradigm kaempferol and its glycosides showed significant antioxidant activity but β -sitosterol glucopyranoside demonstrated negligible activity. These results demonstrated the contribution of flavonoids extracted from lotus stamens to the plant's antioxidant qualities^[10].

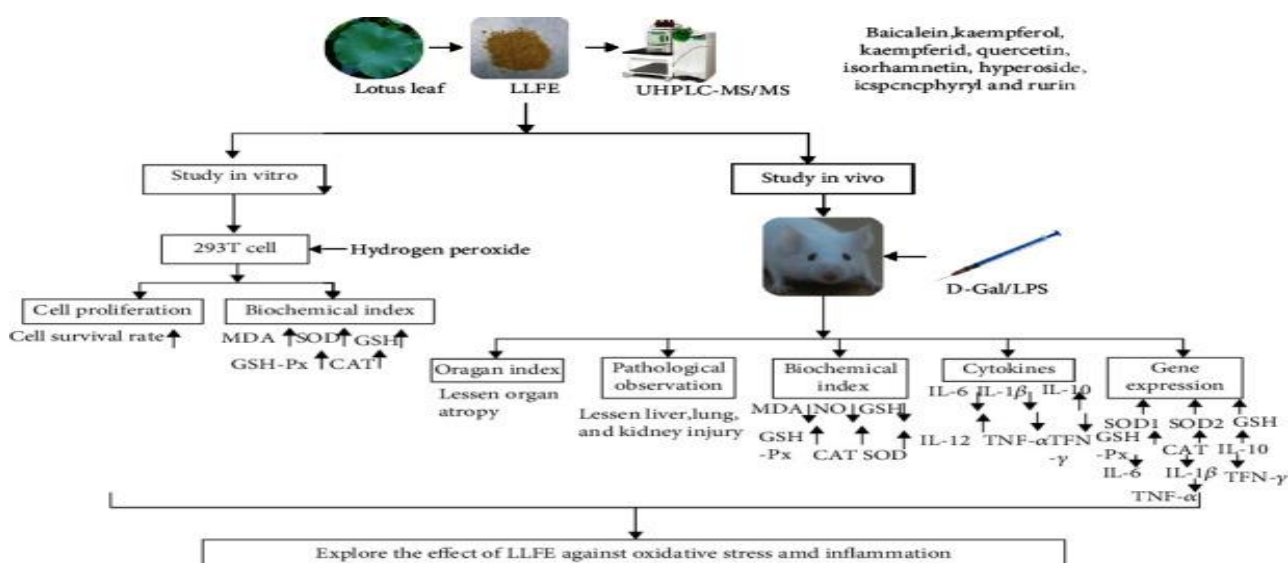


Figure 3. Summary of the antioxidant and anti-inflammatory effects of *Nelumbo nucifera* leaf flavonoid extract. Adapted and modified from Li et al^[36].

6. In Vivo Antioxidant Experimental Evidence of *Nelumbo nucifera*

6.1 Lotus Leaf Flavonoid Extract in D-Galactose/LPS-Induced Oxidative Stress

With the help of a mouse model of D-galactose and lipopolysaccharide (LPS)-induced oxidative stress one of the most comprehensive antioxidant studies collected in this review involved lotus leaf flavonoid extract (LLFE). Through the induction of a high concentration of free radicals and inflammatory mediators this particular experimental model creates an accelerated aging condition^[16].

Many biologically active flavonoids, such as baicalein, quercetin, kaempferol, kaempferide, rutin, hyperoside and isorhamnetin were detected in LLFE through chemical analysis using UHPLC-MS/MS. The antioxidant function of experimental mice was greatly enhanced due to oral administration of LLFE. The activity of endogenous antioxidant enzymes, namely GSH, CAT, SOD, and GSH-Px, was greatly increased in comparison to untreated mice.

At the same time, LLFE greatly reduced oxidative membrane damage due to a decreased concentration of malondialdehyde (MDA) which is a marker of lipid peroxidation. Extract in D-Galactose/LPS-Induced Oxidative Stress^[16].

6.2 Hydroalcoholic Lotus Seed Extract Against Carbon Tetrachloride-Induced Oxidative Stress

The literature review provides information about another research that was performed using rats that were treated with carbon tetrachloride (CCl₄). CCl₄ is commonly used for liver oxidation in experimental animals^[11]. Treatment with lotus seed extract decreased oxidation and significantly enhanced the activity of antioxidants in the liver and kidneys. The efficiency of lotus seed extract as an antioxidant at 100 mg/kg was found to be equal to the efficiency of vitamin E in a 50 mg/kg dosage. Thus, lotus seeds have good antioxidant properties protecting tissues against chemical oxidation.

6.3 Excision and incision wound models

- **Excision models**

Evaluation of topical neferine therapy on streptozotocin-induced diabetic rat wounds. A recent study indicates that it utilized a diabetic incision-wound model. However, secondary descriptions of the work also refer to an excision-wound component. The existing indexed information is not enough to solve the experimental nomenclature. Therefore, the model should be carefully reported as a diabetic cutaneous wound study and not merely attached to a category. Topical 10% neferine was applied once every day for fourteen days. Neferine increased the collagen and protein contents in the wound tissue, decreased re-epithelialization time and enhanced wound closure as compared to untreated diabetic controls^[8].

But the study has important limitations. The accessible abstract does not contain all animal characteristics, wound dimensions, treatment vehicle details, randomization protocols, blinding techniques, and full numerical wound-closure data. Furthermore, it is not reported whether systemic exposure and toxicity were evaluated, local skin concentrations were measured or neferine was chemically quantified in the topical preparation. The study only used one purified alkaloid instead of a standardized whole-plant preparation so the results cannot be applied to leaf, flower, seed or rhizome extracts. The current search did not clearly identify *Nelumbo nucifera* crude extracts in standardized excision models that include full reporting of wound size, hydroxyproline, collagen, inflammatory cell infiltration, neovascularization and histopathological scoring^[36,37]

- **Incision models**

The maturity of collagen and the tensile or breaking strength of the skin can be assessed by means of incision wounds. The neferine study which shows faster wound closure together with higher levels of collagen and protein provides the most relevant evidence regarding a lotus-derived compound in the case of a diabetic incision. Yet the previous study fails to properly describe scar structure the orientation of the collagen fibres or the latest stage of remodelling and it does not clearly state the tensile strength or breaking strength. Consequently, it is not possible to conclude that neferine improves the mechanical properties of repaired skin even though it does show an early and intermediate pro-repair effect. Blind measurements of breaking strength, hydroxyproline content, the ratio of type I to type III collagen, Masson's trichrome staining, the number of α -SMA-positive myofibroblasts and a follow-up period long enough to allow assessment of remodelling and scar formation are all essential elements of a proper incision study^[8,36].

7. Potential Applications in Specific Skin Diseases

7.1 Chronic Wounds

Wounds that are chronic such as pressure ulcers, venous leg ulcers and those resulting from trauma that do not heal are characterised by prolonged inflammation, elevated oxidative stress, the presence of bacteria, impaired angiogenesis and defective collagen remodelling^[13].

These abnormal conditions extend the normal phases of wound healing and increase the chance of infection^[40]. The plant *Nelumbo nucifera* contains a variety of bioactive phytochemicals for example flavonoids (such as quercetin and kaempferol) alkaloids (including nuciferine and neferine), polyphenols and polysaccharides all of which contribute to wound healing by means that are different from each other. Experimental studies have demonstrated that lotus extracts stimulate fibroblast growth, promote collagen production, accelerate keratinocyte movement and increase angiogenesis by raising the levels of vascular endothelial growth factor (VEGF). Moreover, the strong antioxidant activity of lotus phytochemicals activates the Nrf2/HO-1 signalling pathway thereby reducing oxidative stress and protecting cells from damage caused by free radicals.

The anti-inflammatory action of *Nelumbo nucifera* leads to a shorter inflammatory phase in the process of wound healing by inhibiting NF- κ B activation and decreasing the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Furthermore, its antibacterial components reduce the microbial load and help to promote tissue regeneration by stopping the growth of common wound-infecting microbes such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Since these effects occur together, lotus-based topical preparations might be useful as supplementary treatments for chronic wounds^[13].

7.2 Diabetic Ulcers

A serious side effect of diabetes mellitus is the occurrence of diabetic foot ulcers a condition characterised by oxidative stress, peripheral neuropathy, delayed collagen deposition, inadequate angiogenesis and persistent inflammation. Advanced glycation end products (AGEs) whose action is to inhibit fibroblast activity and extracellular matrix remodeling are formed more often under conditions of hyperglycemia^[11,16].

The antioxidant compounds present in *Nelumbo nucifera* enhance the body's own antioxidant defences by increasing the activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and as a result reduce the formation of reactive oxygen species (ROS). Moreover, because lotus phytochemicals increase VEGF^[16] expression they also promote angiogenesis which in turn improves the delivery of nutrients and oxygen to damaged tissues. In studies involving diabetic wounds, extracts of the lotus have been shown to promote collagen deposition, accelerate wound contraction increase the amount of hydroxyproline and encourage re-epithelialization. Moreover, the anti-inflammatory substances reduce the tissue damage caused by macrophages and prevent the excessive production of cytokines. These findings indicate that the antioxidant, anti-inflammatory, antibacterial and collagen-stimulating properties of *N. nucifera* have considerable therapeutic potential for the treatment of diabetic ulcers^[42,43].

7.3 Psoriasis

The preclinical findings support the use of *Nelumbo nucifera* pink flower oil in skin inflammation that resembles psoriasis. Based on the imiquimod-induced mouse model, PLO demonstrated tendencies in decreasing erythema, scales and skin thickness; however, the differences in the PASI score were not statistically significant. On the other hand, the results of the experiment were more obvious when there was a decrease in epidermal hyperplasia, reduction in keratinocyte proliferation, decreased levels of pro-inflammatory cytokines and alteration in the JAK2/JAK3/STAT3 pathway^[36].

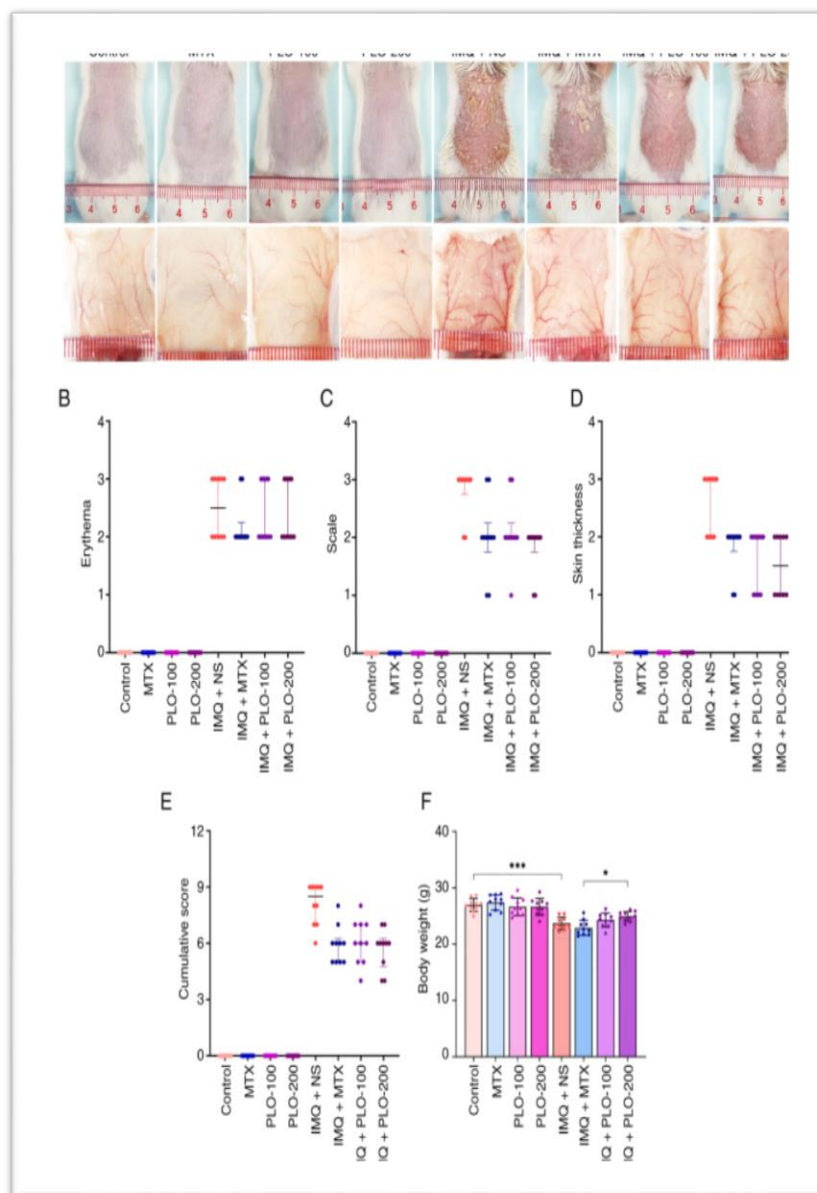


Figure 4. Effect of *Nelumbo nucifera* flower oil extract on imiquimod-induced psoriasis-like dermatitis. Reproduced from Jongsomchai et al ^[36].

7.4 Photoaging

Chronic exposure to ultraviolet (UV) radiation results in photoaging which includes oxidative stress, degradation of collagen, elastin breakdown, abnormal pigmentation and wrinkling. UV radiation activates matrix metalloproteinases (MMP-1, MMP-3, and MMP-9) causing degradation of collagen fibers in the dermis.

The potent photoprotection is attributed to the abundance of flavonoids and phenolic compounds found in *N. nucifera* which act as scavengers of ROS and upregulate endogenous antioxidant defense via the Nrf2 pathway. Lotus extract stimulates the synthesis of collagen through TGF- β /Smad signaling and suppresses the expression of UV-induced MMP. In addition, the anti-inflammatory effect helps maintain skin integrity through reduction of erythema and cytokines induced by UV radiation. The inclusion of lotus-derived phytochemicals into anti-aging skin products designed to prevent photoaging is justified by these biological activities^[5,16].

7.5 Acne

Overproduction of sebum, hyperkeratosis of follicles, colonization of *C. acnes* bacteria and chronic inflammation constitute acne vulgaris which is a complex skin inflammatory disease. Increased oxidative stress is also a contributing factor to the development of lesions^[44].

Due to the presence of flavonoids, alkaloids, tannins, and phenolic acids, *Nelumbo nucifera* demonstrates antibacterial activity against bacteria that can cause acne. It reduces the amount of biofilms produced and stops the development of microorganisms. Production of TNF- α , IL-1 β , IL-6 and other inflammatory mediators responsible for the disease pathogenesis is decreased by phytochemicals with anti-inflammatory properties^[44,45].

Furthermore, its antioxidant properties reduce the oxidative stress in surrounding tissues and sebaceous glands. Besides that some compounds found in lotus can improve the function of skin barrier and regulate the amount of sebum produced. Therefore, *Nelumbo nucifera* can be used as an ingredient in natural anti-acne gels, lotions and face washes.

8. Formulation Strategies and Delivery Systems

Although *Nelumbo nucifera* is effective due to its potent antioxidant, anti-inflammatory, antibacterial and wound healing properties, poor aqueous solubility, phytochemical instabilities, oxidizability and poor skin penetration capabilities reduce its medical utility. Most bioactive components including flavonoids, alkaloids and phenolics degrade readily when exposed to light, oxygen and high temperatures. As a result, advanced formulation strategies need to be adopted to improve the stability, bioavailability, release mechanisms and efficacy of plant-derived compounds^[1,2].

Some of the new drug delivery systems that have been utilized in an effort to improve the topical delivery of the phytochemicals isolated from plants include hydrogels, nanofibers, nanoparticles, liposomes, nano emulsions and polymeric matrices. Such methods preserve a moist environment at the site of application, increase skin penetration provide sustained delivery and protect the unstable phytochemicals from degradation^[6].

8.1 Traditional Topical Formulations

Nelumbo nucifera flower, leaf, seed and rhizome extracts have been used in pastes, ointments, lotions and cosmetic preparations to heal minor cuts and skin inflammation. Contact between the plant extract and the skin surface for a prolonged period of time is facilitated through these preparations and hence, it helps in delivering localized anti-inflammatory and antioxidative properties. Extract of the lotus flower has also been used in many cosmetic preparations owing to its anti-aging, soothing and moisturizing effects^[5].

8.2 Nanoformulation Approaches

There has been very little research conducted on nanoformulations involving *Nelumbo nucifera* even though the use of nanoformulations has dramatically improved the topical delivery of various phytochemicals derived from herbs. The research that has been carried out shows that flavonoids and polyphenols from the lotus can possibly be delivered in liposomes or nanoparticles for better skin penetration, stability and protection against oxidation. More formulation studies are needed prior to applying these delivery methods to a clinical setting^[46].

8.3 Cosmetic and Dermatological Applications

Cosmetics such as creams, lotions, face masks, cleansers and serums have been found to incorporate extracts from the *Nelumbo nucifera* species. In an effort to reduce oxidative stress, hydrate the skin, make it supple and prevent photoaging, lotus plant chemicals with their anti-inflammatory and antioxidant properties are utilized in these cosmetics. Anti-aging skin care preparations contain lotus flower extracts due to the proven ability of these extracts to inhibit matrix metalloproteinase activity and oxidative damage^[5,47,48].

9. Safety, Toxicity and Regulatory Considerations

9.1 Safety Profile

Lotus (*Nelumbo nucifera*) has been utilized as both a food and medicinal herb for many years which implies that it has a good safety record. The different parts of the lotus plant such as flowers, leaves, seeds, rhizomes and embryos have been widely applied in traditional medicine and functional foods. As per the present experimental findings the lotus extracts and their major active compounds such as flavonoids and alkaloids (neferine, nuciferine, liensinine and isoliensinine) exhibit relatively low toxicity when used at pharmacological concentrations. Nonetheless, there is limited literature on well-conducted clinical trials on safety in humans and most of the existing safety literature is based on in vitro and animal studies^[49,50].

9.2 Toxicological Evidence

Nelumbo nucifera plant extracts and chemical isolates have been tested for their toxicities in several preclinical studies. Preclinical evaluations on acute and subchronic toxicity studies revealed that there is neither mortality nor any significant behavioral changes when the plant extracts or isolates are administered in relatively high concentrations^{5,51}. For example, in animal studies the oral median lethal dose of aqueous leaf extract of *N. nucifera* was greater than 5000 mg/kg. The lotus seed extracts were also noted to be safe in repeated-dose studies in rats and dogs without any toxicity symptoms at the tested concentration levels. This indicates that the safety window of *Nelumbo nucifera* products used in experiments is wide. However, carcinogenicity, reproductive toxicity and chronic toxicity studies are not sufficient yet⁵².

9.3 Regulatory Considerations

There is no official approval from major regulatory agencies such as the US FDA and the European EMA of any *N. nucifera* preparation to be used as a prescription drug for treating wounds. Unlike medications, most preparations made from lotus flowers are classified as herbal medicines, dietary supplements or cosmetics. Extracting and characterizing the phytochemicals of the lotus flower through standardized extract extraction and testing its safety and efficacy through randomized clinical trials should first be carried out^[55].

10. Conclusion

Nelumbo nucifera is considered an effective medicinal herb due to the presence of multiple phytochemicals, diverse biological actions and potential applications for wound healing and protection of the skin. This plant contains active ingredients that have antioxidant, anti-inflammatory, antibacterial, angiogenic and collagen-stimulating properties that contribute to faster tissue regeneration and treatment of various skin diseases. However, due to the lack of standardized forms and high-quality human studies, there are obstacles to clinical translation despite good results obtained in preclinical experiments. In order to prove the safety and effectiveness of the use of *Nelumbo nucifera* in the field of dermatology, future research should focus on the standardization of extracts and advanced drug delivery systems.

11. Limitation

- Due to the limited human clinical trials most of the literature is based on in vitro tests and animal experiments.
- It is difficult to compare various experiments because of the large diversity in phytochemicals due to different parts of plants, geographical location, harvest season and extraction process.
- Lack of quality control measures and standardization in the extraction process exists^[62,63].
- Poor understanding of pharmacokinetics, toxicity, skin safety, appropriate dosage and drug-herb interactions remains^[64].
- Limited research is conducted in relation to complex formulations specifically developed for *Nelumbo nucifera* like hydrogels, nanoparticles, liposomes and nanofiber-based wound dressings.
- As a result of limited clinical efficacy and safety trials, regulatory approval is hindered^[68,69].

12. Future Perspectives

Future research should aim at conducting well-designed clinical trials to establish the safety and efficacy of *Nelumbo nucifera* for use in the treatment of wound healing and skin conditions. It is important to develop standardized approaches to plant extraction, phytochemical profiling and quality control in order to make the treatment results repeatable and reliable. Moreover, there is an opportunity to increase the stability, penetration and bioavailability of active compounds derived from the plant by developing advanced technologies of topical drug delivery such as hydrogels, nanoparticles and nanoemulsions. The efficient clinical application of dermatological agents based on *Nelumbo nucifera* will be ensured by further research on the mechanisms involved.

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