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PHARMACOGNOSTIC INSIGHTS INTO THE ANTI-INFLAMMATORY AND ANALGESIC POTENTIAL OF *Nelumbo nucifera* LEAF EXTRACT

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ABSTRACT

Nelumbo nucifera Gaertn., known as the sacred lotus, is an aquatic medicinal plant with significant traditional, cultural, and therapeutic importance in various Asian medical systems. Modern research has uncovered a range of bioactive compounds, such as aporphine alkaloids (like nuciferine), flavonoids (including quercetin derivatives and hyperoside), phenolic acids, and polysaccharides, which contribute to its antioxidant and anti-inflammatory properties (Bishayee et al., 2022; Tungmunnithum et al., 2018). Recent molecular studies show that lotus leaf extracts influence key inflammatory pathways like NF-κB, MAPK, and JNK, which help reduce the levels of pro-inflammatory substances such as TNF-a, IL-6, and nitric oxide (Liu et al., 2014; Kim et al., 2022). This review presents an overview of the botanical features, chemical composition, and pharmacological effects of N. nucifera leaves, with a focus on the pathways related to inflammation and pain management.

KEYWORDS: *Nelumbo nucifera; Lotus leaf extract; Flavonoids; Hyperoside; Aporphine alkaloids; Anti-inflammatory activity; Analgesic potential; NF-κB signaling pathway; MAPK pathway; Oxidative stress; Phytochemical standardization*

1. INTRODUCTION

Inflammation is a natural body response to infection, injury, or oxidative stress, but if it becomes chronic, it can lead to pain and serious health problems (Wang et al., 2023). There is growing interest in natural anti-inflammatory treatments due to the side effects of synthetic NSAIDs (Bishayee et al., 2022).

Nelumbo nucifera belongs to the family Nelumbonaceae and has been widely used in Ayurveda, Traditional Chinese Medicine, and Unani systems to treat fever, bleeding issues, diarrhea, and inflammation (Chen et al., 2019; Sheikh, 2014). Modern studies support these traditional uses and show that the plant has strong antioxidant and anti-inflammatory properties (Yang et al., 2024).

Among the different parts of the plant, the leaves are especially rich in flavonoids and alkaloids, which are known for their anti-inflammatory properties (Liu et al., 2014; Park et al., 2017). Therefore, the focus of this review is on the leaf extract.

2. BOTANICAL DESCRIPTION

Nelumbo nucifera is a long-lived aquatic plant known for its large, round, leaf-like structures with a waxy surface that makes them water-repellent, which helps it adapt to its environment (Yang et al., 2024). The plant is commonly found in India, China, Japan, and Southeast Asia and grows well in freshwater areas like ponds and lakes (Chen et al., 2019). The leaves are circular with veins spreading out and long stems that grow from the rhizome (Sharma et al., 2017).

3. PHYTOCHEMICAL CONSTITUENTS OF N. NUCIFERA LEAVES

Studies show that lotus leaves contain a variety of bioactive substances that can be broadly grouped into different categories:

3.1 Alkaloids

The primary active compounds in lotus leaves are aporphine alkaloids. Nuciferine, the most studied of these, has anti-inflammatory, antioxidant, and neuroprotective effects (Ren et al., 2024; Zhao et al., 2023). Research indicates that nuciferine reduces the activity of p38 MAPK and NF-κB pathways, which helps lower the production of inflammatory cytokines (Kim et al., 2022). It also plays a role in immune signaling that affects the body's response to oxidative stress (Zhu et al., 2022).

3.2 Flavonoids

Lotus leaves are rich in flavonoids like quercetin, hyperoside, and quercetin-3-O-glucuronide (Tungmunnithum et al., 2018). These compounds have strong antioxidant capabilities by neutralizing free radicals and preventing fats from breaking down (Wang et al., 2023). Flavonoids extracted from lotus have been shown to have significant anti-inflammatory effects by reducing nitric oxide in laboratory models of macrophages (Li et al., 2017).

3.3 Phenolic Compounds and Polysaccharides

Phenolic acids and polysaccharides in lotus leaves contribute to antioxidant and liver-protective effects (Wang et al., 2023; Yang

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et al., 2019). Polysaccharides have also been found to influence immune responses (Wang et al., 2023).

4. ANTIOXIDANT POTENTIAL OF LOTUS LEAF

Oxidative stress is closely linked to the activation of inflammation (Wang et al., 2023). Extracts from lotus leaves show strong abilities to remove free radicals, thanks to their high levels of flavonoids and phenolic compounds (Li et al., 2021). Lab tests show that lotus leaf extract lowers the production of harmful free radicals inside cells and improves the function of enzymes like superoxide dismutase (SOD) (Lee et al., 2015; Li et al., 2021). By reducing oxidative stress, lotus leaves indirectly prevent tissue damage caused by inflammation (Liu et al., 2014).

5. ANTI-INFLAMMATORY MECHANISMS OF NELUMBO NUCIFERA LEAF

Inflammation happens when the body's immune system becomes overactive. This leads to increased production of harmful substances called reactive oxygen species (ROS) and the release of pro-inflammatory signals like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), nitric oxide (NO), and prostaglandins (Wang et al., 2023). Many studies show that the extract from Nelumbo nucifera leaves can help reduce these inflammatory signals by affecting the pathways inside cells.

5.1 Inhibition of NF-κB Signaling Pathway

The NF-κB pathway plays a key role in controlling the expression of genes involved in inflammation. When this pathway is activated, it increases the production of cytokines, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) (Liu et al., 2014). Liu et al. (2014) found that lotus leaf extract significantly reduced the activation of NF-κB caused by lipopolysaccharide (LPS) in macrophage cells. The extract lowered the movement of the NF-κB p65 protein into the cell nucleus and reduced the production of iNOS and COX-2, which in turn cut down nitric oxide levels. Nuciferine, a compound in lotus leaves, also inhibits NF-κB activation, which helps lower TNF-α and IL-6 levels (Kim et al., 2022). These findings suggest that the alkaloids and flavonoids in lotus leaves help reduce the expression of inflammatory signals through transcriptional suppression.

5.2 Modulation of MAPK and JNK Pathways

Mitogen-activated protein kinases (MAPKs), including p38 MAPK and JNK, help regulate how cells respond to inflammation. Liu et al. (2014) showed that lotus leaf extract stops the activation of JNK and p38 MAPK in macrophages, leading to a decrease in inflammatory cytokine production. Nuciferine was also found to block p38 MAPK activation, which helps reduce inflammation (Kim et al., 2022; Ren et al., 2024). By inhibiting both the NF-κB and MAPK pathways, lotus leaf extract has a broad anti-inflammatory effect.

5.3 Suppression of Pro-Inflammatory Cytokines

Many studies have confirmed that lotus leaf extracts can reduce the levels of cytokines involved in inflammation. Lee et al. (2019) observed that ethanolic extracts from lotus leaves significantly reduced TNF-α and IL-6 production in immune cells. Zhou et al. (2013) identified active anti-inflammatory compounds in different parts of the lotus plant and found that leaf extract strongly inhibits the release of inflammatory signals. Li et al. (2021) also showed that lotus leaf extract decreases inflammatory markers in cells under oxidative stress, linking its antioxidant and anti-inflammatory effects.

5.4 Antioxidant-Mediated Anti-Inflammatory Action

Oxidative stress worsens inflammation by increasing ROS, which triggers the activity of certain proteins that drive inflammatory responses (Wang et al., 2023). Flavonoids in lotus leaves, such as hyperoside and quercetin derivatives, are strong ROS scavengers (Tungmunnithum et al., 2018). Hyperoside helps reduce inflammation by regulating the body's antioxidant defenses (Wang et al., 2023). Lee et al. (2015) found that lotus leaf extract boosts the activity of antioxidant enzymes and reduces oxidative damage, which helps suppress inflammatory signals.

6. ANALGESIC RELEVANCE OF ANTI-INFLAMMATORY ACTIVITY

Pain is often linked to the release of inflammatory mediators, especially prostaglandins and cytokines (Bishayee et al., 2022). By reducing COX-2 expression and cytokine levels, lotus leaf extract may ease the sensitivity of pain-sensing nerves. Nadvi et al. (2023) found that lotus-based treatments showed strong anti-inflammatory and pain-relieving effects in experimental models. Additionally, nuciferine might help ease inflammatory pain by lowering cytokine levels (Ren et al., 2024). Thus, the pain-relieving potential of lotus leaf extract comes from its ability to inhibit NF-κB, suppress MAPK pathways, reduce cytokines, boost antioxidant activity, and lower nitric oxide production. These effects together support its potential use in topical products for pain relief.

7. COMPARATIVE ANALYSIS WITH STANDARD ANTI-INFLAMMATORY AGENTS

Several studies have compared lotus extracts with standard anti-inflammatory drugs.

Lee et al. (2019) found that lotus leaf extract and standard reference compounds had similar effects in inhibiting inflammatory signals in laboratory tests.

Keshri et al. (2024) made a topical anti-inflammatory gel with herbal extracts and reported good results in reducing swelling compared to standard treatments.

Although lotus extracts may not be as powerful as synthetic NSAIDs in cases of severe inflammation, their multi-target approach and lower risk of side effects make them a promising alternative or support treatment (Bishayee et al., 2022).

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8. SAFETY AND TOXICOLOGICAL CONSIDERATIONS

The available research shows that lotus leaf extracts are generally safe at doses used for medical purposes (Sahu et al., 2024).
However, more long-term studies and skin safety tests are needed to fully understand the risks and benefits (Ren et al., 2024).

9. EXTRACTION STRATEGIES AND PHYTOCHEMICAL OPTIMIZATION

The effectiveness of Nelumbo nucifera leaves in terms of their medicinal properties largely depends on the method used to extract the compounds and the type of solvent used.

Alkaloids like nuciferine dissolve better in moderately polar organic solvents, while flavonoid glycosides are more effectively extracted using hydroalcoholic solutions (Tungmunnithum et al., 2018).

Liu et al. (2025) showed that using ultrasound to assist in the extraction process significantly increases the amount of flavonoids obtained from lotus leaves compared to traditional methods like soaking. Similarly, Zhang et al. (2022) used bioaffinity ultrafiltration techniques to identify active anti-inflammatory components from lotus leaf extracts, which highlights the importance of optimizing extraction methods to improve the biological activity of the compounds.

Studying different solvents suggests that hydroalcoholic extracts may capture a wider range of phytochemicals, including both alkaloids and flavonoids, potentially leading to a more effective anti-inflammatory effect (Park et al., 2017).
Therefore, choosing the right solvent is crucial for achieving the best therapeutic results.

10. ANALYTICAL STANDARDIZATION AND BIOACTIVE QUANTIFICATION

Standardization helps ensure that herbal products are consistent and reliable in their effects. High-performance liquid chromatography (HPLC) is often used to measure the levels of nuciferine and flavonoids in lotus leaf extracts (Sharma et al., 2017).

Studies on how the structure of a compound relates to its activity show that the aporphine structure of nuciferine helps in reducing inflammation by inhibiting certain signaling pathways (Zhao et al., 2023).

Accurately measuring key compounds such as nuciferine and hyperoside is essential for ensuring the reliability of the medicinal effects (Ren et al., 2024). In addition, antioxidant tests like DPPH and ABTS are commonly used to link the amount of phenolic compounds to their biological activity (Li et al., 2021).

11. RESEARCH GAPS AND FUTURE PERSPECTIVES

Even though there is promising evidence from preclinical studies, there are still several areas that need more research:

- Not enough studies on how well the compounds can penetrate the skin for topical use.
- Not enough human clinical trials to evaluate the anti-inflammatory effects.
- The need for standardized procedures for extraction.
- A lack of long-term studies on the safety of topical applications.

Future research should focus on standardized hydroalcoholic extraction methods, accurate measurement of key compounds, and controlled experiments to ensure consistent therapeutic outcomes (Sahu et al., 2024).

12. CONCLUSION

Nelumbo nucifera leaves are a rich source of bioactive compounds like alkaloids and flavonoids that show strong antioxidant and anti-inflammatory effects. Studies have confirmed that these compounds can inhibit pathways such as NF-κB, MAPK, and JNK, which reduce the activity of pro-inflammatory substances like TNF-α, IL-6, nitric oxide, and COX-2 (Liu et al., 2014; Kim et al., 2022). The multi-target nature of lotus leaf extracts supports their use in developing topical anti-inflammatory and pain-relief products. However, to turn these findings into actual therapeutic products, it is necessary to carry out thorough standardization, optimize formulations, and conduct clinical trials.

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