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Synthesis of Literature on Antioxidant Activity and Safety of *Seroja* (*Nelumbo nucifera* Gaertn.) Plant Relative to Pharmacological Potential

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ABSTRACT

Nelumbo nucifera Gaertn. (Nelumbonaceae), known as the sacred lotus, is widely distributed across Asia and has long been used as food and traditional medicine, although its utilization in Indonesia remains largely ornamental. Interest in its antioxidant potential and its role as a source of bioactive compounds has increased. This review aims to systematically summarize in vitro and in vivo evidence on the antioxidant activity of N. nucifera, identify key plant parts and active compounds, compare extraction and assay methods, and evaluate preclinical bioactivity and safety. Literature searches in Google Scholar, NCBI, and PubMed using the keywords "Seroja" or "Nelumbo nucifera" and "antioxidant" yielded 27 eligible articles. Antioxidant activity is mainly attributed to flavonoids, alkaloids, and phenolic compounds, particularly quercetin and neferine. Flowers and seeds generally show higher in vitro antioxidant capacity, whereas leaves and rhizomes are more frequently studied in vivo. Variations in extraction and assay methods contribute to heterogeneous results. Preclinical data suggest a favorable acute safety profile; however, long-term toxicity data remain limited, and no clinical trials have been conducted. Overall, N. nucifera shows promising antioxidant potential, but further standardized toxicological studies and clinical trials are needed to support its therapeutic use.

INTRODUCTION

Seroja (*Nelumbo nucifera* Gaertn.) is an aquatic plant of the family *Nelumbonaceae* and the order *Proteales* widespread in Asia and Oceania (Tungmunnithum et al., 2018). The plant is known by various names, such as padma, Chinese seroja, and Indian seroja, and grows naturally in muddy shallow waters such as swamps and ponds. In Indonesia, *seroja* is commonly used as an ornamental plant. In contrast, in other Asian countries, including

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China, India, Japan, Thailand, and Korea, all parts of the plant have long been used as food and traditional medicine.

Various studies report that *N. nucifera* has a wide spectrum of pharmacological activities, including antioxidant, anti-inflammatory, hepatoprotective, immunomodulatory, antibacterial, antiviral, antidiabetic, antiobesity, and anticancer activities, as well as protective effects on the circulatory and reproductive systems. The activity is associated with the presence of a wide variety of bioactive compounds, especially flavonoids, alkaloids, and phenolic compounds, which are scattered on the flowers, seeds, leaves, and rhizomes of plants (Tungmunnithum et al., 2018).

In recent years, attention to the antioxidant potential of medicinal plants, including *N. nucifera*, has increased alongside the recognition of oxidative stress in the pathogenesis of various degenerative diseases, such as cancer, cardiovascular disease, and metabolic disorders. Study In vitro and in vivo suggests that the bioactive compounds in *seroja* can capture free radicals and modulate the endogenous antioxidant system, thereby contributing to a decrease in oxidative stress (Li et al*.,* 2021; Chen et al*.,* 2019; You et al*.,* 2018; Harishkumar & Selvaraj, 2020; Priya et al*.,* 2018; Yang et al*.,* 2023).

In addition to the therapeutic potential, the safety aspects of *N. nucifera* are also an important concern. Early toxicology studies showed that seed and rhizome extracts were relatively safe at certain doses in animal models. However, long-term safety data and clinical evidence in humans are still limited, so further evaluation is needed before broader therapeutic applications can be recommended (Priya et al., 2018).

Although several studies have reported on the antioxidant activity of *N. nucifera*, the available scientific evidence is still heterogeneous and fragmented, with variations in plant parts, extraction methods, antioxidant test types, and experimental models. In addition, studies that integrate bioactivity potential with preclinical safety aspects are still limited. Therefore, this literature review aims to systematically summarize the results of in vitro and in vivo research on the antioxidant activity *of N. nucifera*, identify the most contributing parts of the plant and active compounds, compare extraction and testing methods, and examine potential bioactivity and safety aspects based on available preclinical data.

RESEARCH METHODS

Study Design

This literature review is a systematic study that aims to collect and analyze secondary data on the antioxidant potential and safety aspects of *N. nucifera*. Literature searches were conducted on three main online databases, namely Google Scholar, PubMed, and NCBI, with a PICO (Population, Intervention, Comparison, Outcome) framework approach. The study population included in vitro, in vivo, and clinical studies evaluating different parts of the *seroja* plant, including roots/rhizomes, seeds, leaves, and flowers. The intervention studied was the antioxidant activity of the plant part, with outputs in the form of potential antioxidant bioactivity and preclinical safety profile. The flow of article selection is presented in **Figure 1**.

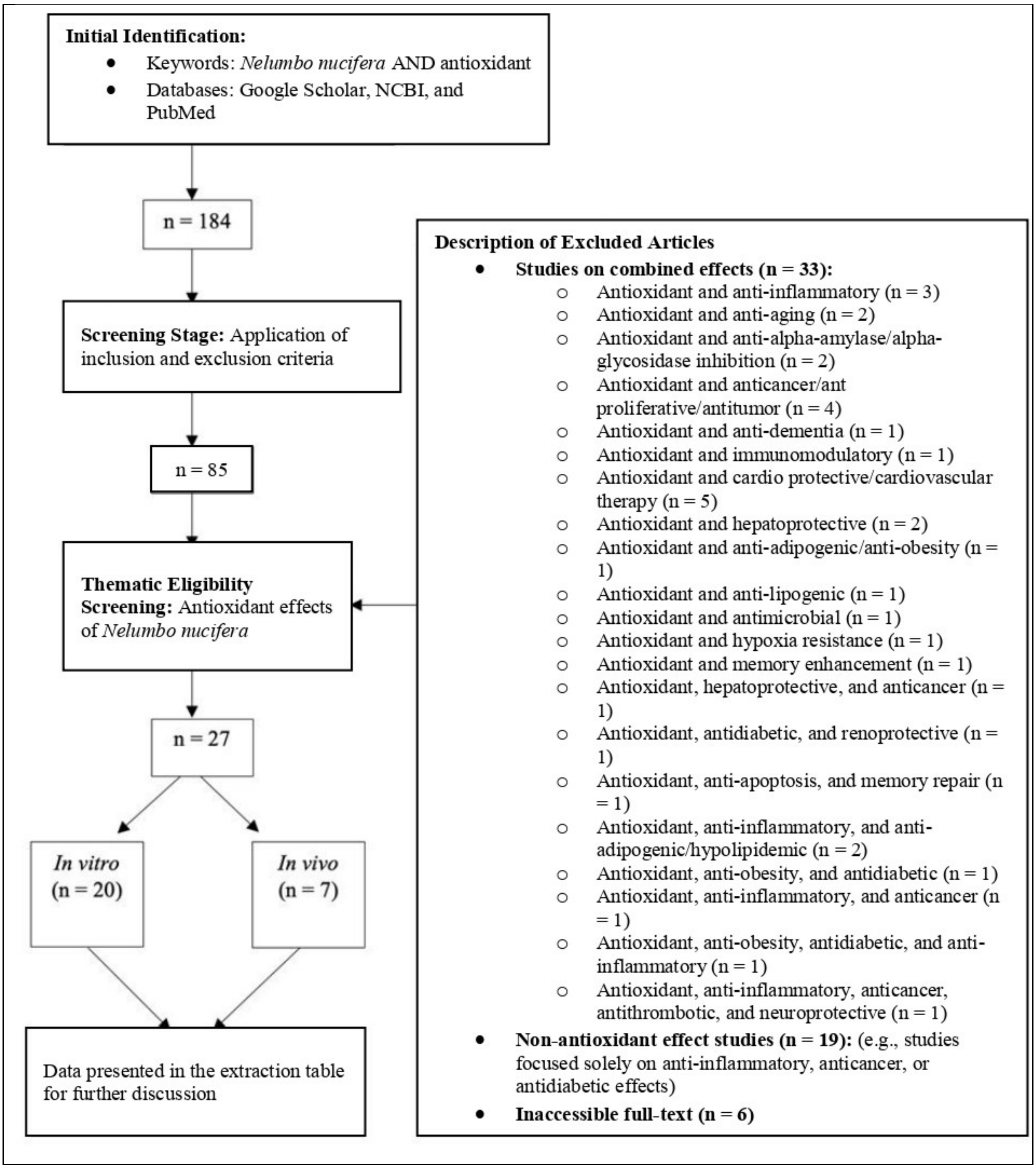

Figure 1. Article selection flow chart
Source: Author's document

Data Collection

Article searches were conducted using the keywords "Seroja" or "*Nelumbo nucifera*" and "antioxidant." Included studies were primary research articles published between 2014–2024, written in English or Indonesian, and available in full text. Reviews, duplicates, irrelevant studies, and articles without full-text access were excluded.

Data Analysis

Article selection is carried out in stages: title and abstract screening, followed by full-text evaluation. A total of 27 articles that met the inclusion criteria were analyzed descriptively to assess antioxidant activity, the part of the plant responsible for the effect, and safety aspects related to the therapeutic use of *N. nucifera*.

RESULTS AND DISCUSSION

The literature indicates that antioxidant activity of *N. nucifera* has been largely evaluated through in vitro and in vivo studies, with no reported clinical trials in humans.The experimental approach used includes measurement of total antioxidant capacity, such as Total Polyphenol Content (TPC) and Total Flavonoid Content (TFC), free radical scavenging activity test using DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid) methods, reduction power test via Ferric-Reducing Power Assay (FRAP), as well as evaluation of endogenous antioxidant systems, including catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH) in cell and animal models. The data obtained were analyzed thematically in accordance with the research objectives, including the identification of active compounds, the contribution of plant parts, extraction methods, potential clinical applications, and safety aspects of use.

Botanical Characteristics, Traditional Uses, and Biopharmacological Profile *of Nelumbo nucifera* Gaertn.

N. nucifera is an aquatic plant of the family *Nelumbonaceae*, widespread in Asia and Oceania, and has long been used as a food and traditional medicine. Almost all parts of the plant, including leaves, flowers, seeds, and rhizomes, can be utilized, with rhizomes being the most consumed part as a functional food due to their high mineral content (Tungmunnithum et al., 2018). This plant grows best in muddy, waterlogged environments and can be propagated by rhizomes and seeds. However, it has a morphological resemblance to the lotus (*Nymphaea lotus*); *N. nucifera*, however, has a different taxonomy and belongs to the order *Proteales*.

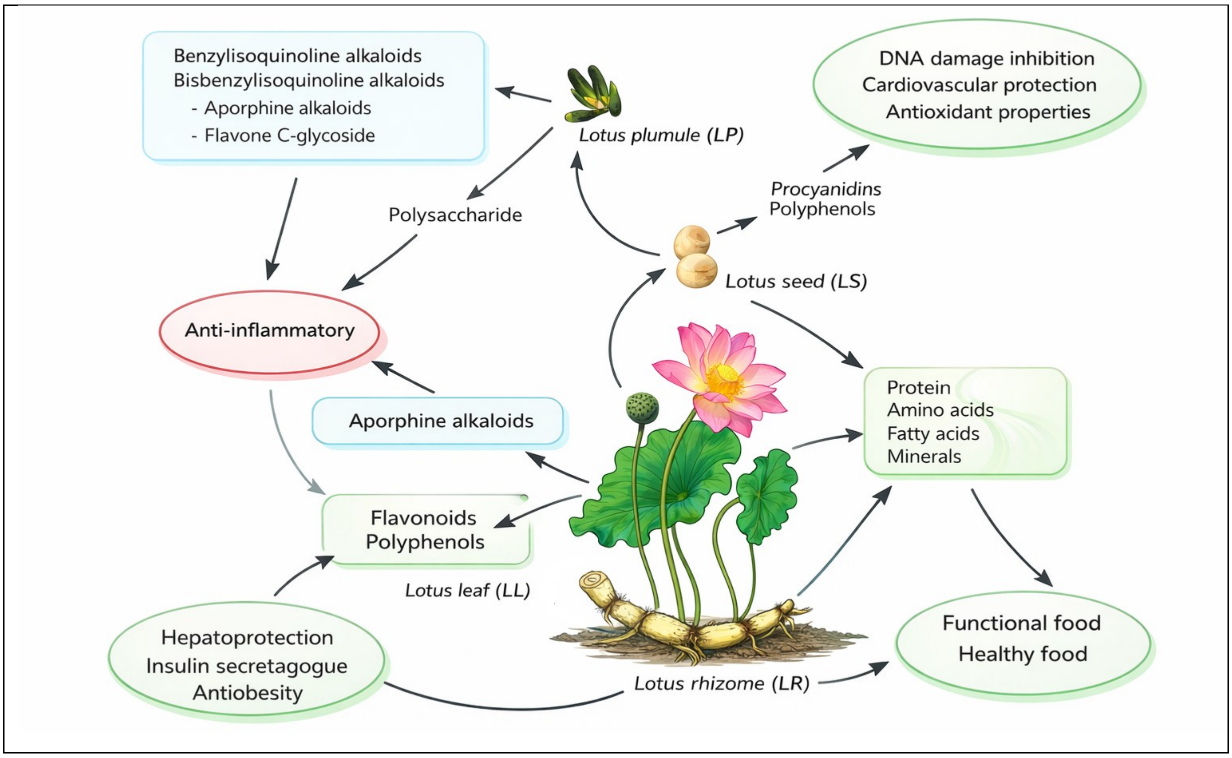

Figure 2. Details of plant parts and active compounds of *N. nucifera*
Sources: Zhou et al. (2013) re-illustrated

Each part of the *seroja* plant exhibits a specific therapeutic potential (**Figure 2**). Various studies report a broad spectrum of biopharmacological activity, including antioxidant, anti-inflammatory, hepatoprotective, antidiabetic, anticancer, and immunomodulatory effects, as well as cardiovascular effects. This activity is related to the content of major phytochemicals, especially flavonoids, alkaloids, triterpenes, and phenolic compounds. The literature review shows that roots and leaves are the most studied parts of plants (10 and 7 studies, respectively), followed by seeds (6 studies), flowers (5 studies), and fruits and tubers, each reported in one study. In terms of bioactivity, antioxidant activity was the most dominant reported (71 publications), followed by anti-inflammatory activity (15 publications) and anticancer or antitumor activity (14 publications). These findings confirm the potential of *N. nucifera* as a source of bioactive natural materials relevant for the development of therapeutic applications based on antioxidant activity (Ma et al., 2023; Chen et al., 2019; Shen et al., 2019; Sranujit et al., 2021; Sim et al., 2019; Tungmunnithum et al., 2022).

Antioxidant Active Compounds in *N. nucifera*

The results of the literature review summarized in Table 1 show that the antioxidant activity of *N. nucifera* is mainly associated with flavonoids, phenolics, and alkaloid compounds.

Table 1. Plant parts and active compounds contained

No.	Plant parts	Plant extracts	Tools for identification methods	Compounds contained
1	Root	Optimization of the extraction of antioxidant components from *seroja* root. Slices of fresh *seroja* root are soaked in a melatonin solution. Treatment of *seroja* root with oxalic acid to increase the release of active compounds. Enzymatic browning to modify the quality of the *seroja* root slices. Methanol extract of *seroja* root as a concentrate of bioactive compounds. *Seroja* root powder is obtained through drying and grinding.	3-(4,5-dimethyla-zol-2-yl)-2,5-diphenyltetrazolium bromide (MTT)	Flavonoids Terpenoids Alkaloids Tannins Phenylpropanoid Tyrosine Phenylalanine Lignans Phenolics **Neferin***
2	Flowers (petals, pollen)	Water and ethanol extract from *N. nucifera* buds Coarse extraction and fractionation of bee pollen Extraction of flavonoids from stamens of *N. nucifera* by the liquid-solids method Ethanol extract of the stamens of *N. nucifera*	Ultrahigh-performance liquid chromatography (UPLC) High-performance liquid chromatography (HPLC)	Flavonoids: **Quercetin***, Gallic acid, catechin, epicatechin, p-hydroxybenzoic acid, kaempferitrin, flavonoid diglycoside, flavonoid monoglycoside, myricetin Phenolics Tannins Isorhamnetin
3	Leaves	Extraction using hot water and precipitation with ethanol Preparation of *N. nucifera* leaf powder with measurable phenolic content Liquid extraction using *N. nucifera* leaf tea water Extraction of multi-stage ethanol on *N. nucifera* leaves using the maceration method.	HPLC Analysis	Pectic polysaccharides Phenolics: kaempferol, **quercetin*** (including quercetin 3-O-beta-glucuronide), isoquercetin, luteolin, catechin, orientin, hyperoside, rutin Ethylene **Nuciferin*** Pigments
4	Seeds (embryo)	Fractionation of flavonoids from *N. nucifera* seed embryos using macroporous resin chromatography Soluble fractions of dry materials	High-performance liquid chromatography (HPLC) combined with tandem mass spectrometry (MS/MS) Proteomics analysis using Tandem Mass Tag (TMT) Parallel reaction monitoring	Abscisic acid Fatty acids Terpenoids Steroids Flavonoids: Luteolin, Schaftoside, Lonicerin Alkaloids: **Neferin***, **Norcoclaurine***, isolysinin, liensinin, armepavin, flavonoid C-

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No.	Plant parts	Plant extracts	Tools for identification methods	Compounds contained
				glycoside, flavonoid D-glycoside **Nelumbosida A-D***
5	Fruit	-	-	**Neferin*** Procyanidin
6	Red rhizome	Rhizome powder, *N. nucifera* Rhizome decoction extracts consisting of primary compounds include straight-chain aliphatic compounds, cyclic alkane compounds, and aromatic hydrocarbon compounds.	Transcriptomic analysis to study gene expression thoroughly Soluble fractions of dry materials	Phenolic: pentose phosphate shikimate Flavonoids Phenylpropanoid A mixture of straight chains, cyclic alkanes, and aromatic hydrocarbons Methylated derivatives Hydroxyl butyl butyl Dimethyl disulfide Gallic acid

*Compounds shown in **bold** represent signature metabolites of *N. nucifera* consistently reported in the retrieved studies.
Source: Author's Document

Flavonoids such as quercetin, kaempferol, luteolin, catechin, and their derivatives are consistently reported in the leaves, flowers, and seeds. In addition, *N. nucifera* contains characteristic alkaloids. These include neferine, nuciferine, liensinine, and isoliensinine, which are mainly found in the seed and embryo (Tungmunnithum et al., 2018; Priya et al., 2018).

Among the various compounds identified, neferine and quercetin, along with their glycosides, appear to be the main candidates as antioxidants. These compounds not only showed significant free radical scavenging capacity in vitro, but are also reported to activate endogenous antioxidant systems through the Nrf2/HO-1 and PI3K/Akt signaling pathways in the model in vivo and in mobile. It indicates that the antioxidant mechanism of *N. nucifera* is not solely a direct chemical reaction, but also involves adaptive molecular regulation in the cell's response to oxidative stress (Khan et al., 2022).

Parts of Plants That Contribute to Antioxidant Activity and Their Range of Activity

Based on the results of in vitro and in vivo tests (**Tables 2** and **3**), *N. nucifera* flowers and seeds showed the highest antioxidant activity in vitro, especially using the DPPH, ABTS, and FRAP methods. In contrast, in vivo studies use more leaves and rhizomes due to their high availability, better stability of extracts, and ease of administration in test animals.

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Table 2. In vivo test summary table of *N. nucifera* as an antioxidant agent

No.	Subject	Extract	Effects
1	Old mice were induced with a combination of D-Galactose/LPS of 30 mg/kg body weight (bb) and 3 µg/kg bb, respectively.	A total of 20 grams of dried lotus leaves (produced in Anhui, China) is mashed, then 100 mL of 70% ethanol is added with a ratio of ingredients to solvent of 1:10 (w/v). The mixture is incubated for 3 hours in a water bath at 60°C. After cooling, the solution is filtered to obtain a liquid fraction as the first extract. The filtered residue is recovered by a similar method, and the two extracts obtained are then combined to produce a crude extract of lotus leaf flavonoids.	Lotus leaf flavonoid extract (LLFE) has been shown to reduce oxidative damage and edema in injured mouse models. LLFE inhibits elevated levels of tissue-damage marker enzymes, such as aspartate transaminase (AST), alanine transaminase (ALT), malondialdehyde (MDA), and nitric oxide (NO). On the other hand, LLFE increases endogenous antioxidant activity, as evidenced by elevated levels of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GSH-Px). In addition, the mRNA expression of genes related to antioxidant activity showed patterns consistent with those biochemical outcomes.
2	Sprague–Dawley male mice with type 2 diabetes were induced using a high-fat diet (HFD) followed by streptozotocin (STZ) injection. Mouse glomerular mesangial cells (MES-13) were treated with a high concentration of glucose (HG), which is 25 mM of glucose.	The lotus leaf *N. nucifera* was obtained from a local farmer in Tainan, Taiwan. Lotus leaf extract (NLE) is extracted and purified from dried leaves, then analyzed and identified using the HPLC-UV method.	*N. nucifera* (NLE) leaf extract shows potential to improve kidney injury due to diabetes by increasing antioxidant enzyme activity in kidney tissue. Treatment with NLE significantly lowered levels of malondialdehyde and 8-hydroxy-2-deoxyguanosine, and increased serum insulin levels. It increased the expression of the enzymes superoxide dismutase, catalase, and glutathione peroxidase, as well as the glutathione content in the kidneys. Histological observations also showed that NLE inhibited Bowman's capsule dilation, indicating a renoprotective effect in diabetes. These findings suggest that NLE has the potential to exert antidiabetic and renoprotective effects against diabetes induced by high-fat diets (HFD) and streptozotocin (STZ), at least in part through antioxidant pathways.
3	The protective activity of a mixture of water and ethanol extracts of Houttuynia cordata Thunb., leaves of *N. nucifera* and seeds of Camellia sinensis (HNC) has been evaluated in mice of the C57BL/6 strain.	*Seroja* leaves	Mice treated with HNC showed a significant decrease in triglyceride levels, decreased activity of the CYP2E1 enzyme, as well as an increase in antioxidant enzyme activity and lipogenic mRNA levels. These findings indicate that HNC has the potential to be a hepatoprotective candidate against ethanol-induced oxidative damage, through its mechanism of increased antioxidant activity and antilipogenic effects.
4	Pretreatment of embryonic-derived mouse cardiomyocytes (H9c2) with the phytochemical compound lotusine showed potential in preventing oxidative stress mediated by doxorubicin (DOX).	Lotusin	Increased levels of endogenous antioxidants, accompanied by decreased lipid peroxidation, were observed in cells treated with lotusine. In contrast, decreased antioxidant levels and increased lipid peroxidation occurred in cells exposed to doxorubicin. The decrease in reactive oxygen species production is evidenced by staining with 2′,7′-dichlorofluorescein diacetate (DCF-DA).

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No.	Subject	Extract	Effects
5	This study aimed to examine the protective role of neferine against doxorubicin-induced toxicity (DOX) in the H9c2 mouse cardiomyoblast cell line.	Neferine is obtained from Sigma (Bangalore, India).	Neferine activates IGF-1R signaling during pre-treatment, increases cellular antioxidant levels, and enhances the expression of IGF-1R downstream targets, including the PI3K/Akt/mTOR pathway. This compound significantly inhibits mitochondrial superoxide formation and autophagy by inducing Nrf2 translocation and increasing HO-1 and SOD1 expression.
6	Animal models of mice with acute alcoholism	Lotus root is obtained from Hangzhou, Zhejiang Province, China. The fresh lotus root sample is then pounded using a mortar and pestle until it becomes a fine powder.	Experiments in mice showed that lotus root extract increased the activity of liver enzymes, including alcohol dehydrogenase (ADH), acetaldehyde dehydrogenase (ALDH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px). In addition, this extract increases glutathione (GSH) levels, decreases malondialdehyde (MDA) levels, and decreases serum enzymes indicative of liver damage, namely aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (AKP), in mice with acute alcoholism models. This treatment also speeds up the metabolism of alcohol after consumption. This study reveals the mechanism of action of lotus root extract in alleviating the effects of acute alcoholism, which may serve as a basis for further research on the development of functional foods based on lotus root, as well as open up new opportunities in the therapy of acute alcoholism.

Sources: (Li et al., 2021; Chen et al., 2019; You et al., 2018; Harishkumar & Selvaraj, 2020; Priya et al., 2018; Yang et al., 2023)

Table 3. Summary of *in vitro* test methods used and minimum to maximum range of antioxidant effects of *seroja* plant (*N. Nucifera*)

No.	Method	Plant parts	Minimal	Maximum
1	TPC	Seeds	34.23 ± 4.84	550.00 ± 0.00
		Flowers	210.00 ± 0.00	370.00 ± 0.00
		Leaves	8.00 ± 0.00	49.97 ± 0.37
2	TFC	Flowers	38.67 ± 0.70	68.11 ± 3.53
		Seeds	25.12 ± 3.58	320.00 ± 0.00
		Leaves	26.02 ± 0.46	73.43 ± 1.30
3	DPPH	Flowers	0.26 ± 0.00 (IC50)	634.79 ± 21.65 (IC50)
		Seeds	1900.00 ± 0.00 (umol TE/g)	4800.00 ± 0.00 (umol TE/g)
			24.49 ± 0.00 (SC50)	>500.00 ± 0.00 (SC50)
4	ABTS	Flowers	0.56 ± 0.03 (CI50)	173.89 ± 25.52 (IC50)
			2800.00 ± 0.00 (umol TE/g)	5000.00 ± 0.00 (umol TE/g)
		Seeds	12.07 ± 0.00 (SC50)	>500.00 ± 0.00 (SC50)
5	FRAP	Flowers	5.21 ± 0.34	18.74 ± 1.97
		Seeds	150.00 ± 0.00	650.00 ± 0.00
		Rhizome	7.00 ± 0.00	899.00 ± 0.00
6	TEAC	Flowers	83.19 ± 1.33	850.00 ± 0.00
7	H2O2	Flowers	60.38 ± 6.72	1965.88 ± 4.48
8	TBARS	Seeds	1.55 ± 0.80 (nmol MDA/mg Protein)	3.10 ± 1.30 (nmol MDA/mg Protein)
		Rhizome	0.60 ± 0.00 (mg MDA/kg)	0.90 ± 0.00 (mg MDA/kg)

Sources: (Ma et al., 2023; Chen et al., 2019; Shen et al., 2019; Sranujit et al., 2021; Sim et al., 2019; Tungmunnithum et al., 2022; Jiang et al., 2018; Chheng et al., 2020; Asano et al., 2019; Khan et al., 2022)

Among all plant parts, the rhizome is the most well-researched, both in vitro and in vivo. It is related to its relatively high phenolic and flavonoid content, as well as consistent antioxidant activity across various rhizome fractions, including skin and nodes, which show strong responses in DPPH, ABTS, and FRAP assays (Zhu et al., 2022). In addition, the rhizome *N. nucifera* has long been consumed as a functional food and traditional medicine in Asia. Hence, its availability, ease of processing, and translational relevance make it a more applicable research focus than flowers or seeds, despite their high bioactivity potential.

In vitro and in vivo (**Tables 2** and **3**) show a discrepancy between the laboratory findings and the translational approach. Plant parts with high antioxidant capacity, particularly flowers and seeds, have not been the main focus in the in vivo study, which uses more leaves and rhizomes. For example, Asano et al. (2019) evaluated the antioxidant activity of *seroja* tubers in vitro, while Li et al. (2021) used leaf extracts in animal models (Asano et al., 2019; Li et al., 2021). This pattern indicates that the selection of plant parts in the study in vivo is more influenced by the availability of ingredients and ease of formulation than by the highest bioactivity potential; hence, the antioxidant potential of *N. nucifera* has not been fully explored in a translational setting.

Extraction Methods and Their Effects on Antioxidant Activity

N. nucifera extraction methods show wide variation, with the main solvents being water, ethanol, and methanol, generally using temperatures below 105°C to prevent the degradation of phenolic compounds and flavonoids. Until now, there has been no standard extraction method, so procedural differences contribute to variations in antioxidant activity across studies. Polar solvents such as ethanol and methanol generally yield higher phenolic and flavonoid content than water, although their use may be limited by residue and regulatory concerns.

The antioxidant test method also affects the interpretation of the results. The DPPH and ABTS assays are simple and suitable for initial screening, but they only reflect radical-scavenging capacity chemically. The FRAP method assesses the ability to reduce, but is less sensitive to non-electron antioxidant mechanisms. In contrast, enzymatic approaches (SOD, CAT, GSH) to cell or animal models provide a more relevant biological picture, although they require higher techniques and costs (Do et al., 2014; Apak et al., 2007; Prior et al., 2005; Chranioti et al., 2014). In the context of the development of phytopharmaceuticals in Indonesia, water-based extraction methods or non-alcoholic fractionation are more applicable, given the BPOM regulations on the alcohol content in herbal products (Shen et al*.,* 2019).

Potential Clinical Applications of *N. nucifera* Antioxidant Activity

To date, no clinical trials have directly evaluated the effectiveness of *N. nucifera* in humans. Most research is still limited to the preclinical stage, with a primary focus on antioxidant activity and anti-inflammatory and anticancer effects. This preclinical study is limited by the absence of a standard method to produce stable preparations with consistent active compound content, while the DPPH test remains the most widely used method to assess free radical scavenging activity.

Pre-clinically, extracts of *N. nucifera* are reported to have the potential to play a role in the prevention of skin aging, inhibition of osteolytic processes, reduction of oxidative and inflammatory stress, and exhibit antiobesity, antidiabetic, and renoprotective effects (Li et al*.,* 2021; Chen et al*.,* 2019; Tungmunnithum et al*.,* 2022). Several studies report a protective effect against amyloid beta-induced neuroblastoma cells using the herbal formulation Kleeb Bua Daeng (KBD), a mixture of several plants including *N. nucifera*, *Centella asiatica*, and *Piper nigrum*. However, because KBD is a multicomponent formulation, the observed biological effects cannot be attributed specifically to *N. nucifera* (Chheng et al*.,* 2020).

Thus, despite its promising potential, current evidence on *N. nucifera* remains preclinical. Therefore, its clinical benefits have not yet been fully confirmed. Until controlled clinical trial data are available, it should be positioned as an adjuvant therapy rather than a substitute for standard treatment.

Safety Data and Therapeutic Use Considerations

Regulatory-wise, all parts of *N. nucifera* are not included in the negative lists of traditional medicine at the ASEAN or Indonesian levels. However, comprehensive standardized safety studies are still lacking, as most evidence comes from preclinical research, particularly acute toxicity tests in animals. Several studies indicate that *N. nucifera* is relatively safe at high doses; seed alcohol extract up to 1,000 mg/kg body weight and the herbal formula Kleeb Bua Daeng up to 2,000 mg/kg showed no death or toxicity signs. It is even associated with increased activity of endogenous antioxidant enzymes and decreased markers of oxidative stress (Zhao & Wang, 2024).

Nonetheless, the security of *N. nucifera* is also affected by the potential accumulation of heavy metals, such as cadmium, copper, and lead, due to its growing habitat in muddy water environments. Therefore, quality control of raw materials and monitoring of heavy metal content are crucial aspects in the development of plant-based therapeutic preparations. Special attention should also be paid to the higenamine content of *N. nucifera* shoots, given that the compound has been classified as a prohibited substance by the World Anti-Doping Agency (WADA) and possesses a cardiostimulatory effect. Thus, the use of plant parts other than shoots—such as leaves, seeds, and rhizomes—is considered safer and more applicable for the development of traditional medicine and functional foods (Yen et al*.,* 2020).

Overall, although preclinical evidence suggests a relatively good acute safety profile, the available data remain insufficient to assess *N. nucifera*'s safety fully. Key limitations include the lack of subchronic and chronic toxicity tests, target organ evaluation, potential long-term accumulation, and the use of mixed herbal formulations, which make it difficult to attribute specific effects (Singh et al*.,* 2024). Therefore, the translation of *N. nucifera* Clinical trials still requires standardized long-term toxicology evaluation and human tolerability tests.

CONCLUSION

This literature review systematically summarizes in vitro and in vivo evidence on the antioxidant activity *of N. nucifera*. The activity is primarily associated with the content of flavonoids, alkaloids, and phenolic compounds, with quercetin and neferine as the most consistently reported compounds. Flowers and seeds showed the highest antioxidant capacity in in vitro assays. At the same time, leaves and rhizomes were more commonly used in in vivo studies due to considerations of the extract's availability and stability. Variations in extraction and testing methods contributed to heterogeneity in results across studies. Pre-clinically, *N. nucifera* showed bioactivity potential relevant to oxidative stress protection with a relatively good acute safety profile, but limited long-term toxicity data and the absence of clinical trials confirm the need for further research before broader therapeutic applications are recommended.

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