REVIEW ARTICLE

Phytochemical Composition and Pharmacological Activities of *Orthosiphon stamineus:* A Review

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Abstract

Orthosiphon stamineus Benth. (Lamiaceae), commonly known as Java tea or cat's whiskers, is a medicinal herb widely used in Southeast Asian traditional medicine for the management of renal and metabolic disorders. This review aims to synthesize current knowledge on its phytochemical constituents, pharmacological activities, and underlying molecular mechanisms. The plant is rich in bioactive compounds, including phenolic acids, flavonoids, and terpenoids, which contribute to a broad range of biological activities. Experimental studies have demonstrated anti-inflammatory, antioxidant, anticancer, and nephroprotective effects in both cell-based and animal models. These pharmacological properties are associated with the regulation of oxidative stress pathways, suppression of inflammatory signaling, and modulation of metabolic processes. Toxicological investigations generally indicate a favorable safety profile at experimentally evaluated doses. Recent research has focused on the development of standardized extracts and nano-based delivery systems to enhance the solubility, stability, and bioavailability of its phytochemicals. Despite promising pre-clinical findings, clinical evidence supporting its therapeutic efficacy remains limited. Future research should prioritize well-designed human clinical studies and improved standardization strategies to facilitate the translation of *O. stamineus* into evidence-based therapeutic applications.

Key words: Anti-inflammatory activity, Antioxidant activity, Nephroprotective activity, *Orthosiphon stamineus*, Phenolic compounds, Phytochemicals

INTRODUCTION

Orthosiphon stamineus Benth., belonging to the family Lamiaceae, commonly known as Java tea or Cat's Whiskers, is an edible herbal plant widely grown and distributed in Southeast Asia, particularly Malaysia, Indonesia, Thailand, and the Philippines.[1,2] The plant is known and has been used in Asian medicine to treat metabolic and inflammatory diseases, including diabetes, hypertension, gout, rheumatism, as well as urologic disorders (nephritis, cystitis, and urolithiasis).[3-6]

The phytochemical profile of Java tea is highly variable, and it includes phenolic acids, flavonoids, diterpenoids, triterpenoids, and volatile components that account for its pharmacological characteristics. The main compounds identified include sinensetin, eupatorin, and rosmarinic acid, which have been documented for various properties such as antioxidant, anti-inflammatory, diuretic, nephroprotective, and anticancer action – primarily *in vitro* or in animal models.[7-9] The fact that these effects are mediated by several molecular targets points to a polypharmacological mechanism of action as opposed to single-pathway specificity.

The translational value of *O. stamineus* is still unfamiliar despite a wealth of pre-clinical evidence because of the lack

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of human trials, uneven dosage, bioavailability data, and variations in extraction and standardization procedures. The usefulness of current reviews for directing clinical translation and regulatory development is limited because they frequently concentrate on separate bioactivities or individual drugs with inadequate integration of mechanistic insights, safety evaluation, and formulation techniques.

Hence, this review provides a comprehensive and updated overview of the botanical characteristics, phytochemical composition, pharmacological properties, molecular mechanisms of action, as well as safety profile and novel formulation techniques for *O. stamineus.* The aim is to highlight existing restrictions and determine priorities for further research and translational development.

MORPHOLOGICAL DESCRIPTION

O. stamineus is a herbaceous perennial plant with a height of up to 75 cm and a purplish stem, which is quadrangular and purplish in color.[10,11] The serrated margins of the leaves are the main distinguishing characteristic of the genus, which have a length of 5–10 cm and are simple, glabrous, and lanceolate. They are located in pairs opposite each other. Campanulate flowers, normally white and pale purple, are borne on maroon terminal racemes. There are two distinct varieties of this plant found in Malaysia with respect to their leaf characteristics and floral coloring (corolla and calyx).[10,12] They have also found that the purple variety contains large amounts of bioactive chemicals compared to the white variant, which is associated with quantitative variation also in phytochemical content. After pollination, the plant yields oblong-ovoid nutlet fruits, which are 1.5–2 mm in diameter, to complete the reproductive cycle.[10]

PHYTOCHEMICAL COMPOSITION

The phytochemical composition of *O. stamineus* underlies its traditional medicinal use and pharmacological activities. The plant contains a wide range of secondary metabolites, including phenolic acids, flavonoids, terpenoids, alkaloids, saponins, tannins, coumarins, and glycosides [Table 1]. Phenolic acids such as rosmarinic acid, caffeic acid, and salvianolic acids contribute significantly to antioxidant, anti-inflammatory, and cytotoxic activities.[8] Flavonoids, including sinensetin, eupatorin, salvigenin, cirsimaritin, rhamnazin, and trimethyl apigenin, are associated with anticancer, antimicrobial, vasodilatory, and enzyme inhibitory effects.[13-15] Terpenoids and β-sitosterol further contribute to anti-inflammatory, cytotoxic, and metabolic regulatory activities,[8] whereas other constituents support diuretic, nephroprotective, and antimicrobial properties.[6,12]

Metabolomic and network pharmacology studies have identified more than 90 compounds in *O. stamineus*, many of which interact with molecular targets involved in inflammation, metabolism, and cancer-related pathways, including PI3K/protein kinase B (Akt) and nuclear factor kappa B (NF-κB) signaling.[8,16] The phytochemical profile is influenced by extraction methods and environmental factors, with methanolic and ethanolic extracts generally yielding higher concentrations of phenolic acids and flavonoids than aqueous extracts.[13]

MAJOR BIOACTIVE COMPOUNDS

The pharmacological activities of *O. stamineus* are said to be due to three important bioactive compounds: Sinensetin, eupatorin, and rosmarinic acid. Sinensetin is a polymethoxylated flavonoid whose increased chemical stability and lipophilicity show antioxidant, anti-inflammatory, anticancer, antidiabetic, and antihyperuricemia effects.[17] Experimental studies have revealed its modulation of the Wnt/β-catenin signaling pathway,[18] inhibition of α-glucosidase and α-amylase enzymes,[19] and its effect on uric acid transport through ATP-binding cassette subfamily G member 2 (ABCG2) inhibition.[20] Another polymethoxylated flavonoid known as eupatorin is shown to be very active in terms of its anticancer activities through the regulation of the Akt signaling pathways, induction of apoptosis, and inhibition of tumor cell proliferation and metastasis.[21] Besides, eupatorin has also been reported to boost immune responsiveness via greater activation of natural killer cells and CD8+ T-cell activities in pre-clinical models.[22] A common phenolic acid found in *O. stamineus* extracts, rosmarinic acid, is often selected as a marker compound for their standardization.[23] It has significant antioxidant, antiproliferative, and nephroprotective properties[24] and can maintain high antioxidant activity after thermal processing, which indicates it is suitable for the formulation of phytopharmaceutical and functional foods.[25] These are found to act by complementary and multi-target mechanisms to render *O. stamineus* with a wide therapeutic potential.

EFFECTIVE CONCENTRATIONS (HALF MAXIMAL INHIBITORY CONCENTRATION [IC_{50}])

When comparing the IC_{50} values from different investigations, one must be careful because of alterations in experimental methodology, specifics of the testing process, and the degree of purity of the compounds. Significant variations in potency can be shown by comparing the effective concentrations, which are compiled in Table 2. Potency is the amount of a substance needed to have a particular effect. This is commonly quantified using the IC_{50} number, which stands for IC_{50}. The IC_{50} is a number that serves to indicate the concentration of a substance that is required to accomplish a given biological reaction (such as the proliferation of cancer

Table 1: Phytochemical compounds

S. No.	Class	Chemical compound	Formula	Medicinal properties	References
1.	Phenolic acid	Rosmarinic acid	$C_{18}H_{16}O_8$	Antioxidant	[8]
		Caffeic acid	$C_9H_8O_4$	Antihyperglycemic activities	[16,50]
		Gallic acid	$C_7H_6O_5$	Anti-inflammatory effects	[6,10]
		Salvianolic acids	$C_{26}H_{22}O_{10}$	Cytotoxic and kidney protective effects	[50,55]
2.	Flavonoids	Sinensetin	$C_{20}H_{20}O_7$	Anticancer	[15,26]
		Eupatorin	$C_{18}H_{16}O_7$	Induces apoptosis and also acts as a vasodilator and P450 enzyme inhibitor	[14]
		Rutin	$C_{27}H_{30}O_{16}$	Reduces oxidative stress	[50]
		Trimethoxyflavone	$C_{18}H_{16}O_5$	Inhibits cyclooxygenase and lipoxygenase enzymes	[26]
		Rhamnazin	$C_{17}H_{14}O_7$	Antioxidant	[15,26]
		Pilloin	$C_{17}H_{14}O_6$	Modulates cellular oxidative stress and inflammation	[26]
3.	Terpenoid	Ursolic acid	$C_{30}H_{48}O_3$	Hepatoprotective	[8,51]
		Oleanolic acid	$C_{30}H_{48}O_3$	Metabolic regulation and liver health protection	[8,51]
		Betulinic acid	$C_{30}H_{48}O_3$	Cytotoxic effect	[8]
		β-sitosterol	$C_{29}H_{50}O$	Anti-inflammatory and cholesterol-lowering	[6,10]
		Vomifoliol	$C_{13}H_{20}O_3$	Modulation of key targets involved in inflammation	[16]

Table 2: Comparative pharmacological potency of major bioactive compounds from *Orthosiphon stamineus*

S. No.	Compound	Biological activity	Pathway	IC_{50}/effective concentration	Assay	References
1.	Sinensetin	Anticancer	Wnt/β-catenin	15 μM	MCF-7 cells	[18]
		Antidiabetic	α-glucosidase	48 μM	Enzymatic assay	[19]
		Anti hyperuricemic	ABCG2 inhibition	22 μM	MDCK-II cells	[20]
2.	Eupatorin	Anticancer	Akt signaling	8 μm	MDA-MB-231 cells	[21]
		Immunomodulatory	IFN-γ activation	20 mg/kg	*In vivo* (Murine)	[22]
3.	Rosmarinic Acid	Anticancer	PI3K/Akt/mTOR	10 μM	HeLa cells	[24]
		Antioxidant	Nrf2/SOD activation	25 μM	HepG2 cells	[25]

IC_{50}: Half maximal inhibitory concentration, ABCG2: ATP-binding cassette subfamily G member 2, IFN-γ: Interferon-gamma, Akt: Protein kinase B, MCF-7: Michigan Cancer Foundation-7, Nrf2: Nuclear factor erythroid 2-related factor 2, SOD: Superoxide dismutase

cells). Therefore, the lower the IC_{50}, the higher the strength.[21] Found that eupatorin has the highest anticancer potency of the three major bioactive compounds, which had an IC_{50} of 8 μM in MDA-MB-231, a triple-negative breast cancer cell line. This is succeeded by rosmarinic acid, which produced an IC_{50} of 10 μM in HeLa cells,[24] and sinensetin showed an IC_{50} of 15 μM in Michigan Cancer Foundation-7 cells.[18]

PHARMACOLOGICAL ACTIVITIES

Java tea is claimed to exert various pharmacological activities due to its phytochemical makeup, and the trend is evident in the increasing literature on experimental research. This plant provides flavonoids, phenolic acids, terpenoids, and essential oils; all of which have been shown to protect the liver, reduce inflammation, act as antioxidants, combat cancer, manage diabetes, promote urine production, and be effective against bacteria.[8,15,26] demonstrate that these therapeutic effects result from diverse actions at multiple points within the body, encompassing the destruction of cancerous cells, the reduction of oxidative stress, influences on metabolic routes, and modulation of enzymes and signaling molecules driving inflammation. The pharmacological actions listed below are based on representative *in vitro*, *in vivo*, and computational research.

Anti-inflammatory activities

Inflammation is a protective physiological response; however, chronic inflammation contributes to the development of cardiovascular, metabolic, autoimmune, neurodegenerative, and cancer-related disorders.[15] Although conventional

anti-inflammatory drugs are effective, their long-term use is often associated with gastrointestinal, renal, and cardiovascular adverse effects.[27,28]

Pre-clinical studies have demonstrated significant anti-inflammatory activity of *O. stamineus*, largely attributed to its phenolic acids, flavonoids, and terpenoids.[15] Oral administration of leaf extracts (100–400 mg/kg) reduced inflammatory responses in experimental models, with greater suppression of nitric oxide and pro-inflammatory cytokines observed at higher doses.[15,26] These effects are mainly associated with rosmarinic acid and polymethoxylated flavonoids such as eupatorin, sinensetin, and tetramethyl luteolin.[26] *In vitro* studies further showed inhibition of macrophage-mediated inflammation and nitric oxide production, supporting its therapeutic potential.[15] However, clinically validated human dosage recommendations are still lacking.

Antioxidant activities

Reactive oxygen species (ROS) and antioxidative defenses are important factors that contribute to the development of cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders, among others, through oxidative stress.[29] Polyphenols such as phenolic acids and flavonoids are responsible for most of the antioxidant activity observed in *O. stamineus*,[30] which they use to quench ROS and prevent lipid peroxidation.[31] The primary antioxidants are rosmarinic acid and danshensu and related phenols, which are also anti-inflammatory and antibacterial.[32] The extraction methods and post-harvest processing can affect the antioxidant activity of *O. stamineus*. In general, polar solvents (ethanol and water) gave phenol extracts and higher antioxidant activity results compared to non-polar solvents.[33,34] The fermentation by *S. cerevisiae* provides additional benefits for antioxidants as more bound phenolics are released. Furthermore, the phenolic extraction and antioxidant capacity are increased in the steam explosion.[36,37] by disrupting the plant cell walls and increasing the porosity of the tissues. The antioxidant property is the main reason for hepatoprotective effects, such as protection against non-alcoholic fatty liver disease, improvement of glucose metabolism, and reduction of oxidative stress in animal models.[34] In summary, the therapeutic potential of the above, based on its high phenolic and flavonoid content and optimized extraction techniques, is supported by its advantageous effects on oxidative stress-related disorders.[37]

Anticancer and antitumor activities

Cancer is a complex disease in which cancer cells undergo proliferation, invasion, and metastasis without any control, which occurs due to the dysregulation of the apoptotic pathways and the cell cycle. Although conventional chemotherapy is effective, systemic toxicity and drug resistance limit the outcomes of treatment, suggesting that there is a need for other methods of therapy. *O. stamineus* has shown potential as an anticancer agent in pre-clinical studies; this is mostly attributed to the flavonoids and phenolic acids it contains, especially sinensetin, eupatorin, and rosmarinic acid.[13] Both sinensetin and rosmarinic acid have cytotoxic and antiproliferative effects via the p53–p21 signaling pathway, leading to cell-cycle arrest and apoptosis, as well as inhibition of oxidative stress and regulation of pathways involved in tumor growth and progression.[13] These compounds could work together in addition through different mechanisms to boost the anticancer results. *O. stamineus* is particularly interesting in the treatment of pancreatic cancer because ethanolic extracts of *O. stamineus* significantly improved the ability of gemcitabine to kill Panc-1 cells, leading to decreases in cell viability and the efficacy of the therapy compared to that achieved with gemcitabine alone.[8] A standardized extract containing sinensetin, eupatorin, and rosmarinic acid, Nuvastatic™, exhibited broad antiproliferative activity in various cancer cell lines,[23] and was very well tolerated in clinical trials testing its efficacy in reducing cancer-related fatigue in people undergoing chemotherapy.[38]

O. stamineus has also been shown to inhibit the development of antibodies against the tumor. In oral squamous cell carcinoma models, Nuvastatic™ demonstrated a significant antitumor activity through the inhibition of pro-angiogenic mediators such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and tumor necrosis factor-beta.[44,45] Further, the ethyl acetate fractions were significantly cytotoxic toward tamoxifen-resistant breast cancer (MCF-7) cells by depressing protein tyrosine phosphatase 1B, as this inhibitor may be useful for cancers resistant to therapy. *O. stamineus* induces apoptosis, inhibits cell proliferation, inhibits cell migration and angiogenesis, regulates cell oncogenic signal molecules, increases sensitivity to mainstream drugs, and suppresses the metastatic process to cancer in general.[46] Evidence to date is promising, but more clinical studies need to be conducted to demonstrate its efficacy as a therapy and its place in cancer treatment.

Antidiabetic and antihyperglycemic activity

Type 2 diabetes mellitus is a major global health concern characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia, leading to complications such as nephropathy, retinopathy, cardiovascular disease, and neuropathy.[6,39] Oxidative stress further contributes to disease progression by damaging pancreatic β-cells and disrupting insulin signaling pathways.[40,41]

O. stamineus exhibits hypoglycemic and insulin-sensitizing effects primarily through its flavonoid- and phenolic-rich phytochemical profile. Methanolic extracts have demonstrated greater antidiabetic activity than aqueous extracts due to their

higher content of bioactive compounds involved in glucose regulation.[6] Experimental studies showed that methanolic extracts reduced blood glucose levels and improved glycemic control by promoting glucose transporter type 4 (GLUT4) translocation and enhancing glucose uptake in diabetic mice.[6] In addition, their antioxidant properties help reduce oxidative stress, preserve β-cell function, and improve insulin sensitivity. Despite promising pre-clinical findings, further clinical studies are required to confirm efficacy and establish optimal dosage.

Antihyperuricemic and nephrolithiasis activity

Hyperuricemia, characterized by elevated serum uric acid levels, is associated with gout, hypertension, and cardiovascular disorders. Methanolic extracts of *O. stamineus* demonstrated significant antihyperuricemic activity in animal models by reducing xanthine oxidase and adenosine deaminase activities, lowering serum uric acid levels, and modulating renal urate transport (URAT) through downregulation of URAT1 and GLUT9 and upregulation of organic anion transporter (OAT)-1 and OAT3.[32]

O. stamineus has also shown potential against nephrolithiasis. Flavonoid-rich extracts reduced renal calcium deposition and improved kidney function markers, including serum creatinine and blood urea nitrogen, in experimental models.[42] Additional studies suggest nephroprotective effects through modulation of PPAR-α and NF-κB signaling pathways and improvement of gut microbiota composition associated with renal health.[43] These findings indicate the potential of *O. stamineus* in the prevention and management of hyperuricemia and kidney stone formation.

Antiviral activity

O. stamineus has shown potential antiviral activity against several viral pathogens. Methanolic leaf extracts demonstrated moderate antiherpes simplex virus type 1 activity by inhibiting viral entry and replication while maintaining a favorable selectivity profile in host cells.[47] *In silico* studies have also identified flavonoids such as ladanein, sinensetin, and rhamnazin as potential inhibitors of dengue virus replication through interactions with NS2B/NS3 protease, HSP70, and other viral targets.[9] In addition, computational docking studies suggest that rosmarinic acid, sinensetin, eupatorin, gallic acid, and caffeic acid may interact with key severe acute respiratory syndrome-CoV proteins, including the main protease and spike glycoprotein.[48] Although these findings indicate promising antiviral potential, further experimental and clinical validation is required.

Antimicrobial activity

The antimicrobial activity of *O. stamineus* is largely attributed to its phenolic and flavonoid constituents. Leaf extracts have demonstrated inhibitory effects against Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*, as well as the fungus *Candida albicans*.[5] These effects are mediated through multiple mechanisms, including disruption of microbial cell membranes, inhibition of DNA and protein synthesis, and inactivation of essential microbial enzymes. Such multi-target actions may reduce the likelihood of resistance development and highlight the potential of *O. stamineus* as a source of alternative antimicrobial agents, although further studies are needed to establish its clinical relevance.[49]

MECHANISM OF ACTION

The multi-target mode of action of Java tea is attributed to the complex phytochemical composition that consists of flavonoids (sinensetin, eupatorin, tetramethyl luteolin, and trifolin), phenylpropanoids (rosmarinic acid and caffeic acid), and triterpenoids such as ursolic acid. The combined effect of these chemicals is to regulate oxidative stress, inflammatory signaling, and cell survival pathways. Network pharmacology analyses show that the phytochemicals react with about 65 molecular targets associated with the inflammatory pathway, cancer development, metabolic, and drug-resistance pathways. This pathway-scale control offers a molecular basis for the vast range of pharmacological activity of this plant, despite the fact that many of these predicted interactions need further experimental support.

Anti-inflammatory mechanism

The anti-inflammatory activity of *O. stamineus* is mediated through the inhibition of multiple inflammatory pathways [Figure 1]. Flavonoids and terpenoids such as trifolin and ursolic acid suppress NF-κB activation, thereby reducing the production of pro-inflammatory mediators.[15] Pinocembrin and pinostrobin inhibit inducible nitric oxide synthase (iNOS), limiting excessive nitric oxide production and associated tissue damage.[15] In addition, tetramethyl luteolin exhibits strong cyclooxygenase-2 (COX-2) inhibitory activity comparable to celecoxib,[26] whereas rosmarinic acid and eupatorin further contribute through modulation of lipoxygenase-related pathways.[2] Collectively, these compounds suppress inflammation by targeting NF-κB, iNOS, COX-2, and related inflammatory signaling pathways.

Anticancer mechanism

The anticancer activity of *O. stamineus* is largely mediated through inhibition of angiogenesis and induction of apoptosis [Figure 2]. The standardized extract Nuvastatic™ suppresses key growth factors involved in tumor vascularization, including VEGF, FGF, EGF, interleukin (IL)-2, IL-7, and transforming growth factor alpha, thereby limiting tumor growth and metastasis.[23]

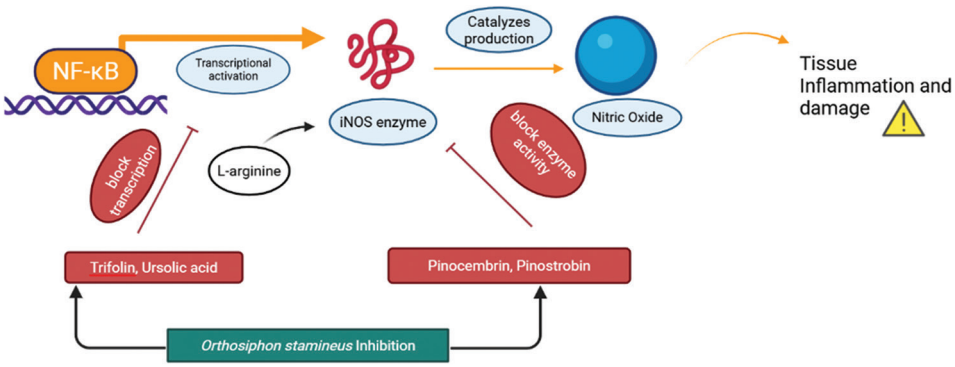

Figure 1: Anti-inflammatory mechanism of *Orthosiphon stamineus* phytochemicals showing inhibition of nuclear factor kappa B transcriptional activation and nitric oxide synthase enzyme activity, preventing tissue inflammation and damage. (Created with Biorender.com)

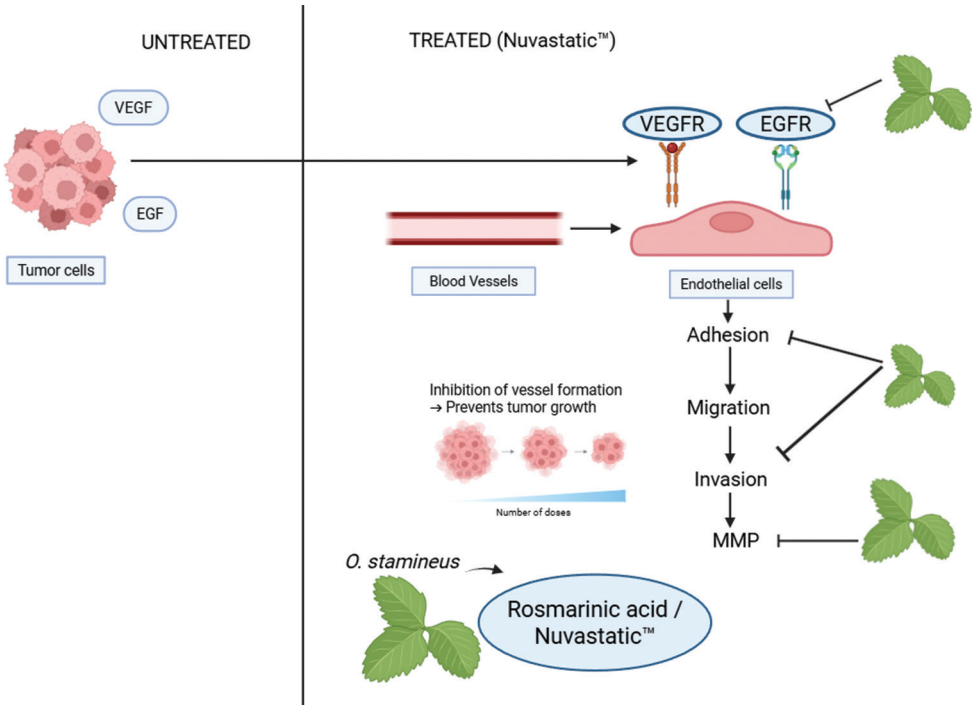

Figure 2: Anticancer mechanism of Nuvastatic™ (*Orthosiphon stamineus* extract) showing inhibition of vascular endothelial growth factor, epidermal growth factor, and subsequent prevention of tumor blood vessel formation (Created with Biorender.com)

Rosmarinic acid contributes to this effect by inhibiting endothelial cell adhesion, migration, and invasion, while also promoting apoptosis in cancer cells.[13] In addition, sinensetin modulates the p53–p21 signaling pathway, leading to cell-cycle arrest and programmed cell death.[13] Together, these bioactive compounds exert complementary anticancer effects through antiangiogenic, antiproliferative, and pro-apoptotic mechanisms.

Direct cytotoxicity and cell cycle arrest

The cytotoxic effects of *O. stamineus* are mediated through multiple signaling pathways involved in cancer cell survival and proliferation [Figure 3]. Rosmarinic acid inhibits the PI3K/Akt/mTOR pathway, restores phosphatase and tensin homolog activity, induces mitochondrial apoptosis, and arrests the cell cycle at the S phase.[24] In animal models, Nuvastatic™ demonstrated greater tumor reduction than rosmarinic acid alone.[23] Eupatorin suppresses Akt signaling,[26] inhibits cancer cell invasion and migration, and enhances immune responses through activation of natural killer and $CD8^+$ T cells.[21,22] Sinensetin induces G_0/G_1 cell-cycle arrest by inhibiting Wnt/β-catenin signaling, whereas tetramethyl luteolin promotes apoptosis in various cancer cell lines.[3,17]

Antioxidant and cytoprotective mechanisms

Oxidative stress is a consequence of ROS, and it leads to the development of cancer and the evolution of chronic

conditions. Figure 4 depicts the antioxidant defense response caused by rosmarinic acid through the Nrf2 signaling pathway. Research done by[4,35] found that the polyphenolic chemicals in Java tea have a direct scavenging effect on ROS and the activation of the Nrf2 pathway that increases the production of endogenous antioxidant enzymes, including catalase and superoxide dismutase.[23,51] This dual antioxidant system provides complete cellular defense. The traditional usage of Java tea for kidney problems is explained by the fact that rosmarinic acid preferentially accumulates in the renal cortex, where it activates Nrf2 to protect kidney tissues from oxidative damage and inflammation.[2,50]

TOXICOLOGY AND SAFETY PROFILE

Available pre-clinical and limited clinical studies indicate that *O. stamineus* possesses a favorable safety profile. Acute and subchronic toxicity studies reported no mortality or significant behavioral, hematological, hepatic, or renal abnormalities, with LD_{50} values exceeding 5000 mg/kg, suggesting low toxicity.[23,44] Standardized extracts such as Nuvastatic™ also showed no adverse histopathological changes in major organs following prolonged administration.

Clinical studies in cancer patients receiving chemotherapy reported good tolerability without evidence of hepatotoxicity,

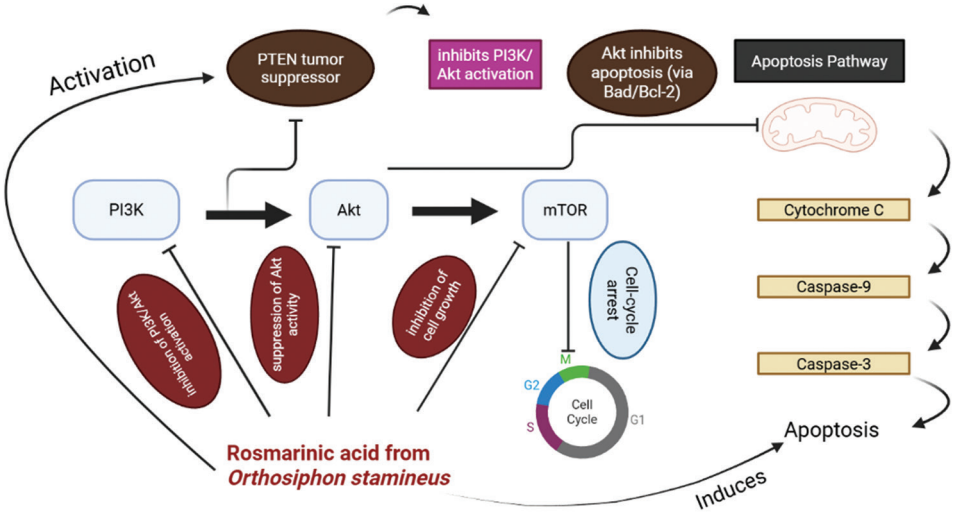

Figure 3: Rosmarinic acid from *Orthosiphon stamineus* inhibits the PI3K/Akt/mTOR signaling pathway, activates the phosphatase and tensin homolog tumor suppressor, and induces apoptosis through the mitochondrial pathway (Created with Biorender.com)

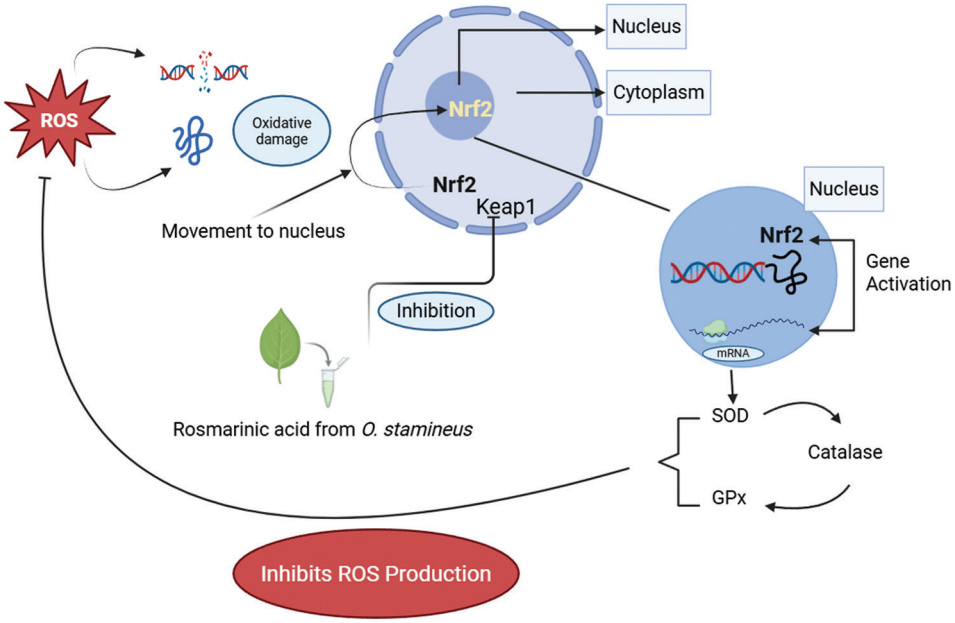

Figure 4: Molecular mechanism of rosmarinic acid from *Orthosiphon stamineus* activating the Nrf2 pathway for antioxidant defense (Created with Biorender.com)

Table 3: Comparative analysis of *Orthosiphon stamineus* formulations and delivery systems

S. No.	Delivery system	Target application	Advantages	Key limitations	References
1.	Emulgel	Topical anti-inflammatory	Enhanced skin penetration, stable, patient-friendly	Limited systemic delivery	[1]
2.	Nanoemulsion	Oral	Improved solubility, faster absorption	Requires surfactant optimization	[1]
3.	Phytosome	Oral/Systemic	Increased permeability, protection from metabolism	Costly preparation	[19]
4.	solid lipid nanoparticle	Sustained systemic release	Controlled release, stability	Low drug loading	[19]
5.	Spray-dried powder	Herbal teas, capsules	Stable, easy storage	Limited dissolution rate	[53]

nephrotoxicity, or hematological toxicity, while reproductive toxicity studies found no teratogenic, mutagenic, or genotoxic effects.[4] Although standardized extracts are generally considered safe at doses of 300–600 mg/day,[23] caution is advised in pregnant or lactating women and in patients with hepatic or renal impairment. Potential herb–drug interactions involving cytochrome P450 enzymes have been suggested, highlighting the need for further pharmacokinetic and interaction studies.[15]

PHARMACEUTICAL FORMULATION AND DELIVERY SYSTEMS

The necessity to address poor water solubility, rapid metabolism, and limited intestinal absorption of key phytoconstituents such as sinensetin, eupatorin, and rosmarinic acid has attracted pharmaceutical development of *O. stamineus*. There are a number of different formulation methods that have been explored to enhance stability, bioavailability, and therapeutic efficacy to address these limitations: Emulgels, spray-dried powders, nanoemulsions, liposomes, and polymeric nanoparticles. An overview of the major *O. stamineus* formulations and delivery systems reported is presented in Table 3.[23,44]

CURRENT RESEARCH GAPS AND FUTURE FINDINGS

The clinical translation of *O. stamineus* is limited by numerous critical limitations, although there are encouraging pharmacological results. There are few large-scale, well-controlled clinical studies; most of the data are provided in *in vitro* studies, animal models, or small groups of humans, limiting extrapolation and clinical certainty.[54] There is a need to conduct expanded trials to demonstrate efficacy and safety in other indications, such as atopic dermatitis, hyperuricemia, and metabolic diseases.[55]

The chemical complexity of Java tea makes standardization and quality control some of the issues. It has not been thoroughly and completely quantified for major bioactives, rosmarinic acid, eupatorin, sinensetin, and orthosiphol isomers, and the interactions of these are not properly explained, and their bioavailability is unclear.[43] More metabolomics, network pharmacology, and formulation science need to be integrated to change these discoveries into clinically consistent medicines.

Mechanistic knowledge also demands optimization, with respect to modulation of gut microbiota, inflammatory and oxidative stress signaling, and transport proteins such as ABCG2, to enable rational dose modulation and target-based application.[43] Simultaneously, there is still a lack of long-term safety and herb-drug interaction studies, particularly in polypharmacy when it comes to the regulation of cytochrome P450 and the impact of diuretics.[15] Even though improved delivery systems are promising, additional efforts in formulation stability, scalability, and regulatory compliance, as well as patient acceptability, are required to achieve successful clinical and commercial translation.[52]

CONCLUSION

O. stamineus is a medicinal plant with diverse pharmacological activities, including anti-inflammatory, antioxidant, antidiabetic, nephroprotective, and anticancer effects. These activities are largely attributed to bioactive compounds such as rosmarinic acid, sinensetin, and eupatorin, which act through multiple interconnected molecular pathways. Although extensive *in vitro* and animal studies support its therapeutic potential, clinical evidence remains limited. Challenges related to phytochemical variability, standardization, bioavailability, and long-term safety continue to hinder clinical translation. Future research should focus on standardized extraction methods, quality control, advanced delivery systems, and well-designed clinical trials to facilitate the development of *O. stamineus* as an evidence-based phytopharmaceutical.

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