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Neuroprotective and Anticancer Potential of Hypericum Species: A Phytopharmacological Review

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ABSTRACT

The genus is taxonomically complex and physically variable; it is frequently separated into sections and subgenera according to glandular structures, floral morphology, and phytochemical markers like the amount of hypericin and hyperforin. The Hypericum genus, notably Hypericum perforatum (St. John's Wort), has long been recognized for its diverse therapeutic potential rooted in rich phytochemical constituents such as hypericin, hyperforin, flavonoids, and phenolic acids. This review critically explores the dual neuroprotective and anticancer activities of Hypericum species, emphasizing their relevance in modern phytopharmacology. Through its antioxidant action, anti-inflammatory properties, neurotransmitter modulation, mitochondrial stabilization, and suppression of glutamate excitotoxicity and amyloid-beta toxicity, hypericum supports neuronal survival in Parkinson's, Alzheimer's, and other associated illnesses. Hypericum targets a variety of tumor types and exhibits anticancer potential through apoptosis induction, cell cycle arrest, anti-angiogenesis, and photodynamic cytotoxicity.Hypericin, in particular, has been explored as a photosensitizer in photodynamic therapy for some malignancies. Despite encouraging pharmacological evidence, clinical translation remains limited due to concerns related to bioavailability, standardization, and herb-drug interaction. This evaluation emphasizes the potential therapeutic benefits of Hypericum species as agents that target multiple pathways and points out the necessity for additional pharmacokinetic, toxicological, and clinical studies to confirm their safety and efficacy. use in neurodegenerative and oncological therapies.

Keywords: *Hypericum perforatum*, hypericin, hyperforin, neuroprotection, anticancer activity, photodynamic therapy, phytochemicals, flavonoids, nanocarriers, drug delivery systems, herbal medicine, oxidative stress, CNS disorders, apoptosis, herbal-drug interactions**.**

INTRODUCTION

Hypericum species, particularly Hypericum perforatum (St. John's Wort), are abundant in bioactive substances with a variety of pharmacological characteristics, including hypericin and hyperforin. Recent data demonstrates their dual potential in anticancer treatment through apoptosis induction, cell cycle regulation, and photodynamic effects, as well as in neuroprotection through antioxidant, anti-inflammatory, and neurotransmitter-modulating activities. The phytochemistry, processes, and potential therapeutic uses of hypericum in the treatment of cancer and neurological illnesses are examined in this paper.

Timeline of Research Milestones

Year	Study / Finding
1996	First reports of hypericin PDT in tumor models
2001–2005	Multiple studies confirmed cytotoxicity in melanoma, glioma, and carcinoma cells
2009	Study showed phototoxic effects of hypericin leading to apoptosis in breast cancer cells
2013	Hypericin shown to inhibit angiogenesis in vitro
2017–2020	Renewed interest in combining hypericin with nanocarriers for targeted therapy
2022–2024	Preclinical studies with nano formulations of Hypericum extracts in colon and prostate cancers

Numerous phytochemicals, including flavonoids, phenolic acids, hypericin, and hyperforin, are found in Hypericum species, especially H. perforatum, and they have a variety of medicinal uses. By lowering oxidative stress, avoiding apoptosis, regulating neurotransmitters, and reducing neuroinflammation, they shield neurons in neurodegenerative disorders. They target different tumor pathways in cancer by exhibiting antiproliferative, pro-apoptotic, anti-angiogenic, and photodynamic effects. Hypericum is a viable option for combined neuroprotective and oncological therapies due to its wide pharmacological profile.

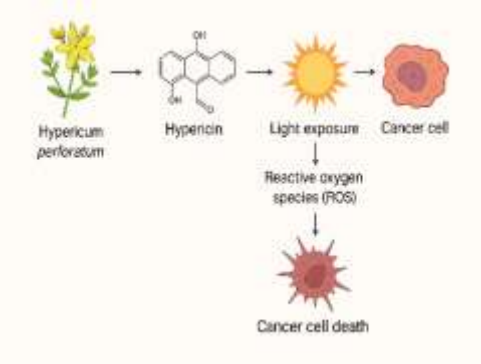

Fig.1-Photodynamic Mechanism of Hypericin from Hypericum perforatum in Cancer Cell Death.

1. Botanical and Pharmacognostic Overview

1.1 Hypericum Species Taxonomy and Classification

With more than 500 species spread around the world, particularly in temperate and subtropical areas, the genus Hypericum is a member of the family Hypericaceae. The species that has been the subject of the greatest pharmacological and clinical research is Hypericum perforatum L., popularly referred to as St. John's Wort. The following is H. perforatum's taxonomic hierarchy:

Category:

Kingdom: Plantae

Division: Angiosperms

Class: Eudicots

Order: Malpighiales

Family: Hypericaceae

Genus: *Hypericum*

Species: *H. perforatum* L.

1.2 Anatomical and Morphological Features

Growth Habit: Stems that are upright and branching, perennial plants or shrubs.

Leaves: sessile, opposite, and speckled with black and transparent glands that store oil and resin.

Vibrant yellow blossoms featuring five petals, numerous clusters of stamens, and an elevated ovary.

Fruits: Numerous tiny seeds enclosed in dry capsules.

The anatomy of leaves is dorsiventral, with glandular trichomes and secretory canals.

Stem anatomy includes schizogenous secretory chambers and well-developed vascular bundles.

Diagnostic Features: Identification is aided by vivid yellow blooms and glandular spots.

1.3 Worldwide Dispersion and Ecological Importance

Worldwide distribution; found in large quantities in portions of Africa, Australia, North America, South America, Asia, and Europe's temperate and subtropical zones.

Roadsides, disturbed areas, meadows, grasslands, and woodland edges are examples of habitats.

Ecological Role: Assists pollinators (bees, butterflies), stops soil erosion, and shows how healthy the soil is.

Adaptability: Its ability to withstand a range of soil types and climates makes it ecologically resilient.

1.4 Customary and Ethnomedicinal Applications

It has long been used to treat burns, wounds, and skin infections.

It serves as a mood stabilizer and an antidepressant in conventional medicine

For sciatica, muscular damage, and nerve discomfort.

Utilized in liver and intestinal diseases.

European, Asian, and American rituals and cultural healing practices all involve infusions and oils.

2. Phytochemical Constituents of *Hypericum* Species

2.1 Overview of Phytochemistry

Hypericum is abundant in naphthodianthrones having photodynamic action, such as hypericin and pseudohypericin.

It has anticancer and neuroprotective phloroglucinols (like hyperforin).

It is rich in biflavonoids with anti-inflammatory and antioxidant qualities as well as flavonoids (rutin, quercetin).

Include phenolic acids and xanthones, which have cytoprotective and antibacterial properties.

Processing techniques, habitat, and species all affect the phytochemical profile.

2.2 Major Bioactive Compounds and Their Classes

Hypericin and pseudohypericin (photodynamic and anticancer) are naphthodianthrones.

Hyperforin and adhyperforin are phenolglucinols that have neuroprotective and anticancer properties.

Quercetin, rutin, and kaempferol are flavonoids that have anti-inflammatory and antioxidant properties.

Biflavonoids: biapigenin (cytoprotective and anti-inflammatory) and amantoflavone.

Mangiferin, 1,3,6,7-tetrahydroxyxanthone (antimicrobial & anticancer) are examples of xanthones.

Phenolic acids include caffeic acid (an antioxidant) and chlorogenic acid.

2.3 Distribution of Phytochemicals in Plant Parts

The black glands of the flowers, leaves, and stems contain hypericin and pseudohypericin, which give the plant its distinctive red colour.

The flowers and higher leaves contain the most of the hyperforin.

Quercetin, rutin, and kaempferol are among the flavonoids that are widely found in leaves, stems, and flowers.

The aerial parts include phenolic acids and xanthones, which support cytoprotective and antioxidant properties.

2.4 Phytochemical Methods of Analysis

These chemicals are isolated and quantified using standard analytical procedures, such as:

Utilizing High-Performance Liquid Chromatography (HPLC) to quantify hypericin and hyperforin

UV-Vis Spectrophotometry for the concentration of flavonoids and phenols

Essential oil profiling using Gas Chromatography-Mass Spectrometry (GC-MS)

Utilizing FTIR and Thin Layer Chromatography (TLC) for qualitative analysis

These techniques support therapeutic formulation standardization, quality assurance, and dosage optimization.

2.5 Correlation with Pharmacological Activities

The pharmacological effects of Hypericum species are intimately associated with their bioactive substances. Both hypericin and pseudohypericin have potent antiviral, anticancer, and photodynamic properties. By modifying neurotransmitters and lowering inflammation, hyperforin and adhyperforin support neuroprotection. While biflavonoids like amentoflavone have cytoprotective and anticancer properties, flavonoids like quercetin and rutin have

strong antioxidant, anti-inflammatory, and neuroprotective properties. Mangiferin is one of the xanthones that exhibit anticancer, antibacterial, and antioxidant properties. Phenolic acids also improve neuroprotection and increase antioxidant capacity.

3. Neuroprotective Potential of *Hypericum*

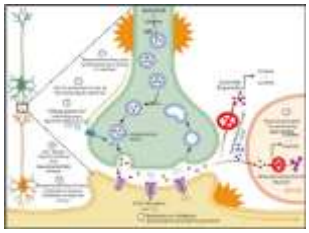

Fig.2-Mechanism of Acetylcholine Neurotransmission and Degradation in Cholinergic Synapses.

3.1 Mechanisms of Neuroprotection

Numerous molecular and cellular processes that support the preservation of brain structure and function in pathological situations are responsible for the neuroprotective benefits of Hypericum species, particularly Hypericum perforatum. These systems work together to combat the neurodegenerative processes that are prevalent in conditions including multiple sclerosis, Parkinson's, Alzheimer's, and Huntington's disease.

3.1.1 Antioxidant and Anti-inflammatory Pathways

The pathophysiology of the majority of neurodegenerative disorders is largely influenced by oxidative stress and persistent inflammation. Flavonoids (quercetin, kaempferol) and phenolic acids (chlorogenic acid) found in hypericum extracts have strong antioxidant properties through scavenging reactive oxygen species (ROS), chelating metal ions, and boosting endogenous antioxidant enzyme systems such as glutathione peroxidase (GPx) and superoxide dismutase (SOD). At the same time, pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 are downregulated, while enzymes like COX-2 and iNOS are inhibited, resulting in an anti-inflammatory effect.

3.1.2 Neurotransmitter Modulation

The neurochemical actions of Hypericum, especially through hyperforin, include the inhibition of neuronal reuptake of serotonin, dopamine, norepinephrine, glutamate, and GABA. By restoring synaptic function and lowering excitotoxicity—a major cause of neuronal damage in a number of CNS disorders—this mechanism not only supports H. perforatum's antidepressant action but also improves neuroprotection.

3.1.3 Mitochondrial Support and Anti-apoptotic Effects

One of the hallmarks of neurodegeneration is mitochondrial malfunction. Hypericum contains compounds that promote ATP synthesis, decrease oxidative mitochondrial damage, and improve mitochondrial membrane potential. Additionally, they prevent programmed cell death in neurons by lowering cytochrome c release, blocking caspase activation, and modifying the Bcl-2/Bax ratio.

3.2 Effects in Neurodegenerative Diseases

3.2.1 Alzheimer's Disease (AD)

Acetylcholinesterase inhibitory action in hypericum extracts improves cholinergic transmission in Alzheimer's disease. In preclinical models, antioxidant and anti-inflammatory qualities improve memory and learning processes and lessen amyloid-beta-induced neurotoxicity.

3.2.2 Parkinson's Disease (PD)

Hypericum species have been demonstrated to mitigate mitochondrial oxidative stress, inhibit microglial activation, and lessen dopaminergic neuronal loss in PD models. Flavonoids and hyperforin help restore motor function and guard against MPTP-induced neurotoxicity.

3.2.3 Huntington's Disease (HD)

Compounds from Hypericum have shown anti-glutamatergic activity and mitochondrial support, both of which are critical in HD pathophysiology, despite their less thorough research. Their therapeutic promise is further supported by their function in regulating apoptotic signals.

3.2.4 Multiple Sclerosis (MS)

By inhibiting pro-inflammatory cytokines and boosting antioxidant defense, hypericum extracts may lessen MS-related neuroinflammation, thereby lowering demyelination and encouraging axonal preservation.

3.3 Preclinical and Clinical Studies

The neuroprotective effects of Hypericum perforatum in in vitro neuronal cells and in vivo mouse models of neurodegeneration have been confirmed by numerous preclinical investigations. These investigations frequently demonstrate reductions in oxidative and inflammatory indicators, enhancements in neuronal survival, and increases in cognitive function.

H. perforatum is a popular herbal antidepressant in therapeutic settings, and there is evidence that it also improves mood and cognitive function in older adults. Its positive safety profile, multitarget activity, and natural origin make it a potential option for the creation of future integrative therapies, even if its neuroprotective benefits have not yet been thoroughly investigated in extensive clinical studies for neurodegenerative illnesses.

4. Anticancer Potential of *Hypericum*

By causing apoptosis and preventing tumor growth, hypericin-mediated photodynamic therapy is the main way that hypericum species demonstrate their anticancer potential. Through cytotoxic, anti-inflammatory, and antioxidant processes, hyperforin, flavonoids, and xanthones help reduce metastasis, inhibit the growth of cancer cells, and induce cell cycle arrest.

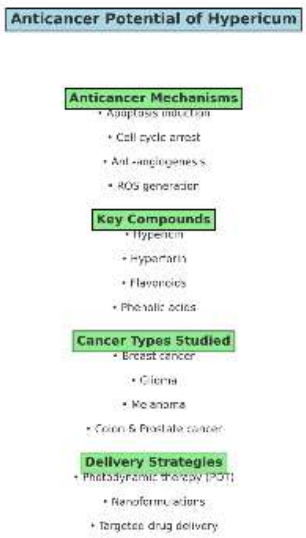

Fig.-3. Anticancer potential of Hypericum

4.1 Mechanisms of Anticancer Activity

a) Induction of Apoptosis

By inhibiting anti-apoptotic proteins like Bcl-2 and triggering caspases and pro-apoptotic proteins like Bax, hypericin and hyperforin cause cancer cells to undergo intrinsic and extrinsic apoptosis.

b) Cell Cycle Arrest

Hypericum species have compounds that can stop the cell cycle at the G1 or G2/M stages, which stops cancer cells like gliomas, breast cancer, and melanoma from growing.

c) Inhibition of Angiogenesis

Hypericin suppresses VEGF expression and blocks new blood vessel formation, limiting nutrient supply to tumor and slow their growth.

d) Generation of Reactive Oxygen Species (ROS)

In photodynamic therapy, hypericin functions as a light-activated photosensitizer, generating reactive oxygen species (ROS) that cause oxidative damage and destroy tumor cells.

4.2 Preclinical and Experimental Evidence

Preclinical research on Hypericum species shows strong anticancer properties; different cancer cell lines are cytotoxically affected by hypericin and hyperforin. Tumor growth inhibition, apoptosis induction, and anti-angiogenic actions are demonstrated in in vivo models, indicating their potential for more clinical research.

4.3 Cancer Types Investigated

CANCER TYPE	OBSERVED EFFECT
Breast Cancer	Phototoxic apoptosis, growth inhibition
Glioma	Cytotoxicity, oxidative damage
Melanoma	ROS generation, cell cycle arrest
Colon and prostrate cancer	Improved bioavailability via nanoformulations

4.4 Advanced Drug Delivery and Therapeutic Strategies

Recent developments concentrate on enhancing solubility and tumor selectivity by fusing chemicals derived from Hypericum with nanotechnology and customized delivery systems. Hypericin-based photodynamic therapy (PDT) is a noteworthy approach for treating localized cancer with few side effects.

5. Advances in Drug Delivery Systems

Poor water solubility, low bioavailability, and significant first-pass metabolism have hampered the therapeutic use of Hypericum species, particularly H. perforatum. Recent developments have concentrated on innovative drug delivery strategies, especially those incorporating nanotechnology, to get around these pharmacokinetic obstacles and improve its neuroprotective and anticancer potential.

5.1 Nanotechnology in Hypericum Formulations

A revolutionary method for enhancing the stability, bioavailability, and site-specific delivery of chemicals produced from hypericum, such as hypericin and hyperforin, is nanotechnology. These molecules are shielded from deterioration, their solubility is improved, and regulated release is made possible by encapsulation within nanocarriers.

5.2 Liposomes, Nanoparticles, and Nanogels

Solid lipid nanoparticles (SLNs), liposomes, polymeric nanoparticles, and nanogels are among the different nano-formulations that have shown encouraging outcomes. Both hydrophilic and lipophilic substances can be encapsulated by liposomes, providing defense against metabolic degradation. Conversely, SLNs and polymeric nanoparticles guarantee longer systemic circulation, improved permeability across the blood–brain barrier (BBB), and regulated release. For CNS and skin applications, nanogels' mucoadhesive and thermoresponsive qualities are helpful.

5.3 Targeted Delivery to CNS and Tumor Tissues

Targeted medication delivery to particular tissues, such as the central nervous system (CNS) and tumor microenvironments, can be accomplished by engineering these nanocarriers. Nanoparticles can be functionalized with ligands that enable BBB penetration for neuroprotective applications, guaranteeing efficient delivery of neuroactive ingredients. Photodynamic therapy (PDT) in oncology has employed hypericin-loaded nanoparticles, which exhibit preferential accumulation in tumor tissues, enhancing phototoxic effects while preserving healthy cells.

5.4 Overcoming Bioavailability and Solubility Issues

All things considered, the pharmacokinetic profiles of Hypericum drugs are much improved by nanocarrier-based systems, which address important problems such low gastrointestinal absorption, quick systemic clearance, and poor solubility. By lowering the necessary dosages, these technologies not only improve treatment efficacy but also lessen the possibility of adverse effects and drug interactions.

6. Safety, Toxicology, and Herb–Drug Interactions

The safety profile, toxicity risks, and potential for drug interactions of Hypericum perforatum, also known as St. John's Wort, must be critically understood due to its extensive usage in herbal therapy. Although hypericum-based preparations are usually thought to be safe when used at therapeutic dosages, inappropriate or unsupervised use might result in interactions and side effects that are clinically relevant, especially in situations involving polypharmacy.

6.1 Potential Side Effects and Contraindications

H. perforatum frequently causes photosensitivity, gastrointestinal issues, exhaustion, dry mouth, lightheadedness, and minor allergic reactions as side effects. Rarely, excessive dosages or extended use have been connected to manic episodes in bipolar illness patients. A well-established worry is photosensitization, particularly in people with pale skin or those who are exposed to strong sunshine.

Due to its enzyme-inducing qualities, it is contraindicated for usage in pregnant and lactating women, people with bipolar affective disorder, and patients undergoing organ transplantation or immunosuppressive medication.

6.2 Known Interactions with Antidepressants, Anticancer Drugs, and Others

Hypericum has strong enzyme-inducing properties, especially on P-glycoprotein (P-gp) and cytochrome P450 (CYP3A4), which can change the plasma concentrations of medications taken together. The combined serotonergic effects of antidepressants are known to cause serotonin syndrome, which is characterized by agitation, disorientation, tremors, and hyperthermia.

Furthermore, by speeding up their metabolism, Hypericum has been demonstrated to lessen the efficiency of immunosuppressants (like cyclosporine), oral contraceptives, anticoagulants (like warfarin), antiviral drugs, and anticancer drugs. Depending on the situation, this could result in toxicity or therapeutic failure.

6.3 Dosage Considerations and Regulatory Status

Depending on the indication, standardized extracts of H. perforatum are given in doses ranging from 300 to 900 mg/day and usually include 0.3% hypericin. However, determining a therapeutic window is difficult because formulations differ in terms of content and bioactivity.

Global regulatory monitoring differs: although H. perforatum is sold over-the-counter in several European nations to treat mild-to-moderate depression, the U.S. FDA restricts its clinical regulation by classifying it as a dietary supplement. Therefore, when Hypericum is added to treatment regimens, practitioners are encouraged to keep an eye on patients for potential interactions and side effects.

7. Challenges and Future Perspectives

Inconsistent phytochemical profiles, a dearth of clinical studies, and inadequate extract standardization are the main obstacles to current research on Hypericum species. Furthermore, important chemicals' limited solubility and bioavailability lessen their therapeutic effect.

To increase efficacy, future research should focus on clinical validation, standardized formulations, and cutting-edge delivery methods like nanoparticles. Developing successful contemporary treatments from Hypericum's potential will require an interdisciplinary approach.

8. Conclusion

Because of its diverse phytochemical makeup, which includes hypericin, hyperforin, and other flavonoids, Hypericum species—especially H. perforatum—show encouraging neuroprotective and anticancer properties. Through processes including neurotransmitter regulation, antioxidant action, anti-inflammatory pathways, and inducing apoptosis in cancer cells, these substances produce therapeutic benefits.

Hypericum's dual pharmacological potential emphasizes how beneficial it is for treating complicated illnesses like cancer and neurodegeneration. To fully achieve its therapeutic promise, however, more clinical trials, standardized formulations, and sophisticated drug delivery methods are required. Converting preclinical data into secure, efficient clinical applications should be the main goal of future studies.

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