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Advancing St. John's Wort Therapy through Nanotechnology: A Comprehensive Review

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ABSTRACT

Hypericum perforatum (St. John's Wort) has been widely employed in traditional and modern phytotherapy for its antidepressant, anti-inflammatory, antimicrobial, antioxidant, and wound-healing activities. These effects arise from bioactive constituents such as hypericin, hyperforin, flavonoids, and phloroglucinols. However, its therapeutic potential is restricted by poor aqueous solubility, low oral bioavailability, photodegradation, and rapid metabolic breakdown, which collectively limit its clinical effectiveness. Nanotechnology-based drug delivery systems have emerged as an effective strategy to overcome these limitations and enhance the pharmacokinetic and pharmacodynamic performance of *H. perforatum*.This review presents a comprehensive overview of the nanoherbal formulations developed for *H. perforatum*, including polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, phytosomes, nanoemulsions, niosomes, and nanogels. Formulation strategies, preparation methods, and key characterization parameters—such as particle size distribution, zeta potential, encapsulation efficiency, release profile, and stability—are discussed to highlight the advantages offered by different nanocarrier systems.Published findings demonstrate that nanoformulations significantly improve the solubility, stability, permeability, and controlled release of *H. perforatum* constituents. Enhanced pharmacological outcomes have been reported in areas such as neuroprotection, wound healing, anti-inflammatory action, and antimicrobial activity, primarily due to improved cellular uptake and sustained therapeutic levels. Safety, toxicity considerations, and known herb–drug interactions, particularly involving hyperforin-mediated CYP450 modulation, are also addressed to ensure a balanced evaluation.Overall, nanoherbal delivery systems offer a promising approach to optimize the therapeutic performance of *Hypericum perforatum*, enabling more targeted, stable, and efficacious clinical applications of this traditional medicinal herb.

Keywords: Hypericum perforatum, Nanoherbal formulations, Nanocarriers, Phytoconstituents, Drug delivery systems

1. INTRODUCTION

Herbal medicines have formed the backbone of traditional healthcare systems across civilizations, offering therapeutic benefits from nature's own pharmacy. Despite their remarkable pharmacological potential, most herbal extracts face a persistent obstacle in modern medicine — poor solubility, limited bioavailability, chemical instability, and lack of site-specific delivery. The active phytoconstituents, often polyphenolic or lipophilic in nature, undergo rapid metabolism and degradation, resulting in diminished therapeutic outcomes. To bridge this gap between traditional efficacy and modern pharmaceutical precision, **nanotechnology** has emerged as a transformative platform.

Nanoformulation —Embedding herbal actives or purified phytochemicals into nanocarrier platforms—such as liposomes, phytosomes, nanoemulsions, polymeric particles, solid lipid systems, and nanostructured lipid carriers—boosts their therapeutic performance by enhancing solubility, stability, membrane penetration, and overall bioavailability.[1] These nanosystems enable targeted and controlled drug release, minimize dose frequency, and offer protection against environmental degradation (light, oxygen, temperature). Moreover, nanoformulations can modulate pharmacokinetic parameters and improve patient compliance, thus aligning the age-old wisdom of herbal therapy with the scientific rigor of contemporary drug delivery.

Recent years have witnessed an explosion of **nanoherbal formulations** across various pharmacological domains — from antioxidant-rich curcumin nanoparticles, resveratrol-loaded liposomes, and quercetin nanoemulsions, to phytosomal systems of ginkgo and green tea. This union of nanotechnology and phytotherapy, often referred to as *"herbonanotechnology,"* represents a paradigm shift — transforming crude extracts into precision therapeutics with quantifiable pharmacodynamics.

Among the many botanicals investigated, ***Hypericum perforatum* L. (St. John's Wort)** has attracted considerable attention for its diverse pharmacological properties and its well-documented clinical use in mood disorders, wound healing, inflammation, and infections. *H. perforatum*, a perennial herb belonging to the family **Hypericaceae**, contains bioactive constituents such as **hypericin, pseudohypericin, hyperforin, flavonoids (quercetin, rutin), phenolic acids, and xanthones**, which collectively contribute to its antidepressant, antioxidant, anti-inflammatory, antimicrobial, and neuroprotective effects[2].

However, despite its broad therapeutic potential, the clinical utility of *H. perforatum* is hampered by **poor water solubility, low bioavailability, and photosensitivity** of its key compounds — particularly hypericin and hyperforin[3]. These compounds degrade under light exposure and undergo extensive first-pass metabolism, leading to inconsistent plasma concentrations and therapeutic variability. Such limitations have motivated the application of **nanocarrier-based systems** to optimize the delivery of *H. perforatum* extracts and isolated constituents.

Recent research has explored a variety of **nanoformulation approaches** for *H. perforatum*, including **liposomes, nanoemulsions, phytosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), niosomes, polymeric nanoparticles, and electrospun nanofiber scaffolds**.[4] These delivery platforms have demonstrated significant improvements in pharmacological outcomes — enhanced wound healing, stronger antioxidant effects, improved neuroprotection, and better stability of hypericin/hyperforin under physiological conditions.

Thus, nanoformulation of *Hypericum perforatum* exemplifies how **traditional herbal wisdom can be refined through nanotechnology** to overcome physicochemical and pharmacokinetic challenges. This review consolidates the current advancements, preparation techniques, pharmacological implications, and translational prospects of *H. perforatum* nanoformulations, with a focus on their potential to enhance therapeutic efficacy while preserving the herb's natural integrity.

Phytochemical Profile and Therapeutic Essence of *Hypericum perforatum* L. (St. John's Wort)

Hypericum perforatum L., widely celebrated as St. John's Wort, is a resilient perennial herb that belongs to the family *Hypericaceae*. For centuries, it has stood as a botanical cornerstone in traditional and modern medicine, revered for its diverse therapeutic virtues. Its remarkable healing capacity arises from a rich constellation of bioactive compounds, each weaving a unique thread into its vast pharmacological tapestry.

Phytochemical Composition

The chemical makeup of *H. perforatum* is a harmonious blend of several potent groups of phytoconstituents that together contribute to its wide-ranging biological effects:

- **Naphthodianthrones** — chiefly *hypericin* and *pseudohypericin* — form the hallmark pigments of the plant. These compounds are renowned for their antidepressant, antiviral, and photodynamic activities, serving as key modulators in neural and cellular processes.[5]

- **Phloroglucinol derivatives**, primarily *hyperforin* and *adhyperforin*, are pivotal to the herb's mood-enhancing action. By regulating neurotransmitter reuptake and ion channel functions, they manifest strong antidepressant, antimicrobial, and anti-inflammatory effects.

- **Flavonoids** such as *quercetin*, *rutin*, *isoquercitrin*, *hyperoside*, and *kaempferol* enrich the plant's antioxidant arsenal. These compounds act as powerful free-radical scavengers, protecting cellular structures from oxidative damage and supporting anti-inflammatory balance.

- **Phenolic acids** including *chlorogenic*, *caffeic*, and *ferulic acid* further augment its antioxidant and hepatoprotective properties, enhancing resilience against metabolic and environmental stressors.

- **Xanthones and essential oils**, though present in trace amounts, contribute synergistically to the herb's antimicrobial and anti-inflammatory potential, amplifying the collective efficacy of the extract.

Together, these phytochemicals orchestrate a multi-dimensional pharmacological response, enabling *Hypericum perforatum* to act not merely as an antidepressant, but as a neuroprotective, regenerative, and systemically harmonizing herb. Its ability to bridge neural health with cellular repair underscores its enduring significance in both traditional healing and modern pharmacotherapy.[6]

Pharmacological Profile of *Hypericum perforatum* L.

The pharmacological significance of *Hypericum perforatum* lies in the intricate synergy of its phytochemical constituents, which act across multiple physiological pathways. The herb's therapeutic breadth encompasses neurological, antimicrobial, anti-inflammatory, and wound-healing domains, establishing it as one of the most versatile botanicals in contemporary phytotherapy[7].

1. Antidepressant and Neuroprotective Activity

The antidepressant efficacy of *H. perforatum* is primarily attributed to the combined actions of *hyperforin*, *adhyperforin*, *hypericin*, and various flavonoids. These compounds modulate the levels of key neurotransmitters such as serotonin, dopamine, and norepinephrine by inhibiting their synaptic reuptake. Additionally, they influence the hypothalamic–pituitary–adrenal (HPA) axis, mitigating stress-induced neurochemical imbalances.
Hyperforin has been shown to enhance neuronal plasticity, promote synaptogenesis, and exert neuroprotective effects by regulating calcium influx and oxidative stress. The result is a gentle yet effective stabilization of mood and cognitive function, often comparable to standard synthetic antidepressants but with fewer side effects.

2. Anti-Inflammatory and Antioxidant Effects

Flavonoids and phenolic acids in *H. perforatum* serve as potent inhibitors of inflammatory mediators such as prostaglandins, cytokines, and nitric oxide. Their antioxidant properties protect lipid membranes, DNA, and proteins from oxidative degeneration, which plays a critical role in chronic inflammatory and degenerative diseases.[8]
Quercetin and kaempferol strengthen the plant's defense against reactive oxygen species, while ferulic acid and chlorogenic acid help restore oxidative balance in the tissues."

3. Antimicrobial and Antiviral Potential

Naphthodianthrones like *hypericin* exhibit broad-spectrum antimicrobial and antiviral properties, acting against gram-positive bacteria, fungi, and enveloped viruses. The mechanism involves disruption of microbial membranes and inhibition of viral replication. Under light exposure, *hypericin* generates reactive oxygen species that further enhance its photodynamic antimicrobial action — a property being explored in photodynamic therapy (PDT).

4. Wound Healing and Tissue Regeneration

The flavonoid-rich extracts of *H. perforatum* accelerate epithelialization, collagen synthesis, and angiogenesis in damaged tissues. These effects are partly mediated by antioxidant protection and modulation of growth factors such as VEGF and TGF-β. Traditional uses of St. John's Wort oil for burns, cuts, and ulcers are now scientifically validated through in vivo studies confirming its regenerative efficacy.[9]

5. Analgesic and Neurocalming Effects

The herb's interaction with opioid and GABAergic systems contributes to its analgesic and anxiolytic potential. Through mild inhibition of pain perception and muscle relaxation, *H. perforatum* offers a natural alternative for managing neuropathic pain, mild anxiety, and sleep disturbances.

Collectively, these pharmacological attributes position *Hypericum perforatum* as a multifaceted therapeutic agent capable of addressing both psychological and physiological disorders through a holistic biochemical mechanism. Its balanced pharmacodynamics — rooted in natural synergy — make it a model candidate for developing standardized phytopharmaceuticals and novel drug delivery systems.

Types of Nanocarriers Applied to *Hypericum perforatum* and Methods of Preparation

To overcome the intrinsic drawbacks of *Hypericum perforatum* (poor solubility, light sensitivity, rapid metabolism, and low bioavailability), various **nanocarrier systems** have been developed. Each type of nanocarrier offers unique physicochemical and biological advantages, allowing tailored delivery for topical, oral, or neuroprotective applications.

Below is a comprehensive overview of the principal nanocarriers employed for *H. perforatum*, along with their preparation methods and pharmaceutical significance.

1. Liposomes

Description:
Liposomes are round vesicular structures made of single or multiple phospholipid bilayers that enclose a water-filled center. Their architecture allows them to carry hydrophilic molecules inside the core and lipophilic compounds within the lipid layers. For *H. perforatum*, liposomes are particularly useful to protect hypericin and hyperforin from light-induced degradation and to enhance their dermal and mucosal permeation.[10]

Preparation Methods:

- **Thin Film Hydration Method:** Phospholipids and cholesterol are first dissolved in an organic solvent, after which the solvent is evaporated to leave a thin lipid film. This film is then rehydrated using an aqueous solution containing *H. perforatum* extract under controlled temperature and agitation.

- **Reverse Phase Evaporation:** Lipid and aqueous phases are emulsified, followed by solvent removal under reduced pressure, producing unilamellar vesicles.

- **Sonication or Extrusion:** Used to reduce size of particle and obtain small unilamellar vesicles (~100–200 nm).

Advantages:

- Enhanced stability of hypericin and hyperforin.

- Improved penetration in skin and mucosal layers.

- Controlled release and reduced photodegradation.

Applications:
A liposomal in-situ hydrogel of *H. perforatum* demonstrated significantly faster wound closure and improved collagen synthesis compared to conventional ointments.

2. Nanoemulsions and Nanoemulsion-based Hydrogels

Description:
Nanoemulsions are colloidal mixtures of oil, water, surfactants, and co-surfactants that, although not thermodynamically stable, maintain kinetic stability. Their droplets generally fall within the 20–200 nm size range.*H. perforatum* oil or ethanolic extract can be loaded in the oil phase to form nanoemulsions suitable for oral, dermal, or intranasal delivery[11].

Preparation Methods:

- **High-energy techniques:** Methods like high-pressure homogenization or ultrasonication are used to break down droplets to the nanoscale.

- **Low-energy techniques:** Approaches such as spontaneous emulsification or phase inversion rely on optimized surfactant and co-surfactant ratios to form nano-sized droplets.

Advantages:

- Enhanced solubility of lipophilic hyperforin and hypericin.

- Increased permeation through biological membranes.

- Suitable for brain targeting via intranasal route.

Applications:

Nanoemulsions of *H. perforatum* exhibited neuroprotective effects against cisplatin-induced neurotoxicity and enhanced antioxidant enzyme activity in preclinical studies.

3. Phytosomes and Nanophytosomes

Description:

Phytosomes are **phospholipid–phytoconstituent complexes** where the polar functional groups of the plant compounds interact with phosphatidylcholine to form stable molecular complexes. This improves lipid compatibility and membrane permeability.

Preparation Methods:

- Dissolve *H. perforatum* extract and phospholipid (e.g., phosphatidylcholine) in an organic solvent like dichloromethane or ethanol.
- Evaporate the solvent to obtain a thin film, then dry and collect the phytosome complex.
- The resulting nanophytosomes can be further dispersed in aqueous media for topical or oral application.

Advantages:

- Enhanced bioavailability and membrane absorption.
- Protection against hydrolytic degradation.
- Stable complex formation suitable for solid dosage forms.

Applications:

H. perforatum phytosomes showed superior neuroprotective and anti-inflammatory effects in neuropathic pain.

4 Solid Lipid Nanoparticles (SLNs)

Description:

SLNs are **submicron-sized lipid particles** made of solid lipids stabilized by surfactants. They encapsulate lipophilic drugs within a solid lipid matrix, providing controlled release and high stability.

Preparation Methods:

- **Hot Homogenization and Ultrasonication:** The lipid (melted) and aqueous phases are emulsified at elevated temperature, followed by homogenization and rapid cooling to form solid particles.
- **Solvent Evaporation Method:** Lipids are first dissolved in an organic solvent, then mixed with an aqueous surfactant solution to form an emulsion. Once the solvent is evaporated, nanoparticles are obtained.

Advantages:

- Protection of hyperforin from oxidation and degradation.
- Controlled release profile with improved bioavailability.
- Biocompatible and non-toxic carriers suitable for topical and oral routes.

Applications:

SLNs loaded with *H. perforatum* extract exhibited enhanced antimicrobial and antiherpetic activity, making them potential candidates for topical antiviral formulations.

5 Nanostructured Lipid Carriers (NLCs)

Description:

Nanostructured lipid carriers represent an advanced form of lipid nanoparticles, combining solid and liquid lipids to form a loosely arranged matrix. This structure enhances drug-loading capacity and reduces the risk of drug leakage during storage.

Preparation Methods:

Similar to SLNs but involve both solid and liquid lipids in the lipid phase before homogenization and cooling.

Advantages:

- Higher encapsulation efficiency than SLNs.
- Better stability and sustained release.
- Improved dermal delivery and antimicrobial performance.

Applications:

NLCs containing *H. perforatum* extracts demonstrated potent antimicrobial and antiherpetic effects and faster wound healing due to enhanced skin permeation.

6 Polymeric Nanoparticles

Description:

Polymeric nanoparticles are solid colloidal particles composed of biodegradable polymers such as PLGA, chitosan, or Eudragit, which can entrap or adsorb herbal extracts.

Preparation Methods:

- Emulsion–Solvent Evaporation: The polymer and herbal extract are dissolved in an organic solvent, dispersed into an aqueous phase to create an emulsion, and then the solvent is removed, resulting in nanoparticle formation.
- **Nanoprecipitation:** Rapid mixing of organic and aqueous phases leads to spontaneous nanoparticle formation.

Advantages:

- Precise control over size and release kinetics.
- Suitable for both hydrophilic and lipophilic constituents.
- Potential for targeted delivery to the brain or inflammatory sites.

Applications:

Polymeric nanoparticles of *H. perforatum* have been explored for sustained neuroprotective delivery and antioxidant therapy.

7 Niosomes

Description:

Niosomes are **non-ionic surfactant-based vesicles** structurally similar to liposomes but more stable and cost-effective.[12]

Preparation Methods:

- **Thin Film Hydration:** Similar to liposome preparation using non-ionic surfactants (e.g., Span, Tween) and cholesterol.
- **Microfluidization:** To obtain uniform vesicle size.

Advantages:

- Enhanced chemical stability compared to liposomes.
- Improved transdermal and topical delivery.
- Simple preparation and scalable production.

Applications:

Niosomal *H. perforatum* formulations improved dermal penetration and provided sustained wound-healing activity in animal studies.

8. Metallic Nanoparticles (Gold, Silver, etc.)

Description:

In biogenic synthesis, extracts of *H. perforatum* function simultaneously as reducing and stabilizing agents, producing environmentally friendly metallic nanoparticles that naturally exhibit antimicrobial and antioxidant properties.

Preparation Methods:

- Mixing *H. perforatum* aqueous extract with a metal salt solution (e.g., $HAuCl_4$ for gold nanoparticles) under mild heating or stirring until color change indicates nanoparticle formation.
- Characterization through UV–Vis, TEM, and DLS analyses.

Advantages:

- Green synthesis without toxic reagents.
- Combined biological and metallic therapeutic effects.
- Potential for photothermal or immunomodulatory applications.

Applications:

H. perforatum-derived gold nanoparticles have shown neuroprotective and immunomodulatory effects in experimental autoimmune models.

9. Electrospun Nanofiber Scaffolds

Description:

Electrospinning is a versatile method to create **nanofibrous mats** capable of encapsulating *H. perforatum* oil or extract for topical wound-healing applications.

Preparation Methods:

- A polymer solution (e.g., gelatin, PCL, or chitosan) containing *H. perforatum* oil/extract is subjected to a high-voltage electric field to produce nanofibers collected on a grounded substrate.

Advantages:

- Sustained local release of actives.
- High surface area promoting cell adhesion and tissue regeneration.
- Ideal for wound dressings and tissue engineering.

Applications:

Gelatin nanofiber scaffolds loaded with *H. perforatum* oil exhibited accelerated epithelialization and enhanced collagen deposition in vivo.

Nanocarrier Type	Key Components	Preparation Method	Particle Size (nm)	Major Application
Liposomes	Phospholipids, cholesterol	Thin film hydration	100–300	Wound healing, topical delivery
Nanoemulsion	Oil, surfactant, water	Ultrasonication	50–200	Neuroprotection, dermal delivery
Phytosome	Phospholipid complex	Solvent evaporation	100–250	Oral bioavailability
SLN	Solid lipid + surfactant	Hot homogenization	100–200	Antimicrobial, antiviral
NLC	Solid + liquid lipids	Hot homogenization	120–250	Topical/wound healing
Polymeric NP	PLGA, chitosan	Solvent evaporation	100–300	Neuroprotective systems
Niosome	Non-ionic surfactant	Thin film hydration	100–400	Transdermal delivery
Metallic NP	Gold/silver salts	Green synthesis	20–100	Antioxidant, anti-inflammatory
Nanofiber Scaffold	Gelatin/PCL polymer	Electrospinning	Fiber diameter 100–500	Wound dressing

3. Preparation and Characterization of Nanoherbal Formulations of *Hypericum perforatum*

Preparation Techniques

The selection of the preparation method depends upon the type of nanocarrier (lipid-based, polymeric, or metallic) and the physicochemical properties of *H. perforatum* extracts, particularly **hypericin** and **hyperforin**, which are highly lipophilic and sensitive to light and oxidation.

Below are the **major preparation techniques** employed for nanoformulations of *H. perforatum*:

a) Nanoprecipitation (Solvent Displacement Method)

Principle: he polymer and plant extract are first dissolved in a water-miscible organic solvent such as acetone or ethanol. When this solution is quickly introduced into a stabilizer-containing aqueous medium (like PVA or Tween 80), rapid solvent diffusion leads to the formation of nanospheres or nanocapsules.[13]

Procedure:

1. Dissolve hypericin or SJW extract and polymer (e.g., PLGA, PCL) in organic solvent.
2. Inject the solution into an aqueous surfactant under magnetic stirring.
3. Evaporate the organic solvent under reduced pressure.
4. Collect and purify nanoparticles via centrifugation.

- **Advantages:** Simple, reproducible, and suitable for thermolabile phytoconstituents.
- **Limitation:** Low encapsulation efficiency for highly hydrophilic compounds.

b) High-Pressure Homogenization (HPH)

- **Principle:** Lipid and aqueous phases containing the herbal extract are forced through a narrow gap at high pressure, producing nanolipid dispersions (SLNs/NLCs).
- **Procedure:**

1. Melt lipid (e.g., glyceryl monostearate, Compritol 888 ATO) and dissolve SJW extract.
2. Mix with hot surfactant solution (Tween 80, Poloxamer 188).
3. Homogenize under 500–1500 bar pressure for multiple cycles.
4. Cool rapidly to form solid lipid nanoparticles.

- **Advantages:** Solvent-free, scalable, suitable for lipophilic constituents like hyperforin.
- **Limitation:** May cause thermal degradation if not optimized.

c) Emulsion–Solvent Evaporation

- **Principle:** The herbal extract and polymer are dissolved in an organic solvent (oil phase) and emulsified in water containing surfactant; solvent evaporation leads to nanoparticle formation.
- **Procedure:**

1. Prepare an oil-in-water (o/w) emulsion using ultrasonication.
2. Evaporate solvent under reduced pressure.
3. Collect nanoparticles by centrifugation and lyophilize for storage.

- **Applications:** Used for polymeric nanoparticles (PLGA, Eudragit) encapsulating hypericin.[14]

d) Thin-Film Hydration (for Liposomes and Phytosomes)

- **Principle:** Lipid films are formed by solvent evaporation and hydrated with an aqueous herbal extract.[13]

- **Procedure:**

1. Dissolve phospholipids and cholesterol in chloroform–methanol (2:1).
2. Evaporate under rotary evaporator to form a thin lipid film.
3. Hydrate the film with SJW extract under gentle agitation.
4. Sonicate or extrude to reduce vesicle size.

- **Applications:** Ideal for *Hypericum*-loaded liposomes and phytosomes to improve membrane permeability and oral bioavailability.

e) Green Synthesis of Metal Nanoparticles

- **Principle:** Polyphenols and flavonoids in *H. perforatum* act as reducing and stabilizing agents to form metal nanoparticles (Ag, Au, ZnO).

- **Procedure:**

1. Prepare aqueous extract of SJW.
2. Mix with metal salt solution (e.g., $AgNO_3$, $HAuCl_4$).
3. Observe color change (indicative of nanoparticle formation).
4. Purify by centrifugation and wash repeatedly.

- **Applications:** Exhibits potent antimicrobial and wound-healing activity.

Characterization of Nanoherbal Formulations

A detailed physicochemical and biological characterization is essential to ensure the stability, efficacy, and safety of *Hypericum* nanoformulations.

a) Particle Size and Polydispersity Index (PDI)

- **Method: Measured by Dynamic Light Scattering (DLS).**
- **Interpretation:** Nanoparticles typically range between **50–300 nm**; PDI < 0.3 indicates uniform distribution.[14]

b) Zeta Potential

- **Purpose:** Determines surface charge and colloidal stability.
- **Method:** Measured by electrophoretic light scattering.
- **Ideal Range:** ±30 mV ensures electrostatic repulsion and suspension stability.

c) Morphology and Surface Topography

- **Techniques:**
  - **Transmission Electron Microscopy (TEM):** Determines size and shape (spherical or irregular).
  - **Scanning Electron Microscopy (SEM):** Reveals surface texture and aggregation pattern.

- **Atomic Force Microscopy (AFM):** Provides 3D surface topology.

d) Encapsulation Efficiency (EE%) and Drug Loading (DL%)

- **Method:** Centrifuge nanoparticles, quantify unentrapped drug via UV–Vis or HPLC.
- **Formulas:**

$$EE\% = \frac{(Total\ drug - Free\ drug)}{Total\ drug} \times 100 \quad DL\% = \frac{Entrapped\ drug}{Total\ weight\ of\ nanoparticles} \times 100$$

- **Significance:** Determines effectiveness of drug entrapment — critical for poorly soluble hypericin.

e) Fourier Transform Infrared Spectroscopy (FTIR)

- Used to detect **chemical interactions** between plant constituents and excipients (lipids/polymers).
- Confirms successful encapsulation without degradation of active compounds.

f) Differential Scanning Calorimetry (DSC) & X-Ray Diffraction (XRD)

- **DSC:** Analyzes thermal behavior and crystallinity of lipid matrices.
- **XRD:** Confirms amorphous or crystalline nature — amorphous form enhances dissolution rate.

g) In Vitro Drug Release Studies

- Conducted using **dialysis bag** or **Franz diffusion cell** in simulated gastrointestinal or physiological fluids.
- **Kinetic Models:** Zero-order, first-order, Higuchi, and Korsmeyer–Peppas models help determine release mechanisms (diffusion, erosion, or swelling).

h) Stability Studies

- Nanoformulations are stored under **accelerated (40°C/75% RH)** and **room temperature** conditions.
- Evaluated for changes in particle size, zeta potential, EE%, and color degradation (especially for light-sensitive hypericin).

i) Biological Characterization

- **Cytotoxicity assays (MTT, LDH)** on fibroblast or keratinocyte cell lines to confirm biocompatibility[15].
- **Antioxidant (DPPH, ABTS)** and **anti-inflammatory (NO inhibition)** assays assess biological potency compared to crude extract.

Pharmacological Outcomes from Nanoformulated *Hypericum perforatum* (St. John's Wort)

Nanoformulations of *Hypericum perforatum* (SJW) have demonstrated **enhanced pharmacological potential** compared to conventional extracts, mainly due to **improved solubility, stability, and bioavailability** of its active constituents like **hypericin, hyperforin, quercetin, and flavonoids**.[16] Below is a brief overview of key pharmacological outcomes observed:

1. Antidepressant Activity

Nano-SJW formulations (such as liposomes, polymeric nanoparticles, and SLNs) show **improved penetration across the blood–brain barrier (BBB)** and **sustained drug release**, leading to **enhanced antidepressant efficacy**. The nanoformulated form ensures stable plasma concentration of hyperforin and hypericin, reducing mood fluctuations and side effects.

2. Antioxidant & Anti-inflammatory Activity

Nanocarrier-loaded SJW exhibits **superior radical scavenging activity** due to increased surface area and controlled release of flavonoids. This enhances **cellular protection against oxidative stress** and reduces inflammatory cytokines, beneficial in neurodegenerative and skin inflammatory disorders.

3. Wound Healing and Dermatological Effects

Nanoemulsion and nanogel forms of SJW improve **skin permeability**, leading to **accelerated wound healing**, better collagen synthesis, and **enhanced antimicrobial protection**. These formulations maintain stability of hypericin, which is otherwise light-sensitive.

4. Neuroprotective and Anticancer Effects

Nanoformulated SJW protects neurons from oxidative damage and apoptotic cell death. In cancer models, nanoparticle delivery enhances **cytotoxicity against tumor cells** while minimizing toxicity to normal cells due to targeted delivery.

5. Improved Bioavailability and Stability

The encapsulation of hypericin and hyperforin within nanocarriers prevents **degradation by light and oxidation**, improving **oral absorption and systemic circulation**. This leads to prolonged pharmacological action and reduced dosing frequency.

Safety, Toxicology & Herb–Drug Interactions of Nanoformulated *Hypericum perforatum* (St. John's Wort)

The increasing use of *Hypericum perforatum* (SJW) in nanoformulated systems—such as liposomes, solid lipid nanoparticles (SLNs), nanoemulsions, and polymeric nanoparticles—has raised important considerations regarding its **safety, toxicology, and herb–drug interactions**. While nanoformulation enhances therapeutic efficacy, it also alters **pharmacokinetics, biodistribution, and cellular interactions**, necessitating careful toxicological assessment.

1. Safety and Biocompatibility of Nanoformulated SJW

Nanoformulations of SJW are generally considered **biocompatible and non-toxic**, especially when formulated with biodegradable polymers (e.g., PLGA, chitosan, PEG) and natural lipids. However, safety depends on the **carrier type, surface charge, and particle size**.

a. Cytotoxicity Studies

- **In vitro studies** using fibroblast, keratinocyte, and neuronal cell lines have shown that nanoencapsulated SJW extracts have **low cytotoxicity** up to concentrations of 100 µg/mL.

- Nanoencapsulation reduces the **direct phototoxicity** of hypericin by shielding it from light exposure and preventing reactive oxygen species (ROS) generation.

b. Hemocompatibility and Immunocompatibility

- Lipid-based nanoparticles exhibit **minimal hemolysis** and no significant immune activation.

- Polymeric nanoparticles show **negligible complement activation**, making them suitable for systemic administration.

c. **Phototoxicity Reduction**

- Free hypericin is known to be **highly photosensitive**, leading to skin irritation and phototoxic reactions.

- Nanoencapsulation (especially in liposomes and SLNs) significantly **reduces light-induced cytotoxicity**, allowing safe use in topical and oral formulations.[17]

d. In Vivo Toxicity

- Animal studies have demonstrated that nanoformulated SJW does **not induce hepatotoxicity or nephrotoxicity** at therapeutic doses.

- Chronic administration studies reveal **no significant histopathological changes** in liver, kidney, or brain tissues.

2. Toxicological Concerns with Nanoformulations

While nanoformulation offers safety advantages, certain risks remain:

- **Nanoparticle Accumulation:** Prolonged exposure may cause nanoparticle retention in organs such as the liver and spleen, depending on surface charge and size.

- **Altered Pharmacokinetics:** The nanoform may change the **metabolic rate or plasma half-life**, possibly amplifying adverse reactions when combined with other drugs.

- **Excipient Toxicity:** Some surfactants and stabilizers (e.g., polysorbates, CTAB) used in nanoformulations may cause local irritation or allergic reactions.

Hence, **long-term toxicity, genotoxicity, and reproductive toxicity** assessments are essential before clinical use.

3. Herb–Drug Interactions

Both standard and nanoformulated SJW are known to strongly activate cytochrome P450 enzymes—particularly CYP3A4 and CYP2C9—as well as the efflux transporter P-glycoprotein (P-gp) [18]. These interactions can lead to **significant alterations in plasma concentrations** of co-administered drugs.

a. Mechanisms of Interaction

1. **Induction of CYP3A4:** Leads to enhanced metabolism and reduced plasma levels of many drugs.

2. **Activation of P-glycoprotein Efflux:** Reduces drug absorption and increases excretion.

3. **Influence on MAO and serotonin levels:** Can lead to **serotonin syndrome** when combined with antidepressants (SSRIs, SNRIs, MAO inhibitors).

Drug Class	Example Drugs	Type of Interaction	Clinical Effect
Antidepressants	Sertraline, Fluoxetine	Additive serotonergic effect	Risk of serotonin syndrome
Oral Contraceptives	Ethinylestradiol	CYP3A4 induction	Reduced contraceptive efficacy
Immunosuppressants	Cyclosporine, Tacrolimus	CYP3A4 induction	Risk of graft rejection
Anticoagulants	Warfarin	Increased metabolism	Reduced anticoagulant effect
Antiretrovirals	Indinavir, Nevirapine	Enhanced clearance	Decreased antiviral efficacy
Anticancer agents	Irinotecan, Docetaxel	Altered metabolism	Decreased efficacy or toxicity

4. Strategies to Minimize Toxicity & Interactions

- **Controlled Release Systems:** Sustained-release nanocarriers reduce peak plasma concentrations, minimizing CYP enzyme induction.[19]

- **Surface Modification:** PEGylation or ligand-functionalized nanoparticles can reduce off-target effects.

- **Topical and Localized Delivery:** Reduces systemic exposure, ideal for dermatological and wound-healing applications.

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Conclusion

Nanoherbal formulations of *Hypericum perforatum* (St. John's Wort) represent a remarkable advancement in merging traditional phytotherapy with modern nanotechnology. Through encapsulation in various nanocarriers—such as liposomes, solid lipid nanoparticles, polymeric nanoparticles, and nanoemulsions—the inherent challenges of SJW's poor solubility, light sensitivity, and inconsistent bioavailability have been effectively addressed. These nanoformulations have demonstrated **enhanced stability, targeted delivery, controlled release, and superior therapeutic efficacy** across multiple pharmacological domains, including antidepressant, antioxidant, anti-inflammatory, neuroprotective, and wound-heal.

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