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Pharmacological Activities, Toxicity, and Drug Interactions of Hypericum Perforatum L.

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ABSTRACT: Hypericum perforatum L. (St. John's Wort) has been utilized throughout history as an herbal remedy. Today, it continues to attract attention from researchers due to the wide variety of bioactive constituents present in the plant. These include naphthodianthrones, phloroglucinols, flavonoids, biflavonoids, xanthones, phenolics, and volatile oils. While St. John's Wort has gained popularity primarily for its use in treating depression, research has demonstrated that the plant exhibits a broad spectrum of biologic actions, including anti-inflammatory action, antibacterial activity, antioxidant properties, protection against neurodegenerative disorders, enhanced healing of wounds and possibly some anticancer properties. As a monotherapy, St. John's Wort appears to be relatively safe; however, the potential for photosensitivity as well as mania induction has been documented. One of the primary concerns regarding the clinical use of St. John's Wort is its capacity to activate cytochrome P-450 enzymes and P-glycoprotein, resulting in decreased levels of many co-administered medications. Drug interactions have been documented with several classes of medication, including warfarin, cyclosporine, theophylline, digoxin, HIV protease inhibitor drugs, certain antiepileptic drugs (i.e., carbamazepine), selective serotonin reuptake inhibitors (SSRIs), triptans, oral contraceptive pills, antiretrovirals and various chemotherapy agents. Given this complex pharmacology and significant potential for drug interactions, the use of H. perforatum should be accompanied by caution and professional supervision.

1. INTRODUCTION

St. John's Wort (H. perforatum L.) has been extensively studied due to both its long-standing medicinal usage, as well as the wide variety of biological effects that it has been reported to produce. The wide variety of biological effects reported for H. perforatum is thought to be associated with its phytochemical diversity [1]. The major types of biologically active compounds found in Hypericum perforatum include flavonol derivatives, biflavones, proanthocyanidins, xanthones, phloroglucinols, and naphthodianthrones [2]. H. perforatum has a therapeutic history dating back thousands of years; ancient Greek physicians used preparations from H. perforatum for many different conditions inside and outside of the body [3]. H. perforatum was also commonly used throughout traditional medical practices for treating various types of wounds, eczema, burns, and mental health issues [4]. Current research into H. perforatum has greatly broadened the previous therapeutic views toward this plant. In addition to its recognized relationship with depression, current studies have examined the potential usefulness of H. perforatum in fighting against infectious diseases caused by bacteria or viruses, reducing oxidative stress related problems, inhibiting cancer growth, and providing protection against neurodegenerative disease [3]. As such, there are at least two reasons why researchers today are showing great interest in Hypericum perforatum: it represents one of the most widely utilized plants in ethnomedicine and the large number of pharmacologic actions associated with numerous bioactive compounds present in this plant.

1.1 Traditional applications

The genus Hypericum comprises approximately 400 species distributed worldwide. Of these, H. perforatum is probably one of the best known. Although native to Europe, western Asia, northern Africa, the Azores, and Madeira, H. perforatum has become established as an introduced species in large parts of North America and Australia [5].

St. John's Wort, because of its extensive use historically, had many functions prior to the advent of modern pharmacology. Traditionally, Western herbalists used this plant medicinally and symbolically for centuries. From ancient Greece to the Middle Ages, it was thought to be able to protect people from negative forces and thus was used in rituals and practices to protect individuals' health. Historically, it also was used therapeutically for conditions such as wounds, kidney problems, neurological diseases conditions historically described as 'insanity' [5] and it continued to be applied internally or externally in order to treat various types of disorders throughout the entire course of history [6]. The medicinal record of H. perforatum spans more than 2,400 years. Its use for wound care was already known by the fifth century BC, and the plant was later documented in the herbal works of Gerard in 1597 and Withering in 1796. Traditional use was not restricted to Europe. The Montagnais, Iroquois, and Cherokee peoples are also reported to have used H. perforatum. Among some of these groups, it was taken for cough and fever, whereas the Cherokee also employed the plant for other purposes. Gerard regarded preparations of St. John's wort as especially valuable for wound care and described one such use as follows:

"Saint John's Wort with his flowers and seed boiled and drunken, provoketh urine, and is right good against the stone in the bladder, and stoppeth the laske. The leaves stamped are good to be laid upon burnings, scalding's, and all wounds; and also, for rotten and filthy ulcers." [7]

Historical medical authorities also attributed numerous therapeutic uses to SJW. Hippocrates, Dioscorides, Galen, and Pliny are reported to have recommended the plant during the first century for diuresis, wound treatment, menstrual complaints, intestinal parasites, and snakebite [3]. Its use continued into the sixteenth century and beyond. Herbalists including Paracelsus, Gerard, and Culpeper recommended preparations of St. John's wort for wound management and the relief of pain. Paracelsus, writing in 1525, also proposed the herb for melancholy, sadness, and states of excessive excitement. The medicinal use of St. John's Wort (SJW) has been extensively practiced throughout much of the world during the last few hundred years. In addition to the use of tinctures and teas for anxiety, sadness, sleep disorders, gastritis, and edema, oil-based formulations were typically used for inflammation and hemorrhoids. In addition to these internal uses, topical SJW formulations have been used for a variety of purposes, including abrasions, sores, minor burns, cuts, scrapes and injuries which cause peripheral nerve damage [3]. In Europe, it was primarily the oil-based preparations of SJW that gained popularity. As early as the sixteenth century, the first oleoresins or extracts made from Hypericum perforatum had become common remedies for bruises and cuts. Surgeons began to utilize them in surgery for two reasons; they believed that the herb promoted the healing process for wounds and, they felt that the herb provided an effective method for cleansing wounds. The first pharmacopeia developed in London included this particular remedy known as Oleum Hyperici [7].

1.2 Bioactive constituents

Chemical variability in H. perforatum contributes to a wide variety of biological effects ascribed to it. There are at least 5 classes of chemically identifiable, biologically active compounds. However, the concentrations of these compounds vary among individual plant samples and are influenced by several factors that include (but are not limited to) genetic variation among individuals of the same species, adulteration with other plants, environmental growing conditions, harvesting method, processing and preparation after harvest, and length of exposure to light [8].

1.2.1 Naphthodianthrones

The main components found in the above ground parts of H. perforatum include the naphthodianthrones hypericin and pseudohypericin. Hypericin and pseudohypericin have been considered for many years to be significant factors that contribute to the antidepressive characteristics of this herb. Hypericin is found primarily within the flowers of H. perforatum and is localized in the dark glands on the surface of the flower petals. Chemically, hypericin is a polycyclic quinone with four adjacent hydroxyl substituents surrounding two carbonyls. The chemical structure of hypericin is highly associated with high levels of photo-reactivity [3,9].

1.2.2 Flavonoids and Biflavonoids

Hyperoside, Isoquercitin, Rutin, Quercetin, Camphor, Luteolin, Myricetin (flavones), along with Biflavonoids (I3, II8- Bipigenin & I3', II8-Bipigenin / Amentoflavin) constitute the majority of flavonoid compounds in St. John's Wort. Hyperoside makes up approximately 7% of the flavonoids found in the stem portion of the plant while an approximate amount of 12% was measured in flower portions [3,8,9].

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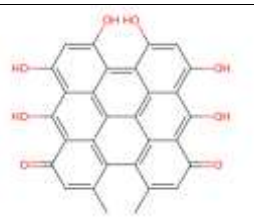
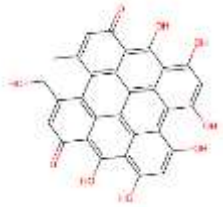
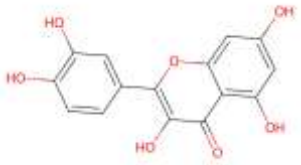
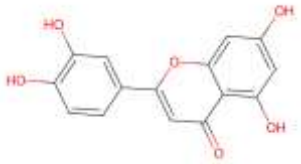
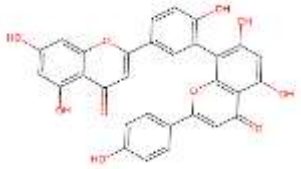
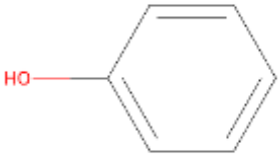
1.2.3 Phenolic and Other Constituents

Additional components of H. perforatum include various phenolic compounds. Tannins and phenolic acids are among the compounds classified within this category [8,9]. The distribution of additional active substances varies across the different parts of the plant. Phloroglucinol derivatives (hyperforin & adhyperforin), which are primarily found in flower and bud parts, whereas xanthones were primarily located within the root [10].

Table 1. Chemical structures of the primary bioactive constituents in Hypericum perforatum L.

Chemical class	Compound	Chemical structure
Naphthodianthrones	Hypericin	
	Pseudohypericin	
Flavonoids	Hyperoside	
	Quercitrin	
	Isoquercitrin	

	Rutin	
	Quercetin	
	Luteolin	
Biflavonoids	Amentoflavone	
Phenolic compounds	Tannins (representative structure: tannic acid)	
	Phenol	

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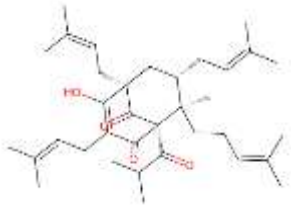
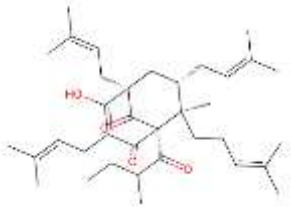
Phloroglucinol compounds	Hyperforin	
	Adhyperforin	

Note: Because "tannins" represent a broad polyphenolic group rather than a single molecule, tannic acid is shown as a representative structural example.

2. PHARMACOLOGICAL ACTIVITIES

2.1. Antidepressant Activity

H. perforatum has had many therapeutic uses; however, the most widely studied are the antidepressant effects. It is well understood that all of the components of St. John's Wort contain biological activity. It remains unclear whether a single constituent is primarily responsible for the therapeutic effects or whether the standardized whole extract has greater pharmacological relevance [11]? There are numerous clinical investigations that support the use of H. perforatum for the treatment of depressive disorders. Many have found that the antidepressant effectiveness of St. John's Wort is similar to or better than traditional antidepressants. There are also some clinical investigations that do not support this claim and report only mild or no benefit compared to placebo [12]. Hyperforin has been shown to contribute to the reduction of depressive symptoms, with rutin also potentially contributing to this effect [13]. Research into the mechanism of how hyperforin exerts its antidepressant effects has primarily examined its ability to modulate the transient receptor potential canonical 6 (TRPC6) channels. By doing so, hyperforin can alter behaviors commonly seen in individuals suffering from depression and anxiety [14]. It is possible that the therapeutic actions of SJW could be due to cooperative effects between the different constituents. Phytochemical synergism was suggested by demonstrating that SJW extracts exhibit diminished antidepressant activity in the absence of rutin [15].

As stated previously, several neurochemical mechanisms have been proposed to explain how H. perforatum exerts its antidepressant effects. In addition to influencing MAO-A and MAO-B activity and reducing the synaptosomal reuptake of serotonin, norepinephrine, and dopamine with similarly broad affinities, St. John's Wort has also been reported to interact with other neurochemical systems [2, 16]. As such, SJW may provide additional monoamines to areas of the CNS that would otherwise be lacking. However, SJW's pharmacological activity extends beyond monoaminergic systems. Adenosine, GABA(A), GABA(B), and glutamate receptors have also been identified as sites at which SJW binds in vitro. Additionally, exposure to SJW has been associated with decreased β-adrenergic receptor expression and increased serotonin 5-HT2 receptor expression. Such receptor level changes could contribute to alterations in neurotransmitter transmission within brain regions typically involved in depression [2].

2.2 Anti-Inflammatory Activity

H. perforatum appears to be composed of a variety of components capable of exerting anti-inflammatory action via various molecular pathways. The potential interference of Janus Kinase (JAK) signaling by hypericin and other related compounds is one area where JAK1 has emerged as a critical target molecule for the inflammation response [17]. Dellafiora et al. indicated that hypericin and some of its analogous and structurally related metabolites bind competitively to ATP which could explain why the plant's anti-inflammatory actions occur via JAK signaling [17].

SJW extracts' impact on inflammatory cytokine production has also been researched. A study conducted by [18]. studied the mediators interleukin-1β, interferon-γ, and tumor necrosis factor-α and found that St. John's Wort treatment produced a significant reduction in the expression of all three inflammatory cytokines [18].Additional mechanisms through which hyperforin exerts its anti-inflammatory effect include the inhibition of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and microsomal prostaglandin E2 synthase, enzymes that are central to the process of inflammatory signaling and relevant to tumorigenic processes [1].Flowers of H. perforatum can potentially create a condition of reduced inflammation in cells through suppression of pro-inflammatory mediators while promoting anti-inflammatory activities. Hatano et al. showed that SJW extract inhibited the activation of NF-kappa B in cultured adipocytes thereby inhibiting inflammatory signaling [19]. Traditionally, oils derived from flowers of H. perforatum have been used to treat topical inflammatory conditions [20].

2.3 Antimicrobial Activity

Considerable interest has also focused on the antimicrobial potential of H. perforatum. The diverse chemical makeup of this plant (naphthodianthrones, flavonoids, prenylated phloroglucinol derivatives, tannins and volatile oils) [7] likely provides the basis for its antimicrobial properties'-derived preparations, both pharmaceutical and herbal, consisting of crude extracts, creams/ointments and pure substances, demonstrate a wide range of biological and pharmacological activities [7]. This property could contribute to the traditional use of SJW as a remedy for wounds and cuts.

Hyperforin is thought to be one of the primary antibacterial compounds isolated from H. perforatum. As a tetraketone, it shows greater inhibition against Gram-positive bacteria when compared to Gram-negative bacteria. In addition to the chemical structure of these compounds, extraction methods can impact their antimicrobial efficacy. Methanolic and ethanolic preparations have exhibited greater levels of antibacterial activity than aqueous preparations [21]. H. perforatum has been used in some studies for treatment of various dermatologic conditions. For example, [22] investigated a topically applied cream containing H. perforatum extract standardized to contain 1.5% hyperforin in patients with mild atopic dermatitis. Compared to a matched placebo vehicle, the cream showed significant improvement over the study period [22].

Additionally, there are studies evaluating the antibacterial effects of lipophilic (oil-based) formulations of H. perforatum. Three different concentrations of oleum hyperici (H. perforatum oil), i.e. 30%, 40%, and 50%, were tested for possible use as either skin or vaginal products. All but one of the test bacterial species were inhibited by each of the three formulations, however, Lactobacillus acidophilus, an organism that typically maintains a healthy vaginal community, was not affected. Therefore, these preparations appear capable of providing effective antibacterial activity while maintaining healthy flora in the vagina. Furthermore, there appeared to be a positive correlation between increasing amounts of oleum hyperici in the formulation and increasing antibacterial activity [7]. There are reports of antimicrobial activity of aqueous preparations of H. perforatum, especially against Gram-positive bacteria, such as methicillin-resistant Staphylococcus aureus. However, all of these aqueous preparations produced less effect than their ethanolic counterparts. The authors also found that ethanolic preparations exhibited a more potent antistaphylococcal effect against methicillin-resistant S. aureus than methicillin-sensitive S. aureus [23]. Oil-based preparations of H. perforatum remain common traditional remedies for burns, bruising and other types of injury. Most often they are prepared using fresh flower material which is macerated in oil and then exposed to sunlight for weeks, resulting in an oily product characterized by a bright red color and orange-red fluorescence under UV light. Additionally, essential oils extracted from H. perforatum have demonstrated antimicrobial activity against numerous microorganisms tested [24], [25].

2.4 Antioxidant and Neuroprotective Activities

The antioxidant effects of H. perforatum have been demonstrated by a number of different models [26] found that standardized extracts of the plant can reduce lipid peroxidation [26], which is pharmacologically relevant because elevated lipid peroxidation contributes to cellular damage in many oxidative stress-related diseases. [27] examined the effects of H. perforatum in SK-N-MC human neuroblastoma cells exposed to hydrogen peroxide and observed protection against oxidative injury [27]. These findings suggest that attenuation of oxidative stress may contribute to the neuroprotective potential of the plant. Extracts standardized for hypericin and hyperforin have additionally demonstrated substantial free-radical-scavenging capacity in both human vascular and cell-free experimental systems. This activity has also been demonstrated using the 2,2-diphenyl-1-picrylhydrazyl radical-scavenging assay [26]. Methanolic extracts of H. perforatum have shown considerable antioxidant activity in multiple experimental models. Of particular interest is their nitric oxide-scavenging capacity, which may provide a mechanistic

connection between the antioxidant properties of the plant and its previously reported anti-inflammatory and central nervous system effects [31].

2.5. Anticancer Potential

The potential anticancer relevance of H. perforatum is linked partly to its antioxidant constituents and partly to the distinctive photochemical properties of hypericin. Phenolic compounds present in plant extracts contribute substantially to antioxidant activity and may have relevance to pathological conditions associated with oxidative stress, including atherosclerosis, cardiovascular disease, neurodegenerative disorders, and cancer [30]. Hypericin is of particular interest in cancer research because of its strong photosensitizing properties. It has been studied as a candidate agent for antitumor photodynamic therapy and is considered one of the most powerful naturally occurring photosensitizers. The potential advantages of hypericin include its effective absorption of longer wavelengths compared with hematoporphyrins, potentially allowing treatment of deeper tumors; lower dark toxicity than some other photosensitizers; preferential accumulation in tumor tissue; and more rapid elimination than hematoporphyrins [28].Kladar et al. further demonstrated that H. perforatum flower extracts contained high levels of antioxidants along with significant inhibitory activities against biologically relevant enzymes such as alpha-glucosidase, as well as demonstrating cytotoxic and genotoxic activities [29]. Therefore, based on the antioxidant properties of the various phenolics present within H. perforatum; the photosensitizing capabilities of hypericin; and their respective abilities to inhibit enzyme activity and exhibit cytotoxicity, there remains sufficient rationale for additional investigations into the use of H. perforatum and/or its constituent compounds in therapeutic treatment of cancer [28-30].

2.6 Wound-Healing Activity

Beginning with a focus on the growth of herbal and complementary therapy for wound treatment globally, H. perforatum has historically been used throughout the world in traditional practices, either as an oral or topical preparation. The global use of H. perforatum for wound care is well-documented and appears to be consistent across cultures and medical systems [32]. The ability of H. perforatum to promote wound healing appears to be due to its chemical makeup. Flavonoid extracts obtained from H. perforatum contain flavonoids; amentoflavone; hypericin; tannins; hyperforin; flavonoids; xanthones and other compounds. These chemicals likely function in various ways. For example, flavonoids such as amentoflavone and hypericin are believed to reduce inflammation which can assist with repairing damaged tissues. In addition, hyperforin may inhibit the ability of certain Gram-positive bacteria (such as S. aureus) to colonize wounds thereby reducing bacterial colonization and potentially supporting wound healing [1]. In addition to the above laboratory data, clinical research has provided additional evidence for the benefit of using topical preparations of H. perforatum. Specifically, Samadi et al. studied the safety and effectiveness of a topical preparation of H. perforatum ointment when applied to post-cesarean section wounds in women. Results indicated that application of H. perforatum ointment resulted in accelerated healing, less scarring, and reduced postsurgical discomfort and itching than those who did not receive the ointment [33].

Similar results were found regarding oil-based preparations. Oily extracts of H. perforatum appeared to stimulate repair of epithelial layers and decrease the size of the wound area. Lavagna et al. reported that application of preparations containing Hypericum oil enhanced the rate of epithelial layer closure and promoted better healing of surgically created wounds in women undergoing cesarean sections [34]. Studies examining cellular responses suggest that H. perforatum stimulates fibroblast proliferation and increases collagen production thereby promoting the development of new connective tissue that closes damaged areas [32]. Similar results have been observed in experimental animal models where oral administration of tinctures made from Hypericum species accelerated healing time in incision, excision, and dead space wound healing experiments [32].

3. TOXICITY AND SAFETY

The medicinal application of H. perforatum should be evaluated in relation to its possible negative effects and its ability to interact with standard medications. Commercial preparations of St. John's wort typically come from the leaves and flowering aerial parts of the plant, with hypericin and hyperforin being the constituents most commonly linked to its biological effects [35]. When used by adults, SJW is typically considered to have a fairly positive safety record. Nonetheless, significant adverse effects have been recognized, especially photosensitivity and the possibility of triggering manic symptoms [36].

The likelihood of photosensitivity is closely associated with the photoreactive characteristics of hypericin. Experimental findings suggest that ultraviolet light exposure, in conjunction with hypericin, can induce oxidative damage to cells. In human lens epithelial cells, exposure to hypericin and subsequent ultraviolet A irradiation led to a significant reduction in α-crystallin and a

corresponding rise in N-formylkynurenine, an oxidation byproduct of tryptophan [37]. These results indicate that individuals might still be at risk for phototoxic effects even when wearing ultraviolet-protective eyewear.Another safety issue relates to the impact of SJW on drug metabolism and transport. The herb can induce components of the cytochrome P450 system as well as P-glycoprotein, thereby accelerating the metabolism or transport of simultaneously administered drugs and lowering their circulating concentrations [38,39]. Its safety during pregnancy and lactation is also incompletely established. This issue is particularly relevant because SJW is commonly used for depressive symptoms. Gregoretti et al. examined exposure to H. perforatum during pregnancy and breastfeeding in rats and reported considerable hepatic and renal injury in offspring assessed on postnatal days 0 and 21. Significant liver and kidney lesions were observed at 100 mg/kg/day, with greater severity in animals exposed during breastfeeding for 21 days. Severe hepatic and renal abnormalities were also detected in offspring exposed to Hypericum only during the lactation period [40].

By contrast, Borges et al. found no clear evidence of significant maternal toxicity following administration of H. perforatum to pregnant rats [41]. The difference between these experimental findings indicates that additional research is required before the safety of SJW during pregnancy and breastfeeding can be defined with confidence.

4. DRUG INTERACTIONS

Many of the most significant clinical concerns related to St. John's Wort are related to potential drug-drug interactions. Although adverse interactions are generally rare when SJW is taken as a single agent, some potentially serious and life-threatening interactions have been reported when it is coadministered with other agents [42]. One of the primary mechanisms by which SJW interacts with other drugs is through the induction of various cytochrome P450 enzymes that metabolize drugs. Specifically, SJW has been shown to induce CYP3A4, CYP2C9, and CYP1A2. Additionally, SJW induces the efflux transporter P-glycoprotein. These changes result in enhanced drug metabolism and decreased systemic exposure to drugs that are co-administered with SJW [43]. Consequently, many prescription medications have been found to be susceptible to this effect. For example, warfarin, ciclosporin, theophylline, digoxin, oral contraceptives, and HIV protease inhibitors are among those that may experience diminished efficacy when given concurrently with SJW [43]. The variability in drug interactions may not always be predictable since there are considerable differences in the chemical composition among commercial preparations of SJW (i.e., constituent(s), concentration(s), and bioavailability).Pharmacodynamic interactions between SJW and serotonergic drugs should also be considered. Concomitant use with serotonin reuptake inhibitors or serotonin receptor agonists, including triptans prescribed for migraine, may increase the risk of adverse serotonergic effects [43]. Hyperforin is significant in this regard. Though it has been described as being one of the primary contributors to the antidepressant effects of SJW, it is also considered to have strong implications regarding the interaction potential of SJW [42]. Preparations containing lower concentrations of hyperforin may be associated with a lower risk of interactions; however, clinically significant interactions cannot be eliminated entirely. Products delivering less than 1 mg of hyperforin per day appear to be less frequently associated with major interactions involving CYP3A4 or P-glycoprotein substrates [44].

Several specific herb–drug interactions are especially well documented. These include decreased blood concentrations of ciclosporin, supported by both clinical trials and case reports; serotonin syndrome or marked lethargy when SJW is administered with serotonin reuptake inhibitors; unintended pregnancies in women taking oral contraceptives together with SJW; and reduced plasma concentrations of antiretroviral agents such as indinavir and nevirapine and anticancer medications including irinotecan and imatinib [42,45].Because St. John’s wort can modify the pharmacokinetics or pharmacodynamics of a wide range of medications, patients receiving warfarin, ciclosporin, theophylline, digoxin, anticonvulsants, antiretroviral therapy, oral contraceptives, selective serotonin reuptake inhibitors, triptans, or other drugs with narrow therapeutic ranges should obtain professional advice before starting or discontinuing SJW. In some circumstances, adjustment of the dose of the conventional medication may be required.

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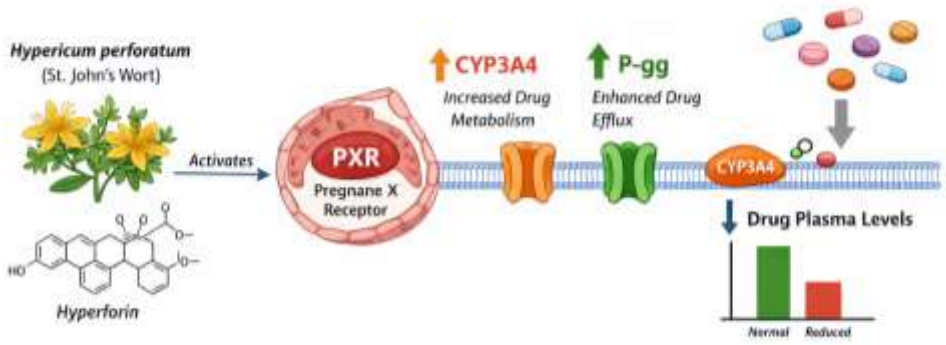

Figure 1. Mechanism of drug interactions via PXR activation leading to CYP3A4 and P-glycoprotein induction.

5. CONCLUSION

The therapeutic profile of Hypericum perforatum encompasses a wide range of reported biological effects, including antidepressant, anti-inflammatory, antimicrobial, antioxidant, neuroprotective, wound-healing, and potential anticancer activities. Hypericum perforatum has been used for centuries to treat a variety of ailments, but it has recently gained popularity for depression. Its antidepressant effects appear to arise from multiple bioactive constituents, particularly hyperforin, hypericin, and flavonoids, including hypericin, hyperforin, flavonoids, etc. It was found that hyperforin has properties similar to some antidepressants and antibacterial agents, while hypericin has properties that lead to photodynamic activity, anti-inflammatory activity and photosensitivity. Although there have been many studies on the benefits of using Hypericum perforatum for depression, further research is required before it can be used in the treatment of depression due to the possibility of herb-drug interactions. Although substantial evidence supports several therapeutic effects of H. perforatum, its clinical use requires caution because of its potential for herb–drug interactions. Induction of cytochrome P450 enzymes and P-glycoprotein can reduce the systemic exposure and therapeutic efficacy of numerous coadministered medications. Further clinical research is therefore required to clarify its efficacy, safety, optimal standardization, and interaction profile.

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AUTHOR CONTRIBUTIONS

Lorem A. Ipsum: Conceptualization, Investigation.

Dolor B. Sit: Methodology, Laboratory Analysis.

Amet C. Consectetur: Data Curation, Formal Analysis.

Adipiscing D. Elit: Supervision, Writing—Review & Editing.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study because it is a review article based exclusively on previously published literature and did not involve human participants, animals, or the collection of primary data.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed in this study. All information presented in this review was obtained from previously published sources cited in the manuscript.

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