

**POSSIBLE DRUG INTERACTIONS AND ADVERSE REACTIONS  
OF FOOD SUPPLEMENT CONTAINING *HYPERICUM  
PERFORATUM L.***

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**Abstract**

*Hypericum perforatum* is a perennial plant from *Hypericaceae* family known as St. John's Wort. It is used in our traditional medicine in liver disease and externally as an oil in wound healing. The aim of this study was to reveal the most important chemical constituents of *Hypericum perforatum* and to correlate them with the pharmacologic activity. St. John's Wort can increase the level of certain drugs metabolizing enzymes, reducing their blood levels. Hyperforin is responsible for interactions with other drugs that are metabolized by CYP450 isoenzymes. This interactions appear when using *Hypericum perforatum* in the case of treatments with contraceptive hormones, anticoagulants, digoxin, theophylline, serotonergic antidepressant, antiviral, immunosuppressant, antiepileptic agents.

**Keywords:** *Hypericum perforatum*, hypericin, hyperforin, drug interactions, adverse reactions

**INTRODUCTION**

*Hypericum perforatum L.* is a perennial plant from *Hypericaceae* family, flowering around 24 June, the day of St John. For these reason *Hypericum perforatum L.* is known as St John's wort. The plant's traditional use in the past was hanging over a religious icon in the house during St John's day in order to avoid the evil.

The genus name *Hypericum* is derived from the Greek words *hyper* (above) and *eikon* (picture). In Romanian popular tradition it is also named fire flower, grass blood or measles (Ardelean A. et al, 2008, Coste I. et al, 2004, Toma C, 2008), because when crushing flower buds or seed pods, a reddish/purple liquid is produced.

St John's wort is a herbaceous perennial plant which shows a short rhizome from which emerge numerous adventitious roots. The stem is

lignified at base, 25-60 cm high, 3-5 mm thick, with two longitudinal edges. The leaves are opposite, 2-3.5 cm long, sessile, ovate or elliptical. The leaves have a perforated aspect because of secreting glands with volatile oil. Flowers are grouped in a corymb consisted of 5 sharp sepals, 5 asymmetrical petals yellowish-gold with black glandular dots on edge. Stamens are arranged in three bundles. The fruit is a capsule with three lodges (Coste I. et al, 2004, Gîtea D. et al, 2011, Şipoş M. et al, 2014).

The upper parts of the stem are harvested in early bloom (*Hyperici herba*) Drying is done in the shade or in drying at temperature of 30-35°C.



Fig.1 *Hypericum perforatum* L. ([www.uniprot.org/taxonomy](http://www.uniprot.org/taxonomy))

### Ecology

The plant is adapted to both aridity and humidity. It grows in meadows in the plains and hills throughout much of the world's temperate regions (Gîtea D. et al, 2011, Savulescu T. et al, 1953). *H. perforatum* L. blooms from June to August. The plant grows wild throughout Europe, especially in forests, pastures and roadsides.

In Romania it is common in drier meadows, edges of woods, along roads. It is widespread in Transylvania (Arad, Bihor, Bistrita County, Braşov, Caras-Severin, Harghita, Hunedoara, Maramures, Salaj, Suceava), Muntenia (Arges, Buzau, Dambovita, Ilfov), Oltenia (Gorj, Mehedinti, Olt), Moldova (Bacau, Botosani, Neamt, Suceava) and Dobrogea (Tulcea), but can harvest and in all other counties. The most favorable areas of cultivation are Cluj, Salaj and Dambovita counties; there are favorable conditions also in Arad, Arges, Bacau, Bihor, Botosani County, Neamt, Suceava, Vrancea (Ardelean A. et al, 2008).

*Hypericum perforatum* grows best in a land made of sand and clay mixture. Clay soils are beneficial for them, does not like excess water.

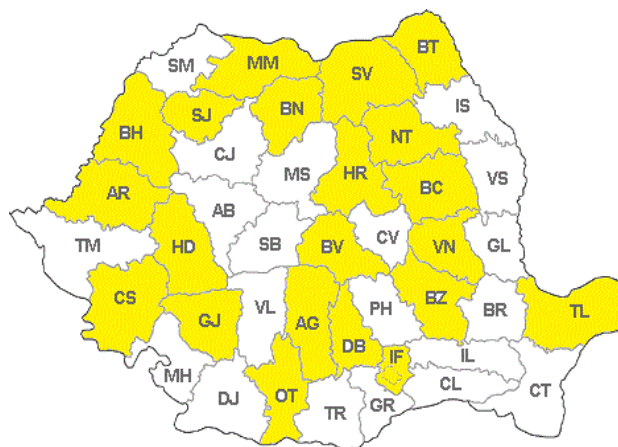


Fig.2. The area of distribution of the species *Hypericum perforatum* L. in Romania

In our traditional medicine is widely used in liver disease, hypotension, and externally as an oil in wound healing. It was used in folk medicine for treating nervous, digestive, respiratory diseases and wounds. Because of its wound healing, St. John's Wort is used to treat traditionally burns and irritation (Luo L. et al, 2004 , Neag T. et al, 2015, Toma C. et al, 2007).

Chemical investigations into the constituents of *H. perforatum* have detected following compounds (\*\*PDR for herbal medicines, 2007):

- anthracene derivatives (hypericin, pseudohypericin),
- flavonoids (hyperoside, quercitrin, rutin, isoquercitrin, biflavonoids),
- xanthenes (1,3,6,7-tetrahydroxy-xanthenone),
- acylphloroglucinols (hyperforin),
- volatile oil (2-methyl-octane, undecane, alpha-pinene),
- oligomers,
- tannins,
- caffeic acid derivatives

Table 1

Class	Chemical compounds
NAPHTODIANTHRONES	Hypericin, pseudohypericin, dehydrohypericin, protohypericin, isohypericin
FLAVONOIDS	Hyperoside, rutozide, luteolin, quercetin
PHENYL-PROPANE DERIVATIVES	caffeic acid, chlorogenic acid
PHLOROGLUCINOL DERIVATIVES	Hyperforin
TANNINS	Catechin, epicatechin
VOLATIL OIL	2-methyl-octan, undecane, dodecane, $\alpha$ -pinene, caryophyllen, humulene, myrcene

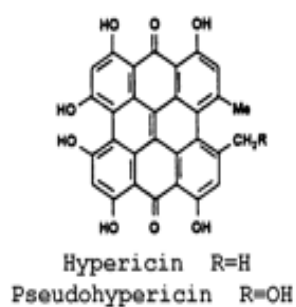


Fig. 3. Chemical structure of hypericin and pseudohypericin  
(\*\*\*PDR for herbal medicines, 2007)

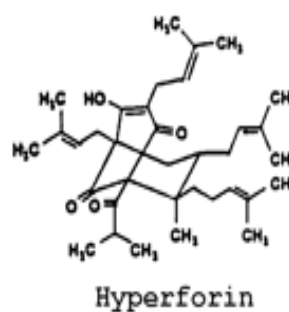


Fig. 4. Chemical structure of hyperforin  
(\*\*\*PDR for herbal medicines, 2007)

## Pharmacology

The active substance hypericin is responsible for the pharmacological action. In addition to traditional antimicrobial actions, collagogue, healing, showed a very good antidepressant action, acting as monoamine oxidase inhibitor. It stimulates the body to produce the hormone melatonin which regulates sleep-wake cycle and helps in treating insomnia in substance depressive states. It is significant that at present pharmacological and clinical research and studies are focused especially on the old Hippocratic recommendation of psychiatric disorders (Ardelean A. et al, 2008, Hanganu D. Et al, 2002, Klemow K.M. et al, 2012, Pallag A. et al, 2014).

According to studies and clinical outcomes of the European Commission and the European Association of Phytotherapy which are affiliated with USA, India, Australia etc, the efficiency of therapeutics with St. John's wort has been shown to be comparable to imipramine and maprotiline.

The mechanism of action is related to the inhibition of post-synaptic serotonin level as well as second-generation antidepressants. Another scientifically proven is the hypotensive action due to peripheral vasodilation. This action is due procianide fractions rich in inhibiting phosphodiesterases, acting as a vasodilator. Those actions should not be overlooked in traditional medicine and therapy for diarrhea due to the content in tannins and flavonoids due to enuresis as a diuretic, rheumatism and gout. Some plant extracts have been proven effective against gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis*.

The latest research on the pharmacological activity of the species *H. perforatum* focused on the effects of antidepressants.

Antimicrobial activity was evaluated against a number of bacterial and fungal strains. The plant has a wide range of medical applications, including skin sores, eczema, burns, diseases of the digestive and mental disorders. Plant extracts showed strong antibacterial activity against a number of bacterial strains. The active principles that have proven antibacterial identified so far are hyperforin and hypericin (Gîtea D. et al, 2011, Öztürk Y.S. et al, 1992, Pallag A. et al, 2014, Savulescu T. et al, 1953).

A study presented the inhibitory effects of six flavonoids from *Hypericum perforatum* which were assessed spectrophotometrically using nitric oxide synthase (NOS) in blood and cerebral homogenate of rats. Of the assayed compounds, quercetin and hyperoside showed concentration-dependent enzyme inhibitory actions. The results suggested that the galactose moiety in hyperoside may be associated with the selectivity of the NOS inhibition (Luo L. et al, 2004 , Neag T. et al, 2015).

The hepatoprotective effect of *H. perforatum* was investigated *in vivo* by cannulating the rat bile duct for choleric activity and by barbiturate sleeping time following CCl<sub>4</sub>-induced hepatic injury. It was observed that the extract shortens the barbiturate sleeping time of CCl<sub>4</sub>-treated mice suggesting hepatoprotection (Öztürk Y.S. et al, 1992, Pallag A. et al, 2014, Zeb Saddiqe et al, 2010).

### **Contraindications, Precautions, Adverse reactions**

St. John's wort supplements should not be used during pregnancy and lactation because high concentrations of St. John's Wort *in vitro* were mutagenic to sperm cells and adversely effected oocytes (\*\*PDR for herbal medicines, 2007).

St. John's wort can increase the level of certain drugs metabolizing enzymes, reducing their blood levels. Treatment with hyperforin is responsible for interactions with other drugs that are metabolized by CYP450 isoenzymes. Alert in the case of treatments: contraceptive hormones, anticoagulants, digoxin, theophylline, serotonergic antidepressant, antiviral (such as: HIV-1 protease inhibitors, nucleoside reverse transferase), immunosuppressant, antiepileptic agents.

It may have photosensitizing effect (to avoid prolonged exposure to sunlight or ultraviolet radiation) (Hanganu D. Et al, 2002, Jurcă T. et al, 2011, Zeb Saddiqe et al, 2010). When administering any preparation St. John's wort (creams, ointments, oils, tinctures, infusions) should be avoided the sun exposure due to the effect of photosensitivity.

### **Drug interactions**

Cytochrome P450 3A4 is an important enzyme in the body, mainly found in the liver and in the intestine. Its purpose is to oxidize small foreign organic molecules (xenobiotics), such as toxins or drugs, so that they can be removed from the body.

Cytochrome P450 enzymes involved in interacting with *Hypericum perforatum* are CYP3A4, CYP1A2, CYP2D6, CYP2E1.

CYP3A4 is a family member of oxidizing enzyme cytochrome P450 enzyme present in the liver and the gut. It is the isoform most represented in the human liver. It oxidizes foreign organic molecules (toxins, drugs) to eliminate from the body. Substrates: nifedipine, verapamil, statins, estradiol, progesterone, anxiolytics.

CYP1A2 is localized to the endoplasmic reticulum and expression is induced by some PAHs. Substrates: tricyclic antidepressants, antipsychotics, theophyllin, melatonin.

CYP2D6 is responsible for the metabolism and elimination of about 25% of the drugs used clinically in a process known as O-demethylation.

Substrates: tricyclic antidepressants, antipsychotics, beta-blockers, class I antiarrhythmic drugs, opioid analgesics.

CYP2E1 biotransforms few drug structures. It has important role in the metabolism of paracetamol. Substrates: anesthetics, paracetamol, ethanol.

**Acitretin:** The concomitant use of *Hypericum perforatum* and acitretin may lead to an unwanted pregnancy.

Clinical Management: avoid concomitant use with acitretin women  
Advice to avoid self-medication during treatment with *Hypericum perforatum*

**Amiodarone:** *Hypericum perforatum* induce cytochrome P450 CYP 3A4. Concomitant use with amiodarone amiodarone decreases.

Clinical Management: amiodarone is not recommended with *Hypericum perforatum*. Because of the long half-life of amiodarone the potential interactions may continue even after treatment with amiodarone.

**Anesthesia:** *Hypericum perforatum* used before surgery with anesthesia lead to complications such as hypotension during anesthesia and waking from anesthesia delayed.

Management clinics: stop at least 5 days prior to surgery with anesthesia treatment with *Hypericum perforatum*.

**Anticoagulants:** Concomitant administration of *Hypericum perforatum* leads to lower anticoagulant effect of anticoagulants. Several case reports show a decrease in INR in patients taking warfarin concomitantly with *Hypericum perforatum*.

Clinical management: if patients choose to continue treatment with *Hypericum perforatum* symptoms and decrease the effect of anticoagulants prothrombin time should be carefully monitored.

**Antidiabetics:** Concomitant use with hypoglycaemic *Hypericum perforatum* may lead to hypoglycaemia. The study hypoglycemia occurred between 7:12 to healthy patients under treatment with *Hypericum perforatum* after receiving one of tolbutamide. Other antidiabetic could be affected in the same way *Hypericum perforatum*, because the effect does not appear to be linked to the metabolism of CYP 2C9 tolbutamide.

Clinical Management: caution should be even greater in diabetic patients treated with hypoglycemic event. It is closely monitoring the symptoms of hypoglycaemia.

**Barbiturate:** *Hypericum perforatum* may decrease the effect of barbiturates central depressing. This counteracts the depressant effects of barbiturates in mice. *Hypericum perforatum* induce CYP3A4 and P-glycoprotein in humans.

Clinical Management: *Hypericum perforatum* if patients administered concomitantly with barbiturates, monitored alternations between therapeutic

effects and adverse effects of barbiturates. Until this interaction will be more studied, *Hypericum perforatum* association with drugs metabolized by cytochrome P450 such as barbiturates should be avoided.

**Antihypertensive:** Concomitant administration of *Hypericum perforatum* with beta blockers leads to decreased effect of beta-blockers (metoprolol).

*Hypericum perforatum* decreases the effect of calcium channel blockers (nifedipine)

**Statins:** *Hypericum perforatum* decrease the plasma concentrations of statins and their effect. (simvastatin, rosuvastatin, fluvastatin, lovastatin).

**Benzodiazepines:** Concomitant use of benzodiazepines with *Hypericum perforatum* lowers the benzodiazepine effect. *Hypericum perforatum* significantly induce the metabolism of alprazolam and midazolam (studied as marker substances in the metabolism of CYP P450 3A4 humans).

**Caffeine:** Concomitant use of caffeine with *Hypericum perforatum* may increase the metabolism of caffeine.

**Contraceptives:** *Hypericum perforatum* may decrease the effect of contraceptives. There have been reports of pregnancy and bleeding. the combination of the two.

**Digoxin:** The concomitant use of *Hypericum perforatum* lead to reduced plasma concentrations of digoxin. The probable mechanism is the induction of P-glycoprotein [20].

## CONCLUSIONS

Herbal preparations and other dietary supplements may have some secondary effects or exacerbate the effects of medicinal products on prescription. Information about drug interactions are often deficient.

*Hypericum perforatum* is used in folk medicine to treat nervous, digestive, respiratory and wounds healing. The documented pharmacological activity of *Hypericum perforatum* include antidepressant, antibacterial, antiviral activity.

When administering any preparation St. John's Wort (creams, ointments, oils, tinctures, infusions) should be avoided the sun exposure due to the effect of photosensitivity. Hypericism is manifested by: itchy, painful rash, skin necrosis, neurological phenomena (psychomotor excitement, seizures, death by brain hyperemia).

St. John's Wort can increase the level of certain drugs metabolizing enzymes, reducing their blood levels. Hyperforin is responsible for interactions with other drugs that are metabolized by CYP450 isoenzymes. This interactions appear when using *Hypericum perforatum* in the case of treatments with contraceptive hormones, anticoagulants, digoxin,



theophylline, serotonergic antidepressant, antiviral, immunosuppressant, antiepileptic agents.

*Hypericum perforatum* L. may induce cytochrom P450 3A4. The substrat-drugs of CYP 3A4 are benzodiazepines (alprazolam, midazolam, diazepam), contraceptives (estradiol, progesteron, etinilestradiol), calcium channel blockers (nifedipine, amlodipine, felodipine, verapamil, diltiazem), statins (simvastatin, atorvastatin, lovastatin), antidepressants (citalopram, sertraline, amitriptyline) This activity of *Hypericum perforatum* decreases the plasma concentrations of drugs metabolised by CYP 3A4.

*Hypericum perforatum* may induce cytochrom P4502D6. One of the substrates of CYP2D6 are beta blockers (metoprolol, carvedilol, nebivolol, timolol, propranolol). *Hypericum perforatum* decreases the effect of beta-blockers.

Caffeine is substrat of CYP 1A2 and concomitant use of caffeine with *Hypericum perforatum* may increase the metabolism of caffeine.

Anesthetics (halothane, enflurane, isoflurane) are substrats of CYP2E1. *Hypericum perforatum* used before surgery with anesthesia lead to complications such as hypotension during anesthesia and waking from anesthesia delayed.

St. John's Wort (*Hypericum perforatum*) is one of the most commonly used antidepressant agents. For this reason we have to take account of possible interactions and side effects that may occur with concomitant use with other drug classes.

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