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Recent Studies on Antioxidant, Antimicrobial and Ethnobotanical Uses of *Hypericum perforatum* L. (*Hypericaceae*)

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Abstract: *Hypericum perforatum* L. (*Hypericaceae*) is one of the medicinal plants whose value has increased rapidly in recent years. It is especially popular for its use in the treatment of mild and moderate depression, as well as for the treatment of skin diseases, internal and external inflammatory wounds, neurological disorders, and the metabolism-disrupting effects of free radicals. Besides, it shows inhibitory effects against different kinds of microorganisms such as bacteria, fungus, and protozoa. Antimicrobial biofilms generated by the plant are its most potent output, unlike its essential oil which does not have much value in itself as much as its ingredients that can be converted into more valuable products. Its usage as a folk remedy has a wide application area in various cultures. It is thought that compiling studies on various aspects of this plant will benefit future studies. The present paper reports on studies on the antibacterial, antioxidant, and therapeutic properties of *Hypericum perforatum*, as well as on the composition of its essential oil.

Keywords: *Hypericum perforatum*, medicinal plants, antioxidants, antimicrobials, essential oil.

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INTRODUCTION

Hypericum is a genus belonging to the *Hypericaceae* family and comprising about 500 species that are growing widely and has been utilized in folk medicine for many centuries (1,2). *Hypericum perforatum* is a herbaceous perennial plant growing in the tropical and sub-tropical regions of Europe, Asia, North Africa, and North America. It is usually 30-60 cm tall but can grow up to 1.5 m on the Pacific coast of America. The leaves can be arranged singly, oppositely, or spirally (Figure 1). There are five sepals and five petals in the flower's bud. Its leaves are oval in shape and its flowers are bright yellow. (3–5). It grows mostly on roadsides, with thorny plants and in arid lands. Because it blooms about June 24, the Memorial Day of Baptist John, the plant is commonly known as St. John's Wort in English, Johanniskraut in German, Herbe de la Saint-Jean in French, Erba di San Giovanni in Italian, and Hierba de San Juan in Spanish (6).

Figure 1: Flower and leaves of *H. perforatum.*

The name of the "*perforatum*" epithet belonging to the genus *Hypericum* was given because of the oil guts in its flowers and leaves. The red or black oil glands of the *H. perforatum* are made up of hypericin and its derivatives, whereas the transparent ones are made up of essential oils and other active ingredients that are not found in hypericins (7,8). The fact that *H. perforatum,* which has been used for various purposes in alternative medicine since ancient times, is widely pharmacologically effective has led to studies in many fields such as pharmacy, medicine, dentistry, agriculture, and cosmetics.

Hypericum species contain many secondary metabolites in at least 11 different classes, including naphthodianthrones, phloroglucinol derivatives, flavonoids, organic acids, essential oils, amino acids, xanthones, tannins, procyanidins, and other water-soluble compounds. From the main active ingredients, those of naphthodianthrones' class are effective in the treatment of depression up to moderate severity, while those of the phloroglucinol class are effective in the treatment of wounds, burns, and inflammation (9). Another issue that has come to the fore in recent years is the increase in the use of organic and alternative medicine products. Medicinal and aromatic plants and products derived from them are often used as medicines, both in strengthening immunity and for treating diseases. This necessitates a deeper understanding of the beneficial and harmful properties of plants to produce more useful products. In recent years, the consumption of products obtained from *Hypericum* species has increased, and nowadays, it is one of the most consumed medicinal plants in the world (10). Although its extracts are used generally, it is known that its essential oil has good neuroprotective, antimicrobial, and antioxidant effects (5).

According to a review of literature, there have been several studies, about 300 publications per year regarding *H. perforatum*, in many fields, primarily chemistry, biology, and medicine.

In this paper, studies on the plant's activity against microorganisms, antioxidant content, medicinal use, essential oil qualities, extraction methods, drying procedures, and active components (hypericin and hyperforin) were reviewed.

ANTIMICROBIAL ACTIVITY

One of the most prominent features of the plant is its antibacterial and antimicrobial properties (11). These properties gain more value when taken together with its wound healing and anti-inflammatory effect. The effectiveness of the plant against harmful microorganisms has been evaluated in many studies. The degree of inhibitions in various culture media have been assessed, in vivo and in vitro (12,13).

The most effective parts of the plant were flowers against gram-positive bacteria (*S. aureus*), gram-negative bacteria (*K. pneumoniae, P. aeruginosa, S. enteritidis, E. coli*), and yeast (*C. albicans*). Leaves were effective against *Aspergillus niger*. The antibacterial effect of the plant was stronger against gram-positive microorganisms than against gram-negative ones (14). Furthermore, the properties of various biofilms with *H. perforatum* were also studied. The inhibition efficiency of the biofilm produced with ethanolic extract and polyurethane foam remained low against gram-negative, *E. coli* and against *C. albicans*. However, the gram-positive *S. aureus* inhibition rate reached 90.85% (15). Güneş and Tıhmınlıoğlu (2017) achieved the same result (16). On the other hand, biofilms made from chitosan, gelatin and the plant were more inhibitory against gram negative *S. typhi* than against *E. coli* and gram positive *S. aureus* (17). Methanolic macerate and aqueous decoction extract showed the best results after vancomycin, while liquid commercial ethanolic extract, methanolic solution of a commercial tablet product, macerates in sunflower, olive, and two unknown vegetable oils did not show any effect against the *S. aureus* (18). Also, among three different *Hypericum* species, *H. perforatum* showed the strongest anti-infectious effect against *Toxoplasma gondii*, an intracellular parasite, due to the hyperforin it contains (19).

pH, water permeability (17), mechanical testing, swelling behavior, surface hydrophobicity (16), water activity test, Low-Field Nuclear Magnetic Resonance (LF-NMR) analysis, texture analysis, and L*-a*-b* color tests (20), were investigated as the physical properties of biofilms in different studies. Vapor permeability and stretching ratio are higher in films with oil additives, but decrease as the oil concentration increases. The degree of swelling is lower, the tensile stress decreases further as the oil additive increases. The contact angle is slightly increased. Cell renewal rate is highest with 0.5% oil (16).

Studies that evaluated the effectiveness of *H. perforatum* against microorganisms are summarized in Table 1.

Table 1: Antibacterial and antifungal activities of *H. perforatum.*

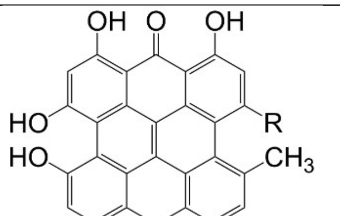
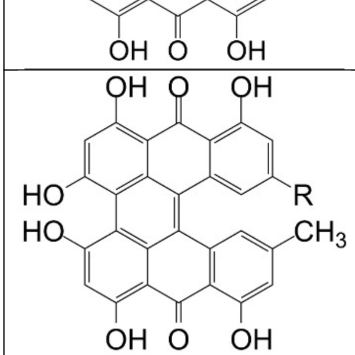
Reference	Microorganism	Classification
(12–18,21–29)	*Staphylococcus aureus*	gram-positive bacterium
(12,22)	*Staphylococcus epidermidis*	
(23,28)	*Sarcina lutea*	
(12,17,28,30)	*Bacillus subtilis*	
(28,30)	*Bacillus mycoides*	
(23,26,31)	*Bacillus cereus*	
(28)	*Mycobacterium phlei*	
(28)	*Corynebacterium michiganes*	
(27,32)	*Corynebacterium diphtheriae*	
(27)	*Streptococcus pyogenes*	
(27)	*Streptococcus agalactiae*	
(12,21,27,33)	*Enterococcus faecalis*	
(31,34)	*Listeria monocytogenes*	
(21–23)	*Micrococcus luteus*	
(13,14,30,33)	*Klebsiella pneumoniae*	gram-negative bacterium
(13,14,22,23)	*Salmonella enteritidis*	
(17,22,33)	*Salmonella typhimurium*	
(31)	*Salmonella infantis*	
(13–17,21,26–28,31,33)	*Escherichia coli*	
(21,28)	*Proteus vulgaris*	
(21,23)	*Proteus mirabilis*	
(13,14,23,33)	*Pseudomonas aeruginosa*	
(20)	*Pseudomonas plecoglossicida*	
(20,30)	*Pseudomonas fluorescens*	
(20,26,27)	*Pseudomonas aeruginosa*	
(20)	*Pseudomonas sp. MChB*	
(30)	*Pseudomonas phaseolicola*	
(30)	*Pseudomonas glycinea*	
(22,23)	*Pseudomonas tolaasii*	
(30)	*Erwinia caratovora*	
(30)	*Entrobacter cloaceae*	
(23,30)	*Agrobacterium tumefacies*	
(30)	*Azotobacter chrococcum*	
(35,36)	*Aeromonas hydrophila*	
(31)	*Helicobacter pylori*	
(31)	*Campylobacter coli*	
(26)	*Chronobacter sakazakii*	
(28)	*Penicillium chrysogenum*	fungi
(22)	*Penicillium funiculosum*	
(37)	*Penicillium canescens*	
(28)	*Fusarium avenaceum*	
(37)	*Fusarium oxysporum*	
(37)	*Alternaria alternata*	
(28)	*Mucor plumbeum*	

(22)	*Cladosporium cladosporioides*	
(22)	*Trichoderma viride*	
(13–15,22–24,27,28,33,38)	*Candida albicans*	
(38)	*Candida utilis*	
(38)	*Candida tropicalis*	
(38)	*Candida krusei*	
(38)	*Candida parapsilosis*	
(38)	*Candida glabrata*	
(13,14,22)	*Aspergillus niger*	
(24)	*Aspergillus fumigatus*	fungi
(37)	*Aspergillus glaucus*	
(37)	*Phialophora fastigiata*	
(21)	*Pythium ultimum*	
(21)	*Trichophyton mentagrophytes*	
(24)	*Trichophyton rubrum*	
(39)	*Plasmopara halstedii*	
(25)	*Rhizopus stolonifer*	
(24)	*Leishmania infantum*	
(24)	*Trypanosoma rhodesiense*	protozoa
(24)	*Plasmodium falciparum*	
(24)	*Trypanosoma cruzi*	

ANTIOXIDANT ACTIVITY

Hypericum perforatum contains many important bioactive substances, some of which, such as naphthodianthrones and phloroglucinols have direct medical effect (Figure 2). Others contribute to human health in various ways due to its antioxidant effects. Antioxidant substances defend the metabolism against free radicals, especially reactive oxygen species formed in the body. Thus, the development of diseases such as cancer is prevented, and overall immunity is enhanced.

Secondary metabolites occur as plants' response to biotic and abiotic stress factors like water, light, temperature, CO_2, abundance of nitrogen and other nutritious compounds, geographical environment, genetic features, harvest time, contaminants, elicitors, harmful microorganisms, herbivores, etc (40,41). In their studies, Eray et al. (2020) and Karimi et al. (2022) investigated how the different growing conditions of *H. perforatum* affect the formation of secondary metabolites. In this way, it may be possible to prepare cultural planting conditions for specific purposes (8,42). Another cultural planting study has prepared for the aim of producing a powerful radical scavenger (43). Pan et al. (2004) isolated the protoplast from the calluses obtained from the hypocotyl parts of the plant and used it in the regeneration of the plant. With this work, an important step was taken towards the production of designed plants (44). In a study about genes expression according to the growing conditions, especially temperature, the mechanisms that are activated by various genes are mentioned (45).

<table>
<tr><td rowspan="2">
</td><td>Hypericin</td><td>R = CH_3</td></tr>
<tr><td>Pseudohypericin</td><td>R = CH_2OH</td></tr>
<tr><td rowspan="2">
</td><td>Protohypericin</td><td>R = CH_3</td></tr>
<tr><td>Protopseudohypericin</td><td>R = CH_2OH</td></tr>
</table>

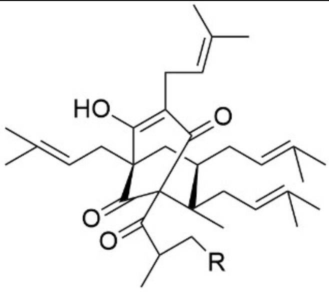
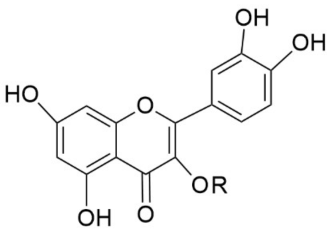
	Hyperforin	R = H
	Adhyperforin	R = CH_3
	Rutin	R = Glucose-Rhamnose
	Hyperoside	R = Galactose
	Quercetin	R = H
	Quercitrin	R = Rhamnose
	Isoquercitrin	R = Glucose
	Pentose	R = Quercetin-3-*O*-pentoside

Figure 2: Major ingredients of *H. perforatum* extracts.

In a warmer and lighter environment, the proportion of all bioactive components was higher. While phenolic and flavonoid substances were more abundant in vegetative and flowering stages, hyperforin decreased continuously, unlike previous studies. While hypericin increased with high temperatures and light, it started to decrease with flowering in low temperatures and light (46). Rutin content was higher in the budding phase. Quercitrin, quercetin, and I3, II8-biapigenin were higher in the full-flowering phase. Hyperoside content did not change (47). Almost all bioactive ingredients were found to be reduced in a plant afflicted with ash yellows phytoplasma infection. The rate of essential oil also decreased significantly (40).

The main chemical components and biological activities of *H. perforatum* subspecies and other *Hypericum* taxa were compiled by Kladar et al. (48). *H. perforatum* subsp. *perforatum* is richer in flavonoids, tannins, and phenolic acids compared to the *angustifolium* subspecies and contains rutin unlike others (12). *Hypericum perforatum* ssp *veronense* includes a higher rate of hypericin, hyperforin and phenolic components than *Hypericum perforatum* ssp *perforatum* (49). Inhibition rates and antioxidant capacities of 9 *Hypericum* species against 7 microorganisms were investigated after a three-day maceration period. *H. perforatum* could not stand out in terms of antibacterial effect, but especially the flowers of the plant showed the highest antioxidative effect (73100 μmol α-tocopherol acetate/g extract). The antioxidant capacity of the plant organs varied depending on flavonoid contents in flowers (11.7%), leaves, and stems (7.4%) (13). It has been understood that different parts of the plant contain different major components. Ciccarelli et al. (2001) examined the composition of oil glands in plant parts (7). Total phenolic and flavonoid contents as well as 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging power, β-carotene-linoleic acid total antioxidant activity, ferric reducing antioxidant power, Cupric reducing antioxidant capacity (CUPRAC) metal chelating power and antimicrobial effects of some *Hypericum* species were measured. *H. perforatum*, *H. salsugineum* and *H. aviculariifolium* epithets were compared to Butylated Hydroxy Anisole (BHA) and Butylated Hydroxy Toluene (BHT). While *H. perforatum* had the lowest antioxidant activity, total phenolic content, and Fe chelating power, *H. aviculariifolium* exhibited the highest Cu chelating power and total flavonoid content (14).

In terms of antioxidant activity, it is recommended to brew for 5-10 minutes at 80-100°C as the best method of use. Preparation of the tea, which became red in 3 minutes, was not enough to see naphthodianthrones. Apart from this, phenolic acids and chlorogenic acid also increased significantly after 3 minutes (50). While the rates of bioactive components increased with the decoction time up to 20 minutes, the rates decreased with infusion time. Decoction process was more efficiently than infusion. Likewise, it gives products whose antioxidant activities are more than twice as high (51).

Quercetin is an important phenolic compound that has powerful antioxidant and antiradical activity even in minor amounts (52). It is higher in palm oil macerate and lower in olive oil macerate, compared with the sunflower oil macerate of *H. perforatum*. While it was claimed that quercetin has a protective effect on the stomach against cold restriction stress, the highest protection was obtained when working with the lowest quercetin (53). Firenzuoli et al. (2004) discussed the effects of flavonoid content in nutrition as risks and therapeutic opportunities (54).

After a period of exposing to sunlight in olive, sunflower, and palm oil for 40 days, 0.02% (v/v) BHA or α-tocopherol antioxidants were added in some extracts, separately. The appearance, odor, relative density, and acid number of the extracts were analyzed during a shelf life for 3, 6, and 12 months at room conditions. Although palm oil is a more stable vegetable oil to heat effect, it gives a lower quality extract. Characteristics of the extracts with antioxidants are satisfying after 12 months, but the samples without antioxidants degrade after 6 months. BHA and α-tocopherol affect the extracts similarly (55). According to Arsić (2016), a homemade *H. perforatum* olive-oil macerate made easily can have some unique properties such as longer shelf life and higher total flavonoid content (56).

Methanolic extracts contained more hypericin and hyperforin, but the aqueous solutions were rich in antioxidant compounds (57). In particular, the extracts with epicatechin, catechin, protocatechuic acid, gallic acid, quercetin, and kaempferol as components were effective against colon cancer cells (58–60).

In addition to antioxidant content (61–64), total chlorophylls, total carotenoids, phenolic substances (65,66), polysaccharides (67), and xanthones contents (68) were also examined. Accordingly, the antioxidant activity was enhanced by all these compounds.

Different active oxygen sources were used to describe the antioxidant and antiradical effects of various medicinal plants. By voltamperometric electrical experiments, *H. perforatum* has been found to be more effective against hydrogen peroxide than hydroxyl radical and more useful in oxidizing molecular oxygen (69).

When studies were compared, it was discovered that as the water ratio increased in the ethanol-water mixture, the phenolic substance content increased as well, but the aqueous extract had a low content: 14.35-16.72, 53.84, 128.82, and 4.44 mg gallic acid equivalent per g dry matter of extracts with ethanol/water (7:3) (70), ethanol/water (1:1) (66), ethanol/water (3:7) (71), and water (72), respectively. In terms of DPPH scavenging effectiveness, the first and third extracts had almost the same concentration for eliminating 50% of the DPPH radical (IC50) (3.17 and 3.48-5.68 g/ml), but the extract of equivalent volumes was not so effective (242.323 g/ml). Likewise, in terms of phenolic material content, the activity in the form of acetone>ethanol>petroleum ether was as ethanol>acetone>petroleum ether in terms of DPPH scavenging potential (37).

The high bioactive properties of methanolic extracts have also attracted attention in many studies (14,26,61,63,73,74). When chloroform or acetone were added, the DPPH removal efficiency of the extracts increased (26,49), while water, ethyl acetate, and chloroform alone had a low effect (26,73).

Öztürk et al. (2009) showed that leaves contained more phenolic substances and flavonoids than flowers. After the step with the solvent of methanol:water (7:3), the yield of the plant, which was treated twice with ethyl acetate, increased. Similarly, the leaves were generally more effective than flowers in terms of DPPH scavenging effect (75).

MEDICINAL USES

The medicinal effects of the plants are quite diverse, they are mostly used for their antidepressant and wound healing properties. They are good for many ailments and provide benefits in different ways, especially in the treatment of neurological and oncological disorders. Although they are often classified as over-the-corner drugs from a medical point of view, in recent years there has been an increase in the usage of *H. perforatum* as an alternative treatment method and as a supportive practice for the main treatments.

Hypericum perforatum, which is one of the commonly used over-the-corner psychotropic herbal remedies, is especially used in the treatment of depression, anxiety, and insomnia. There are also studies on bipolar disorder (76). A study has been conducted to show that antioxidant and antidepressant effects work together against restraint stress, which is one of the important events that cause oxidative damage in the brain (77). The genes it affects were included in a study conducted to better understand its neuroprotective effect (78).

Strong anti-MAO-A, anti-α-glucosidase activity, antihyperglycemic agents, treatment of cognitive impairments such as Alzheimer's Disease are determined (79). It has been stated that its using before Alzheimer's Disease treatment has a positive effect due to some components like (+)-catechin and (-)-epicatechin (80). One of the most effective plant's mechanisms to relieve the symptoms of Alzheimer is the inhibition of neuronal acetylcholinesterase activity (70). Hyperforin and hypericin are known to be highly effective components against Alzheimer's disease, particularly (81,82).

Preventive for myringosclerosis (83), therapeutic for renal ischemia reperfusion injury (84), acute injuries or contusions, myalgia, first-degree burns (85,86), protective of central nervous system (73,87,88), and immune booster (89) effects are given comprehensively. As neuroprotective products, methanolic extracts have good inhibition activities against enzymes of acetylcholinesterase and butyrylcholinesterase and free radicals such as DPPH, DMPD, and NO (73).

There have been many studies on the usage of hypericin in photodynamic therapy processes. During photodynamic therapy using the extract of the plant or hypericin directly, it is desirable to treat diseased cells, not healthy cells. It has been understood that the use of hypericin, which inhibits neutrophilic respiratory burst oxidase together with the enhancing effect of vitamin C, will give a much better result in this regard (90). On the other hand, the probable reason why the plant causes less photosensitivity than pure hypericin is that the antioxidants it contains, strengthen the cells against harmful effects (91). Interaction between occurring photodynamic effect of hypericin and some proteins was investigated in a few aspects (92). It is effective in protection from UV irradiation induced lipid peroxidation (93). When hypericin uptake sensitizes eye epithelial cells to sunlight, it was observed that 0.1-10 μM hypericin uptake developed necrosis and apoptosis in UV-A and visible light. Considering the information in the literature, it was understood that the possibility of cataractogenesis in the eye would increase in the case of sun exposure by taking the herb (94). Using yeast genes, *H. perforatum* has been found to affect 52 genes that work on intra and intercellular transports and signal transduction in humans (95).

Preventing the adverse consequences of lipid dysregulation in some physiological cases such as obesity, fatty liver, and type 2 diabetes by hypericin are other prominent features, in addition to the long-lasting protective effect of hyperforin on pancreatic β-cells (96,97). It shows not only therapeutic but also protective properties. For example, it provides antimutagenic protection against the harmful effects of the chemotherapeutic cyclophosphamide (98). The oxidizing low-density lipoprotein shows an atherogenic effect in the body and can cause cholesterol-related deaths. Thanks to lipophilic active ingredients of the plant such as hypericin, pseudohypericin and hyperforin, *H. perforatum* has been found to provide antiatherogenic benefit by inhibiting this protein together with its antidepressant and antioxidant effects (99). It can be used as an alternative to mouthwashes after third molar surgery (100). To understand its antiaging effect, its usage against D-galactose has been studied (101). It has been found that the antidepressant mechanism of action includes a decrease of concentrations of corticosterone and pro-inflammatory cytokines in plasma (102). Antioxidant activity, causing apoptosis and modulating Ca^{2+} influx effects, can be used in the treatment of oxidative stress in neutrophil cells against Behcet's disease (103). It was reported that the wound healing effect of the plant was not related to its hypericin content but to components such as quinoids, xanthones, and flavonoids (104). High contents of xanthones were reported in the methanolic *H. perforatum* seeds' extract. These compounds are also associated with antioxidant and antimicrobial activities (74).

It was shown that the plant has no effect on intraperitoneal adhesion formation (105) and smoking cessation (106) but reduce alcohol addiction due to its antidepressant effect (107).

Information on the usage of the herb in the treatment of different illnesses, especially depression, and its drug interactions have been compiled in many studies, because many medicinal and aromatic herbs can have harmful effects on the metabolism as well as positive effects. Over-the-corner drugs like *H. perforatum* should not be used without consulting the pharmacists, and maximum attention should be paid to their interactions with prescription drugs (108–115). Although it has high interactions with many antidepressant drugs and synergistic effects with different plants, it can be used by adding it to various herbal teas (65).

On the one hand, the use of *H. perforatum* by local people has been reported in many reviews, where some gave suggestions for using it (1,116–126). On the other hand, the report prepared by the European Medicines Agency is a study that should be taken into consideration regarding the use of the plant for various medicinal purposes (127). While undiluted hypericin and hyperforin show prooxidant effects, they start to show a stronger antioxidant effect as they are diluted. When ingested, they will not be possible to remain undiluted, so the prooxidant effects are not encountered, but excessive intake may be harmful in this regard. The recommended dose is 300 mg consumed three times a day. In this case, it was diluted 1:10-1:20 so that sufficient antioxidant effect was provided (128).

Hypericum perforatum can be used alone or with other plants for feeding cattle. When used as a forage additive, it improves the ruminal nitrogen cycle and volatile fatty acid formation without damaging local beneficial microorganisms (129). When added to Atlantic salmon (*Salmo salar*) feed, it strengthens the immune system and shows an antioxidative effect against crowding stress (130).

Studies on the harmful side of the plant are also continuing. It is known that long-term or high dose usage causes sensitivity to light, oedema, and alopecia on the skin. Along with antidepressant effects, side effects such as itching, dizziness, constipation, fatigue (131), anxiety, insomnia, restlessness, diarrhea (132), gastrointestinal upset, and dry mouth (133) might be detected depending on the person using it. It has been determined that its use as a nutritional supplement creates anomalies in liver and testicular cells by causing a decrease in nucleic acid and nonprotein sulfhydryl and an increase in malondialdehyde (134). A remarkable study on the use of the plant in cosmetics was published in 2014. Both the methods of use and the points to be considered are discussed in a very broad scope (135).

It can induce disorders when used with other antidepressants, monoamine oxidase (MAO) inhibitors, cytochrome P-450 mixed function oxidases (MFO), reserpine, narcotics, or substances that increase photosensitivity (85,136,137). It was found that various *Hypericum perforatum* extracts prepared with ethanol or DMSO significantly inhibited the CYP1A2, CYP2A6, CYP2C9, CYP2C19, and CYP3A4 cytochrome P-450 enzymes. These enzymes actually convert the drug into a form that your body can use more effectively and makes some drugs be excreted from the body without being effective, so more care should be taken with the consumption of this plant when using drugs. (110,133,138,139). Also, the enzyme group has a healing effect on 2,4,6-trinitrobenzenesulfonic acid (TNBS) colitis, inflammatory bowel disease, and intestinal cerulein-induced pancreatitis (60,140,141).

In different studies, heavy metals were found in herbalists' products. The high levels of Al, Cd, K, Mg, Mn, Pb, Zn, Co, Cu, Cr, Ca, Ba, B, Li, Na, Fe, and Ni in the samples once again showed that uncontrolled producers play with public health (142–147)). When the fatty acid composition and other quality values of 23 Turkish homemade and commercial olive oil macerates were examined, it was found that some products were adulterated (148).

The production of antioxidant and anticancer effective nanoparticles obtained from the solution prepared with the aqueous extract of the plant and silver nitrate has emerged as a new trend that can be used in different fields. These nanoparticles, which can be used in medical device coatings, antibacterial products, cosmetics, food, and pharmacy, can also be employed both as medicine and as drug carrier thanks to their unique physical and chemical properties (86,149). Utilization *of H. perforatum* in nanoparticular carrier systems was investigated in many studies (150–152).

ESSENTIAL OIL COMPOSITION

There are many papers on the essential oil analysis of *Hypericum perforatum*. According to those, it is understood that not only oil composition, but also major compounds are changed due to internal and external factors of the plant, such as genetic characteristics, plant organs, climate, soil, season, growth phase, collection time and procedures, drying method, analysis method, etc (153,154). A summary of the studies on the essential oil of the plant is given in Table 2.

Table 2: Main essential oil components of *H. perforatum.*

Reference	Main compounds (Concentration %)	Harvesting location
(33)	α-Pinene (30.92%) β-Pinene (18.32%) Caryophyllene (15.26%) Germacrene d (9.23%) β-cis-Ocimene (7.85%)	Arad county, Romania
(38)	Germacrene D (23%) β-Caryophyllene (14%) Bicyclogermacrene (5%),	Kirklareli, Turkey
(40)	Caryophyllene (30.0%) Germacrene D (19.64%) β-Copaene (7.09%) γ-Amorphene (6.28%)	Bologna, Italy (Ash yellows infected samples)
(146)	α-Pinene (8.1%) n-Nonane (7.0%) Globulol (5.5%)	Southern Estonia
	(E)-β-Caryophyllene (19.2%) γ-Muuorulene (8.7%) γ-Amorphene (6.5%)	Central Estonia
	α-Pinene (14.3%) Germacrene d (13.7%) 2-Methyloctane (11.3%) β-Pinene (6.8%)	Northern Estonia
(154)	β-Selinene Bicyclogermacrene 2-Tetradecene α-Amorphene	Gaziantep and Tunceli, Turkey
(155)	Caryophyllene oxide (15.3%) β-Caryophyllene (7.3%) 1-Tetradecanol (7.0%)	Provence–Alpes–Côte d'Azur, France (Vegetative stage)
	Caryophyllene oxide (17.0%) β-Caryophyllene (16.8%) Spathulenol (12.7%)	Provence–Alpes–Côte d'Azur, France (Floral budding stage)
	β-Caryophyllene (18.3%) Caryophyllene oxide (15.9%)	Provence–Alpes–Côte d'Azur, France (Flowering stage)
	Caryophyllene oxide (18.5%) β-Caryophyllene (9.1%)	Provence–Alpes–Côte d'Azur, France (Fruiting stage)
(156)	2-Methyl-octane (20.5%) α-Pinene (13.7%) Spathulenol (9.8%) n-Hexadecanoic acid (4.0%)	Different locations of Southeast Serbia
(157)	β-Caryophyllene (14.8%) (E)-β-Farnesene (7.1%) ar-Curcumene (13.0%) Germacrene D (17.8%)	Val-d'Arc, Provence–Alpes–Côte d'Azur, France
	β-Caryophyllene (28.4%) Germacrene D (37.3%)	Pertuis, Provence–Alpes–Côte d'Azur, France
	β-Caryophyllene (26.1%) Dodecanol (7.5%) α-Selinene (15.5%) Germacrene D (6.3%)	Saint-Cyr, Provence–Alpes–Côte d'Azur, France
	β-Caryophyllene (24.1%) β-Selinene (6%) Bicyclogermacrene (5.8%) Germacrene D (29.1%)	Mérindol, Provence–Alpes–Côte d'Azur, France
	Spathulenol (21.1%) γ-Muurolene (7.7%) Nerolidol (6.5%) Branched Tetradecanol (9.1%)	Bandol, Provence–Alpes–Côte d'Azur, France

	β-Caryophyllene (13.3%) γ-Muurolene (6.9%) (E,E)-α-Farnesene (8.4%) Spathulenol (21.5%) Caryophyllene oxide (18.4%)	Meailles, Provence–Alpes–Côte d'Azur, France
(158)	β-Caryophyllene (22.3%) 2-Methyl octane (17.3%) 2-Methyldodecane (6.0%)	Panèevo, Serbia
	α-Pinene (35.0%) β-Pinene (23.4%) 2-Methyl octane (13.5%)	Termi, Greece
(159)	2,6-Dimethylheptane α-Pinene β-Caryophyllene 2-Methyl-3-buten-2-ol	Izmir, Turkey
(160)	n-Triacontane (16.3%) n-Heneicosane (14.4%) n-Tetracosane (13.8%) n-Nonacosane (13.3%)	Sobina, Serbia
	n-Tetratriacontane (25.96%) 1,2-Benzenedicarboxylic acid (13.4%) Phytol (7.1%)	Sobina, Serbia
(161)	α-Pinene (61.8%) 3-Carene (7.5%) β-Caryophyllene (5.5%)	Gaziantep, Turkey
(162)	α-Pinene (21.0%) 2-Methyl-octane (12.6%) γ-Muurolene (6.9%) Spathulenol (6.4%)	Ioannina, Greece
(163)	β-Caryophylene (14.2%) 2-Methyl-octane (13.1%) 2-Methyl-decane (7.9%)	Rujan mountain, Serbia
(164)	β-Caryophyllene (11.7%) Caryophellene oxide (6.3%) Spathulenol (6.0%) α-Pinene (5.0%)	Tashkent, Uzbekistan
(165)	Longifolen (18.7%) γ-Eudesmole (10.7%) Spathulenol (6.9%) Bicyclogermacrene (5.5%)	Mashhad, Iran (Before flowering)
	α-Cadinene (27.17%) Bicyclogermacrene (16.93%) Spathulenol (6.95%) γ-Eudesmole (6.52%)	Mashhad, Iran (Full flowering)
	Longifolen (22%) β-Bisabolene (9%) Spathulenol (8.45%) Glubulol (5.15%)	Mashhad, Iran (Fruit set)
(166)	δ-Cadinene (11.6%) 2,6-Dimethyl-heptane (10.9%) (E)-Caryophyllene (9.9%) α-Humulene (7.1%)	Galogah, Iran
	δ-Cadinene (22.6%) (E)-Caryophyllene (12.2%) α-Humulene (11.3%) α-Pinene (9.0%) 2,6-Dimethyl-heptane (7.4%)	Nor, Iran
	2,6-Dimethyl-heptane (15.0%) n-Nonane (11.1%) δ-Cadinene (11.0%) α-Pinene (8.7%) β-Funebrene (6.7%)	Javaherdeh, Iran

	α-Pinene (14.4%) δ-Cadinene (10.6%) 2,6-Dimethyl-heptane (9.8%) 3-Methyl-nonane (8.1%)	Darrod, Iran
	α-Pinene (21.9%) n-Nonane (9.8%) 2,6-Dimethyl-heptane (9.1%) n-Dodecanol (6.8%) γ-Himachalene (6.0%)	Tonekabon, Iran
	α-Pinene (23.6%) 2,6-Dimethyl-heptane (13.5%) γ-Cadinene (8.7%) 3-Methyl-nonane (5.7%)	Toskestan, Iran
	α-Pinene (26.0%) 2,6-Dimethyl-heptane (15.2%) β-Pinene (11.6%) δ-Cadinene (10.2%)	Kharw, Iran
	α-Pinene (25.7%) 2,6-Dimethyl-heptane (15.1%) β-Funebrene (12.4%) γ-Cadinene (9.6%)	Lahijan, Iran
	γ-Cadinene (16.9%) 2,6-Dimethyl-heptane (6.3%) n-Tetradecanol (6.3%) α-Pinene (6.2%)	Mashhad, Iran
	2,6-Dimethyl-heptane (36.1%) α-Pinene (23.6%) 3-Methyl-nonane (10.1%)	Azadshahr, Iran
(167)	Ledene oxide II (8.91%) Humulene epoxide II (7.90%) *cis*-Phytol (7.89%)	10 accessions from the field collection, Vilnius, Lithuania
	Docosane (10.80%) Spathulenol (9.10%) Caryophyllene oxide (7.76%)	
	Spathulenol (10.01%) Eicosane (9.01%) Caryophyllene oxide (6.92%)	
	Dodecanoic acid (9.63%) Caryophyllene oxide (9.27%) Hexadecanoic acid (7.61%)	
	Hexadecanoic acid (12.87%) Spathulenol (12.16%) Caryophyllene oxide (7.99%) Tetradecanol (6.94%)	
	Hexadecanoic acid (10.05%) Caryophyllene oxide (9.28%) Spathulenol (8.17%)	
	Ledol (9.31%) Caryophyllene oxide (8.41%) Spathulenol (6.71%)	
	Caryophyllene oxide (18.73%)	
	Caryophyllene oxide (11.31%) Spathulenol (8.51%)	
	Salvial-4(14)-en-1-one (8.44%) Hexadecanoic acid (8.13%) Tetradecanol (7.88%)	
(168)	Germacrene D (29.5%) β-Eudesma-4(15),7-dien-1-ol (9.1%) α-Cadinol (6.2%) Caryophyllene oxide (6.1%)	Varéna district, Lithuania

	Germacrene D (14.8%) β-Eudesma-4(15),7-dien-1-ol (11.7%) funebrol (6.7%)	Svencioniai district, Lithuania
	Germacrene D (23.2%) Funebrol (6.1%) Caryophyllene oxide (6.0%) α-Cadinol (5.8%)	Ukmerge district, Lithuania
	Germacrene D (12.7%) Caryophyllene oxide (11.9%) β-Caryophyllene (9.6%)	Zarasai district, Lithuania
	Germacrene D (15.7%) β-Caryophyllene (8.8%) Caryophyllene oxide (7.0%)	Marijampole district, Lithuania
	Germacrene D (14.0%) β-Caryophyllene (7.8%) β-Eudesma-4(15),7-dien-1-ol (6.5%)	Vilnius district, Lithuania
	Germacrene D (12.0%) β-Caryophyllene (10.5%)	Marijampole district, Lithuania
	Germacrene D (16.1%) Caryophyllene oxide (13.1%) (Z)-β-Farnesene (8.2%)	Vilnius city, Lithuania
	Germacrene D (12.7%) (Z)-β-Farnesene (9.0%) β-Caryophyllene (8.2%) Dodecanol (6.1%)	Vilnius city, Lithuania
	Germacrene D (13.6%) Tetradecanal (9.4%) Tetradecanol (9.4%) Caryophyllene oxide (7.2%) β-Caryophyllene (6.8%)	Moletai city, Lithuania
(169)	Caryophyllene oxide (35.8%) β-Caryophyllene (11.1%) Spathulenol (8.0%) Dimethylheptane (6.6%)	Varéna district, Lithuania
	Caryophyllene oxide (17.5%) Germacrene D (9.8%) Spathulenol (7.5%) α-Cadinol (5.3%) β-Caryophyllene (5.2%)	Varéna district, Lithuania
	Caryophyllene oxide (14.2%) β-Caryophyllene (11.4%) Germacrene D (10.1%) β-Farnezene (8.0%) Spathulenol (7.1%)	Alytus district, Lithuania
	Caryophyllene oxide (13.4%) β-Caryophyllene (12.0%) Germacrene D (7.8%) α-Pinene (6.9%)	Vilnius district, Lithuania
	β-caryophyllene (18.3%) Caryophyllene oxide (15.7%) Germacrene D (10.1%) Spathulenol (7.1%)	Elektrénai district, Lithuania
	β-Caryophyllene (19.1%) Caryophyllene oxide (12.5%) Spathulenol (8.5%) Germacrene D (6.8%)	Vilnius city, Lithuania
	β-Caryophyllene (13.2%) Caryophyllene oxide (11.8%) Germacrene D (5.9%) Spathulenol (5.6%)	Vilnius city, Lithuania
	β-Caryophyllene (10.5%) Caryophyllene oxide (7.0%)	Rokiškis district, Lithuania

	Spathulenol (6.9%) δ-Cadinene (6.7%) β-Farnezene (6.1%)	
	Germacrene D (16.1%) Caryophyllene oxide (13.1%) β-Farnezene (8.2%) Spathulenol (5.6%)	Vilnius city, Lithuania
	Germacrene D (31.5%) α-Muurolene-14-hydroxy (9.1%) α-Cadinol (6.2%) Caryophyllene oxide (6.1%)	Lazdijai district, Lithuania
(170)	Germacrene D (22.8%) 2-Methyloctane (10.8%) α-Pinene (10.1%) β-Caryophyllene (6.6%)	Vermion mountains, Greece (Wild samples)
	Germacrene D (18.9%) 2-Methyloctane (17.8%) β-Caryophyllene (10.3%) T-Muurolol (5.6%)	Vermion mountains, Greece (Cultivated samples)

The plant with the lowest essential oil yield in the growth phase reaches the highest yield when it starts to bud. Its main components remain the same, but the total number of components changes. Since it starts to grow, the proportion of aliphatic compounds has decreased. On the other hand, sesquiterpenoids reach the highest level during budding and sesquiterpenes at flowering stage. The monoterpene rate has also increased gradually and approached 10% (155). Essential oil contents of flowers, leaves, and stems were investigated. The prominent class in leaves (74%) is sesquiterpenes, while about half of the oil in flowers (44%) and stem (50%) is non-terpenes (156).

Major compounds in the essential oils obtained in different research are given in Figure 3.

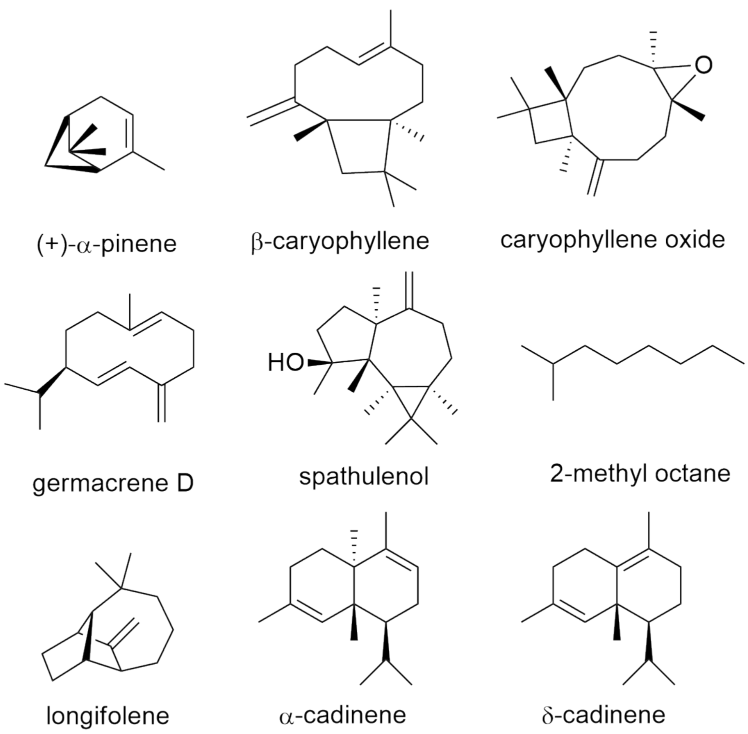


Figure 3: Major ingredients of different *H. perforatum* essential oils.

Essential oils of five different *H. perforatum* samples from France were examined. The major constituents were β-caryophyllene, caryophyllene oxide, ar-curcumene, germacrene D, and spathulenol (157). A study comparing the essential oil contents of herbs collected from Greece and Serbia gave interesting results. β-caryophyllene, which represented 22% in Serbian oil, was found to be less than 1% in Greek oil, whereas there were higher rates of α and β-pinene. While a very important part of Greek oil consisted of monoterpenes, sesquiterpenes and aliphatic hydrocarbons were prominent in other oils (158). Hışıl et al. (2005) reported that 2,6-dimethylheptane, α-pinene, β-caryophyllene, and 2-methyl-3-buten-2-ol were found as the main volatile components (159). The major essential compounds were: β-selinene (19.4%), bicyclogermacrene (15.3%), 2-tetradecene (8.2%), and α-amorphene (8.1%), in the air-dried aerial parts from Turkey (154). A review has been prepared on the essential oil of the plant and its ingredients (171).

Hatami et al. (2012) studied the SC-CO_2 extraction of *H. perforatum* and determined the required assumptions for modelling. It was assumed that temperature and pressure are homogeneously distributed in the reactor, all of the solid particles were of equal-sized and round-shaped, the concentration did not change radially, the local equilibrium was established at the fluid and solid interfaces and this equilibrium was linear, the amount of solid and therefore the reactor volume did not change during the process, the physical properties of the solvent remained constant and it flowed through the reactor in the plug flow model (172).

The difference created using CO_2 in the extraction of the herb collected from Albania was investigated. Soxhlet extraction with hexane and hydrodestilation were performed for comparison. A yield very close to hexane (2.73% vs 2.5%) was obtained at half the temperature (40°C) and half the time (1.5 h) with CO_2 (173). The efficiency was lower in the operation with liquid CO_2, but the rate of essential oil was higher (6.4%) than with supercritical CO_2. It was observed that the increase in pressure enhanced the efficiency but did not change the essential oil yield after a certain point. The main components in the liquid phase were n-triacontane (16.33%), n-heneicosane (14.41%), n-tetracosane (13.83%), n-nonacosane (13.26%) and in the supercritical phase were n-tetratriacontane (25.95%), 1,2-benzenedicarboxylic acid (13.44%), phytol (7.13%) (160). While either the temperature or pressure was lower, the other had to increase. On the other hand, since the solubility of CO_2 was directly dependent on its density, 313 K and 20 MPa were determined as the optimum extraction conditions (172).

Solvent-free microwave extraction (SFME) is one of the most interesting extraction methods in recent times. Moisture content, microwave power, and microwave time were investigated (72). All these three parameters increase the extraction efficiency. The parameters other than the duration were effective on the extracted content. Experimentally, the highest efficiency was found to be 0.365 g/100 g (d.m.) under conditions of high radiation power (468 W), high radiation duration (33 min) and low moisture content (43%). Efficiency was calculated as 0.405 g/100 g (d.m.) with response surface method. Although SFME made the extraction effective, the antioxidant content of the product was lower than ascorbic acid. The prominent ingredients in the product are phenolic components. A product with higher sesquiterpene content was obtained with hydrodistillation, and a product with higher terpenoid content was obtained with SFME. The reason for their increased ratio is that terpenoids absorb radiation better because they are more polar (174).

CONCLUSION

In this study, a comprehensive and actual review of the studies on *Hypericum perforatum* is given. When looking at the studies, different aspects can be seen, such as botanic, medicine, organic chemistry, chemical engineering, etc. In summary, *H. perforatum* has a wide range of uses thanks to certain active ingredients in its composition. It is not the species that contains the most hypericin and hyperforin substances, but it is the most commonly used species of *Hypericum* because it can grow in many places, has been studied for a long time, and contains a wider range of components. It is used not only as over-the-corner medicine but also in prescription treatment processes. It can also be used as a food additive due to its antimicrobial and antioxidant effects. Although maceration is a common method of use when it is fresh, there are no studies on the drying process. Its extraction can be carried out with traditional methods (soxhlet extraction, stirred extraction) as well as modern methods (accelerated solvent extraction, supercritical fluid extraction). Its essential oil generally includes derivatives of caryophyllene, pinene, germacrene, selinene, and cadinene compounds, although its composition varies regionally.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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