ST. JOHN'S WORT:
Its Properties and Medicinal Effects

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FOREWORD

St. John's wort is a plant that has been used for various therapeutic purposes since ancient times and can grow in a wide area. The use of the plant is an alternative treatment method that stands out in the therapy of lower and moderate depression and skin problems such as wounds and burns. It also has strong antimicrobial effects and contains antioxidant components.

We wanted to prepare this book and inform the relevant people about St. John's wort in a wide scope in order to ensure both better utilization of this plant and agricultural sustainability.

We hope this book will help you to appreciate it better if you see this golden-colored plant while walking around the countryside.

December 2022

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LIST OF ABBREVATIONS

WHO	: World Health Organization
EMA	: European Medicines Agency
FDA	: U.S. Food and Drug Administration
LC	: Liquid Chromatography
HPLC	: High Pressure Liquid Chromatography
GC	: Gas Chromatography
IR	: Infrared
UV	: Ultraviolet
NMR	: Nuclear Magnetic Resonance
DAD	: Diode Array Detector
SC	: Supercritical
Hz	: Hertz
W	: Watt
K	: Kelvin
°C	: Degree Celsius
MPa	: Mega Pascal
h	: Hour
min	: Minute
mM	: Millimolar
µmol	: Micromole
µg	: Microgram
ml	: Milliliter
nm	: Nanometer
d.w.	: dry weight

1. INTRODUCTION

According to the report of the WHO, 4000 of the 20 thousand plant species growing in the world have commercial value. While there are 12 thousand plant species all over Europe, there are more than 10 thousand plants, 3 thousand of which are aromatic, in Turkey. One of them is *Hypericum perforatum* L. (St. John's wort).

Hypericum perforatum L. is belongs to Plantae (plants) kingdom, Magnoliophyta (angiosperms) division, Magnoliopsida (dicotyledons) class, Malpighiales order, Hypericaceae family. The family has nearly 400 species in the World and 46 of 96 Hypericum species growing in Turkey are endemic [1]. While it grows naturally in Anatolia, Europe, North Africa, West Asia, and America, it is cultivated culturally in some European countries, Australia, China, North and South America.

Hypericum perforatum L. (St. John's wort), which grows in many regions of the World, is historically and locally known with different names. As the plant blooms around June 24, when St. John is commemorated, it is called St. John's wort. In other European languages, it is also named after St. John such as "hierba de San Juan" (Spanish), "erva de São João" (Portuguese), "erba di San Giovanni" (Italian), "Johanniskraut" (German) etc.

It is a bushy, multi-branched and perennial herb. It grows on roadsides and fences, in meadows, in dry summer, humid winter and mostly slightly acidic-neutral soils. Even though the plant generally has a 25-60 cm length, which can be reached to more than 1 m on the western America. Its oval leaves can be organized individually, contrarily, or spirally. It has five green sepals and five bright yellow petals in the flower. The plant, which can be seen abundantly on sun-drenched hills, is easily recognized by its golden petals in summer [2]–[7].

The most well-known types of proprietary developed are Authos, Hyperimed, Hyperixtrale and Motiv in Germany, Topaz in Poland, Uperikon, Hypera and Gold in Slovakia. Topaz is the most cultivated species in the world

due to its high hypericin content.

It is a plant with high economic return. If it is desired to be grown from seed, it is recommended to prepare a quality soil and plant 50-200 g of seeds per decare in autumn. In seedling production, after sowing seeds in the cultivating field between October and December and obtaining the seedlings, the time to transfer to the field is between March and April. For vegetative production, five cm stem cuttings are taken from the shoots of the adult plant in the spring. Rooted cuttings can be planted in the field between March and April.

The plants are seen between 65 meters and 1600 meters in Turkey. It can also grow in poor soils, but it prefers humus and neutral soils. Phosphorus fertilizers increase the rate of active substance, while nitrogen fertilizers decrease the rate of hypericin. Other harms of nitrogen fertilizers are that they increase fungal-related plant diseases, delay flowering and reduce yield. In the use of organic fertilizers, it is recommended to fertilize at least 3 months before the harvest or to give it to the plant sown before St. John's wort. Grains are the best choice as a pre-plant, as the part remaining in the field after harvest does not contain disease agents. It is recommended to pass 4-5 years in order to plant St. John's wort again in a place where St. John's wort was planted before, because it is non-resistant in terms of disease.

It is suitable to be collected during the full flowering period. It can be harvested once in the first planting year and twice in the second planting year. A qualified product is taken from the upper 1/3 part. After the harvest, it should be kept in bulk for a maximum of 4 hours and the drying process should be started. The drying temperature must also be below 40°C in order to be able to influence in a healthy way [8].

Hypericum genus grows widely and utilizes as herbal remedies for centuries [9], [10]. The history of using the plant as an alternative medicine method in the treatment of various ailments, both in the Anatolian geography and in the European and American continents, is old. For example, in the historical books, it is mentioned that the Ottoman armies carried St. John's wort oil with them when they set out to use it in the treatment of the wounds they received during the wars.

The medicinal properties of the plant have been recorded by many botanists since the Middle Ages, starting with Hippocrates and Plinius. Its prominent features at first are that it heals wounds, is diuretic and relieves

back pain. In the book The Herball, written by John Gerard in 1633, it was mentioned that the plant was used as an ointment on burns. It is as effective as common antidepressants and has fewer side effects when used correctly. The above-ground part of the plant collected in summer is dried in the shade. If it is desired to be used internally, it is boiled with water. If it is to be used externally, the fresh or dry plant is placed in olive oil and kept in the shade for a few weeks. After the solid parts it contains are filtered, the oil can be kept in a cool and sun-free place. The oil can be rubbed into the body or a few drops can be drunk. If it is desired to be drunk as tea, it is expected to be brewed by pouring boiling water on the fresh or dried herbs [11].

Considering the prominent uses of the plant, it is seen that its antimicrobial and anti-inflammatory properties have been utilized from the ancient times. This feature is used by applying the oil to the skin. It is also seen that the oil can be diluted with water and drunk and its tea is brewed in the healing of digestive system wounds. It is possible to use the essential oil in aromatherapy and respiratory diseases. Another prominent medicinal effect is that it can be used as a natural antidepressant. There are studies showing that the symptoms of mild and moderate depression and various neurological disorders can be eliminated by consuming the dried extract.

The species name of perforatum to one of the Hypericum genus is using because of the transparent oil glands on the plant. Pharmacological benefits of *Hypericum perforatum* L. encourage to study in different fields. Ingredients of Hypericum species can be assorted at least 11 classes as naphthodianthrones, phloroglucinols, flavonoids, organic acids, terpenoids, amino acids, xanthones, tannins, procyanidins and hydrophilic substances. Naphthodianthrones and phloroglucinols are efficient in the medication of depression in low-moderate level and of wounds, burns and inflammation, respectively [12].

Besides these, use of natural and alternative medicines is using more in recent years. Medicinal and aromatic plants and products of those are used as remedies, in strengthen immunity and in the treatment of diseases. Thus, knowing beneficial and harmful sides of the plant better is necessary to produce more efficient products. In nowadays, Hypericum extracts and supplements has been using increasingly as one of the most consumed medicinal products in the world [13].

According to the literature survey, there are studies on this plant in many

fields of chemistry, biology, and medicine. An average of 300 publications a year are about *Hypericum perforatum* L.

In this book, studies on the antimicrobial activity of the plant, its antioxidant content, its use for medicinal purposes, essential oil properties, extraction by different methods, drying processes, hypericin and hyperforin active ingredients were reviewed.

2. CHEMICAL COMPOSITION

In 1830, Buchner named the red pigment obtained from *Hypericum perforatum* L. as hypericumrot (Hypericum red). The name hypericin was coined by Cerny in 1911. Cerny stated that the compound he isolated 1.2 g from 1 kg of dried flowers had the formula $C_{16}H_{10}O_5$. It was understood by Brockmann and Sanne that hypericin, which was thought to belong to the anthocyanidin class in 1927, was 10-11-dimethyl-1,3,4,6,8,12,-hexahydroxynaphthodiantron ($C_{30}O_{16}O_8$) molecule in 1953. It is said that hypericin is the substance that gives the red color to the oil of the plant and that the pigments are determined at 590 nm in the UV spectrum. Then, it is thought that |3,||8-biapigenin and 1,3,6,7-tetrahydroxyxanthone may also be responsible for this color [14].

The composition of the St. John's wort oil is given in Table 1 [9].

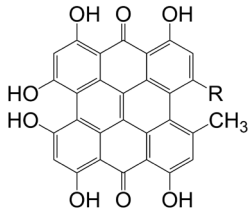
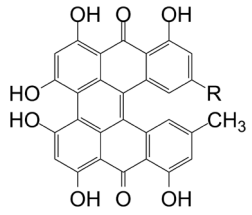
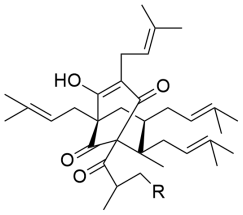
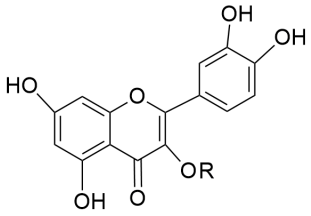
Table 1. The composition of St. John's wort oil

Class	Total percentage in plant (g/g %)	Active component	Percentage in plant (g/g %)
Naphthodianthrones	0.03-3 (Flowers/buds)	Hypericin	0.09
		Pseudohypericin	0.23
Phloroglucinols	2-5 (Flowers/buds)	Hyperforin	2.0-4.5
		Adhyperforin	0.2-1.8
Flavonoids	12 (Leaves) 7 (Stem) 2-4 (Buds)	Quercetin	2.0
		Hyperoside	0.7
		Quercitrin	0.5
		Isoquercitrin	0.3
		Rutin	0.3
		Campherol	*
		Myricetin	*
		Amentoflavone	0.01-0.05
		|3,||8-Biapigenin	0.1-0.5
Procyanidins	12 (Vegetative parts) 8 (Flowers/buds)	Procyanidin	*
		Catechin	*
		Epicatechin polymers	*
Tannins	6-15	Tannic acid	*
Essential oil	0.06-1.0 (Flowers/leaves)	Terpenes, alcohols	*
Amino acids	0.01	GABA	0,0007
		Cysteine	*
		Glutamine	*
		Leucine	*
		Lysine	*
		Ornithine	*
		Proline	*
		Threonine	*
Phenylpropanes	0.1	Caffeic acid	0,1
		Chlorogenic acid	<0,1
Xanthones	0.01 (Roots) 0.0004 (Leaves/stem)	Kielcorin, Norathyriol	*
Other water-soluble compounds	0.5	Organic acids, peptides, polysaccharides	*

*Trace amount

All components are efficient in the formation of the unique characteristics of the plant. However, naphthodianthrones (hypericin and its derivatives) and phloroglucinols (hyperforin and its derivatives) are the most prominent in terms of industry. Apart from these, antioxidant components are also important depending on the reason for use. The structures of the main components in the composition of St. John's wort oil are as in Table 2:

Table 2. Main components of St. John's wort oil

	Hypericin	$R = CH_3$
	Pseudohypericin	$R = CH_2OH$
	Protohypericin	$R = CH_3$
	Protopseudohypericin	$R = CH_2OH$
	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-pentoyde

The secondary metabolite types of *Hypericum perforatum* L., which is the most used species in Asia and Europe, are higher than those of other

Hypericum species. The main component groups found in the plant are naphthodianthrones, phloroglucinols, phenylpropanes, flavonoids, flavonol glycosides, biflavones, tannins, proanthocyanidins, xanthones, essential oil components, amino acids, and phenolic acids. It has been reported that naphthodianthrones have a wound-healing effect and flavonoids have an anti-inflammatory effect [7], [15].

The compounds contained in the oil in general are hypericin, pseudohypericin, protohypericin, protopseudohypericin, isohypericin, cyclopseudohypericin, hyperforin, adhyperforin, hyperoside, rutin, quercitrin, isoquercitrin, quercetin, biapigenin, amentoflavones, campherol, luteolin, myricetin, catechins, procyanidins, chlorogenic acid, caffeic acid, ferulic acid, isoferulic acid, p-coumaric acid, p-hydroxybenzoic acid, vanillic acid, isovalerianic acid, nicotinic acid, myristic acid, palmitic acid, stearic acid, carotenoids, nicotinamide, pectin, β-sitosterol, vitamin A, vitamin C, straight chain hydrocarbons, alcohols and terpenoids [2], [3], [6], [7], [12].

2.1. Hypericin

A large-scale study on the chemical and biological means by which hypericin can be synthesized was conducted in 2004 [16]. The compound is synthesized in 27 of 36 Hypericum species. Respectively, *Hypericum boissieri* Petr. and *Hypericum barbatum* Jacq. species contained 0.512% and 0.306% total hypericin, only 0.125% was detected in *Hypericum perforatum* [17]. Ayan and Çırak found hypericin in 9 Hypericum species grown in Turkey. The species with the most hypericin were *Hypericum triquetrifolium* (3.092 mg/g d.w.), *Hypericum montbretii* (2.959 mg/g d.w.) and *Hypericum perforatum* (2.91 mg/g dry matter). Pseudohypericin contents were determined as 4.166, 4.288 and 1.8 mg/g d.w., in order of the species [18].

Drying, light and extraction methods do not change the yield of naphthodianthrone whether it is done during flowering or fruiting. Maceration of fresh plants collected from nature in the shade yields elevated levels of hyperforin, regardless of the plant's developmental stage [19]. In a study conducted in Australia, it was determined that narrow-leaved specimens had higher hypericin than broad-leaved specimens throughout the year. It was observed that the hypericin ratio increased and decreased more rapidly in the broad-leaved biotype, while the hypericin ratio was significantly higher in the

narrow-leaved plants in the spring [20]–[22]. When the samples with different morphological characteristics were examined, it was seen that the hypericin ratio changed directly with the density of the dark glands on the leaves and inversely with the area of the leaves. A statistical relationship could not be determined between the length/width ratio of the leaves, the height of the plant and the bioactive components it contains, and the hypericin ratio [23].

In the analysis by HPLC, 0.44-2.82 mg/g hypericin, 0.0-1.86 mg/g chlorogenic acid, 0.0-8.77 mg/g rutin, 5.41-22.28 mg/g hyperoside, 1.64-3.98 mg/g quercitrin, and 1.01-1.76 mg/g quercetin have been determined in samples collected from northern Turkey [23]. In the LC-MS/MS analysis of 8 samples from India, 1.68-4.62 mg/g pseudohypericin, 1.19-2.68 mg/g hypericin, 3.84-24.58 mg/g hyperforin, 6, 54-23.77 mg/g rutin, 13.74-41.64 mg/g hyperoside, 1.33-12.85 mg/g quercitrin and 0.19-1.54 mg/g quercetin were found. The reason for the variation between the amounts of these secondary metabolites was determined as genetic, environmental, and climatic factors [24]. Extracts of the plant are usually prepared with ethanol/water or methanol/water. These extracts, which generally contain 0.1-0.3% hypericin, 0.6-11% hyperforin, 4-16% flavonoids, 19-25% sugars, around 10% tannin compounds, 2-3% citric and malic acids [25].

In the study of Ekren et al. (2010), St. John's wort clones were derived at Bornova ecological conditions and an average of 0.208% hypericin content was obtained, with the highest rate in the commercial Topaz species [4]. Pseudohypericin is 2-3 times more abundant than hypericin [26].

Separation of lipophilic compounds can be accomplished by reverse electro-osmosis flow anhydrous medium capillary electrophoresis system. The electrophoresis medium was a 3:2:1 by volume methanol/dimethyl sulfoxide/N-methyl formamide mixture with 50 mM ammonium acetate and 150 mM sodium acetate electrolytes added. The flow was reversed by adding the polycation hexadimethrine bromide (0.001-0.05%). Readings on the DAD were made at 300 nm for hyperforin, 590 nm for hypericin, and 350 nm for flavonoids and found 26.5 µg/ml hypericin, 51.0 µg/ml pseudohypericin and 1715.0 µg/ml hyperforin and derivatives [27].

Hypericin can be used as a natural fluorophore in a chemiluminescence system with energy obtained from bis-(2,4,6-trichlorophenyl)oxalate, H_2O_2 and imidazole catalyst. This system has also been applied to determine the

antioxidant activity of quercetin and β-carotene [28].

According to the analysis performed at 284 nm in HPLC, while there are many components in the oil composition as a result of ultrasonic extraction, the oil consists only of hyperforin and adhyperforin due to the fact that supercritical extraction is a highly selective process [29].

When studied under the same conditions, hypericin was almost not seen in the products of n-hexane, ethyl acetate, 2-propanol and SC-CO_2 extractions, while it was seen in the ethanol extract. In applications with ethanol, plants collected in July (35 mg/kg with Soxhlet extraction and 60 mg/kg with pilot scale extraction) were found to contain more hypericin than plants collected in September (17 mg/kg with Soxhlet extraction and 38 mg/kg with pilot scale extraction). Considering the total amount of hypericin, it was observed that the yields of 2-propanol (0.57 g/kg) and ethyl acetate (0.41 g/kg) lagged behind the ethanol yield (1.15 g/kg with Soxhlet extraction and 0.85 g/kg with pilot scale extraction)) [29].

Soxhlet extraction processes were performed with ethanol, chloroform, and ethanol, and it was observed that the products contained 8.2-8.8 μM total hypericin and 124-135 μM total flavonoids. However, these substances were not found during the extraction with chloroform. Since the aim of the study was the toxicity and oxidative stress caused by hypericin under the influence of light, it was determined that 10 μg/ml chloroform extract had the effect of eliminating the cytotoxicity of hypericin [30].

Hypericin and flavonoids were not found even if ethanol co-solvent was used in CO_2 extraction in liquid and supercritical phases. Only oleoresin with liquid CO_2, oleoresin and essential oil phases with SC-CO_2 were separated. While it was stable before, the extraction rate decreased rapidly when the SC phase transitioned. With the addition of ethanol, the yield increased (from 6.69% to 10.72% as d.w.) while the hyperforin content decreased (from 2.56% to 2.29% as d.w.) [31].

Maceration is one of the methods used for a long time to extract active ingredients from plants. Vegetable oils are often used as solvents. Depending on the nature of the solvent used, it is also possible to obtain more useful products than those obtained by other methods. The biggest disadvantage of this method, which is carried out by keeping the herbal substance in a solvent, is to take a long time.

It has been observed that macerates prepared under the sun for 40 days do not contain hypericin or its derivatives due to photodegradation [32]. The hypericin content of the products obtained by using three oils in maceration was sunflower, olive and palm oil macerate, from the most to the least. When quercetin, one of the important antioxidant substances contained in the plant, was examined, it was seen that palm oil gave a more efficient product in this respect. Contrary to expectations, olive oil macerate was the product with the lowest antioxidant content [33].

In a study conducted in Italy in 2007, it was found that the hyperforin and adhyperforin ratios of the oils obtained from the plant, which were kept in olive oil at 50°C, were low and the highest ratios were found as a result of the 28-day maceration of fresh fruits (90 g) in olive oil (512 ml). 36.90 µg/100 mg hyperforin and 17.58 µg/100 mg adhyperforin) were obtained. In addition, trace amounts of hypericin and its derivatives were found in all oils produced by olive maceration [2]. The oil quality of homemade and commercial macerates (*oleum hyperici*) produced in Turkey was examined and it was said that the fatty acids and therefore the quality of olive oil used in maceration improved the therapeutic properties of the ointment [34].

Solvent extraction using organic solvents provides higher yields in a shorter time as the solvent can be selected according to the desired product. Some molecules dissolve better in polar solvents because they are polar, while others dissolve better in nonpolar solvents because they are nonpolar. A common method of solvent extraction is Soxhlet extraction. In this method, by using the special Soxhlet apparatus, it is ensured that the solvent comes into contact with the herbal substance repeatedly and is saturated with the active substances at this time.

In a study comparing various solvents in Soxhlet extraction, the extraction efficiency decreased as the chain length of the solvent increased. For example, Cossuta et al. (2012) showed that ethanol was superior to 2-propanol, ethyl acetate and n-hexane in terms of total hypericin yield [29]. In another study, it was observed that the ethanol-water mixture gave better results than the use of ethanol alone [35].

In an extraction study with methanol, a total hypericin content of 3.814 g rutoside equivalent flavonoids and 0.163 g total hypericin content were determined [36].

In the comparison of Soxhlet and supercritical fluid extractions, the products were listed as ethanol (255.78-358.25 g/kg), 2-propanol, ethyl acetate and n-hexane products in terms of the amount of product obtained, and the amount of product obtained as a result of the treatment with ethanol in the pilot scale system (158.60-250.00 g/kg) was found to be lower. 38.43-31.73 g/kg of product was obtained with SC-CO_2. In terms of the amount of hypericin obtained, the yields were 1.15 g/kg for Soxhlet extraction with ethanol and 38-60 mg/kg for pilot scale production with ethanol [29]. As a result of the experiment performed with SC-CO_2 extraction at 100-450 bar and 40-60°C conditions, 6 times less product was obtained compared to the Soxhlet extraction with ethanol [37].

It was stated that the extraction of St. John's wort plant with SC-CO_2 yielded the purest oil [38]. With its low polarity, CO_2 shows high selectivity to lipophilic compounds such as essential and vegetable oils and fat-soluble vitamins. Thus, SC-CO_2 has a high selectivity to highly lipophilic phloroglucinols and lipophilic naphthodianthrones, essential oils, and biflavones [39]. Many bioactive compounds in plants have relatively higher polarity, so more hydrophilic plant substances (such as flavonoids, procyanidins, and tannins) can be extracted with a polar co-solvent such as ethanol or methanol instead of pure SC-CO_2. In the study, which includes information that hyperforin compound is easily extracted with SC-CO_2, hypericin and flavonoids cannot be recovered even with ethanol co-solvent, and liquid CO_2 is as effective as SC-CO_2, 60 g of extract was obtained with 5 kg CO_2/kg plant at 300 bar and 50°C [31]. In another study, it was stated that liquid and SC-CO_2 gave almost the same amount of extract with similar content and grinding the vegetable raw material into smaller sizes provided higher efficiency [40]. Cui and Ang (2002) determined that 380 bar pressure and 50°C temperature is as the most suitable conditions for the extraction using pure SC-CO_2 of phloroglucinols in their study with dried St. John's wort leaves and flowers taken from herbalists [41].

After 3 hours of treatment under 90 bar pressure and 1 hour under 120 bar pressure, 32-33% of the extract was transformed into hyperforin. As the pressure and time increased, the extraction efficiency increased and the hyperforin content in the extract decreased. The conversion of hyperforin to orthophorin increased with the effect of time and temperature [25]. In the

next study, oil was extracted and analyzed with SC-CO_2 from the extract [25]. The oil contains phloroglucinols such as hyperforin (36.5%) and adhyperforin (4.6%) as well as alkanes, fatty acids and wax esters, while apolar components are concentrated in the wax phase, which remains above the hyperforin-rich phase. Compounds with high polarity such as naphthodianthrones have not been seen. In another extraction study with SC-CO_2, it was studied in the range of 10-20 MPa at 40 and 50°C [38]. Up to 526 mg of phloroglucinol could be obtained in each gram of the resulting extract, and this ratio did not change much according to the amount of the extract formed. The highest yield of hyperforin and adhyperforin was obtained at 313 K and 10 MPa by consuming 7-8.5 grams of CO_2 for 1 gram of dry St. John's wort. However, the total amount of extract decreased with temperature and increased with pressure. Since the extraction power is high at high CO_2 density, the best hyperforin and adhyperforin content was achieved under conditions where 600-700 kg/m^3 CO_2 concentration was provided. In addition, ultrasonic extraction with methanol was performed after 2 hours of pretreatment at 50°C and 10 MPa without CO_2 feeding, and it was observed that the amounts of hyperforin and hypericin increased compared to ultrasonic extraction without pretreatment. In the study of Mannila et al. (2002), the most suitable condition was 30°C and 60 atm where a CO_2 concentration of 0.64 g/ml was provided, and at this point, 12 mg of hyperforin was obtained from one gram of St. John's wort [42].

If one of the temperature or pressure is lowered, the other must be increased. Since the density of the solvent is one of the most important parameters in extractions with supercritical fluids, the best working condition for SC-CO_2 was determined as 313 K and 20 MPa [43].

Another extraction method that has attracted attention in recent years is solvent-free microwave extraction. Moisture content, microwave power and time were examined by Abdelhadi et al. (2015). All three parameters increased the extraction efficiency. Parameters other than duration are also effective on extract content. The yield obtained from the material with a moisture content of 43%, which was treated at 468 W power for 33 minutes, was measured as 0.365 g/100 g d.w. Although the yield of the products produced by this method is high, the antioxidant effects were found to be low when compared to Vitamin C. The prominent component class of the product was phenolic substances.

In the same study, according to the comparison trials with hydrodistillation, the hydrodistillation product was rich in sesquiterpenes, and the solvent-free microwave extraction product was rich in terpenoids. The reason for this was explained as the more polar terpenoids absorbing the radiation more [44], [45].

Punegov et al. (2015) took 500 mg of sample with 6% humidity into 25 ml containers, added 15 ml of chloroform, put them in an ultrasonic bath for 30 s and kept them at room temperature for 30 min. After the chloroform extract of chlorophyll and lipids was taken 3 times under vacuum with silk and paper filters, the degreased raw material was dried in a cylindrical polypropylene manifold with air flow. It was mixed with 15 ml of solvent containing 20-90% ethanol by volume and extracted in 60 seconds at a frequency of 2450 MHz with a power density of 0.0205 W/cm^3 using a household microwave oven in a 1-liter container. It was heated to 65°C for 60 seconds and the first extract was taken and diluted with ethanol in a 25 ml container. The process was repeated two more times and hypericin and pseudohypericin in the product were detected at 590 nm. In the experiments with ethanol, a higher rate (0.09%) of naphthodianthrone was obtained than the ones made with isopropyl alcohol. The best results were obtained from the experiment with 55% ethanol [46].

The conditions under which the extraction is carried out directly affect the result. In studies on herbal products, it is necessary to work at a temperature as low as possible against the possibility of deterioration of the content. Ensuring that the cell walls are broken down before extraction increases the yield. For example, high pressure application before ultrasonic extraction increased the amount of other components as well as the yield of hypericin and hyperforin [38]. Similarly, disintegration of the cell walls using an ultrasonic bath before maceration reduced the process time from hours to minutes [47].

Direct sonication is more effective than ultrasonic bath application, and as the power increases, the efficiency increases. Sonication, Soxhlet extraction, maceration, accelerated solvent extraction experiments do not provide selectivity between the main components, while their amounts vary depending on the total product yield. Among the methods, maceration had the lowest efficiency [48].

In the study conducted with a microwave oven operating at 600 W, the best product was obtained with an ethanol solution with a concentration of 55-70% and approximately 0.09% total hypericin was reached. Isopropyl

alcohol solution, which provides almost the same yield, was measured at a concentration of 45-60% [46].

Ramezani and Zamani (2017) tried various adsorbent and leaching solvent mixtures to separate hypericin by column chromatography in their study. Dichloromethane provided better removal from dichloromethane, hexane, diethyl ether and petroleum ether to remove chlorophyll-like components of *Hypericum perforatum* L. leaves. After this step, the vegetable matter was extracted with ethanol:acetone (2:1). Among activated carbon, silica gel, the amberlites of XAD-7, CG-400 and CG-50 used to obtain the total hypericin content of the extract, silica gel gave the best results. Washing solvents of chloroform, chloroform:methanol (8:1), acetonitrile, ethanol:acetonitrile (1:1), chloroform:acetonitrile (1:1), ethanol, dichloromethane:acetone:methanol (15:10:75) were tried. It was observed that the last mixture left a long trace to give the best separation. It has also been stated that the narrow and long column works better than the wide and short column [49].

Direct sonication was performed using 40 and 60 W power at 20 kHz for 5-60 minutes in methanol, and indirect sonication with an ultrasonic bath at 35 kHz. Maceration and Soxhlet extractions lasted 24 h with methanol. Accelerated solvent extraction was carried out with methanol at 40°C, under 100 bars in 5 minutes. The stainless-steel cell is 33 ml, the flush volume is 60%. It has been observed that power increases efficiency, direct working is more effective than indirect work. Analyses were made in terms of hypericin, hyperforin, rutin, hyperoside, and quercitrin. It was observed that their amounts changed with the total yield. Neither method showed any selectivity. Accelerated solvent extraction, a new method, and ultrasonic bath was behind Soxhlet extraction. The lowest efficiency was obtained with maceration [48].

Purification studies with silica, polyamide or Sephadex LH-20 columns are costly and challenging. Karioti et al. (2009) observed that naphthodianthrones and other polar components are introduced in the separation process with vacuum liquid chromatography. In size exclusion column chromatography with Sephadex LH-20 or LH-60, proanthocyanins pass through the column along with naphthodianthrones. Based on this, hypericin-pseudohypericin mixture at 98% purity was obtained by using a series of liquid-liquid extraction stages with diethyl ether-ethyl acetate-methanol and Sephadex LH-20, LH-60 columns [50].

2.2. Hyperforin

Only one of the Hypericum species contains hyperforin up to 5% that is *Hypericum perforatum* [51]. Since there are creams containing hyperforin in the market, studies on this subject are continuing. In a study examining effect of hyperforin against solar simulated radiation, it was seen that even 0.45% hyperforin showed a high rate of anti-inflammatory effect and was useful in the treatment of erythema and atopic dermatitis in the skin [52]. Radical formation on the skin is prevented by 80% with hyperforin-rich *Hypericum perforatum* cream via stabilization of *Stratum corneum* while preventing rate was 60% with placebo [53], [54].

While the hyperforin-rich product is produced from fresh plants by maceration under daylight, drying and artificial light negatively affect this process. If the process is carried out in a hot environment, it is observed that hyperforin turns into furohyperforin. In the study investigating temperature, light and drying factors in Hypericum perforatum maceration in olive oil, no flavonoid or naphthodianthrone was found except for I3,II8-biapigenin [55]. It was understood that hyperforin and adhyperforin degrade in a lightened or dark room even at 5°C rapidly [56]. The compound degrades completely in daylight in 4 hours, under fluorescence at 60% in 6 hours, and not in the dark in 6 hours [57].

It creates unique pharmacological effects by inhibiting the uptake of many neurotransmitters such as 5-HT, serotonin, norepinephrine, dopamine, glutamate, and GABA, affecting the conductivity of ion channels and changing the pH of the environment. It can slow down tumor formation with its apoptosis-enhancing and antiproliferative effects and calm anxiety [58]–[60]. The plant precludes the toxicity occurred by β-amyloid and spatial memory debilitations by disaggregation of β-amyloid accumulations [61]. Brahmachari has prepared a recent review on the antidepressant effects and synthesis of hyperforin [51].

The contributions of ultrasound, microwave, and pressure to classical extraction with alcohol-water mixture were investigated. The best method for hyperforin has been to work in a pressurized condition [62].

Hyperforin, which is overly sensitive to heat and contact with air, was found in the SC–CO_2 extraction (23.97 g/kg and 10.39 g/kg from two *Hypericum perforatum* samples gathered when two separate times) but not in Soxhlet

extraction with organic solvents [29]. Römpp et al. (2004) tried to obtain hyperforin with SC-CO_2. In the processes at 9 MPa for 3 h and at 12 MPa for 1 h, 35% of hyperforin was gained. However, at higher pressures, the content was decreased. Low temperature was more effective as hyperforin degraded with temperature. As the time increased from 1 hour to 3 hours, the efficiency increased, but the hyperforin content decreased. No change was observed at higher durations. The conversion rates of hyperforin to orthophorin was 0.10 around [25]. It has been suggested that the SC-CO_2 density should be 600-700 kg/m3 in order to obtain the product with the optimal hyperforin and adhyperforin content [38]. It has been decided that temperature of 60°C and pressure of 400 atmospheres are the optimum conditions for 60-min SC-CO_2 extraction process with the acetone addition [57].

There have been several studies using semipreparative HPLC for the purification of hyperforin. The generally accepted procedure is a single or multi-stage extraction process and evaporation of solvent(s) followed by the lyophilization and feeding into HPLC using the appropriate column and eluting solvent [63].

3. MEDICAL USES

The plant has various effects medicinally. It is mostly used for its antidepressant and wound-healing effects directly; besides this, it is useful for many ailments. It is beneficial in different treatments, especially which of neurological and oncological disorders. It is one of the kind of medicines called over-the-counter drugs. Still, its use as both of an alternative and a supportive treatment method is increasing considerably in recent years.

It has been determined that it reduces stress, anxiety, and depression, relieves digestion, is diuretic, relieves pain, reduces bleeding by narrowing the vessels, prevents inflammation, fungi, germ and bactericidal effects.

If the plant is to be used for medicinal purposes, the most suitable harvest time is July. It is collected between June and September in Turkey. St. John's wort is collected in many regions of our country and dried as soon as possible so that its content does not deteriorate. Its oil can be produced in secretory ducts or glands that can be found in leaves, flowers, and the pistil. The amount

and composition of the oil may vary depending on factors such as the genetic characteristics of the plant, its state of development, which part is processed (leaf, flower, stem…), environmental conditions in which it is grown, and the method used to extract the oil.

With the effect of temperature, flowering stops, biomass decreases and the rate of hypericin increases in the plant that starts to consume the stored food [64]. Likewise, the increase in CO_2 increases this rate, while the rate of hypericin decreases as the plant becomes dehydrated [35]. On the other hand, since acetate and malonate formed as a result of photosynthesis constitute the source of hypericin biosynthesis via emodin and protohypericin, factors that decrease the rate of photosynthesis also reduce the formation of hypericin and its derivatives [65]. In a study examining the effect of temperature on the total hypericin content, the rate of total hypericin increased up to 30 mg in the plant and reached its highest level at a temperature of 25°C, where the photosynthesis rate is the highest [66].

Content and quality are unpredictable in the production of herbal products classified as dietary supplements by the FDA. The contents of the extracts may vary with temperature, light, light intensity, amount of soil nutrient components, or production method. Therefore, the composition of St. John's wort extracts and oils may differ from each other. In general, St. John's wort medicinal preparations contain 3-5% hyperforin or 0.3% hypericin. In short-term treatments and continuous therapies, 600-1200 mg of extracts are used in three doses throughout the year [6]. The results of the studies on *Hypericum perforatum* L. indicate that taking the preparations containing the standardized extract of the plant in doses ranging from 500-1000 mg daily may be beneficial in the treatment of mild and moderate depression. The standard dose is 300 mg of an extract containing 0.3% hypericin, 3 times a day. Some products are standardized for 2-3% hyperforin, not hypericin [67].

As an over-the-counter psychotropic herbal drug, the plant is used especially in the therapies for depression, anxiety and insomnia. There are also studies examining the effect on bipolar disorder [68]. It has been observed that antioxidant and antidepressant effects make a difference against restraint stress, that is an oxidative damage reason in the brain [69]. In order to better understand its neuroprotective effect, the genes it affects have been tried to be determined [70].

In terms of public health, one of the most important reasons for using St. John's wort is its antidepressant effect. In 1997, this herb accounted for a quarter of the antidepressant substances sold in Germany [67]. Both the use of antidepressants and the production and consumption of plants with antidepressant effects, such as St. John's wort, are increasing year by year. At least 40% of patients with depression in European countries consume this herb. St. John's wort extract is more effective than placebo and commonly used antidepressants. It has been determined that the rate of discontinuation of treatment in the treatment of moderate depression is lower than those who use drugs. Today, most people tend to use herbal sources rather than drugs [71]. According to Linde et al. (2008), St. John's wort is much more effective than placebo treatment and gives the same effect as conventionally used antidepressants with fewer side effects [72]. In a study examining the effect on the central nervous system of mice, the herb was as effective as desipramine and trimipramine [73].

Its beneficial effects on neurological problems such as Alzheimer's disease, anti-MAO-A, anti-α-glucosidase activity, and antihyperglycemic components have been studied [74]. Thanks to substances such as (+)-catechin and (-)-epicatechin, its use before the treatment of Alzheimer's disease has been reported to increase the effect of the treatment [75]. Its inhibition of neuronal acetylcholine esterase activity is most useful in improving the symptoms elicited by the disease [61]. It has been understood that the most beneficial component against this disease is hyperforin [76].

Protection against myringosclerosis [77], ameliorating renal ischemia-reperfusion injury [78], its effect in healing first degree burns, myalgia, acute injuries and bruises [79], central nervous system protection [80]–[82], immune-enhancing [83] were studied in various articles. Extracts with methanol have a neuroprotective effect through the removal of free radicals such as DPPH, DMPD and NO with acetyl and butyryl cholinesterase enzymes [80].

There are also many studies on the use of hypericin in photodynamic therapies. The use of plant extract or directly hypericin during photodynamic therapy ensures that healthy cells are protected, and diseased cells are eliminated. Hypericin, when supplemented with Vitamin C, inhibits the neutrophil respiratory burst oxidase enzyme [84]. On the other hand, the probable reason of the plant's lower sensitivity to light than pure hypericin is

that antioxidants in metabolism protect cells against harmful effects [30]. The interaction between the formation of the photodynamic effect of hypericin and some proteins has been studied from various aspects [85]. The plant is effective in protecting from UV-induced lipid peroxidation [86]. Hypericin uptake makes eye epithelial cells more sensitive to sunlight. Uptake of 0.1-10 μM hypericin causes cell rupture or death in UV-A and visible light. Exposure to sunlight after consuming the plant may cause cataractogenesis in the eye [87]. In the study conducted using yeast genes, it was understood that the plant affects 52 different genes that function in both intracellular and intercellular transport and signal transduction [88].

Hypericin is effective against leukemia and solid tumors by disrupting the mitochondria of cancerous cells. It shows antineoplastic, antiproliferative, apoptotic effects. The 0.5 μM dose of hypericin showed the same cytotoxic effect as the 1/10000 diluted extract. Accordingly, the main cytotoxic component of the plant is hypericin, inducing the programmatic death of HL-60 cells by affecting h-TERT mRNA suppression [89]. It directly inhibits protein tyrosine kinase activity, which is effective on processes such as epidermal growth factor receptors, which are effective in tumor formation, and phosphorylation of proteins through tyrosine residues, control of cell cycle and transformation [90]. However, high amount of application to normal cells does not cause any harmful effect [3]. Agostinis et al. (2002) reviewed the effects of hypericin on cancer cells and Theodossiou et al. (2009) examined its intracellular effects [91], [92].

Other noticeable features of St. John's wort are that hypericin defends against the negative consequences of lipid dysregulation seen in troubles such as obesity, fatty liver, and type 2 diabetes, and the long-term protective effect of hyperforin on pancreatic β cells [93], [94].

The plant has many therapeutic and protective properties. For example, its antimutagenic protection provides a power against the detrimental effects of the chemotherapeutic cyclophosphamide [95]. As a result of that the oxidizing low-density lipoprotein causes atherogenic effects in the body, cholesterol-related deaths occur. Thanks to the lipophilic active components of the plant such as naphthodianthrones and phloroglucinols, it has been determined that St. John's wort has antidepressant and antioxidant effects, as well as providing antiatherogenic advantages by inhibiting this protein [96]. The extract can be

used instead of mouthwash after third molar surgery [97]. It has been studied to understand its anti-aging effect [98] and determined that the antidepressant mechanism of action includes decreased corticosterone and proinflammatory cytokine concentrations in plasma [99]. The antioxidant activity of the plant, which causes apoptosis and adjusts the Ca^{+2} entry effects, possible to use in the eliminate oxidative stress in neutrophil cells against Behçet's disease [58]. It has been reported that its wound-healing effect is not related to the hypericin content, but to quinoids, xanthones and flavonoids [100]. A large amount of xanthone was found in the methanolic St. John's wort seed extract. These ingredients are also associated with antioxidant activity and antimicrobial effect [56].

The benefits of St. John's wort oil in the wound- and burn-healing have been studied in many studies. Suntar et al. (2010) observed that this oil improves break resistance, blocks inflammatory cells in the tissue, and enhances connective tissue formation [101]. In a study conducted in 2013, it was revealed that the presence of subcutaneous edema, necrosis, hyperemia decreased, and collagen formation and PMNL infiltration increased considerably when compared with 1% silver sulfadiazine (Silverdin) [7].

Studies have shown that the plant is not affected on intraperitoneal adhesion formation [102] and smoking cessation [103], but its antidepressant effect helps to reduce alcohol dependence [104].

There are many review studies about the plant and drug interactions. This issue is very considerable because many medicinal and aromatic plants, besides their positive effects, can also have harmful effects on metabolism. Over-the-counter drugs should not be used without consultation, and it should be careful to their drug-interactions [105]–[112]. In spite of having synergistic effects with many antidepressants and herbs, it can be used as additive in various herbal teas [113].

The use of St. John's wort as folk remedy has been included in many studies. Some publications have recommendations for use [9], [114]–[119]. EMA prepared a report about the use of the plant for various medicinal objectives [120]. Hypericin and hyperforin show a strong antioxidant effect when diluted, while they are acting as prooxidants without dilution. Naturally, it is impossible to remain undiluted when taken into the body, thus a prooxidant effect is not encountered. Still excessive intakes can be harmful in this respect.

The recommended dose for use in many publications is 300 mg of extract three times a day. In this case, dilution rate can be 1:10-1:20 to provide sufficient antioxidant effect [121].

The plant can be used as cattle feed alone or mixed with other herbs. When used as a feed additive, it enhances ruminal nitrogen turnover and volatile fatty acid formation without harming local helpful microorganisms [122]. When added to the diet of Atlantic salmon (*Salmo salar*), it makes the immune system stronger and has an antioxidant effect against crowd stress [123].

The production of antioxidative and anticancerogenic nanoparticles obtained from aqueous extract of the plant has developed as a new movement for different areas. Those nanoparticles can be prepared with some booster compounds such as silver nitrate and can be used in coatings especially for medical devices, antibacterial products, cosmetics, food, and pharmaceuticals. Their unique physical and chemical properties can be helpful in using both as drugs and drug carriers [124]. Investigation of nanomolecular lipid carrier systems is another growing area [125], [126].

To understand the harms of the plant is also studying continuously. It causes light sensitivity on the skin, edema, hair loss, itching, dizziness, constipation, fatigue [127], anxiety, insomnia, restlessness, diarrhea [128], gastrointestinal discomfort, and dry mouth [129] while long-term or high dose using. Of course, many of these side effects may occur depending on the user's metabolism and generally while using it with other antidepressants. It has been determined that using it as a foodl supplement, triggers to seen abnormalities in liver and testicular cells because of decreasing in nucleic acids and non-protein sulfhydryl and increasing in malondialdehyde [130].

Taking it with other antidepressants, MAO inhibitors, cytochrome P-450, MFOs, reserpine, narcotics or photosensitizers creates a situation as if the plant is used more than normal dose and this causes discomfort for the user [79], [131], [132]. The extracts in ethyl alcohol or dimethyl sulfoxide notably withhold CYP1A2, CYP2A6, CYP2C9, CYP2C19 and CYP3A4 cytochrome P-450 enzymes. This group of enzymes has a curative effect on TNBS colitis, inflammatory bowel disease, and intestinal cerulein-induced pancreatitis and decide to activate or removing from the body without being effective. Thus, there is more necessity of attention to the consumption of this plant with drugs

[109], [129], [133], [134].

Many heavy metals were found in studies examining the products sold in herbalists. Raised levels of chemical elements such as Al, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, K, Li, Mg, Mn, Na, Ni, Pb and Zn showed that uncontrolled producers are playing with public health [135]–[140]. Since cadmium element accumulates especially in the upper parts of the plant, it should be preferred to plant in cadmium-poor soils or to collect it from there. It is important for human health that the plant does not contain cadmium higher than 0.5 mg/kg [8]. Adulteration is one of the big problems in homemade and commercial macerates of the plant [34].

4. ANTIMICROBIAL ACTIVITY

One of the major features of St. John's wort is its antibacterial and antimicrobial effect [141]. These effects' value advances, especially with the wound-healing and anti-inflammatory effects of the plant. Inhibition rates of the plant's microorganisms have been investigated by numerous in vivo and in vitro studies [142], [143].

Considering its behavior against the most known microorganisms, flowers for *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Escherichia coli*, *Candida albicans*, leaves for *Aspergillus niger* are more effective. It inhibits gram-positive bacteria better than gram-negative bacteria [144]. The biofilm produced from its use with polyurethane foam was more effective against *Staphylococcus aureus* bacteria than against *Candida albicans* and *Escherichia coli* bacteria. On the other hand, it restrained up to 90.85% of the gram-positive *Staphylococcus aureus* [145], [146]. Again, in a study examining the effect against *Staphylococcus aureus*, extracts prepared with methanol and boiling water were more beneficial than commercial ethanolic extract, methanolic solution of commercial tablet, sunflower oil, olive oil and two other unknown vegetable oil [32]. The biofilms with chitosan, gelatin and the plant were more efficient against to gram negative *Salmonella typhi* than gram positive *Staphylococcus aureus* and gram-negative *Escherichia coli* [147].

There are studies showing that it is effective against *Staphylococcus aureus*,

Proteus vulgaris, *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Micrococcus luteus* ATCC9341, *Moraxella catarrhalis*, *Lactobacillus* and *Helicobacter pylori* bacteria [2], [3], [5], [7], [26], [148].

Also, in three different Hypericum species, *Hypericum perforatum* was found the powerful anti-infectious species owing to its hyperforin against *Toxoplasma gondii*, an intracellular parasite [149].

Mechanical properties, swelling behavior, surface hydrophobicity [146], pH, water permeability, [147], water activity, LF-NMR, texture, and L*-a*-b* color tests [150] of biofilms were investigated in different studies. Oil additives advance the vapor permeability, stretching ratio and cell renewal rate of biofilms until an optimum oil content. The degree of swelling and the tensile stress also decrease with the higher oil additives. The contact angle slightly increases [146].

Studies on the effectiveness of *Hypericum perforatum* L. against microorganisms are seen in Table 3.

Table 3. Antimicrobial activities of St. John's wort

Reference	**Microorganism**
gram-positive bacterium	
[32], [142]–[146], [151]–[160]	*Staphylococcus aureus*
[143], [155]	*Staphylococcus epidermidis*
[152], [154]	*Sarcina lutea*
[143], [152], [157], [161]	*Bacillus subtilis*
[152], [161]	*Bacillus mycoides*
[154], [159]	*Bacillus cereus*
[152]	*Mycobacterium phlei*
[152]	*Corynebacterium michiganes*
[151], [162]	*Corynebacterium diphtheriae*
[151]	*Streptococcus pyogenes*
[151]	*Streptococcus agalactiae*
[143], [151], [156], [163]	*Enterococcus faecalis*
[159], [164]	*Listeria monocytogenes*
[154]–[156]	*Micrococcus luteus*
gram-negative bacterium	

[142], [144], [161], [163]	*Klebsiella pneumoniae*
[142], [144], [154], [155]	*Salmonella enteritidis*
[155], [157], [163]	*Salmonella typhimurium*
[159]	*Salmonella infantis*
[142], [144]–[146], [151], [152], [154]–[160], [163]	*Escherichia coli*
[152], [156]	*Proteus vulgaris*
[154], [156]	*Proteus mirabilis*
[142], [144], [154], [163]	*Pseudomonas aeruginosa*
[150]	*Pseudomonas plecoglossicida*
[150], [161]	*Pseudomonas fluorescens*
[150], [151]	*Pseudomonas aeruginosa*
[150]	*Pseudomonas sp. MChB*
[161]	*Pseudomonas phaseolicola*
[161]	*Pseudomonas glycinea*
[154], [155]	*Pseudomonas tolaasii*
[161]	*Erwinia caratovora*
[161]	*Entrobacter cloaceae*
[154], [161]	*Agrobacterium tumefacies*
[161]	*Azotobacter chrococcum*
[165]	*Aeromonas hydrophila*
[166]	*Helicobacter pylori*
[159]	*Campylobacter coli*
fungi	
[152]	*Penicillium chrysogenum*
[155]	*Penicillium funiculosum*
[152]	*Fusarium avenaceum*
[152]	*Mucor plumbeum*
[155]	*Cladosporium cladosporioides*
[155]	*Trichoderma viride*
[142], [144], [145], [151], [152], [154], [155], [158], [163], [167]	*Candida albicans*
[167]	*Candida utilis*
[167]	*Candida tropicalis*
[167]	*Candida krusei*
[167]	*Candida parapsilosis*
[167]	*Candida glabrata*
[142], [144], [155]	*Aspergillus niger*

[158]	*Aspergillus fumigatus*
[156]	*Pythium ultimum*
[156]	*Trichophyton mentagrophytes*
[158]	*Trichophyton rubrum*
[168]	*Plasmopara halstedii*
[160]	*Rhizopus stolonifer*
protozoa	
[158]	*Leishmania infantum*
[158]	*Trypanosoma rhodesiense*
[158]	*Plasmodium falciparum*
[158]	*Trypanosoma cruzi*

5. ANTIOXIDANT ACTIVITY

Free radicals are formed as a result of both the respiratory system and other metabolic processes in aerobic metabolisms. Free radicals produced by metabolism or taken from outside are unstable/active atoms or molecules with unpaired electrons that react with other molecules. In metabolism, parts of reactive oxygen, nitrogen and sulfur species are found as free radicals. Molecules such as superoxide (O_2^-), hydroperoxyl (OOH^-), hydroxyl (HO^-), alkoxyl (RO^-), peroxyl (RO_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), ozone (O_3), hypochlorite (ClO), hypochlorous acid (HOCl), hypobromous acid (HOBr) are examples of reactive oxygen species. Nitrate (HNO_3), nitrosyl (NO^+), nitroxyl (NO^-), nitrous tetroxide (N_2O_4), nitrous trioxide (N_2O_3), peroxynitrite ($ONOO^-$), alkyl peroxynitrides (ROONO), peroxy nitrate (ONOOH), nitronium (NO_2^-), nitric oxide (NO^-), nitrogen dioxide (NO_2^-) are free nitrogen species. Free radicals formed from thiols reacting with free oxygen species form reactive sulfur species.

The formation of free radicals can occur in 3 ways:

- One of the common electrons remains in each fragment formed after the homolytic breakdown of a molecule containing a covalent bond.

$X : Y \rightarrow X\bullet + Y\bullet$

- Occurs as a result of loss of an electron from a molecule or heterolytic fragmentation.

$X : Y \rightarrow X\bullet^- + Y^+$

- It is formed by the participation of an electron in a molecule.

$A + e^- \rightarrow A\bullet^{(+,-)}$

When we look at the causes that accelerate the formation of free radicals, we mostly encounter external factors such as stress, foods containing additives, drugs, UV rays, radiation, alcohol and cigarettes, and internal factors such as fat oxidation reactions, immune system reactions, and biochemical reactions. In terms of a healthy body, the state of being equal in the rate of formation of free radicals in metabolism and their disappearance thanks to the antioxidant mechanisms within the body is called oxidative balance. In this balance, free radicals do not harm the body and can play important roles depending on their place. For example, reactive oxygen species are involved in processes such as intracellular and intercellular communications, gene expression, and ion transport. Inflammatory disorders in the body exposed to oxidative stress, which occurs when the balance is disturbed as a result of free radical accumulation in metabolism or insufficiency in antioxidative reactions due to internal and external causes, circulatory system diseases such as heart failure and arteriosclerosis, respiratory system diseases such as kidney failure, bronchitis and emphysema, liver diseases, the development of conditions such as cancer, diabetes, neurodegenerative disorders such as Alzheimer's disease, cataracts, autism and aging increases. In order to prevent this, molecules called antioxidants must complete the unpaired structure of the radicals by gaining or losing electrons.

Antioxidants are truly diverse in structure and function. Fast-acting antioxidants can delay the damage caused by free radicals for a while depending on their concentration and prevent damage during their existence. Delaying effects, on the other hand, allow these damages to occur more slowly. This effect of antioxidants, which protects metabolism by oxidizing themselves and breaking harmful reactions to the body, is as much as their concentrations. After the antioxidant substance in the environment is oxidized, the oxidative process continues its natural flow. Therefore, the power of antioxidants is related to both the number of free radicals they can reduce per unit number of molecules and the speed of the reactions they enter. Therefore, in order to determine how active an antioxidant is, it is necessary to examine its radical scavenging ability, redox reactivity, metal chelating ability and interaction with other antioxidant substances in the same environment [169].

The activity of an antioxidant substance means its free radical scavenging/

eliminating potential. This is measured by looking at radical scavenging, affinity for hydrogen atom or electron exchange, metal chelating potential, and interaction with other antioxidants. Structurally, the activity varies depending on the number and location of hydroxyl groups, the presence of sugar structure and methoxy groups.

Measuring the time required for the depletion of all the antioxidants the sample contains, adding a certain antioxidant to the medium containing free radicals and measuring the amount of depleted free radicals, or determining the reaction rate of a particular free radical and measuring the rate decrease in the antioxidant added medium are on the basis of the methods used to determine the antioxidant capacity of a substance.

The methods used to determine the antioxidant content are based on either electron transfer or hydrogen atom transfer. In electron transfer-based methods, the interaction between the antioxidant and the free radical is determined by measuring the color change. The most well-known ones are the determination of total phenolic substance with Folin-Ciocalteu reagent, trolox equivalent antioxidant capacity, iron ion reducing antioxidant power, total antioxidant potential using copper (II) as oxidant, and 2,2-diphenyl-1-picrylhydrazil methods. Most of the hydrogen transfer-based methods, on the other hand, use the comparison of antioxidant and substrate reactivity against peroxyl radicals from degradation products of azo compounds. The most known of these methods are oxygen radical scavenging antioxidant parameter, total radical scavenger antioxidant parameter and crocin bleaching methods.

Methods based on hydrogen transfer use an artificial free radical generator, oxidizable molecular probe, and antioxidant compound. The antioxidant and the substrate compete for the peroxyl radical obtained from the initiator. Thanks to the hydrogen atoms that the radical receives from the antioxidant, the reaction between the radical and the substrate is delayed.

The components of St. John's wort, such as those from the naphthodianthrone and phloroglucinol class, have direct medicinal effects. Other components contribute to health in separate ways and indirectly. Examples of these are antioxidant compounds. Antioxidants protect metabolism against free radicals such as reactive oxygen species formed in the body. In this way, the formation of many diseases such as cancer is prevented, and immunity is kept strong.

There are many studies on the antioxidant effects of the plant. The total

antioxidant capacity of methanolic extracts of St. John's wort grown in the Balkans was measured as 1560±95, 3630±83, 5430±55, and 73100±49 µmol/g α-tocopherol acetate/extract in the whole plant, stems, leaves and flowers, respectively. A correlation was found between flavonoid content in leaves (7.4%) and flowers (11.7%) and antioxidant effect [142]. In a study carried out in Bulgaria, the antioxidant capacity of the aqueous extract of St. John's wort was found as 3.74±0.14 mM trolox equivalent, and the total amount of phenolic substance as 881.93±6.68 µM quercetin equivalent. It was found to be one of the plants with the highest antioxidant capacity in the study [2].

Ciccarelli et al. (2001) classified the components in the secretions of the ducts and glands in various parts by examining the secretion channels of St. John's wort and the fluids in the transparent sebaceous glands [170].

Hypericum perforatum L. subsp. perforatum subspecies has higher flavonoid, tannin and phenolic content than angustifolium subspecies. It has also been identified as the only subspecies containing rutin [143]. Another study comparing different subspecies found higher hypericin, hyperforin, and phenolic substances in the veronense subspecies than in the perforatum subspecies [171]. Maltas Cagil et al. (2013), on the other hand, found the antioxidant capacity, total phenolic content and iron chelating power of two species (salsugineum and avicullariifolium) not included in this study to be higher than *Hypericum perforatum* L., and found the copper chelating power and total flavonoid content to be at similar levels [144]. Kladar et al. (2015) also compiled the chemical contents and biological activities of various Hypericum species [172].

It has been stated that infusing for 5-10 minutes at 80-100°C is the best method when it is desired to benefit from the antioxidant effect of the plant. The 3-minute period when the tea turned red was insufficient for the naphthodianthrones to be seen. After 3 minutes, phenolic and chlorogenic acids also increase significantly [173]. During boiling, which lasts up to 20 minutes, the number of bioactive substances increases, while a further increase in brewing time reduces the quality. Boiling is a better method than brewing, and it gives up to twice the active product in terms of antioxidant content [174].

The quality of olive oil macerate in terms of total flavonoid content and shelf life Şahin et al. (2020) [6]. While products obtained with methanol are

rich in hypericin and hyperforin, the antioxidant effect of aqueous solutions is stronger [175]. Products rich in catechin, epicatechin, protocatechuic acid, gallic acid, quercetin and kaempferol are the most effective against colon cancer cells [176]–[178]. The antioxidant content [179]–[182], total chlorophyll, total carotenoid and phenolic compounds [113], [183], polysaccharides [184], xanthone content [185], which constitute the biological activity of the plant, were studied.

St. John's wort includes various significant bioactive substances. Some of those such as naphthodianthrones and phloroglucinols affect the metabolism directly. Others support the human health in diverse ways thanks to for example their antioxidant effects. Antioxidant ingredients fight for the metabolism against free radicals, such as reactive oxygen species occurred in the body. By this way, diseases like cancer are prevented and the immunity of the body is strengthened.

Secondary metabolites of plants are responses to biotic (genetic characteristics, elicitors, harmful microorganisms, herbivores, etc.) and abiotic (water, light, temperature, CO_2, abundance of nitrogen and other nutritious compounds, geographical conditions, harvest time, contaminants, etc.) stress factors [186]. Eray et al. investigated effects of the growing conditions of *Hypericum perforatum* on the formation of secondary metabolites. In this wise, to grow the plant for specific purposes can be possible at specific cultural planting conditions [187]. For the producing a strong radical scavenger, another cultural planting procedure has studied [188]. Pan et al. separated the protoplast from the calluses obtained from the hypocotyl parts of the plant and utilized it in reclamation of the plant. With this study, production of designed plants came true remarkably [189]. How the growing conditions of the plant affect the activities and mechanisms of the genes is discussed in an article [190].

Rate of bioactive ingredients in the plant rises with temperature and light. At different growing stages, these rates increase or decrease. For example, phenolic and flavonoid components are higher at vegetative and flowering stages. Hyperforin rate increases according to some studies but not to the study of Radušienė et al. Hypericin reduces with flowering in low temperatures and light [191]. Rutin is higher at the budding stage, while quercitrin, quercetin and I3,II8-biapigenin are higher at the full-flowering stage. Hyperoside is not

changed along the stages [192]. Almost all bioactive substances reduce in the plant affected with ash yellows phytoplasma infection. The rate of essential oil decreases with this illness significantly [186].

Quercetin, a phenolic compound, has a strong antioxidant activity even in lower amounts [193]. Its rate is more in palm oil macerate and less in olive oil macerate as against sunflower oil macerate of *Hypericum perforatum*. It was said that quercetin is protective for the stomach from the cold restriction stress, however the highest protection was seen with the lowest quercetin in a study [33]. Use and effects of the flavonoids in nutrition was discussed in an article [194].

Maceration process lasts for 40 days in general folk remedies. After a maceration time by exposure to sunlight in olive, sunflower, and palm oil, some physicochemical features of the products along shelf lives for 12 months with and without additives of BHA or α-tocopherol antioxidants. Although palm oil is a more stable to temperature as a vegetable oil, it gave a lower qualified product. Characteristics of the products with antioxidants were satisfying after 12 months while the products without antioxidants degraded after 6 months. BHA and α-tocopherol affected the macerates similarly [195]. According to a study, an easy to make, homemade *Hypericum perforatum* macerate in olive oil can have long shelf life and high total flavonoid content [196].

Various active oxygen sources were utilized in a study to describe the antioxidant and antiradical effects of some medicinal plants. Using voltamperometric electrical method, *Hypericum perforatum* has been found more useful against hydrogen peroxide than hydroxyl radical and powerful in oxidizing molecular oxygen [197].

6. ESSENTIAL OIL

Essential oils, also known as essences or aromatic oils, are one of the products of plants used in industries such as food, cosmetics and pharmaceuticals. Although they are different from fixed oils, they are called oils because they do not mix with water. In summary, they differ from other vegetable oils due to the fact that their components are not esters of glycerides, their boiling temperatures are much lower, and their production methods are different.

Essential oils consisting of terpenes, oxygenated-terpenes, phenolic and aliphatic terpene derivatives can be found in plants' leaves (mint, laurel), flowers (rose, jasmine), fruits (citrus, strawberry), roots (ginger), seeds (pepper, anise), bark or stem (cinnamon) or all parts (lavender, thyme) [198].

Essential oils have been used in almost all civilizations in the east and west. Products such as aroma, incense and ointment obtained by using essential oils have been used especially due to their antimicrobial and anti-inflammatory properties and physical properties such as odor and taste. In the field of aromatherapy, which has been developed since the beginning of the 20th century, the subjects of obtaining and using essential oils are studied. It is seen that essential oils, which are used in a wide variety of fields, especially in food, perfumery, cosmetics, cleaning, and pharmacy, are also found in nanotechnological studies in fields such as textiles and paints, or in productivity-enhancing studies in fields such as livestock [199].

One of the traditional and modern uses of essential oils is to benefit from their antimicrobial effect. Essential oils of many plants such as pine, sage, rosemary, cumin, clove, thyme, golden herb can be used for this purpose. The resins leaking from the tissues of pine species after bark injuries and the propolis used by the bees in their honeycombs also contain such large terpenoid compounds.

The most widely used method of using essential oils is inhalation. Non-phototoxic products can be used by applying to the skin. It is also used in the form of drinking by dripping into water, albeit a little.

Factors such as plant type, season, geographical features, part used, method used change the yield and composition of essential oil. Therefore, it can be said that each plant specimen is unique. However, the approximate yield of plant species and the number of components are known. Some

plants have tens of components, while others have hundreds. Although this situation makes essential oils seem to have a complex structure, they can also be considered to be simple because they contain certain component classes [200]–[203]. There are many isomeric molecules. Some of them are called with Greek letters or cis-trans because they are similar to each other, while some of them are called with special names. For example, cis- and trans-citral are known as geranial and neral, respectively.

Most are clear to yellow in color. Since they have a specific gravity close to water, they can be easily entrained by water vapor. They can easily crystallize and deteriorate with factors such as heat and humidity. They have high refractive indices and vapor pressures, low polarity, and molecular weights [201], [202]. Polarity, which is one of the most important properties in terms of solubility, is related to the dielectric constants of the molecules, and the fact that the molecule has functional groups increases this property [204]. Oxygenated-terpenes are more potent aromatically and therapeutically than terpenes. The antioxidant property is prominent in terpenes and phenolic molecules [205].

Determining the quality of essential oils is a critical issue. There are two important points when determining quality: The product must have the essential properties specific to an essential oil and the name and amount of its ingredients. The most commonly used analysis methods to determine the composition and component ratios are GC and UV-Vis, IR and NMR spectroscopy. HPLC is used to detect components with boiling points that are too high to evaporate under GC analysis conditions. In addition, specific gravity, refractive index, melting and boiling point, optical rotation, color, odor, solubility, viscosity, total acid number, iodine number, saponification index, alcohol, ester, aldehyde and ketone content measurements are made and physicochemical properties are determined [206].

Since waxes, pigments, coumarins, psoralens are compounds with different properties and for different areas of use, the presence of these components, which creates adverse conditions such as cloudy appearance and phototoxicity, is undesirable in the use of essential oil in most areas [207]. Long-chain hydrocarbons, heterocyclic molecules, fatty acids, sterols, and carotenoids are the most visible substances as non-volatile components under normal conditions.

The first method of obtaining essential oils is the oil soaking method, also known as enfleurage. Methods such as water and steam distillation, solvent extraction, pressing, supercritical fluid extraction, microwave extraction, solid phase microextraction are frequently used methods in the production of essential oils. Solubility of the components, boiling points and desired properties of the composition are important in the selection of the method.

One of the methods used to prevent deterioration due to heat is the cold pressing of plants placed in cloth bags. The product obtained therefrom can be separated by decantation, filtration, or centrifugation. However, since this product is taken with the water contained in the tissues, there is a possibility of loss of water-soluble components.

Distillation is the most used method in essential oil production, although it has disadvantages such as deterioration caused by heating, loss of water-soluble components and a lengthy process. In water distillation carried out with Clevenger apparatus or still, water and herbs are placed in the boiling pot and heated. In steam distillation, saturated or superheated steam is passed through the plant on a grid at the top.

In microwave extraction, steam of the plant is obtained, which is heated by microwave energy in some water without an organic solvent. Energy efficiency, non-use of organic solvents, and short-time processing are the prominent aspects. By using electromagnetic waves at frequencies between 2.5-75 GHz, the solvent is heated directly and thus, less solvent is heated with less energy to obtain sufficient efficiency. Factors such as the type and amount of solvent, temperature, time, amount of water contained in the plant, heating power are the main factors of microwave extraction.

The absorption of the volatile components of the plant into the cold oil is called enfleurage, and the absorption into the hot oil is called maceration. These traditional methods take a long time and as a result, either a solvent such as alcohol and essential oil must be separated, or a product with a consistency to be applied to the skin is produced.

In solvent extraction, an organic solvent with a hydrocarbon structure is generally used. The product is removed from the solvent by filtration or distillation, and the remaining wax-like substances are separated with a solvent such as alcohol. After evaporation of alcohol, essential oil is obtained. Soxhlet apparatus is often used for solvent extraction. In addition to the negative

aspects such as the complete removal of the solvent and the evaporation of high volatility components, it also has positive aspects such as preventing deterioration due to heat and providing a composition close to nature. The solvent should be inexpensive, low boiling point, immiscible with water, and available in pure form, which does not degrade the structure of the components.

There are also applications such as contacting the vapor of the plant boiled in water with the vapor of the solvent, passing the solvent vapor from the plant in the water, performing the extraction using the solvent at elevated temperature and pressure, and using the solvent in the supercritical phase [200]. In extraction using supercritical fluid, yield and selectivity can be adjusted through pressure and temperature. The positive aspects of supercritical fluid extraction are that the organic solvents are not used, the solvent can be reused, the process is short, the dissolving power as high as that of liquid solvents can be provided with high diffusivity as well as gas solvents, the extraction can be carried out in environments that will prevent thermal and oxidative degradation.

There are many studies on the contents and main components of essential oils. Different contents can be encountered depending on several factors such as genetic characteristics, plant part used, climate, soil, season, harvesting time and method of the plant, drying method, and analysis method [208], [209].

While the essential oil yield is at its lowest during the growth phase, it reaches the highest level with the onset of budding. In this process, the main components stay the same, but the total number of components varies. As growth begins, the proportion of aliphatic hydrocarbons decreases. Meanwhile, the proportion of sesquiterpenoids reaches its highest levels during budding, and the proportion of sesquiterpenes during flowering. The monoterpene ratio increases continuously and reaches to 10% [210]. Smelcerovic et al. (2007) found sesquiterpenes with 74% in the leaves, non-terpenoid components with 44% in the flowers and 50% in the stem [211].

Although it varies according to climatic and geological conditions, it has been understood that there are mostly monoterpenes and sesquiterpenes in essential oils obtained from plants grown in distinct parts [2]. Radusiene et al. (2005) obtained essential oil from St. John's wort grown in Lithuania [212], Schwob et al. (2004) in France [210], Yüce (2016) in Turkey [209]. Contrary to the samples grown in Turkey, β-caryophyllene and caryophyllene

oxide compounds were prominent in the other two studies, while β-selinene, bicyclogermacrene and 2-tetradecane were determined as the main essential oil components in the samples collected from Gaziantep and Tunceli.

β-caryophyllene, caryophyllene oxide, ar-curcumene, germacrene D, spathulenol were the main components in the essential oils of 5 different samples collected from France [213]. In a study conducted in Turkey, β-selinene, bicyclogermacrene, 2-tetradecene and α-amorphene were determined as the components with the highest ratio [209]. The results obtained in a study comparing samples collected from Greece and Serbia showed that the contents were completely different. Accordingly, while the essential oil of the samples collected from Serbia contained β-caryophyllene at 22%, this substance was found below 1% in the essential oil of the samples collected from Greece. The components with the highest ratio in this product were α- and β-pinene. Greek essential oil consists predominantly of monoterpenes, while Serbian essential oil was found to be rich in sesquiterpenes and aliphatic hydrocarbons [214]. In a study conducted in Iran, 0.1-1% by mass of essential oil was obtained. Sesquiterpenes, alkanes and monoterpenes were prominent in the examples. When the contents of all samples were compared, the co-existence of only 2,6-dimethyl-heptane, 1,3-dimethyl-benzene, n-nonane, α-pinene, 3-methyl-nonane, p-cymene, allyl hexanoate, α-humulene, γ-himachalene, (E)-nerolidol and dihydro-eudesmol compounds was found [215]. The prominent volatile components of the product obtained by phytosol extraction were 2,6-dimethylheptane, α-pinene, β-caryophyllene and 2-methyl-3-buten-2-ol [216].

Crockett prepared a review on the content of the essential oil of the plant in 2010 [217]. Hatami et al. (2012) considered some assumptions necessary when trying to extract with SC-CO_2. Accordingly, the temperature and pressure are uniformly distributed in the reactor, all solid particles are in equal sized round shapes belonging to a single substance, the concentration does not change radially, local and linear equilibrium states occur at the fluid and solid interfaces, the amount of solid and therefore the volume of the reactor does not change throughout the process, The modeling study was carried out based on the assumptions that the physical properties of the solvent remain constant and flow in accordance with the piston flow model in the reactor [43].

In the study, where the efficiency remained low when liquid CO_2 was

used instead of SC-CO_2, it was observed that the efficiency increased up to a point with pressure but remained constant thereafter. The main components in the liquid phase are n-tricontan, (16.33%), n-heneicosan (14.41%), n-tetracosan (13.83%), n-nonacosan (13.26%) and in the supercritical phase n-tetratriacontan (25.95%), 1,2-benzenedicarboxylic acid (13.44%), phytol (7.13%) [40].

There are many studies on the essential oil composition of the *Hypericum perforatum* L. According to the investigations, it is seen that not only the whole oil composition, but also major components are altered because of internal and external conditions of the plant such as genetic features, processed part, climate, soil, season, growing stage, harvesting time and method, drying procedure, analysis method, etc. [208], [209]. A compilation on the main substances of St. John's wort essential oil is given in Table 4.

Table 4. Main essential oil components of St. John's wort

Reference	Main compounds (Concentration %)	Harvesting location
[163]	α-Pinene (30.92%) β-Pinene (18.32%) Caryophyllene (15.26%) Germacrene d (9.23%) β-cis-Ocimene (7.85%)	Arad county, Romania
[167]	Germacrene D (23%) β-Caryophyllene (14%) Bicyclogermacrene (5%),	Kirklareli, Turkey
[209]*	β-Selinene Bicyclogermacrene 2-Tetradecene α-Amorphene	Gaziantep and Tunceli, Turkey
[210]	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)

[211]	2-Methyloctane (20.5%) α-Pinene (13.7%) Spathulenol (9.8%) n-Hexadecanoic acid (4.0%)	Different locations of Southeast Serbia
[213]	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
[214]	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)

[215]	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

[216]*	2,6-Dimethylheptane α-Pinene β-Caryophyllene 2-Methyl-3-buten-2-ol	Izmir, Turkey
[40]	n-Triacontane (16.3%) n-Heneicosane (14.4%) n-Tetracosane (13.8%) n-Nonacosane (13.3%)	Sobina, Serbia
[40]	n-Tetratriacontane (25.96%) 1,2-Benzenedicarboxylic acid (13.4%) Phytol (7.1%)	Sobina, Serbia
[218]	α-Pinene (61.8%) 3-Carene (7.5%) β-Caryophyllene (5.5%)	Gaziantep, Turkey
[219]	α-Pinene (21.0%) 2-Methyl-octane (12.6%) γ-Muurolene (6.9%) Spathulenol (6.4%)	Ioannina, Greece
[220]	β-Caryophylene (14.2%) 2-Methyl-octane (13.1%) 2-Methyl-decane (7.9%)	Rujan mountain, Serbia
[221]	β-Caryophyllene (22.3%) 2-Methyl octane (17.3%) 2-Methyldodecane (6.0%)	Panèevo, Serbia
[221]	α-Pinene (35.0%) β-Pinene (23.4%) 2-Methyl octane (13.5%)	Termi, Greece
[222]	β-Caryophyllene (11.7%) Caryophellene oxide (6.3%) Spathulenol (6.0%) α-Pinene (5.0%)	Tashkent, Uzbekistan

[223]	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)
[224]	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%)	

[225]	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

[226]	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%) Spathulenol (6.9%) δ-Cadinene (6.7%) β-Farnezene (6.1%)	Rokiškis district, Lithuania
	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

[227]	Caryophyllene (30.0%) Germacrene D (19.64%) β-Copaene (7.09%) γ-Amorphene (6.28%)	Bologna, Italy (Ash yellows infected samples)
	Caryophyllene (25.41%) Germacrene D (17.24%) β-Copaene (5.97%)	Bologna, Italy (Healthy samples)
[228]	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

*Composition was not given.

The plant harvested from Albania is extracted using SC-CO_2. Soxhlet extraction with hexane and distillation with water were carried out for comparison. With the supercritical procedure, an essential oil yield as almost higher as soxhlet process (2.73% vs 2.5%) was obtained with less heat energy and time [229]. While the efficiency was lower with liquid CO_2, the rate of essential oil was higher (6.4%) than SC-CO_2. To the findings, pressure increases the efficiency but does not change the essential oil yield above of a specific point. The major substances were n-triacontane (16.33%), n-heneicosane (14.41%), n-tetracosane (13.83%), n-nonacosane (13.26%) in the liquid phase and were n-tetratriacontane (25.95%), 1,2-benzenedicarboxylic acid (13.44%), phytol (7.13%) in the supercritical phase [40]. If one of the temperature or the pressure is lower, the other must be increased. However, 40°C and 20 MPa were determined as the optimum extraction conditions because the solubility of CO_2 is influenced by its density [43].

Solvent-free microwave extraction (SFME) is one of the newer methods. Effects of moisture of the plant, microwave power and time were questioned

in a study [44]. All these three parameters make the extraction efficiency higher. First two parameters are efficient on the extract composition. With the investigations, 0.365 g/100 g (d.m.) was found as the highest efficiency at high power (468 W), for longer process time (33 min) with low moisture feed (43%). The efficiency that calculated with response surface analysis is calculated as 0.405 g/100 g (d.w.). SFME process provide an effective extraction, however the product had lesser antioxidant capacity than Vitamin C. The distinguished components of the extract are phenolics. The product produced using hydrodistillation showed higher sesquiterpene ratio, and the product produced using SFME showed higher terpenoid ratio. The reason of the increase in the terpenoid content is radiation absorption power of the terpenoids is stronger owing to their high polar structures [45].

7. EXTRACTION

Maceration is a method that has long been used to obtain active substances from plants. According to the properties of the solvent oil used in maceration, more useful products can be produced than other methods. Soxhlet extraction can be done using organic solvents instead of this time-consuming method, or more advanced methods can be used. *Hypericum perforatum* extraction is usually done to obtain naphthodianthrones or phloroglucinols, so the key point is determined accordingly.

n-Hexane, ethyl acetate, 2-propanol, and ethanol were used in Soxhlet extraction by Cossuta et al. Pilot-scale studies were also carried out with ethanol in the Soxhlet apparatus and with SC-CO_2. The extraction efficiency increases with the solubility parameter of the solvent. Thus, the order of efficiency was in the form of ethanol, 2-propanol, ethyl acetate and n-hexane. The efficiency was lower than the Soxhlet extraction with the same solvent, as the pilot scale study was shorter. The highest extraction efficiency was obtained in Soxhlet studies with ethanol, and it was 255 g/kg in the sample collected at the end of flowering and 358 g/kg in the sample collected at the beginning of flowering [29].

In a study, the herb was extracted with methanol on boiling water. After filtering, diluting to a specific volume, shaking, settling down and filtering

again, 5 ml of 100 g/l sodium acetate in methanol and 3 ml of 25 g/l aluminum chloride in methanol were added onto 5 ml of filtrate. After all was shaken, it was completed to 25 ml with methanol. When the volume decreases, the volume is completed again. Flavonoids and total hypericin were measured against a blank solution at 430 nm and 587 nm, respectively. An equivalent amount to 3.814 g of rutoside flavonoid (%) and 0.163 g total hypericin (%) were measured. In terms of both properties, *Hypericum maculatum* Crantz ssp. typicum has been featured [36]. It has been found that the extraction with ethanol-water gives better results than the treatment with only ethanol [35].

After extracting *Hypericum perforatum* with hydroethanolic solution, filtering and naming as total ethanolic extract, a part of it was subjected to liquid-liquid extraction with hexane, ethyl acetate and butanol. Each solvent was evaporated separately at 35°C under vacuum. Hexane extract was named V_1, butanol extract V_6. The ethyl acetate extract was dissolved in methanol and fractionated by passing through a Sephadex LH-20 column with methanol. The fractions were taken to TLC, evaporated under vacuum, and separated as V_2-V_5, respectively. Washing is done with ethyl acetate: formic acid: glacial acetic acid: water (100:11:11:27), toluene: chloroform: acetone: formic acid (40:25:35:1) and toluene: ethyl acetate: formic acid (6:4:1) eluates. The creamy colored aqueous phase obtained from this step was lyophilized and named as V_7. All fractions were dissolved in ethanol and analyzed on HPLC. Featured components in the products are acylphloroglucinol derivatives (mainly hyperforin) in V_1, bianthraquinones (such as hypericin and some related compounds) in V_2, the precursor composition of cinnamic acid and flavanol glycosides in V_3, quercetin-like flavanol glycosides in V_4, flavonoid aglycones (such as quercetin and I3,II8-biapigenin) in V_5, caffeoylquinic acids and glycosides of flavonoids in V_6, different compounds from various phenolic classes formed in small amounts in V_7. V_5, V_6 and V_4 showed the highest radical scavenging effect. While V_1 and V_2 remained ineffective, V_3, V_5 and V_6 were able to reduce lipid peroxidation [230].

The physical conditions of the extraction directly affect the result. It is important to work at low temperatures. In addition, exposing the plant to high pressure before ultrasonic extraction has been beneficial in terms of recovery of hyperforin, adhyperforin and hypericin [38]. The breakdown of cell walls by ultrasonic effect increases efficiency and shortens the process. In the study

where it was aimed to produce a hypericin-rich macerate, the maceration process was shortened from 5 hours to 20 minutes performing in an ultrasonic bath [47]. The active ingredients of the extracts obtained in a 55°C water bath and an ultrasonic bath were analyzed. In some instances, the water bath and in others, the ultrasonic bath are more efficient. Nevertheless, the water bath increases the proportion of active ingredients generally [231].

Heinrich et al studied the effects of using 12 fatty acids (olive oil, Arachis oil, soybean oil, almond oil, sunflower oil, maize germ oil, macadamia nut oil, sesame oil, *Simmondsia chinensis* seed oil and medium-chain triglycerides) in *Hypericum perforatum* maceration on product ingredients. Remarkable macerates were the almond oil macerate with the highest hypericin content (5.5±0.21 mg/100 g) and macadamia nut oil macerate with the lowest hypericin content but the highest phloroglucinol content (hyperforin (36.7±4.44 mg/100 g oil) and adhyperforin (4.6±0.58 mg/100 g oil)). Contrast to its phloroglucinol content, macerate of medium-chain triglycerides included the maximum flavonoids content [56].

Response Surface Method with Box-Behnken design was used to examine the ultrasound assisted extraction parameters. Based on the concentration of quercetin, one of the most important phenolic compounds, effects of the specified parameters were investigated. According to experiments, optimum conditions were at 67°C, for 67 min, using 77% (v/v) methanol and 1.2 M HCl in acidic alcohol solvent. The best amount of quercetin was found as 11.09 ± 0.40 mg/g d.w. [232]. In another study, the process of obtaining hypericin-rich extract using ethanol, acetone, water, chloroform, and hexane solvents was tried to be expressed by Response Surface Method. In the system in which bioactive compounds are measured, solvent mixture, time, and temperature were determined as important parameters for efficiency. It has been calculated that the best result would be obtained in 5.3-5.9 hours with a solvent mixture in the ratio range of 44-69% ethanol in acetone in a water bath at 55°C [233]. By using glycerol which has extremely low dielectric constant, it has been ensured that water can extract polyphenols better. It has been determined that the process carried out in a magnetic stirrer and illuminated using the Response Surface Method will give the best result at 70°C with 10% glycerol added water [234].

8. DRYING

Drying processes are of particular importance when it comes to medicinal and aromatic plants. If the drying of these plants, which is desired to be used due to certain components in its content, is not done properly, deterioration may occur. Mold and aflatoxin may occur in the packaged products without sufficient moisture loss, and the deterioration of sensory properties such as odor and color are not desired by the consumer. Depending on the method, temperature and time applied during dehumidification, the conversion of components into by-products is also possible. The process must be well designed so that the molecules are not exposed to hot temperature for a long time.

Feverish temperature makes drying in a shorter time. Air velocity (wind) reduces the vapor pressure and moisture evaporates faster. Energy consumption and hypericin ratio decrease with temperature and increase with air velocity. Considering all this, Minaei et al. (2014) showed in their study that the most efficient drying was achieved with air at a temperature of 50-60°C, sent at a speed of 0.7 m/s. Although the energy consumption of the plant placed in the dryer increases with the bed height, it has been determined that the energy cost per unit mass is inversely proportional to the bed height [235].

Drying, which is a prominent issue when it comes to medicinal and aromatic plants, has not been addressed enough in studies on *Hypericum perforatum*. There are only a few studies on drying from the distinctive aspects. It is particularly important to subject the plant to a good drying process after collection for a quality and preferable product. Drying method, applied temperature, processing time, remaining moisture rate affect not only the appearance but also the content. This has an impact on the effects of product and shelf life. According to the paper prepared by Chenarbon et al. (2012), low temperature and air velocity (40°C, 0.3 m/s) and thick bed depth (3 cm) are the suitable drying conditions for the optimum color quality of *Hypericum perforatum* [236].

It has been reported that flowering stops, biomass growth decreases and hypericin ratio increases in the plant due to the effect of temperature [64], hypericin increases with CO_2 and decreases with water stress. Contrarily, water stress increases the hyperforin ratio [35]. As reactive oxygen species

begin to form faster in the plant under water stress, the rate of secondary metabolites increases. This situation, which causes an increase in antioxidant effect, also increases the formation of hyperforin and its derivatives. On the other hand, since acetate and malonate formed by photosynthesis constitute the source of hypericin biosynthesis via emodin and protohypericin, factors that decrease photosynthesis rate also reduce the formation of hypericin and other hypericin species [65]. Seconder metabolites have been increased with the O_3-rich atmosphere [237]. The highest rate of photosynthesis and the highest amount of total hypericin was seen at 25°C (30 mg/plant). The best temperature for hyperforin was 30°C (160 mg/plant). Although the rate of secondary metabolites increased in sprouts at 35°C, no flower was formed [66].

It has been reported that increasing of drying temperature up to 50°C protects hypericin and flavonoids better, flavonoids are not degraded much in freeze-stored plants, only hypericin decreases [238].

Another study includes drying is an encapsulation process. Purified methanolic extract of *Hypericum perforatum* is encapsulated in β-cyclodextrin by freeze drying. It has been a useful product in the preparation of functional foods as it reduces the degree of thermal degradation [239]. Although freeze drying is believed to protect large molecule tannins, in the study of Makarova et al. (2021), it was observed that drying with warm air gave a product with higher polyphenols and flavonoids than freeze drying [35]. In another study, after infusing of herbs in boiling water, filtered and homogenized extract was atomized in a spray dryer. Various physical parameters related to the process were examined in the study [240].

An engineering study for solving the problem of the drying of *Hypericum perforatum* was done in Turkey. It is aimed to reduce the moisture content of 120 kg mass from 64% to below 15% in the warm air tray type dryer operating with LPG. In the study where the process was carried out with 63% drying efficiency in 8 hours, the LPG consumption was 0.290 kg/kg (d.w.). In an application that harvests three times a year and works for 90 days, the payback period is calculated as 0.34 months [241].

In a study examining the thin layer drying of the plant, different oven temperatures, heated air velocities and bed heights were tested. When seven different drying models were compared statistically, Verma, Yagcioglu, Two-

Term (low R^2), Henderson and Habis, Modified Page (high X_2) and Lewis (high RMSE) were found to be unworkable. As a result, it has been determined that the Page drying model is the model best describing the process [242]. Similarly, in another study examining the microwave drying process modelled by the Page model, energy consumption between 1000-650 W remains constant, while it increases significantly between 500-90 W. Although no microwave experiment can yield as high hypericin as natural drying (25-30°C, 5 days), remarkably comparable results were seen at 750-850 W. In total, the best conditions were 150 seconds at 850 W, and energy consumption during this process was calculated as 0.06 kWh [243].

CONCLUSION

This book was prepared for a compilation of the studies on St. John's wort. The plant has been using in botanic, chemistry, pharmacy, etc. for a long time. Thus, reviewing those studies in various aspects is particularly important to use the knowledge about the plant correctly.

In summary, composition of St. John's wort includes many compounds have strong antioxidative and antimicrobial effects in a broad area. Besides these indirect medicinal benefits, antidepressant and wound-healing effects are the most prominent advantages of the plant thanks to two major components of its oil, hypericin and hyperforin, and their derivatives. Studies on the essential oil of St. John's wort show that inner and outer, biotic and abiotic factors influence the whole composition and main ingredients of its products. Besides consuming it freshly, drying it after the harvest immediately is important to keep its composition as close to natural. Among the production methods of St. John's wort products, maceration in vegetative oil is a useful and traditional, soxhlet extraction is a highly efficient and frequently used, and supercritical extraction is the most suitable for the food industry.

Consequently, it can be said that St. John's wort is a useful and efficient plant for the human health in varied ways as a therapeutic over-the-counter drug and supportive food supplement. Still, we would like repeat that it must not be forgotten to be careful drug-interactions while using it.

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