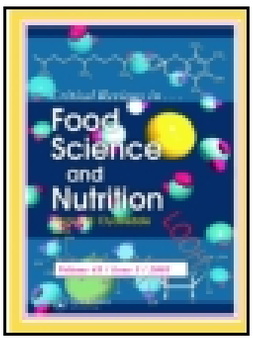

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Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Jose M. Lorenzo, Amin Mousavi Khaneghah, Mohsen Gavahian, Krystian Marszałek, Ismail Eş, Paulo E. S. Munekata, Isabel C. F. R. Ferreira & Francisco J. Barba (2018): Understanding the potential benefits of thyme and its derived products for food industry and consumer health: From extraction of value-added compounds to the evaluation of bioaccessibility, bioavailability, anti-inflammatory, and antimicrobial activities, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2018.1477730

To link to this article: https://doi.org/10.1080/10408398.2018.1477730

Accepted author version posted online: 17 May 2018.
Published online: 14 Jun 2018.

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REVIEW

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Understanding the potential benefits of thyme and its derived products for food industry and consumer health: From extraction of value-added compounds to the evaluation of bioaccessibility, bioavailability, anti-inflammatory, and antimicrobial activities

Jose M. Lorenzo [a], Amin Mousavi Khaneghah [b], Mohsen Gavahian [c], Krystian Marszałek [d], Ismail Eş [e], Paulo E. S. Munekata [f], Isabel C. F. R. Ferreira [g], and Francisco J. Barba [h]

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ABSTRACT

Natural bioactive compounds isolated from several aromatic plants have been studied for centuries due to their unique characteristics that carry great importance in food, and pharmaceutical, and cosmetic industries. For instance, several beneficial activities have been attributed to some specific compounds found in Thymus such as anti-inflammatory, antioxidant, antimicrobial, and antiseptic properties. Moreover, these compounds are classified as Generally Recognized as Safe (GRAS) which means they can be used as an ingrident of may food producs. Conventional extraction processes of these compounds and their derived forms from thyme leaves are well established. Hoewever, they present some important drawbacks such as long extraction time, low yield, high solvent consumption and degradation thermolabile compounds. Therefore, innovative extraction techniques such as ultrasound, microwave, enzyme, ohmic and heat-assisted methods can be useful strategies to enhance the exytraction yield and to reduce processing temperature, extraction time, and energy and solvent consumption. Furthermore, bioaccessibility and bioavailability aspects of these bioactive compounds as well as their metabolic fates are crucial for developing novel functional foods. Additionally, immobilization methods to improve stability, solubility, and the overall bioavailability of these valuable compounds are necessary for their commercial applications. This review aims to give an overall perspective of innovative extraction techniques to extract the targeted compounds with anti-inflammatory and antimicrobial activities. Moreover, the bioaccessibility and bioavailability of these compounds before and after processing discussed. In addition, some of the most important characteristics of thyme and their derived products discussed in this paper.

KEYWORDS

anti-inflammatory; antimicrobial, bioavailability; bioactive compounds; Thyme; thymol

1. Introduction

For centuries, herbs and spices have been preferentially used all around the world, and many of them are included in the category of Generally Recognized as Safe (GRAS) (Kim, Cho, and Ham 2013). The application of their extracts and essential oils is becoming an increasing trend in food and pharmaceutical industries as a potential source of bioactive compounds with antioxidant (Agregán et al. 2017; Barba, Esteve, and Frígola, 2014; Fernandes et al. 2016, 2018; Hashemi, Khaneghah and de Souza Sant'Ana, 2017a; Hashemi et al. 2017b; Hashemi et al. 2018), anti-inflammatory (Habashy et al. 2018), antifungal, antibacterial and even antiviral (Bakhtiary et al. 2018; Mahmoudzadeh et al. 2016; Mahmoudzadeh et al. 2017; Hashemi et al. 2017c; Özogul et al. 2017; Şahin et al. 2017; Asl et al. 2018) properties. In this context, the popularity and consumption of medicinal plants have significantly grown over the last years (Eş et al. 2017; Saljoughian et al. 2017).

Some of the aromatic plants with significant industrial interests such as rosemary, sage, mint, marjoram, oregano, and thyme belong to the family of *Lamiaceae*. Thyme as a pleasant smelling perennial shrub comprises over 350 aromatic plant species with different botanical characteristics and a broad chemical heterogeneity (Adzet et al. 1977; Stahl-Biskup and Venskutonis 2012; Tavakolpour et al. 2017; Kuete 2017). Analysis of world consumption of aromatic plants showed that this genus is among the bestsellers culinary herbs with an expanding market (Dauqan and Abdullah 2017; Krause and Ternes 1999; Kuete 2017).

Essential oils and their compounds obtained from several *Thymus* species have been gaining great interest due to their

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reduced safety concerns, general acceptance by consumers, and multi-functionality, which can be used in pharmaceutical, food and cosmetic industry (Bozin et al. 2006). Spain, Portugal, France, Germany, Italy, Morocco, Canada and the United States (Stahl-Biskup and Venskutonis 2012) are leading countries in thyme production. Due to their aromatic properties, thyme leaves can be used in various industrial food products such as ice-cream, meat, butter, liqueurs, and candy production. Furthermore, their incorporation into the products improves their shelf life by slowing the oxidation process and decreasing color changes (Hęś and Gramza−Michałowska 2017) as well as antimicrobial activities (Dauqan and Abdullah 2017). Thymus components can also significantly contribute to favorable biological activities (Hosni et al. 2013; Nikolić et al. 2014). In this context, thymus can find potential applications in pharmaceutical and cosmetic industries because of its biological and medicinal benefits, including antimicrobial, antitussive, antispasmodic and antioxidant properties (Gavliakova et al. 2013; Khosravipour and Direkvand-Moghadam 2016; Oliveiro et al. 2016). In addition, thyme is frequently employed in the manufacturing of perfumes and toiletries (Boughendjioua and Djeddi 2018).

Therefore, this review focuses on the potential advantages of thyme and its constituents, including anti-inflammatory, antimicrobial and antiviral activities. Besides, its applications in food products along with innovative techniques for thyme essential oil extraction are also presented.

2. Cultivation and production cost

People have known how plant thyme for many centuries. For example, Thyme was mentioned in poetic descriptions of early Persian gardens, indicating its cultivation on that time (Stahl-Biskup and Venskutonis 2012). Although thyme can be found in nature, the growing demand for this aromatic plant and its derivate products, destructive gathering methods and insufficient and irregular rainfall in some regions highlighted the need for its cultivation. The cultivation requirements of thyme genus are different. The common thyme (*T. vulgaris*), as one of the most popular spices, prefers light and permeable soil which is rich in organic materials and minerals (Rey & Sáez, 2002). The harvest yield of thymus varies from 2 to 5 ton of dry plant material per hectare, depending on several parameters such as the planted spices, environmental condition and planting season, agricultural practice, and harvesting season. It was reported that the classical cultivation of thyme needs about 1500–2000 working hours per hectare. According to the statics, global production of thyme is estimated to be about 14,000 tons/year (Stahl-Biskup and Venskutonis 2012). This medicinal plant is produced in several regions of the world including Mediterranean, South American, and Middle Eastern countries. Turkey is the main supplier of this medicinal plant with more than 12,000 ha farms that are cultivated with this plant (in 2016) and exports about 10,000 tons thyme, i.e., 70% of world trade, which is equal to about 43 million USD revenue. The essential oils of this herb also gave a high profit to the thyme producer and processor countries. As an example, the export revenue of Turkey from exporting thyme essential oil was about one million USD in 2010 (Baka, 2012). The major importer countries of thyme are the United States, Canada, France, Hungary, and Poland (Aslan & Mevlüt, 2017).

The production cost is an important parameter that should be considered while using a medicinal plant as a food ingredient/additive. It should be noted that the farming cost of any medicinal plant can vary in different regions of the world, considering variations in plant yield, agricultural materials and machinery, land, and labor costs. Mevlüt, Osman & Sitki (2014) assessed the production inputs, costs, and profitability of thyme farming in Turkey, as the main producer of this plant, and reported that production of one kilogram of thyme cost 1.7 TL, i.e., about 0.4 USD, in 2014. They also illustrated that labor, fertilizer, and machinery are among the cost variables for thyme production (Mevlüt, Osman & Sitki, 2014). It should be noted that in case of thyme that is growing wild on mountain highlands or another area, the cost variables are different from the ones that reported by Mevlüt, Osman & Sitki (2014). A comprehensive study on the production cost of thyme spices is required to explore the economic aspect of production and consumption of thyme as a food ingredient/additive in thyme producing countries.

3. Chemical composition of thyme

Harvesting time, variables related with climate, vegetative development stage, the plant part of interest and the extraction method are among the responsible parameters for fluctuations in the chemical nature of the herbal extracts and essential oils (Tavaklpour et al., 2107). Several bioactive compounds, such as phenolic acids, flavonoids, biphenyl compounds and, most importantly, essential oils, are the main components that constitute phytochemical composition of thyme (Figure 1). Thyme usually contains between 1% and 2.5% essential oil, which is the main reason behind its spicy taste and pleasant aroma (Figueiredo, Barroso, and Pedro 2010). Thymol and its phenol isomer, carvacrol, are usually the major components of extracted essential oil (representing around 30–50%), and are reported to have antioxidant, antimicrobial, antitussive, expectorant, antispasmodic, and antibacterial effects (Fachini-Queiroz et al. 2012; Gavliakova et al. 2013; Höferl et al. 2009; Quiroga, Asensio, and Nepote 2015; Yanishlieva et al. 1999) and are recognized as GRAS by the Food and Drug Administration (FDA) (Burdock 2010; Luna et al. 2018). Thymol ($C_{10}H_{14}O$) is also known as Thymic acid; Thyme camphor; Thymol [USAN: JAN]; Phenol, 5-Methyl-2-(1-methyl ethyl) phenol; 5-methyl-2-(1-methyl ethyl); 6-isopropyl-; p-Cymen-3-ol; 3-hydroxy-; Phenol, 2-isopropyl-5-methyl; m-Thymol; 3-Hydroxy-p-cymene; 1-Hydroxy-5-methyl-2-isopropylbenzene; 5-Methyl-2-isopropyl phenol; 3-Hydroxy-1-methyl-4-isopropyl benzene; Isopropyl cresol; Enichem thymolm-Cresol; 2-Isopropyl-5-methylphenol; 3-p-Cymenol; 6-Isopropyl-m-cresol; 1-Methyl-3-hydroxy-4-isopropyl benzene; 3-Methyl-6-isopropyl phenol; 5-Methyl-2-isopropyl-1-phenol; 6-Isopropyl-3-methylphenol; has a warm odor and produce a sweet, medicinal, spicy flavor.

The annual consumption of this compound is estimated to be about 283.33 lb, and its application in the food product is approved by several organizations, such as FDA and

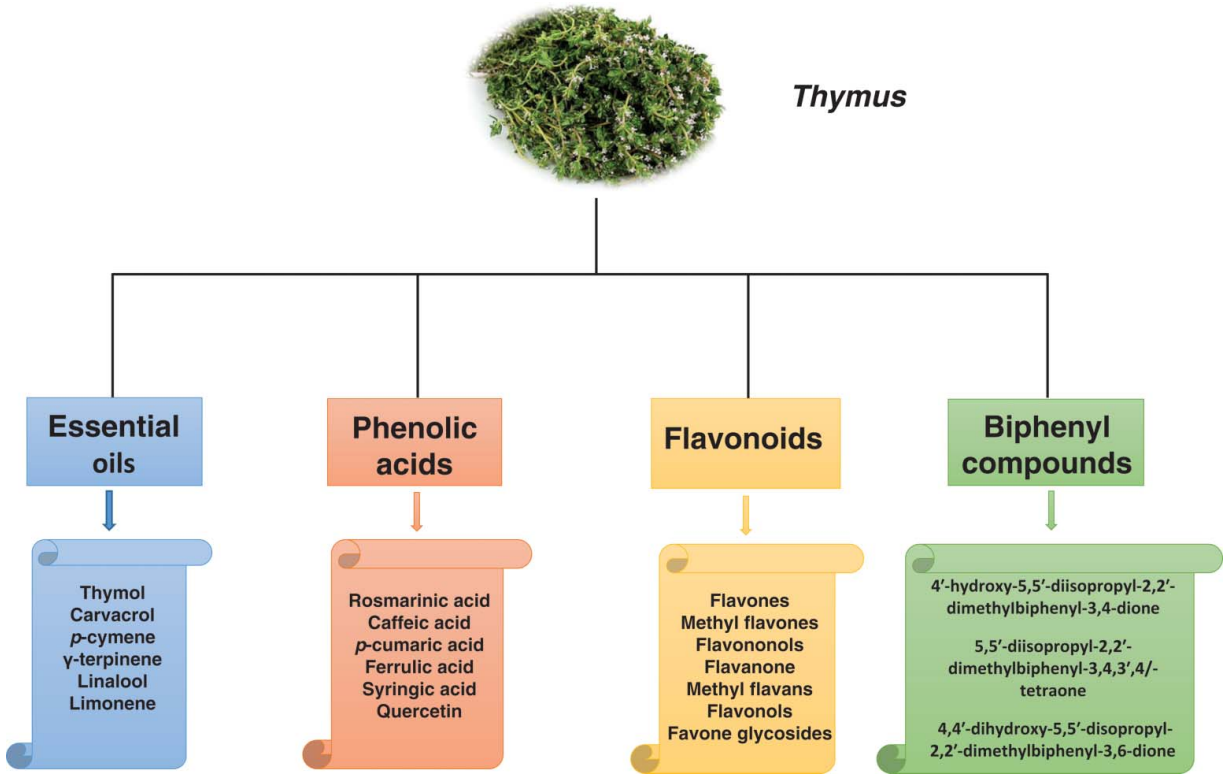

Figure 1. Main components that constitute phytochemical composition of thyme.

the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Thymol was reported to be among the principal compounds of the essential oils of *Thymus vulgaris, T. serpillum*, and *T. capitatus* moreover, many other aromatic herbs. The radical scavenging ability of this natural compound made it a valuable compound with biological activity (Burdock 2016). The *in vivo* effect of thymol and its antioxidant impact on animal tissues, including plasma, brain, and muscle have been comprehensively assessed and it was revealed that dietary consumption of this compound enhanced the oxidative stability and the activity of enzymes such as superoxide dismutase and glutathione peroxidase as well as reduced the malondialdehyde concentration, which is correlated with higher concentrations of polyunsaturated fatty acid precursors such as α-linolenic and linoleic acid (Ezzat Abd El-Hack et al. 2016; Hashemipour et al. 2013).

Moreover, thymol has several modulatory roles in lipid metabolism as its supplementation altered the metabolic pathways of bile acid, cholesterol synthesis and fatty acid metabolism (Koppenol et al. 2014). It was suggested that the desirable effects of thymol could be directly related to its antioxidant activity (Youdim and Deans 1999; Fernandez et al. 2017). This compound was also reported to be a potential food additive in order to prevent obesity as it can enhance the mitochondrial biogenesis, expression of a core set of brown fat-specific markers, and protein level.

Carvacrol ($C_{12}H_{18}O$), which is generally known as Antioxine; o-Cresol, 5-isopropyl; 5-Isoproply-2-methylphenol; Isothymol; p-Cymen-2-ol; 2-hydroxy-; 2-Methyl-5-(1-methylphenol)phenol; 2-p-Cymenol; 1-Hydroxy-2-methyl-5-isopropylbenzene; 2-Hydroxy-p-cymene; Isopropyl-o-cresol; 5-Isopropyl-o-cresol; 3-Isopropyl-6-methylphenol; Karvakrol; 2-Methyl-5-isopropylphenol; Phenol, 3-isopropyl-6-methyl-; Phenol, 5-isopropyl-2-methyl-; Phenol, 2-methyl-5-(1-methyl-ethyl)-; o-Thymol, has a characteristic of a pungent, warm odor. Similarly to thymol, its consumption in food material is permitted by FDA and JECFA (Burdock 2016).

A high concentration of other monoterpenes such as *p*-cymene (15–20%), γ-terpinene (5–10%), and linalool (1–5%) was also found in the essential oil of thyme. A low concentration (0.5–1.5%) of other monoterpenes, such as limonene, *trans*-sabinene hydrate, borneol, α-terpineol camphor, myrcene, ß-pinene, and terpinen-4-ol, were also reported in thyme oil. In addition, less than 3% of sesquiterpenes (ß-caryophyllene) were reported in some thyme essential oils. Figure 2 summarizes the main chemical structures of terpenes found in essential oil of thyme.

Table 1 shows the phenolic compounds identified in thyme species (Vallverdú-Queralt et al. 2014). The predominant phenolic acid in thyme is rosmarinic acid (mean values of 84.04 μg/g dry matter; Vallverdú-Queralt et al. 2014), which is an anti-oxidative polyphenol of great value with numerous other beneficial effects, such as anti-inflammatory and anti-mutagenic properties as well as preventive effect against Alzheimer's disease (Airoldi et al. 2013; Furtado et al. 2008; Rocha et al. 2015). Other phenolic acids that were reported in thyme are: caffeic acid (6. 6 μg/g dry matter), *p*-hydroxybenzoic acid (4.4 μg/g dry matter), *p*-cumaric acid (2.7 μg/g dry matter), protocatechuic acid (2.6 μg/g dry matter), ferrulic acid (1.0 μg/g dry matter), syringic acid (0.9 μg/g dry matter), quercetin (0.8 μg/g dry matter) and chlorogenic acid (0.7 μg/g dry matter) (Vallverdú-Queralt et al. 2014).

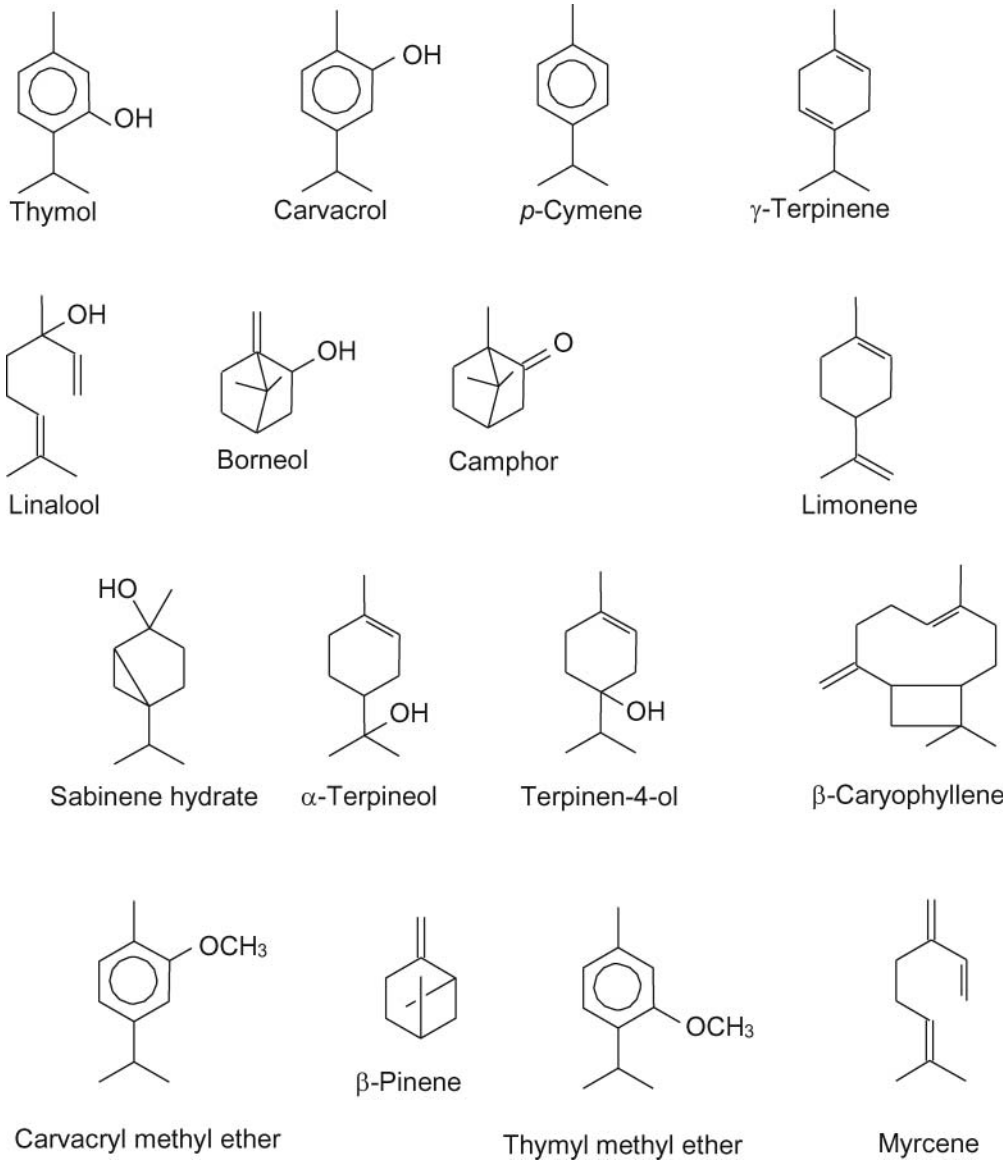

Figure 2. Main chemical structures of terpenes found in essential oil of thyme.

Regarding flavonoids, a great variety of compounds have been described in thyme, including flavones, methyl flavones, flavononols, flavanone, methyl flavans, flavonols, and flavone glycosides (Stahl-Biskup and Venskutonis, 2012). Luteolin and apigenin are the most abundant flavonoids in thyme, which are present in both forms as aglycones and as O-glycosides (Vila 2002; Wang et al. 1998). Together with flavones, there is a great diversity of methylated flavones (such as cirsilineol, cirsimaritin, salvigenin, sideritoflavone, thymonin, etc.), whereas flavonols and flavanones are presented in low number and amount in thyme (Stahl-Biskup and Venskutonis 2012). On the other hand, five biphenyl compounds [4′-hydroxy-5,5′-diisopropyl-2,2′-dimethyIbiphenyl-3,4-dione (1), 5,5′-diisopropyl-2,2′-dimethylbiphenyl-3,4,3′,4/-tetraone (2), and 4,4′-dihydroxy-5,5′-disopropyl-2,2′-dimethylbiphenyl-3,6-dione (3), 3,4,3′,4′-tetrahydroxy-5,5′-diisopropyl-2, 2′-dimethylbiphenyl (4) and 3,4,4′-trihydroxy-5,5′-diisopropyl-2,2′-dimethylbiphenyl (5)] were isolated from thyme leaves. These compounds have shown a deodorant effect and antioxidant activity (Ladopoulou et al. 2015; Okazaki, Kawazoe, and Takaishi 2002). Finally, a great number of monoterpene glycosides (Kitajima et al. 2004; Takeuchi, Lu, & Fujita, 2004) and triterpenes in the form of ursolic acid (0.9%) and oleanolic acid (0.4%) (Jäger et al. 2009) were also isolated from different parts of thyme.

4. Extraction of bioactive compounds from thyme

The typical processes for obtaining bioactive compounds from thyme leaves are a steam distillation, hydrodistillation (HD), and maceration, (Stahl-Biskup and Sáez 2002, Tavakolpour et al. 2017). Although these extraction processes are considered as safe, they involve several drawbacks, including long extraction time, low yield, and may negatively affect thermolabile compounds such as polyphenols.

Recently, some alternative techniques (Roohinejad et al. 2017) such as ultrasound-assisted maceration (UAM) (Kowalski and Wawrzykowski 2009; Kowalski et al. 2015), microwave-assisted hydrodistillation (MAHD) (Golmakani and Rezaei 2008)., enzyme-assisted extraction (EAE) (Hosni et al. 2013), pressurized liquid extraction (PLE) (Villanueva

Table 1. Phenolic compounds identified in thyme species (Vallverdú-Queralt et al., 2014).

Compound	$[M–H]^-$	MS/MS ions	Acc Mass	Molecular Formula
Phenolic acid				
Gallic acid	169	125 (100)	169.0142	$C_7H_6O_5$
Vanillic acid-*O*-hexoside	329	329 (10), 167 (100)	329.0877	$C_{14}H_{18}O_9$
Carnosic acid	331	331 (70), 287 (100)	331.1915	$C_{20}H_{28}O_4$
Rosmarinic acid	359	197 (30), 161 (100)	359.0772	$C_{18}H_{16}O_8$
Syringic acid	197	182 (40), 167 (40),	197.0455	$C_9H_{10}O_5$
Coumaric acid	163	119 (100)	163.0400	$C_9H_8O_3$
Caffeic acid-*O*-hexoside 1	341	179(100), 135 (10)	341.0877	$C_{15}H_{18}O_9$
Neochlorogenic acid (3-*O*-caffeoylquinic acid)	353	191 (100), 179 (40), 135 (20)	353.0877	$C_{16}H_{18}O_9$
Protocatechuic acid	153	153 (40), 109 (90)	153.0193	$C_7H_6O_4$
Caffeic acid-*O*-hexoside 2	341	179(100), 135 (10)	341.0877	$C_{15}H_{18}O_9$
Homovanillic acid-*O*-hexoside 1	343	181 (100), 137 (10)	343.1034	$C_{15}H_{20}O_9$
Dicaffeoylquinic acid 1	515	353 (100), 173 (10), 179 (8)	515.1194	$C_{25}H_{24}O_{12}$
Vanillic acid	167	167 (50), 152 (20), 108 (50)	167.0350	$C_8H_8O_4$
Caffeic acid-*O*-hexoside 3	341	179(100)	341.0877	$C_{15}H_{18}O_9$
Caffeic acid	179	135 (100)	179.0349	$C_9H_8O_4$
p-Hydroxybenzoic acid	137	93 (100)	137.0244	$C_7H_6O_3$
Ferulic acid	193	193 (5), 178 (40), 149 (10), 134 (80)	193.0506	$C_{10}H_{10}O_4$
Chlorogenic acid (5-*O*-caffeoylquinic acid)	353	191 (100)	353.0877	$C_{16}H_{18}O_9$
Coumaric acid-*O*-hexoside 1	325	163 (100), 119 (20)	325.0928	$C_{15}H_{18}O_8$
m-Hydroxybenzoic acid	137	93 (100)	137.0244	$C_7H_6O_3$
Cryptochlorogenic acid (4-*O*-caffeoylquinic acid)	353	191(50), 173 (100), 135 (20)	353.0877	$C_{16}H_{18}O_9$
Homovanillic acid	181	137 (100)	181.0506	$C_9H_{10}O_4$
4-*O*-*p*-Coumaroylqunic acid	337	191 (20), 173 (100), 163 (30)	337.0930	$C_{16}H_{18}O_8$
Ferulic acid-*O*-hexoside	355	193 (100)	355.1034	$C_{16}H_{20}O_9$
Sinapic acid-*C*-hexoside	385	325 (50), 295 (100), 265 (70), 223 (25)	385.1139	$C_{17}H_{22}O_{10}$
Flavonoids				
Apigenin	269	269 (10), 151 (100)	269.0455	$C_{15}H_{10}O_5$
Apigenin-7-O-glucoside	431	269 (100)	431.0983	$C_{21}H_{20}O_{10}$
luteolin	447	357, 258, 327	286.0477	$C_{15}H_{10}O_6$
Naringenin-*C*-hexoside	433	373(50), 343(50), 303 (20)	433.1140	$C_{21}H_{22}O_{10}$
Hesperetin	301	286 (30), 151 (100)	301.0718	$C_{16}H_{14}O_6$
Kaempferol-3-O-glucoside	447	285 (100)	447.0932	$C_{21}H_{20}O_{11}$
Kaempferol	285	285 (40), 151 (100)	285.0405	$C_{15}H_{10}O_6$
Kaempferol-3-O-rutinoside	593	285 (100)	593.1511	$C_{27}H_{30}O_{15}$
Quercetin-3-O-glucoside	463	301 (100)	463.0881	$C_{21}H_{20}O_{12}$
Rutin	609	301 (100)	609.1460	$C_{27}H_{30}O_{16}$
Quercetin	301	301 (10), 151 (100)	301.0353	$C_{15}H_{10}O_7$
Hesperidin	609	301 (100)	609.1825	$C_{28}H_{34015}$

Bermejo et al. 2015), supercritical fluid extraction (SFE) (Palavra et al. 2011), heat-assisted extraction (HAE) (Jovanović et al. 2017) ohmic-assisted hydrodistillation (OAHD), ultrasound-assisted ohmi (UAO) and ultrasound-assisted hydrodistilation (UAHD) (Tavakolpour et al. 2017) have been successfully applied for the extraction of bioactive compounds from thyme areal parts (Figure 3). These innovative extraction technologies are characterized by either reducing processing temperature, extraction time, consumed energy, solvent consumption (Chemat, Vian, and Cravotto 2012; Gavahian and Farahnaky 2018; Gavahian, Chu, and Sastry, 2018; Roselló-Soto *et al.* 2015; Misra *et al.* 2017) or increasing the extraction yield (Rombaut et al. 2014). In addition, the combination of these innovative approaches could lead to developing optimized extraction processes and further improve the performance and efficiency of the extraction process (Chemat, Vian, and Cravotto 2012).

For instance, Jovanović et al. (2017) studied the effects of three extraction methods, including maceration, heat-assisted extraction (HAE) and ultrasound-assisted extraction (UAE), on the total polyphenol content (TPC) and total flavonoid content (TFC) of the extracted essential oil from the thymus. They observed that the highest TPC content was obtained in thyme samples after applying UAE (32.7 mg GAE/L) followed by HAE (29.8 mg GAE/L) and maceration (26.6 mg GAE/L). TFC was also significantly higher in the extracts obtained after UAE (16.7 mg CE/L) compared to HAE (12.4 mg CE/L) and maceration (14.3 mg CE/L).

On the other hand, the recovery of thymol was studied using PLE combined with green solvents (ethyl lactate, ethanol, and limonene) and SFE combined with pure CO_2 and CO_2 and each of the three green solvents as co-solvent (Villanueva Bermejo et al. 2014). These authors displayed that the three solvents studied presented excellent capacity to extract thymol from *T. zygis* and *T. vulgaris* using PLE. Although PLE could be a useful technology to extract thymol, the samples obtained after using supercritical CO_2 presented the highest amounts of thymol.

In another study, Golmakani and Rezaei (2008) compared MAHD with traditional HD regarding chemical compositions of the extracted essential oils and extraction time, cost, and efficiency. According to these authors, a similar extraction yield was obtained at considerably shorter extraction time when MAHD was employed instead of HD. They also reported that MAHD had no adverse effect on the chemical composition of the extracted essential oils. In line with this, OAHD also resulted in an improved extraction time and a substantial energy saving compared to the conventional HD technique (Gavahian et al. 2012). According to the authors, this method produced an essential oil with higher concentrations of thymol

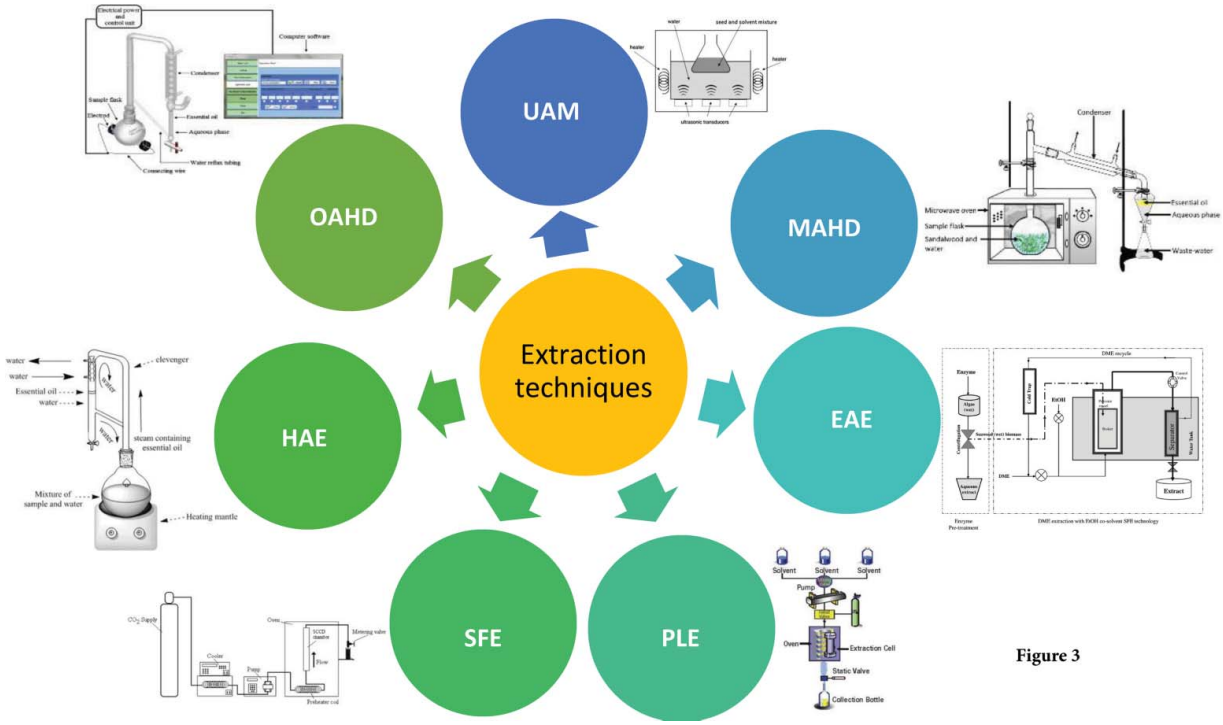

Figure 3. Alternative techniques applied for the extraction of bioactive compounds from thyme areal parts. MAHD: Microwave-Assisted Hydrodistillation; EAE: Enzyme-Assisted Extraction; PLE: Pressurized Liquid Extraction; SFE: Supercritical Fluid Extraction; HAE: Heat-Assisted Extraction; OAHD: Ohmic-Assisted Hydrodistillation; UAM: Ultrasound-Assisted Maceration. Figures was adapted from: Billakanti et al. (2013); Gavahian et al. (2012); Herrero, Cifuentes, & Ibañez (2006); Marszałek et al. (2017); Samadi et al. (2017); Samaram et al. (2014); Vazquez-Roig & Picó (2015).

and carvacrol, due to the selective extraction ability of OAHD (Gavahian and Farahnaky 2018).

On the other hand, the use of 20 min UAM as a preliminary stage before the distillation of essential oil from thyme leaves increased the extraction yield by 9%, as compared with the control method (Kowalski and Wawrzykowski 2009). Hosni et al. (2013) also noticed that enzyme-assisted extraction could be considered as a promising biotechnological method for increasing the release of essential oil from thyme plants. These authors observed that the use of cellulase, hemicellulase and their combination increased the exaction efficiency of essential oil by 64, 24 and 109%, respectively.

4.1. Enzymatic extraction of thymol

The enzymatic extraction is an alternative approach, based on partial or complete hydrolysis of the cell walls by specific enzymes to obtain thymol. The application of enzyme can improve essential oil release yield as well as increasing properties such as antimicrobial or antioxidant activities of the thymol. For a more efficient extraction, appropriate enzymes should be employed for the hydrolysis.

The enzymes such as cellulase or hemicellulases are important candidates for *thymus* leaves for thymol extraction. Hosni et *al.* (2013) pre-treated *Thymus capitatus* leaves with cellulose, hemicellulose and the combination of both enzymes and improved the release of thyme essential oil by 63.55, 23.72 and 109.32%, respectively compared to control (without enzyme). In this study, the use of enzyme combination presented cooperative synergistic effect for thyme extraction. Interestingly, the antimicrobial activity of thyme oils against *S. agalactiae, S. aureus, E. feacium, E. coli* and *S. Typhimurium* was highest for hemicellulose treated samples even this enzyme could not increase thyme release. Cerda et al. (2013) employed two commercial enzymes (Macer 8 FJ and Grindamyl CA 150), and enzymes increased antioxidant activity of essential oils obtained from fresh and depleted thyme up to 100% more in comparison with control.

Another important parameter is the type of solvent used in the extraction process. Most organic solvents can inhibit or decrease the activity of enzymes used for extraction since ethanol is a competitive inhibitor that acts on the active sites of enzymes. Therefore, enzymatic extraction of thymes should be conducted using aqueous solution. Moreover, temperature, time, and enzyme concentration are crucial parameters to be optimized for more efficient extraction of essential oils.

5. Anti-inflammatory activity of thyme and their extracts

Inflammation is a natural and protective way of organism's response to a tissue injury or infections. This protection is induced by combatting invaders in the body (microorganisms and non-self cells) and consequent moving of dead or damaged host cells (Stevenson and Hurst 2007). It was reported that several parameters such as bacterial infection and harmful chemicals could result in inflammatory diseases which are responsible for various chronic diseases, such as cancer, hepatic, and autoimmunity (Sánchez et al. 2015). Thyme has been traditionally used as an herbal medicine for inflammatory diseases (Soković et al. 2009), and several investigations showed that it contains valuable components with anti-inflammatory properties (Rodrigues et al. 2015; Ocaña and Reglero 2012; Afonso et al. 2017).

The collected T. Vulgaris from Brazil (Fachini-Queiroz et al. 2012), Italy (Oliviero et al. 2016) and Greece (Habashy et al. 2018) have been shown to be effective against inflammation. Moreover, thymus extracts and essential oils have shown to have a potent attenuating effect for several inflammatory mediators. In this line, thymus essential oils reduced the gene expression of nuclear factor-kappa (NF-κ)B, cyclooxygenase (COX)-2 and inducible nitric oxide (NO) synthase (iNOS) by 59, 48 and 34%, respectively, and decreased the NO and tumor necrosis factor (TNF)-α protein by 57 and 71%, respectively. Its water extract had a similar reduction effect which was stronger for NF-κB (85%), iNOS (50%), and NO (87%) but weaker for COX-2 (48%) and TNF-α protein (71%), as compared to that of thymus essential oils. According to their result, the attenuating effect of thymus extract and essential oils were superior to that of dexamethasone (Habashy et al. 2018). Rodrigues et al. (2015) evaluated the anti-inflammatory effect (inhibition of NO production) of T. *zygis* subsp. *sylvestris* and its main compounds tested separately, p-cymene, carvacrol, and thymol. These authors showed a considerable reduction of lipopolysaccharide (LPS)-triggered nitric oxide (NO) formation at concentrations up to 0.32 and 0.16 μL/mL, respectively, without decreasing cell viability.

In another study, Ocaña and Reglero (2012) observed that thyme extracts obtained using supercritical-CO_2 presented an important anti-inflammatory activity by (a) decreasing the liberation of pro-inflammatory cytokines, and (b) increasing the anti-inflammatory secretion in activated macrophages. The anti-inflammatory activity of thyme could be related to carvacrol and thymol, which showed inhibitory effects on the enzyme cyclooxygenase, as well as inhibitory effects on the compliment and nitric oxide synthesis (Fachini-Queiroz et al. 2012). Finally, Afonso et al. (2017) also reported that *T. caespititius* seems to have anti-inflammatory properties due to its strong inhibition effect on nitric oxide formation (EC_{50} = 230 μg/mL). Moreover, Kindl et al. (2015) found an important anti-inflammatory activity in six *Thymus* species: *T. pulegioides* (EC_{50} = 69.8 μg/mL), *T. praecox* subsp. *polytrichus* (EC_{50} = 139.0 μg/mL), *T. vulgaris* (EC_{50} = 97.9 μg/mL), *T. serpyllum* subsp. *serpyllum* (EC_{50} = 176.6 μg/mL), T. *longicaulis* (EC_{50} = 71.6 μg/mL) and *T. striatus* (EC_{50} = 91.1 μg/mL).

The valuable components of thyme essential oil, such as thymol (El−Sayed, Mansour, and Abdul−Hameed 2016; Pivetta et al. 2018; Yu et al. 2016) and carvacrol (Landa et al. 2009; da Silva Lima et al. 2013; Mouhi et al. 2017), also exhibit anti-inflammatory activity. According to the published data on anti-inflammatory effects of thymus and its derivatives (Ocaña and Reglero, 2012; Afonso et al. 2017; Habashy et al. 2018; Rodrigues et al. 2015; Oliviero et al. 2016), this herb could be considered as a natural substitute for chemical anti-inflammatory medicines such as dexamethasone, which may have serious adverse effects, including an increase in infection and delayed wound healing (Waldron et al. 2013; Habashy et al. 2018).

6. Antibacterial activity of thyme

According to Marino, Bersani, and Comi (1999), the essential oils from thyme presented antimicrobial activity against Gram-positive (*Bacillus licheniformis, Micrococcus spp., B. thuringiensis, Sarcina flava, Listeria innocua* and *Staphylococcus aureus*) and Gram-negative (*Proteus mirabilis, Yersinia enterocolitica, Escherichia coli, Salmonella* Typhimurium, *P. putida E. coli O157:H7, P. vulgaris, Pseudomonas fluorescens* and *Serratia marcescens*) bacteria (Table 2). In this regard, Rota, Herrera, Martínez, Sotomayor, & Jordán (2008) observed a significant level of effectiveness against bacteria when they used the essential oils from *T. hyemalis* (thymol and carvacrol chemotype) followed by *T. zygis* (thymol chemotype) and *T. vulgaris* (thymol chemotype) with MBC $\leq$0.2 μL/mL against 9, 6 and 6 strains tested, and MIC $\leq$0.2 μL/mL against 9, 8 and 8 strains assayed, respectively.

On the other hand, Abu-Darwish et al. (2012) observed that *T. vulgaris* and *T. serpyllum* isolated essential oils presented the widest range of activity against *S. aureus, E. coli* and *Pseudomonas aeruginosa*, producing inhibition zones of 8–20 mm and 5–20 mm, respectively. They also observed that decreasing amounts of the tested essential oils from *thymus* species lead to a corresponding decrease of the diameters of inhibition zones. In addition, Bogavac et al. (2015) also evaluated the antimicrobial activity of *T. vulgaris* against *Proteus mirabilis, S. aureus, C. albicans, E. coli* and *Enterococcus spp.*, showing MIC values ranged from 2.8 μg/mL to 45.4 μg/mL.

According to Al-Mariri et al. (2013), *T. syriacus* also possessed antimicrobial activity against *P. aeruginosa, E. coli O157: H7, B. melitensis, K. pneumoniae S.* Typhimurium, *Y. enterocolitica O9*, and *Proteus spp.*, showing MIC values ranged from < 0.375 to 1.5 μL/mL. In addition, essential oils from *T. vulgaris* showed high antimicrobial efficacy against *C. albicans, B. cereus, E. coli, M. cattarhalis, E. faecalis, C. tropicalis*, and *S. aureus*, with MIC values ranging from 0.062 to 0.500 mg/mL (Ahmad, van Vuuren, and Viljoen 2014). These authors found that thymol and carvacrol presented the highest microbial activity (MIC $\leq$ 2 mg/mL), while linalool presented moderate activity (MIC 2–4 mg/mL) and p-cymene, borneol, α-terpinene and γ-terpinene exhibited weak antimicrobial activity (MIC $\geq$ 4 mg/mL). According to Juven et al. (1994), timol and carvacrol bin to the amine and hydroxylamine groups of the proteins of the bacterial membrane, changing its permeability and causing the consequent death of the bacteria.

On the other hand, Nikolić et al. (2014) evaluated the antimicrobial activity of three essential oils from *T. vulgaris, T. algeriensis and T. serpyllum* against *Streptococcus sanguinis, Streptococcus mutans, Pseudomonas aeruginosa, Streptococcus salivarius, Lactobacillus acidophilus Streptococcus pyogenes, Enterococcus feacalis* and *Staphylococcus aureus*. They noticed that MIC ranged from 2.5 to 160 μg/mL and MBC ranged from 5 to 320 μg/mL, showing *T. serpyllum* the strongest microbial activity, whereas *T. vulgaris* presented the lowest antimicrobial activity. In addition, Džamić et al. (2015) assessed the antifungal and antibacterial activity of *T. capitatus* and its components (carvacrol and thymol) against Gram-negative bacteria (*S.* Typhimurium, *E. coli, Proteus mirabilis* human isolate, and *P. aeruginosa*), Gram-positive bacteria (*S. aureus, L. monocytogenes, Micrococcus flavus* and *B. cereus* clinical isolate), and fungi (*Penicillium funiculosum, A. niger, A. flavus, Candida albicans* human isolate, *A. fumigatus* human isolate, *Trichoderma viride, A. ochraceus*, and *Penicillium*

Table 2. Antimicrobial activity of thyme species.

Thymus species	Microorganism	Main effect	Reference
Thymus vulgaris	*E. coli, E. coli* O157:H7, *B. thuringiensis, P. mirabilis, P. vulgaris, P. putida, S. typhimurium, P. fluorescens, S. marcescens, Y. enterocolitica, Micrococcus spp., S. flava, S. aureus, B. licheniformis*, and *L. innocua*	*T. vulgaris* presented bacteriostatic activity against the microorganisms tested	Marino et al. (1999)
Thymus vulgaris, Thymus zygis and *Thymus hymalis*	*Y. enterocolitica* O:8, *S. enteritidis* CECT 4155, *S. typhimurium* CECT 443, *E. coli* O157:H7 CECT 4267, *S. aureus* CECT 239, *L. monocytogenes serovar* 1/2c CECT 911, *E. coli* CECT 516, *biotype 1* CECT 4315, *S. flexneri serovar* 2a CECT 585 and *S. sonnei* CECT 457	The most active essential oils was those from T. hyemalis (thymol and carvacrol chemotypes) followed by T. zygis (thymol chemotype) and T. vulgaris (thymol chemotype) with MIC 6 0.2 ll/ml against 9, 8 and 8 strains tested and MBC 6 0.2 ll/ ml against 9, 6 and 6 strains, respectively	Rota et al. (2008)
Thymus vulgaris and *Thymus serpyllum*	*E. coli, S. aureus* and *Pseudomonas aeruginosa*	S. aureus showed high sensitivity to thymol, E.coli show lower sensitivity to thymol and P. aeruginosa are resistant to most of the essential oils tested with the exception of thymol.	Abu-Darwish et al. (2012)
Thymus syriacus	*P. aeruginosa, E. coli* O157:H7, *B. melitensis, K. pneumoniae S. typhimurium, Y. enterocolitica* O9, and *Proteus spp.*	MIC ranged from $<$ 0.375 to 1.5 μL/mL	Al-Mariri et al. (2013)
Thymus vulgaris	*C. albicans* ATCC 10231, *B. cereus* ATCC 11778, *E. coli* ATCC 8739, *M. cattarhalis* ATCC 23246, *E. faecalis* ATCC 29212, *C. tropicalis* ATCC 201380 and *S. aureus* ATCC 126000	MIC ranged from 0.125 to 1 μg/mL	Ahmad et al. (2014)
Thymus vulgaris, Thymus algeriensis and *Thymus serpyllum*	*Streptococcus sanguinis* IBR S002, *Streptococcus mutans* IBR S001, *Pseudomonas aeruginosa* IBR P001, *Streptococcus salivarius* IBR S006, *Lactobacillus acidophilus* IBR L001 *Streptococcus pyogenes* IBR S004, *Enterecoccus feacalis* IBR E001 and *Staphylococcus aureus* ATCC 25923	MIC ranged from 2.5 to 160 μg/mL MBC ranged from 5 to 320 μg/mL	Nikolĭc et al. (2014)
Thymus capitatus	*S. aureus* ATCC 6538, *E. coli* ATCC 35210, *P. aeruginosa* ATCC 27853, *T. viride* IAM 5061, *P. funiculosum* ATCC 36839, *S. typhimurium* ATCC 13311, *P. mirabilis human isolate, A. ochraceus* ATCC 12066, *P. ochrochloron* ATCC 9112, *L. monocytogenes* NCTC 7973, *B. cereus clinical isolate, M. flavus* ATCC 10240, *A. flavus* ATCC 9643, *A. fumigatus human isolate, A. niger* ATCC 6275, and *C. albicans human isolate*	For bacteria MIC ranged from 10 to 100 μg/mL For fungi MIC ranged from 10 to 50 μg/mL	Džamić et al. (2015)
Thymus glabrescens + tetracycline	*P. aeruginosa* ATCC 27853, *P. mirabilis* ATCC 12453, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603 and *S. aureus* ATCC 29213	The combination of thymol and tetracycline against all tested bacteria decreased the MIC value of tetracycline ranging from 2-fold for *K. pneumoniae* ATCC 700603 to 10-fold for *E. coli* ATCC 25922. These results were almost the same of the thyme oil-tetracycline association. In contrast, the association of thymol with tetracycline against *S. aureus* ATCC 29213 showed strong antagonistic effect.	Miladinović et al. (2015)
Thymus vulgaris	*Proteus mirabilis, S. aureus, C. albicans, E. coli* and *Enterococcus spp.*	MIC ranged from 2.8 μg/mL to 45.4 μg/mL	Bogavac et al. (2015)
Thymus herba-barona, Thymus pseudolanuginosus, and *Thymus caespititius*	*E. coli* NCTC 9001, *S. epidermidis* NCTC 11047, *S. typhimurium* NCTC 12023, *S. aureus* NCTC 6571 and *P. aeruginosa* NCTC 10662	MIC ranged from 0.6 to 7.0 mg/mL and MBC ranged from 1.6 to $>$7.0 mg/mL	Afonso et al. (2017)

ochrochloron). These authors obtained a high antibacterial effect of essential oil from *T. capitatus* (MIC ranged between 1–2 μg/mL, and MBC between 1–40 μg/mL), while timol (MIC 10–100 μg/mL and MBC 50–150 μg/mL) and carvacrol (MIC 2.5–50 μg/mL, and MBC 5–100 μg/mL) were slightly less effective. Moreover, the antifungal activity was even stronger, ranging from MIC 0.2–1 μg/mL to MIC 10–50 μg/mL, and MIC 5–50 μg/mL, for essential oil, timol, and carvacrol, respectively. The antifungal activity of thyme oils is mainly attributed to the degeneration effect of thymol and carvacrol against the fungal hyphae, which seems to empty their cytoplasmic content (Zambonelli et al. 1996).

In another study, Miladinović et al. (2015) studied the antibacterial activities of geraniol and thymol, the main constituents of *T. glabrescens* oil against *P. aeruginosa, P. mirabilis, E. coli, K. pneumoniae*, and *S. aureus*. These authors noticed that the combinations, thymol-tetracycline and essential oil-tetracycline, generated synergistic interaction to a greater extent

compared with the geraniol-tetracycline association. This way could be a possible strategy to reduce the minimum effective dose of the given antibiotics and, as a result, minimize its adverse side effects.

Finally, *T. herba-barona* presented antimicrobial activity against *S.* Typhimurium (both MIC and MBC 5.0 μg/mL), whereas higher concentrations (up to 5.0 mg/mL) were required to inactivate *E. coli* and *P. aeruginosa* (Afonso et al. 2017). They also observed that concentrations of *T. pseudolanuginosus* higher than 6.5 mg/mL were not efficient against *S.* Typhimurium, *E. coli*, and *P. aeruginosa*. Essential oils from *T. caespititius* can be lethal to *E. coli* (MBC 7.0 μg/mL) but required higher concentrations than 7.0 mg/mL to eliminate *S.* Typhimurium and *P. aeruginosa*. In this regard, Gram-negative bacteria presented more resistance (MIC ranged from 5.0 to 7.0 mg/mL) than Gram-positive bacteria, more specifically *S. aureus* (MIC between 0.6 and 3.5 mg/mL).

7. Bioaccessibility and bioavailability of nutrients and bioactive compounds from thyme

Bioaccessibility is associated with the amount of thyme constituents, which are present in the gut as a result of their liberation from the food matrix. Additionally, bioavailability can be defined as the proportion of the thymol constituents that are digested, absorbed and consequently metabolized through the specific metabolic pathways. Therefore, bioaccessibility and bioavailability are two important aspects that determine the beneficial properties of these important bioactive compounds and, hence, investigation of their metabolic fate is crucial to develop novel and more efficient functional foods. In order to better understand these aspects, their stability either in food matrix or *in vivo*, as well as their release rate from food matrix, should be well studied.

Several studies showed that thyme constituents, such as thymol, carvacrol, and p-cymene, are absorbed and metabolized in humans and several animals (Baser 2008; Satou et al. 2013; Thalhamer, Buchberger, and Wase 2011). The bioavailability of these biocompounds in the poultry industry is well investigated. Studies in hens, which were fed with *T. vulgaris* plant material, revealed that thymol was still bioavailable in egg yolk. Interestingly, the bioavailability of thymol was simply determined by displaying oxidative stability of liquid yolks since thymol presents antioxidant effect. The results showed that mínimum 278 μg of thymol/g of yolk were required in order to display significant antioxidant activity (Botsoglou et al. 1997).

Another study on the effect of dietary thyme on the oxidative stability of the egg yolk and eggshell revealed that thyme reduced oxidation of liquid yolk. However, their results revealed that thymol, as one of the most antioxidant constituents of thyme essential oils, is not the only responsible compound that prevents egg yolk oxidation. Luna et al. (2018) showed that thymol consumption had a biological effect on female quail birds and contributed to sustaining the metabolic needs during laying period and increased the plasma triglycerides. They proposed thymol as a natural antioxidant additive for poultry feed to improve the oxidative stability.

A similar protective effect of BHT was also observed for thymol when it was included in the poultry feed (Luna et al. 2017). Likewise, it was shown that thymol-dietary supplementation of poultry improved the nutritional quality of their egg and provided the embryo with polyunsaturated fatty acids. (Fernandez et al. 2017). Recent advancements in extraction methods as well as mass spectrometry techniques, determination of bioavailability of these compounds became more rapid and efficient. In this context, thymol was detected and quantified by using headspace solid phase microextraction technique followed by gas chromatography-mass spectrometry in fecal and egg yolk of quails, which were supplemented with thymol (80 mg of thymol/kg of basal diet/day) in their diets (Fernandez, Palacio, and Labaque 2017). The concentration of fresh feces and egg yolk were 31.51 ng/g and 11.83 ng/g, respectively.

Bioavailability of thymol can also be determined by monitoring its antibacterial activity since intake of thymol-enriched foods can eliminate certain species of bacteria. In this respect, study with broiler chickens showed that feeding thymol and carvacrol to these animals (Gallus gallus domesticus) significantly reduced *Campylobacter jejuni* colonization in their cecum (Arsi et al. 2014). However, there are several reasons that affect their absorption before thymol reaches the cecum. One of the principal reasons is the rapid absorption of thymol in the upper intestine, stomach or regions close to the small intestine (Kohlert et al. 2002). This rapid absorption can limit the antimicrobial activity of thymol since thymol will be mostly absorbed before reaching cecum and only very low level of thymol will reach cecum, which will not result in a reduction in the population of *Campylobacter* (Meunier et al. 2006; Hermans et al. 2010).

A study on the passage kinetics of carvacrol and thymol through piglet gastrointestinal tract showed that these compounds were absorbed in the stomach (Michiels et al. 2008). Likewise, Kohlert et al. (2002) assessed the systemic availability of thymol in human and observed that this compound could not be found in plasma and urine after oral intake of 1 mg thymol. However, thymol metabolites were detectable up to 41 h after in the plasma and urine. While tested plasma contained only thymol sulfate, it could be possible to detect both thymol sulfate and thymol glucuronide in urine. The authors suggested that the mean terminal elimination half-life of thymol is about 10 hours. The bioavailability of thymol is estimated to be about 16% (Kohlert et al. 2002; Bhattaram et al. 2002).

These studies have shown that thymus essential oil and their components are usually absorbed quickly, and it is hard to expect them to be available in any target organ. According to Figure 1, the major components of the thymus, such as thymol and carvacrol, have low aqueous solubility (Trombetta et al. 2005), which can accelerate its quick degradation and absorption in the stomach and small intestine (Nieddu et al. 2014; Anderson et al. 2012). A minor fraction of the ingested thymol can be recovered in the small intestine. However, this can be possible only due to the very small amount of thymol escaped solubilization and absorption in the stomach probably because of the physical adsorption by different ingredients present in the feed (Michiels et al., 2008). However, in some cases, depending on the application in food industry, thymol containing food is prepared to be delivered to treat bacteria-related infections in the small intestine. Thus, it is essential to find new methods to avoid absorption in the stomach and pass through barriers until reaching the small intestine.

Therefore, researchers tried to address this issue through encapsulating the valuable compounds of this aromatic plant (Arana-sanchez et al. 2010; Hill, Gomes, and Taylor 2013; Shah, Davidson, and Zhong 2013). Different encapsulation materials have been used to increase the stability of thymol in food matrix as well as its efficient delivery. The encapsulated carvacrol in calcium alginate was successfully delivered to the small intestine of piglet as the calcium alginate layer slowed down thymol absorption in the upper gastrointestinal tract (Wang et al. 2009). It was also reported that co-drug design of thymol with diacerein improved its bioavailability (Dhaneshwar et al. 2013). It should be noted that bioaccessibility of essential oils and their components also depend on their interactions with the food matrix.

Encapsulation technique can be used to enhance the solubility and stability of essential oils and improve their bioavailability. In a recent study, the incorporation of essential oils into farinaceous matrices was proposed in order to allow essential oils to withstand the cooking and digestion processes. In the same study, it was also reported that the incorporation of thyme essential oil into a starch-based solid matrix increased its residual by 25% after the cooking process, as compared to the control sample (Aravena et al. 2016).

On the other hand, liposomes can be an interesting candidate to facilitate the delivery of thymol, which is known to have strong anti-inflammatory properties. However, depending on the solubility of these compounds, its incorporation with liposomes occurs either in the aqueous core or inside the lipid bilayer. Due to the low solubility of thymol, it can be incorporated only into lipid bilayer structures, which can alter its release rate in the body (Coimbra et al. 2011). Moreover, the insertion of PEG polymer into liposomal formulation can significantly prolong the circulation time of thymol-containing liposomes in the bloodstream in order to better control intravenous delivery of the compounds (Gref et al. 2012). Unfortunately, their lipophilic characteristics lead to low loading of thymol since higher thymol content can disrupt lipid bilayer by intense interaction with the phospholipids present in the formulation of liposomes (Ultee et al. 2002).

Beside liposomes, cyclodextrins have also been used for thymol encapsulation. Cyclodextrins are cyclic oligosaccharides, consisting of different numbers of glucose units that give them toroid-like structures (Wang *et al.*, 2018; Yao *et al.*, 2017; Zou *et al.*, 2017). Due to this arrangement, the interior of toroid structure is hydrophobic, while they are hydrophilic outside (Eş et al. 2016). This property makes them attractive delivery agents for compounds with low water solubility such as thymol. In this context, thymol was encapsulated into β-cyclodextrins with a good loading efficiency and accelerated *in vivo* thymol absorption rate without altering bioavailability. Thus, higher doses could be administered, and un-absorbed thymol is kept in the intestine. Thus, it is possible to formulate thymol-containing cyclodextrins, which can be used in the treatment of intestinal bacterial diseases (Nieddu et al. 2014).

According to the studies mentioned above, the consumption of thyme, its essential oils, and isolated compounds, can be beneficial for the consumers. However, the effectiveness of these valuable compounds can decrease during food processing and within the digestion system. Therefore, as discussed before, several techniques such as encapsulation can be used to enhance the bioavailability of thyme and their derived products.

The concentration of thymol in thyme essential oil can reach from 10 to 64% (Salehi *et al.* 2018). Therefore, calculation of recommended dose of thyme or thyme extracts in order to obtain health effect is difficult. Some authors noted that consumption of thymol in dose 1.08 mg per day were insignificant taking into account concentration of this compound in human plasma and urine. Pharmacokinetic data of total absorption and elimination in human plasma indicated that peak plasma concentration was 93.1 ng/ mL and the mean terminal elimination half-life was 10.2 hours (Kohlert *et al.*, 2002). Comonnly, thymol is detected in plasma as thymol sulfate and as both thymol sulfate and thymol glucuronide in urine (Raoof *et al.*, 1996).

Anyway, some studies demonstrate the effect of consumption of olive oil enhanced by thyme extracts in rat diet (1.5 g/kg of body weight). They noted that the bioavailability of olive phenolic compounds was enhanced in the presence of thyme extract (Rubió *et al.*, 2014).

There are also several studies proved helth benefits connected with consumption thyme or thyme extracts on the respiratory, cardiovascular systems as well as anti-inflamatory activity. Ethanolic extracts containing 0.072 and 0.005% thymol and carvacol, respectively as well as thyme preparations with a thymol content ranged from 0.005% to 0.15% demonstrate significant positive effect on the smooth muscles of trachea and the ileum and on the respiratory clearance (Meister *et al.*, 1999; Begrow *et al.*, 2010). Administration of an aqueous extract of thyme in dose 100 mg per kg of body mass per day for 8 weeks positively influenced on the blood pressure reduction. Moreover, supplementation of 3 to 6 mg of thymol per kg of body mass per day for 8 weeks may influence on the reduction of initial lipid lesion as well as lowering serum lipids in rabbits blood (Salehi *et al.* 2018; Yu *et al.*, 2016). Moreover, administered orall of thymol in dose 14 mg per kg of body mass per day significantly influended on reduction of rats obesity (Haque *et al.*, 2014).

Other studies has shown that extracts from thyme contained from 10 to 71% of thymol significantly reduced the production and gene expression of the proinflammatory mediators tumor necrosis factor (Ocaña and Reglero, 2012). Moreover, the results of (Riella *et al.*, 2012) suggested that thymol may exhibit anti-inflammatory activity in dose from 10 to 100 mg per kgof body mass.

On the other hand, the constituents of thyme oil may cause several allergic reactions, even in very low concentration. Several cases have been reported in which people experienced dermatitis or inflammation of the skin after consumption of thymol. Concerning the toxicity of thyme and thymol, although thyme GRAS status, it has been suggested not to exceed oral doses of 10 g of dried leaves (0.03% of phenols calculated as thymol) per day to prevent toxicity. EFSA also suggests a moderate acute toxicity expressed as LD50 for thymol when administered by the oral route in rat, mouse, and guinea pig: 0.98, 1.80 and 0.88 mg per kg of body mass, respectively (Salehi *et al.* 2018).

8. Application of thyme in food products

Microbiological spoilage and chemical deteriorations are the main causes of quality loss of meat, fish, and their derived products during handling, processing, and storage (Lorenzo and Gómez 2012). In this regard, the use of antioxidant and antimicrobial agents delay the lipid and protein oxidation and lead to a retardation of spoilage, allowing maintenance of quality and safety and increasing the shelf-life of these products (Lorenzo et al. 2014; Pateiro et al. 2014).

Table 3 summarizes the application of thyme in food products. Solomakos et al. (2008), evaluated three levels (0.3%, 0.6%, and 0.9%) of thyme essential oil against *E. coli* O157:H7 in minced beef. They observed that thyme essential oil at the concentration of 0.6% inhibited *E. coli* growth at 10°C. Additionally, Fratianni et al. (2010) observed that thyme essential oil at 0.5% presented an inhibition of *E. coli* and lactic acid bacteria in chicken. Moreover, in another study, according to Krisch et al. (2010), the addition of thyme essential oil at 1% increased the shelf-life of minced pork by decreasing of *E. coli* in minced pork by 1 log CFU/g after 24 h of the refrigerated period at 5°C.

Kostaki et al. (2009) observed that the addition of 0.2% (v/w) thyme essential oil decreased the microbial count and extended the product shelf-life. This result could be related because of the antibacterial activity of thyme essential oil which is attributed to its high phenolic content including carvacrol, thymol, *p*-cymene, and γ-terpinene. Besides, lipid and protein oxidation were also lower in treated samples compared to control group. Kykkidou et al. (2009) reported that the addition of 0.1% thyme essential oil extended the shelf-life of fresh Mediterranean swordfish fillets under aerobic conditions by 5 days. They observed that the application of thyme oil decreased the total viable count and H_2S-producing bacteria and inhibited the lipid oxidation.

On the other hand, Karabagias, Badeka, and Kontominas (2011) studied the effect of thyme essential oil (0.1%) on the shelf-life (microbial, physicochemical and sensory properties) of chopped lamb meat stored at 4°C. They observed that microbial populations were reduced up to 2.8 log CFU/g on day 9 of storage and color parameters were improved by the application of thyme oil. Based on the studied sensory properties, the authors suggested that the shelf-life of fresh lamb can be extended by 2–3 days through the addition of thyme essential oil. However, thyme oil did not protect lamb meat from oxidation within the normal shelf-life of meat under atmospheric packaging condition.

The effect of thyme essential oil as a natural preservative on the shelf-life extension of fresh bluefish during storage at 2°C was also assessed (Erkan et al. 2011). Regarding sensorial properties, the use of thyme oil increased the shelf-life from 9 to 11 days. Similarly, total volatile base nitrogen and trimethylamine values considered as acceptable also increased from 9 to 13 days in treated samples. Concerning lipid oxidation, TBARS, free fatty acid, and peroxide values were lower in treated samples than the control group. Finally, lower microbial counts were found in treated samples, increasing the shelf-life by 3–4 days. The addition of thyme (0.25%) essential oil on the microbial, lipid oxidation and sensory properties of fermented poultry sausage was evaluated (El Adab and Hassouna, 2016). The use of thymus improved the hygienic quality of dry fermented sausages by reducing the *Enterobacteriaceae* counts, total coliform counts and S*taphylococcus aureus* counts. In addition, a decrease in lipid oxidation was observed without affecting their sensory properties.

Recently, Jayari et al. (2017) evaluated the inhibitory effect of *T. capitatus* and *T. algeriensis* essential oils against four pathogenic strains (*E. coli, Salmonella* Typhimurium, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*) inoculated experimentally (10^8 CFU/g) in the minced beef meat stored for 15 days. These authors observed that both extracts presented a bacteriostatic effect only against *E. coli* and *S.* Typhimurium at low concentrations (0.01 and 0.05%). In addition, *T. capitatus* also presented an interesting bactericidal activity against *E. coli, Salmonella* Typhimurium and *Staphylococcus aureus* at higher concentrations (1 and 3%). On the other hand, Sharma et al. (2017) assessed the effect of thyme oil at 0.125% on the quality of fresh (raw, ready to cook) chicken sausages. They found that treated samples had a lower microbial count and TBARS values, which increased the shelf-life for 2–3 days, as compared to that of the control sample.

Table 3. Application of thyme in food products.

Food	Dose	Results	Reference
Minced beef	0.6%	Inhibition of the growth of *E. coli* O157:H7 during storage at 10°C	Solomakos et al. (2008)
Se bass filets	0.2%	Extended product shelf-life by 3 days	Kostaki et al. (2009)
Mediterranean swordfish fillets	0.1%	Extended the shelf-life by 5 days	Kykkidou et al. (2009)
Chicken breast	0.5%	Inhibition of the growth of *E. coli* and lactic acid bacteria Decrease on total viable count	Fratianni et al. (2010)
Minced pork	1%	Decrease on *E. coli* counts during storage at 5°C	Krisch et al. (2010)
Chopped lamb	0.1%	Decrease on *Pseudomonads*, LAB, *B. thermosphacta*, and *Enterobacteriaceae* counts Improve color parameter of lamb meat	Karabagias et al. (2011)
Bluefish	1%	Decrease on lipid oxidation and microbial counts	Erkan et al. (2011)
Fermented poultry sausage	0.25%	Decrease on *Enterobacteriaceae* counts, total coliform counts and *Staphylococcus aureus* counts Decrease significantly TBARS values	El Adab, & Hassouna (2016)
Minced beef	0.1–3%	Inhibition of the growth of *E. coli, S. thyphimurium, S. aureus*, and *P. aeruginosa*	Jayari et al. (2017)
Chicken sausages	0.125%	Decrease on TBARS values, total viable, psychrophilic bacteria and yeast and moulds counts	Sharma et al. (2017)

9. Conclusions

Thyme and its derivates, such as extracts and essential oils, have a great industrial value due to their anti-inflammatory, antimicrobials, and antioxidants activities. They can be used in the manufacturing of new foods, additives, nutraceuticals, specific drugs and cosmetic products. For examples, thyme extracts were found to have strong antibacterial activity against several bacterial infections related to intestine and cecum. Moreover, due to the low water solubility of thyme essential oils and their reduced stability in the food matrix, investigations on new encapsulation methods and materials are required to improve *in vivo* effectiveness. Although thyme and its derivates derived active are their categorized as GRAS, they can present potential toxicity to human cells. Hence, new studies are needed to determine optimum dosage of these compounds to deliver into specific cells without showing any toxicity. Moreover, novel methods should be developed detection to monitor their bioaccessibility and bioavailability in the human body. Finally, more in vivo studies and clinical trials should be performed to better understand their effects on consumers.

Disclosure statement

The authors report no conflict of interest.

Acknowledgements

Amin Mousavi Khaneghah likes to thank the support of CNPq-TWAS Postgraduate Fellowship (Grant #3240274290). Mohsen Gavahian wants to thank the support of the Ministry of Economic Affairs, project no. 106-EC-17-A-22-0332, Taiwan, Republic of China.

Funding

CNPq-TWAS Postgraduate Fellowship 3240274290.

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