Received: 17 November 2017 | Revised: 10 April 2018 | Accepted: 11 April 2018

DOI: 10.1002/ptr.6109

WILEY

REVIEW

Thymol, thyme, and other plant sources: Health and potential uses

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Thymol is a naturally occurring phenol monoterpene derivative of cymene and isomer of carvacrol. Thymol (10–64%) is one of the major constituent of essential oils of thyme (*Thymus vulgaris* L., Lamiaceae), a medicinal plant with several therapeutic properties. This plant, native to Mediterranean regions, is commonly used as a culinary herb and also with a long history of use for different medicinal purposes. Nowadays, thymol and thyme present a wide range of functional possibilities in pharmacy, food, and cosmetic industry. The interest in the formulation of pharmaceuticals, nutraceuticals, and cosmeceuticals based on thymol is due to several studies that have evaluated the potential therapeutic uses of this compound for the treatment of disorders affecting the respiratory, nervous, and cardiovascular systems. Moreover, this compound also exhibits antimicrobial, antioxidant, anticarcinogenesis, anti-inflammatory, and antispasmodic activities, as well as a potential as a growth enhancer and immunomodulator. In the present review, these bioactivities have been covered because some of them can contribute to explain the ethnopharmacology of thymol and its main source, *T. vulgaris*. Other important aspects about thymol are discussed: its toxicity and bioavailability, metabolism, and distribution in animals and humans.

KEYWORDS

essential oil, Lamiaceae, medicinal plant, natural food preservative, thyme, thymol

1 | INTRODUCTION

One of the medicinal plant widely used in pharmacology is thyme (*Thymus vulgaris* L., Lamiaceae; Hossain, AL-Raqmi, AL-Mijizy, Weli, & Al-Riyami, 2013). This subshrub is native to Mediterranean regions, where it presents a high chemical variability. This species is commonly used as a culinary herb, and it also has a long history of use for different medicinal purposes (Zarzuelo & Crespo, 2002). In this regard, Table 1 shows several traditional and current uses of thyme and the regions where these uses have been described. From this table, it can be noticed that the ethnopharmacology of thyme includes the treatment of disorders affecting the respiratory, digestive, cardiovascular, and nervous systems (Al-Bayati, 2008; Castillo-España et al., 2009; Essawi & Srour, 2000; European Medicines Agency, 2013; Giordani et al., 2008; Imelouane et al., 2009; Komaki et al., 2016; Nikolić et al., 2014; Ocaña & Reglero, 2012). The application of thyme for its antiparasitic and antimicrobial properties has also been reported, together with other uses as a diuretic, diaphoretic, and antispasmodic agent (Al-Bayati, 2008; Giordani et al., 2008; Imelouane et al., 2009; Kiani, Firoozian, & Moradkhani, 2017; Nikolić et al.,

TABLE 1 Uses of *Thymus vulgaris* in traditional medicine

Medicinal properties	Plant part/plant preparation	Place	Reference
Traditional uses			
Respiratory tract			
Expectorant	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009)
Antitussive	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009)
Antibroncholitic	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009)
In bronchitis	Not defined[a]	Spain	Ocaña and Reglero (2012)
In bronchopulmonary disorders	Not defined[a]	Not defined[c]	Nikolić et al. (2014)
Whooping cough	Aerial parts[b]	Palestine	Essawi and Srour (2000)
Asthma	Not defined[a]	Spain	Ocaña and Reglero (2012)
Nervous system			
Sedative	Infusion[b]	Not defined[c]	Nikolić et al. (2014); Komaki, Hoseini, Shahidi, and Baharlouei (2016)
Digestive system			
Carminative	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009); Nikolić et al. (2014)
Gastroenteric disorders	Not defined[a]	Not defined[c]	Nikolić et al. (2014)
Intestinal diseases	Aerial parts[b]	Palestine	Essawi and Srour (2000)
Treats ulcers of the stomach and the duodenum	Aerial parts[b]	Palestine	Essawi and Srour (2000)
Cardiovascular system			
Hypertension	Not defined[a]	Mexico	Castillo-España et al. (2009)
Antiparasitic and antimicrobial activity			
Anthelmintic	Not defined[a]	Iran	Al-Bayati (2008); Nikolić et al. (2014)
Antifungal agent	Not defined[a]	Algeria	Giordani, Hadef, and Kaloustian (2008)
Antiseptic	Not defined[a]	Not defined[c]	Fani and Kohanteb (2017)
Others			
Diuretic properties	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009)
Diaphoretic properties	Not defined[a]	Not defined[c]	Nikolić et al. (2014)
Antispasmodic	Not defined[a]	Iran, Morocco	Al-Bayati (2008); Imelouane et al. (2009)
Emphysema	Aerial parts[b]	Palestine	Essawi and Srour (2000)
Current uses			
Treatment of respiratory tract diseases (including cough, catarrhs, acute bronchitis, as mucolytic, and expectorant)	Several liquid herbal preparations and dry extracts (using water, ethanol, and solutions containing ammonia, glycerol, ethanol, and water as extraction solvent)	Europe	European Medicines Agency (2013)

[a]The authors have not provided details about the plant part and preparation of *Thymus* used.

[b]The authors have not provided details about the preparation of *Thymus* used.

[c]The authors have not provided details about the place where *Thymus* was traditionally used.

2014), Moreover, evidence has also demonstrated that in traditional medicine, *T. vulgaris* was used in the treatment of anxiety in humans (Komaki et al., 2016).

In traditional medicine, other *Thymus* spp. have been also used for their antiseptic, antihelminthic, expectorant, antispasmodic, antimicrobial, antifungal, antioxidative, carminative, sedative, antivirotic, diaphoretic, antibacterial, antispasmodic, antirheumatic, antihypertensive, and calming effects (Fachini-Queiroz et al., 2012). Other studies have mentioned the use of these plants to treat wounds, water retention, nausea and fatigue, respiratory diseases (such as colds), menstrual and menopausal problems, skin conditions (oily skin and scars), hangovers, and even depression. Moreover, other benefits of *Thymus* plants are strengthening memory and concentration as well as calming the nerves. They can use to prevent hair loss and acne outbreaks. Thyme oil also improves the resistance of body to oral infections. It can keep insects and parasites away, for example, mosquitoes, fleas, lice, and moths (Amiri, 2012; Beers & Berkow, 1966; Rustaiyan et al., 2000; Soliman & Badeaa, 2002).

Studies report that thyme essential oils are among the main ones used in the food industry and in cosmetics as antioxidants and preservatives (Sharifi-Rad, Salehi, Schnitzler, et al., 2017; Zarzuelo & Crespo, 2002). Thyme contains high concentrations of monoterpene phenols, including thymol (2-isopropyl-5-methylphenol or iso-propyl-meta-cresol; $C_{10}H_{14}O$; 10–64%), carvacrol (iso-propyl-ortho-cresol; 0.4–20.6%), and *p*-cymene (9.1–22.2%), and other monoterpenes such as 1,8-cineole (0.2–14.2%), linalool (2.2–4.8%), borneol (0.6–7.5%), α-pinene (0.9–6.6%), and camphor (0–7.3%; Amiri, 2012; Burt, 2004; Nickavar, Mojab, & Dolat-Abadi, 2005). Thymol is a naturally occurring monoterpene derivative of cymene, and carvacrol is its isomer (Figure 1). Among other bioactivities, both thymol and carvacrol have antitussive, antioxidative, antimicrobial, expectorant, antispasmodic, and antibacterial effects (Amiri, 2012; Beers & Berkow, 1966; Höferl et al., 2009; Johns, Johns, & Rudolph, 1992; Nickavar et al., 2005; Rustaiyan et al., 2000; Sharifi-Rad, Salehi, Varoni, et al., 2017; Youdim, Dorman, & Deans, 1999). Therefore, these compounds could contribute to the pharmacology effects of thyme. Other potential therapeutic uses of thymol are for the treatment of disorders affecting the respiratory (Astudillo, Hong, Bye, & Navarrete, 2004; Gavliakova et al., 2013), nervous (Asadbegi, Yaghmaei, Salehi, Komaki, & Ebrahim-Habibi, 2017), and cardiovascular (Yu, Chao, Chang, Chang, & Lee, 2016) systems. In addition, thymol also exhibits anticarcinogenesis (Deb, Parimala, Devi, & Chakraborty, 2011) and anti-inflammatory (Braga et al., 2006; Fachini-Queiroz et al., 2012; Liang et al., 2014) activities, as well as a potential as a growth enhancer and immunomodulator (Hashemipour, Kermanshahi, Golian, & Veldkamp, 2013).

Caspar Neumann extracted thymol for the first time in 1719 (Castleman, 2010). Thymol forms colorless, translucent crystals or plates from ethyl acetate, acetic acid, or dimethyl carbonate, often large, or white crystalline powder with odor of thyme. Its odor has also been described as spicy-herbal, slightly medicinal odor reminiscent of thyme, and aromatic odor. Its taste is described as pungent, caustic, sweet, medicinal, and spicy. It was obtained in its pure form some 134 years later by Lallemand (1853). Nevertheless, thymol extract from the thyme plant was used thousands of years ago by the ancient Egyptians as a preparation to help preserving mummies (Nagoor Meeran, Javed, Al Taee, Azimullah, & Ojha, 2017).

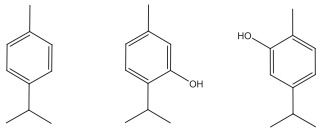

FIGURE 1 Structure of cymene, thymol, and carvacrol

These days, oils from *Thymus* plants and extracts, as well as thymol and carvacrol, are used for several purposes, for example, as medical antiseptics and wound healing agents, food preservatives, and flavorings (Amiri, 2012; European Medicines Agency, 2013). In this sense, thymol is a generally recognized-as-safe food additive according to the Food and Drug Administration (Zhang et al., 2014). It also used as a surface sanitizer, pesticide (insecticide, fungicide, rodenticide, antimicrobial, etc.), antioxidant, and lab reagent, as well as in perfumery and in microscopy (Fachini-Queiroz et al., 2012; Komaki et al., 2016). Thymol, usually combined with glycerin, alcohol, and other volatiles, is used to make mouthwashes. As an example, Listerine® contains 0.06% of thymol together with menthol, eucalyptol, and methyl salicylate. The evidence of its effectiveness in improving oral health has been suggested to be strong in a recent review by Vlachojannis, Al-Ahmad, Hellwig, and Chrubasik (2016). Probably, most of these properties are related to its effectiveness against wide range of bacteria, mold, fungi, and intestinal worms (Barnes, Anderson, & Philipson, 2007; Boyd & Sheppard, 1970; Burrow, Eccles, & Jones, 1983; Dorman & Deans, 2000; European Scientific Cooperative on Phytotheraphy, 2007; Federspil, Wulkow, & Zimmermann, 1997; Frohlich, 1968; Kienholz, 1959; Maruzzella, Balter, & Katz, 1959; Maruzzella & Sicurella, 1960; Shapiro & Guggenheim, 1995; Shubina, Siurin, & Savchenko, 1990; Vila, 2002; Von Schindl, 1972), as well as to their antioxidant properties.

In this context, the objective of the present review is to summarize the main bioactive properties of thymol described until present in vitro, ex vivo, in vivo, and in humans, and as well of thyme, as main source of thymol, and other plant sources. Other important aspects have been also covered: bioavailability, distribution and metabolism, toxicity, and allergenicity.

2 | MATERIALS AND METHODS

2.1 | Information of sources and search

The literature research was carried out by all the authors until September 2017. The following databases were screened: PubMed, Scopus, and Google Scholar. No restrictions were placed on the dates or languages of the publication to cover as much as possible the wide range of pharmacological properties of thyme or their sources, mainly, thyme. Several combinations of keywords used to search literature were "thymus," "*Thymus vulgaris*," "thymol," "bioactivity," "antimicrobial," "respiratory," "nervous," "cardiovascular," "bioavailability," "allergy," "toxicity," "foodborne," "health," "essential oil," and so forth. In addition, the websites of the World Health Organization (http://who.int/en/), the European Medicines Agency (http://www.ema.

europa.eu/ema/), and the European Food Safety Authority (EFSA; https://www.efsa.europa.eu/) were also consulted.

The literature about the healthy properties of thymol was divided in function of their action and organism system in which this compound (or the plant source, mainly, thyme) has a beneficial effect.

2.2 | Chemical structures

Chemical structures were drawn using ChemBioDraw Ultra 12 software.

3 | RESULTS AND DISCUSSION

3.1 | Sources of thymol

Thyme (*T. vulgaris* L., Lamiaceae) is the main source of thymol, as commented before. It contains between 10% and 64% of this compound (Burt, 2004). However, a species from Eastern Morocco contained only 0.24% of thymol in its essential oil. This variability was explained by the fact that the genotype, edafoclimatic conditions, and harvesting time may affect the volatile composition of this plant (Imelouane et al., 2009).

Nevertheless, thymol is widespread in healing Lamiaceae plants, including other *Thymus spp*. (*Thymus zygis*, *Thymus glandulosus*, *Thymus hyemalis*, etc.), *Monarda spp*. (*Monarda fistulosa*, *Monarda punctata*, *Monarda didyma*, etc.), and *Origanum* spp. (*Origanum compactum*, *Origanum dictamnus*, *Origanum onites*, *Origanum vulgare*, etc.; Table 2; Bouchra et al., 2003; Figiel, Szumny, Gutiérrez-Ortíz, & Carbonell-Barrachina, 2010; Goodner et al., 2006; Jordán, Martínez, Goodner, Baldwin, & Sotomayor, 2006; Kanias, Souleles, Loukis, & Philotheou-Panou, 1998; Lagouri et al., 1993; Lee, Umano, Shibamoto, & Lee, 2005; Li et al., 2014; Liolios et al., 2009; Moldao-Martins et al., 2000; Ozkan, Baydar, & Erbas, 2010; Shen et al., 2016; Tilford, 1997; Zamureenko et al., 1989). Some *Satureja* species, such as *Satureja spicigera* (35.1%), *Satureja intermedia* (32.3%), and *Satureja mutica* (26.5%), contain relatively high amounts of thymol. Nevertheless, chemical variation between populations may also occur, as shown for *Satureja sahendica*, whose content of thymol varied from 19.6% to 41.7% (Sefidkon et al., 2004; Sefidkon & Jamzad, 2005). *Zataria multiflora*, another medicinal plant belonging to the Lamiaceae family, contains as major components of its essential oil carvacrol (59%) and thymol (39%; Misaghi & Basti, 2007). This plant geographically grows only in Iran, India, Pakistan, and Afghanistan. Furthermore, thymol

TABLE 2 Examples of other plant sources of thymol

Plant	Part	% of thymol in essential oils	Origin	Reference
Lamiaceae				
Thymus zygis	Aerial parts	15.5–21.0	Portugal	Moldao-Martins, Palavra, da Costa, and Bernardo-Gil (2000)
Thymus glandulosus	Whole plant	43.2	Morocco	Bouchra, Achouri, Hassani, and Hmamouchi (2003)
Thymus hyemalis	Aerial parts	16.09–29.27	Spain	Goodner, Mahattanatawee, Plotto, Sotomayor, and Jordan (2006)
Thymus broussonetii	Whole plant	36.7	Morocco	Elhabazi et al. (2012)
Monarda fistulosa	Aerial parts	0.2–12.6	North America/Russia	Tabanca et al. (2013); Zamureenko, Klyuev, Bocharov, Kabanov, and Zakharov (1989)
Monarda punctata	Flowers	75.2	China	Li, Yang, Li, Yao, and Sun (2014); Shen, Zhou, Li, Hu, and Mo (2016)
Monarda bradburiana	Aerial parts	57.7	North America	Tabanca et al. (2013)
Origanum dictamnus	Aerial parts	0.13–0.61	Greece	Liolios, Gortzi, Lalas, Tsaknis, and Chinou (2009)
Origanum onites	Aerial parts	0.7	Greece	Lagouri, Blekas, Tsimidou, Kokkini, and Boskou (1993)
Origanum vulgare	Aerial parts	13.7	Greece	Lagouri et al. (1993)
Satureja spicigera	Aerial parts	35.1	Iran	Sefidkon and Jamzad (2005)
Satureja intermedia	Aerial parts	32.3	Iran	Sefidkon and Jamzad (2005)
Satureja mutica	Aerial parts	26.5	Iran	Sefidkon and Jamzad (2005)
Satureja sahendica	Aerial parts	19.6–41.7	Iran	Sefidkon, Jamzad, and Mirza (2004)
Zataria multiflora	Aerial parts	39	India, Pakistan, and Afghanistan	Misaghi and Basti (2007)
Apiaceae				
Trachyspermum copticum	Fruits/ seeds	72.3/37.2	Iran	Oskuee, Behravan, and Ramezani (2011); Rasooli et al. (2008)
Lagoecia cuminoides	Aerial parts	72.8–94.8	Turkey	Baser and Tümen (1994)
Verbenaceae				
Lippia multiflora	Leaves	14	Africa	Bassolé et al. (2010)
Lippia gracilis	Leaves	3.83–55.50	Brazil	Ferraz et al. (2013); Guilhon et al. (2011)

represents about 7% of the phenolic constituents of oils extracted from *Coleus aromaticus* (Dutta, 1959).

Plants belonging to other families also contain thymol (Table 2). As an example, it is about one third of the oil from *Trachyspermum copticum* (Apiaceae; Rasooli et al., 2008), which grows in the east of India, Iran, and Egypt, and other study suggests that the essential oils from its fruits contain thymol (72.3%), terpinolene (13.12%), and *o*-cymene (11.97%) as the main constituents (Oskuee et al., 2011). *Lagoecia cuminoides* is another plant of the family Apiaceae, which is taken as an herbal tea in some regions of Turkey. The water-distilled essential oils of its aerial parts contain a high content of thymol (72.8–94.8%; Baser & Tümen, 1994). Additionally, the occurrence of thymol has also been described in essential oils of tropical plants of the family Verbenaceae, for example, the African *Lippia multiflora* (14%; Bassolé et al., 2010; Ku & Lin, 2013), and *Lippia gracilis* (3.83–55.50%) from Brazil (Ferraz et al., 2013; Guilhon et al., 2011; Riella et al., 2012). Interestingly, this genus has been used as substitutes for oregano, which also contains thymol as commented before (Tucker & DeBaggio, 2009). Alternatively, the species *Centipeda minima* (Asteraceae), commonly used in Chinese folk medicine, is rich in derivatives of thymol (Liang et al., 2007). Therefore, all the essential oils of these species can be used as natural sources of thymol and standardized for further uses.

3.2 | Bioavailability, metabolism, and distribution

Due to the potential role of thymol in human health and as feed additive for animals, its bioavailability and metabolism have been determined in humans and animals biological samples, as well as in animal food products and tissues. These studies are essential to understand the mechanism of action of thymol, the active molecules, and the target tissue/organ where thymol as such (without modification or released after its deconjugation) and/or its metabolites may exert a biological role. For that, both gas chromatography (Dong et al., 2012; Fernandez, Palacio, & Labaque, 2017; Passreiter, Wilson, Andersen, & Isman, 2004) and liquid chromatography coupled to mass spectrometry (Kohlert et al., 2002) have been used.

In this way, Kohlert et al. (2002) found that free thymol could not be detected in human plasma or urine after oral administration of tablets containing thymol (1.08 mg). Alternatively, thymol was present in human plasma as thymol sulfate and as both thymol sulfate and thymol glucuronide in urine (Figure 2). So the latter authors quantified thymol in plasma based on the total free thymol concentration after enzymatic hydrolysis of the sulfate, and the main results are shown in Table 3. Peak plasma concentrations (93.1 ng/ml) were reached after above 2 hr, and the mean terminal elimination half-life was 10.2 hr. Urinary excretion of thymol metabolites could be followed over 24 hr. Thymol sulfate was eliminated slowly because a small clearance (Cltot/f) of 1.2 L/hr was found. The renal clearance of thymol was 0.271 L/hr, suggesting high protein binding and reabsorption in the kidney, whereas the volume of distribution was 14.7 L, indicating that thymol sulfate stay mainly in the extra cellular space. The ratio of peak areas of these metabolites was constant over the different urine fractions. Similarly, phenol applied intravenously to mice also resulted in sulfate and glucuronide metabolites (Kenyon, Seeley, Janszen, & Medinsky, 1995). However, the latter study showed a dose-dependent ratio; this means that an increasing dose may shift the ratio from sulfate metabolite toward glucuronide one. Moreover, despite the absence of thymol in plasma, thymol glucuronide was eliminated renally (Raoof, Van Obbergh, De Goyet, & Verbeeck, 1996). Therefore, Kohlert et al. (2002) suggested that thymol sulfate could be reabsorbed in the proximal tubule after glomerulary filtration. Then, cleavage to thymol could be achieved by the activity of aryl sulfatases according to Munroe and Chang (1987). On the other hand, other way could be the cleavage to thymol by brush border enzymes (Hart, Calder, Ross, & Tange, 1980), before being reabsorbed. Moreover, a recent study in vitro on phenolic compounds suggests that glucuronidation, sulfation, and methylation may also occur in enterocytes (Contreras, Borrás-Linares, Herranz-López, Micol, & Segura-Carretero, 2016). In this regard, Abid, Bouchon, Siest, and Sabolovic (1995) showed that at least the generation of thymol glucuronide may start in the intestine after the study of the microsomal fraction of Caco-2 cells.

Concerning other studies in animal models, thymol metabolites were rapidly excreted in urine in rats (Austgulen, Solheim, & Scheline, 1987). In this study, besides the parent thymol itself (major compound), six metabolites were identified: 2,5-dihydroxy-*p*-cymene, 2-(2-hydroxy-4-methylphenyl)propan-1-ol, 5-hydroxymethyl-2-(1-methylethyl)phenol, 2-(4-hydroxymethyl-2-hydroxyphenyl) propan-1-ol, 2-(2-hydroxy-4-methylphenyl)propionic acid, and 3-hydroxy-4-(1-methylethyl)benzoic acid. In rat plasma, thymol sulfate and thymol glucuronide have also been detected after the oral administration of a hydroethanolic thyme extract (1.5 g; Rubió et al., 2012). Thymol is also excreted in the urine as sulfate and glucuronide conjugates in rabbits and dogs (Williams, 1959). In the case of dogs,

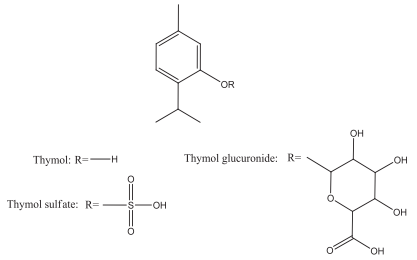

FIGURE 2 Structures of thymol, thymol sulfate, and thymol glucuronide

TABLE 3 Pharmacokinetic data of total thymol absorption and elimination in human plasma (Kohlert et al., 2002)

	Mean value
Dose (mg)	1.08
C_{max} (ng/ml)	93.11
t_{max} (hr)	1.97
$t_{1/2}$ (hr)	10.2
CL_{tot}/f (L/hr)	1.2
Vdss/f (L)	14.7

Note. C_{max} = peak plasma concentration; t_{max} = time to reach C_{max}; $t_{1/2}$ = elimination half-life; CL_{tot}/f = total body clearance with respect to unknown bioavailability f; Vdss/f = volume of distribution at steady state with respect to unknown bioavailability f.

TABLE 4 Antimicrobial properties of thymol and plants containing thymol

Bioactivity	Effect and mechanisms of action	Type of study	Studied plant/compound	Reference
Antifungal activity				
Against *Rhizopus oryzae* strains	Inhibition of the growth, MIC and MFC of *Thymus vulgaris* EO: 256–512 μg/ml and 512–1,024 μg/ml; MIC and MFC of thymol: 128–256 μg/ml and 128–1,024 μg/ml Inhibition of the germination of sporangio-spores and mycelial development by interacting with ergosterol	In vitro	*T. vulgaris* EO (46.6% of thymol) and thymol Control: amphotericin B (MIC, 2–4 μg/mL)	De Lira Mota, de Oliveira Pereira, de Oliveira, Lima, and de Oliveira Lima (2012)
Against two *Candida albicans* strains	Inhibition of the growth, MIC: 125–500 μg/ml To interfere with the architecture of the envelope.	In vitro	Thymol Control: vehicle	Braga, Alfieri, Culici, and Dal Sasso (2007)
Against *C. albicans*	Inhibition of the growth, MIC (80%): *Thymus numidicus* EO (0.0005–0.0006 μg/ml), *Thymus ciliates* EO (1.6690 μg/ml), and *T. vulgaris* EO (3.710 μg/ml)	In vitro	*T. numidicus*, *T. ciliates*, and *T. vulgaris* EOs with 66.3–57.2%, 60.5%, and 25.6%, respectively	Giordani et al. (2008)
Against *Aspergillus flavus*	Inhibition of the growth, MICs: 80 μg/ml (no visible mycelia and no spore growth) Reactive oxygen species involves the fungicidal actions of thymol against spores via the induction of nitric oxide	In vitro	Thymol	Shen et al. (2016)
Antibacterial activity				
Against *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus sanguinis*, *Streptococcus pyogenes*, *Enterecoccus feacalis*, *Pseudomonas aeruginosa*, *Lactobacillus acidophilus*, and *Staphylococcus aureus*	Inhibition of the growth: *Thymus algeriensis* EO (MIC, 20–80 μg/ml); *T. vulgaris* EO (MIC, 80–160 μg/ml); *Thymus serpyllum* EO (MIC, 2.5–5 μg/ml)	In vitro	*T. algeriensis*, *T. vulgaris*, and *T. serpyllum* EOs, with 56.0%, 48.9% and 38.5 of thymol, respectively Control: streptomycin and ampicillin (MIC, 5–625 μg/ml) Hexoral®[b] (MIC, 190–1,560 μg/ml)	Nikolić et al. (2014)
Against *S. aureus*, *Bacillus subtilis*, and *Escherichia coli*	Inhibition of the growth, MICs: 0.0005–0.00025 (%, v/v)	In vitro	*Carum copticum* (72.3% of thymol)	Oskuee et al. (2011)
Against *S. aureus* and *E. coli*	Inhibition of the growth, MICs: 0.3–5.0 mg/ml Hydrophobicity enables them to disturb the cell membrane, which may be dependent on the lipidic composition and net surface charge. Then, thymol might penetrate into the cell and interact with critical intracellular sites	In vitro	Thymol	Cristani et al. (2007)
Against P. aeruginosa	Inhibition of the growth, MIC: 0.05% (v/v) Interfering with the starting phases of adherence and with biofilms	In vitro	Thymol	Koraichi Saad, Hassan, Ghizlane, Hind, and Adnane (2011)
Haemophilus influenzae, *Streptococcus pneumoniae*, *S. pyogenes*, and *S. aureus*	Antibacterial action at high vapor concentration applied for a short time MID 3.13–6.25 mg/L air	In vitro	Three thyme EOs (red, wild, and geraniol)	Inouye, Takizawa, and Yamaguchi (2001)
Against H. influenza, *S. aureus*, and *S. pneumoniae*	Higher antibacterial action in vapor phase (MIC values 128 μg/ml) than in liquid	In vitro	Thymol Controls: amoxicillin, ampicillin, and oxacillin (MICs 0.125–1 μg/ml)	Houdkova, Rondevaldova, Doskocil, and Kokoska (2017)

(Continues)

TABLE 4 (Continued)

Bioactivity	Effect and mechanisms of action	Type of study	Studied plant/compound	Reference
	phase (MIC values, 256 μg/ml)			
Antiviral activity				
Against *Bacillus* phage CP51	Direct inactivation of virus particles	In vitro	*C. copticum* (72.3% of thymol) at 0.1–0.0001 (%, v/v)	Oskuee et al. (2011)

Note. EO = essential oil; MFC = minimal fungicidal concentration; MIC = minimal inhibitory concentration; MID = minimal inhibitory dose.

almost one third of 1-g dose was excreted in urine without any changes, whereas there were no traces of it in the feces (Robbins, 1934).

Although reports on the bioavailability of thymol in humans and model animals have been published since 1934, the scientific interest in the metabolism and distribution of thymol in production animals is strikingly increased. The potential use of thyme and thymol to improve growth performance, to enhance antioxidant status, and to reduce diseases (Tables 4 and 5) is indirectly connected with human health. Thymol can be used as an alternative to chemicals and respond to consumers' concern about naturalness in the food chain, including farm animals (Table 6; Sato, Hötzel, & von Keyserlingk, 2017).

In this context, Ocel'ova et al. (2016) have estimated the concentration of thymol in blood plasma, liver, kidney, and muscle of broiler chickens after a supplementation with thyme essential oil. They found the highest concentrations of thymol in the kidney tissue and plasma and the lowest in the breast muscle and liver tissue. Possibly, an intensive metabolism of thymol occurred in the liver, whereas it was accumulated in the kidney tissue. Nevertheless, these authors only studied total free thymol using gas chromatography–mass spectrometry (GC–MS), and no information about thymol metabolites could be obtained. Afterwards, in another study, thymol glucuronide and thymol sulfate were detected in plasma, liver, and duodenal wall of broiler chickens using liquid chromatography–mass spectrometry (LC–MS), but it was dependent on the administered concentration (Pisarčíková, Oceľová, Faix, Plachá, & Calderón, 2017). In addition, thymol may also pass to egg yolk samples (11.83 ng/g) from quails supplemented with thymol in their diets (80 mg thymol/bird per day; Fernandez et al., 2017). Another study suggested that the concentration of thymol increased in gut and plasma of broiler chickens after the administration of thyme herb, but thymol levels were very low in edible tissues such as liver and flesh (Haselmeyer et al., 2015). Although in some of these studies, the data did not indicate a clear positive effect of thyme on animal performance; it seems that the effects of thymol may depend on the diet formulation and the environment (Haselmeyer et al., 2015). However, other effects of thymol have been reported at intestinal levels such as intestinal injury by improving intestinal integrity and modulating immune responses in chickens infected with *Clostridium perfringens* (Du et al., 2016).

Finally, as far as we know, little is known about the bioactivity of the aforementioned thymol metabolites or whether these compounds are inactive forms. Anyway, Rubió et al. have studied the antioxidant effect and bioavailabity of phenolic compounds from olive oil and thyme extracts, alone or in combination, after their acute administration in rats (1.5 g/k of body weight). Their results indicated that the bioavailability of olive phenolic compounds was enhanced in the presence of thyme, although no synergistic effect was observed in the antioxidant status. From the antioxidant activity measured in plasma, these authors suggested that the antioxidant protection against oxidative stress could occur through a direct antioxidant effect of phenolic metabolites, including thymol sulfate (Rubió et al., 2014).

3.3 | Role in health: Bioactivity

Nowadays, various risks factors such as stress, environmental and biodiversity changes, modern life styles and new food habits, immune pressures, and the impact of exploding populations lead to flaring up of common health problems in humans, to increase the frequency of carcinomas and to compromise the immune system. In addition to this, a deadly issue of the present time is the emergence of antibiotic-resistant pathogens and the toxic effects of residual medicines in the food chain (Dhama et al., 2013; Kuldeep et al., 2014; Sharifi-Rad, Ayatollahi, et al., 2017; Sharifi-Rad, Varoni, et al., 2017; Salehi et al., 2017). These factors act as the driving force for the search of new medicaments. A recent report by the World Health Organization indicates that there is a lack of new antibiotics under development to combat the antimicrobial resistance, including tuberculosis. What is more, most of the new drugs are only short-term solutions because they are modifications of existing antibiotics (http://www.who.int/mediacentre/news/releases/2017/running-out-antibiotics/en/; Sharifi-Rad, Salehi, Stojanović-Radić, et al., 2017). For these reasons, as in the past, looking for medicaments of herbal origin that assure more efficiency with less damaging effects than synthetic ones is the objective to which numerous researchers are addressing their efforts (Sharifi-Rad, 2016).

In this context, thyme possesses numerous compounds and natural antioxidants, which have enormous potential to combat microorganism infections, to enhance immunity, and to be used in therapeutic and management intervention against cancer due to their pharmacological activities (Bagheri, Mirzaei, Mehrabi, & Sharifi-Rad, 2016; Salehi et al., 2018; Sharifi-Rad, Sureda, et al., 2017; Sharifi-Rad, Mnayer, et al., 2018; Stojanović-Radić, Pejčić, Stojanović, Sharifi-Rad, Stanković, 2016). Thymol and carvacrol are two of its active compounds as commented above. Concerning thymol, Tables 4 and 5 show the antimicrobial properties of thymol and some of the bioactive properties related to this compound in vitro, ex vivo, in vivo, and in humans and the potential mechanisms of action. In this sense, the main bioactivities are described here to clarify the ethnopharmacology of thyme, the main source of thymol. In addition, thymol- and thyme-based extracts may improve the productive performance of farm animals, the nutrient bioavailability, and so forth (Table 6).

TABLE 5 Bioactivity of thymol and plants containing thymol, mechanisms of action, type of study (*in vitro*, *ex vivo*, *in vivo* and in humans), dosage and duration

Bioactivity	Effect and mechanisms of action	Type of study	Studied compound/plant, dose and duration[a]	Ref.
Against respiratory system disorders				
Antispasmodic activity	Dose-dependent antispasmodic activity, prostaglandin F2α being more efficiently antagonized than other spasmogens ($BaCl_2$, carbachol, and histamine)	Ex vivo: isolated guinea pig trachea	Ethanolic extract of thyme (0.072% of thymol) at 0.2% to 2.0% (v/v) Control: vehicle	Meister, Bernhardt, Christoffel, and Buschauer (1999)
Antispasmodic effect	Antispasmodic activity in the rabbit jejunum and tracheal relaxant properties	Ex vivo: rabbit jejunum and isolated guinea pig trachea	Thymol: 10^{-10}–10^{-2} M Control: isoproterenol	Astudillo et al. (2004)
Antispasmodic activity and secretomotorics	The extract with higher thymol content was more effective, as a relaxant (rat ileum), as an antispasmodic compound (rat trachea contraction provoked by Ba++ or K+) and in mucociliary transport	Ex vivo: rat ileum and rat trachea In vivo: tracheal mucociliary clearance	Ex vivo: thyme preparations (thymol content of <0.005–0.15%) at 100 μg/ml and thymol (10–191 μg/ml); Controls: papaverine (40 μM) and vehicle In vivo: 0.4 and 4.0 ml/kg BW (thymol content of 0.13–1.3 mg/kg BW); Controls: vehicle and salbutamol (500 μg/kg)	Begrow et al. (2010)
Antitussive effects	Modulation of cough, which could be related to olfactory signaling mechanisms	In humans: healthy volunteers	Nasal treatments of thymol (0.025 ml, 10^{-3} M)	Gavliakova et al. (2013)
Pulmonary function	Reduction of inflammatory cells and oxidant biomarkers, increase of antioxidant biomarkers, and improvement of force vital capacity and peak expiratory flow	In humans: forty-seven sulfur mustard exposed patients (27–30 years after exposed)	*Zataria multiflora* (5 and 10 mg·kg·day), 2 months Control: placebo group	Khazdair, Rajabi, Balali-Mood, Beheshti, and Boskabady (2018)
Asthma	Improvement in lung wheezing and forced expiratory volume in 1-s value, which could be due to anti-inflammatory properties of these agents through reduction of NO_2	In humans: forty asthmatic patients	*Z. multiflora* (5 and 10 mg·kg·day), 2 months. The extract contained initially 55.4 mg/100 ml thymol, 7.7 mg/100 ml carvacrol, and 63.2 mg/100 ml total phenol Control: placebo group	Alavinezhad, Hedayati, and Boskabady (2017)
Against nervous system disorders				
Anxiolytic properties	Anxiolytic effects, which is not influenced by the locomotor activity	In vivo: rats	Oral administration of *Thymus vulgaris* leaves extract (70% ethanol; 50–200 mg/kg infusion for 7 days) Control: saline solution	Komaki et al. (2016)
Neuroprotective	To decrease the effects of amiloid β on memory	In vivo: HFD-fed rat model of Alzheimer's disease	Thymol (30 mg/kg in sunflower oil), 4 weeks Control: standard diet	Asadbegi et al. (2017)
Against cardiovascular system disorders				
Antihypertensive properties	Reduction of blood pressure; improvements on aortic vascular damage and hypertension-related biochemical parameters	In vivo: rats	Aqueous extract of *T. vulgaris* (100 mg·kg·day, orally), 8 weeks	Kensara, Elsawy, El-shemi, and Header (2013)
Antihyperlipidemic effects and aortic intimal thickening	Suppression of the progression of hyperlipidemia and atherosclerosis by reducing aortic intimal lipid lesion, lowering serum lipids, and inhibiting oxidative stress and inflammation	In vivo: HFD rabbits	Thymol (3 or 6 mg·kg·day, for 8 weeks) Control: standard diet	Yu et al. (2016)
Antioxidant properties				
Antioxidant activity in lipids systems	Strong antioxidant activity	In vitro	Purified triacylglycerols of lard and sunflower oil	Yanishlieva, Marinova, Gordon, and Raneva (1999)

(Continues)

TABLE 5 (Continued)

Bioactivity	Effect and mechanisms of action	Type of study	Studied compound/plant, dose and duration[a]	Ref.
			containing 0.02–0.20% of thymol	
	Inhibition of lipid peroxidation			Rhee, Anderson, and Sams (1996)
Antioxidant activity	DPPH scavenging activity, reducing power, β-carotene bleaching and TBARS inhibition: *Thymus algeriensis* (EC_{50} 0.31–1.64 mg/ml), *T. vulgaris* (0.005–4.80), and *Thymus serpyllium* (0.004–0.96 mg/ml)	In vitro	*T. algeriensis*, *T. vulgaris*, and *T. serpyllum* EOs, with 56.0%, 48.9%, and 38.5% of thymol, respectively Control: trolox (EC_{50}s 2.63–43.0 mg/mL)	Nikolić et al. (2014)
Antioxidant activity and modulation of antioxidant enzymes	To increase the antioxidant enzyme activity (SOD and GPx), total antioxidant status, and concentration of polyunsaturated fatty acids in phospholipids of the brain	In vivo: rats	Standard pelleted diet with thyme EO or thymol at 42.5 mg/kg BW per day, 7–28 months	Youdim and Deans (2000)
Anti-inflammatory activity				
Inhibition of the release of elastase	To intervene with elastase enzyme in a concentration-dependent manner	In vitro: PMNs cells	Thymol (2.5–20 μg/ml)	Braga et al. (2006)
Inhibition of LPS-stimulated inflammatory	Inhibition of the production of TNF-α and IL-6, suppression of the expression of iNOS and COX-2, blocking the phosphorylation of p38 mitogen-activated protein kinases, and among others	In vitro: LPS-stimulated mouse mammary epithelial cells	Thymol (10–40 μg/ml)	Liang et al. (2014)
Anti-inflammatory activity	Thyme EO: inhibition of inflammatory edema and leukocyte migration Thymol: inhibition of inflammatory edema and chemoattractant effect	In vitro: chemotaxis in leukocytes In vivo: ear edema in mice (a) and carrageenan-induced pleurisy in rats (b) models	In vitro: thymol (0.3–90 μg/ml) In vivo: (a) Acute administration of thyme (45.5% and 0.9% of carvacrol and thymol; 250–750 mg/kg) and thymol (100–400 mg/kg; 4 hr); controls: indomethacin (5 mg/kg), and celecoxib (10 mg/kg). (b) Topical thyme and thymol (10 mg/ear); controls: indomethacin (0.5 mg/ear), dexamethasone (0.1 mg/ear), and vehicle	Fachini-Queiroz et al. (2012)
Attenuation of allergic airway inflammation	Reduction the level of OVA-specific IgE and the levels of IL-4, IL-5, and IL-13; inhibition of the recruitment of inflammatory cells into airway Amelioration of the pathologic changes of lung tissues and goblet cell hyperplasia Reduction of the development of airway hyperresponsiveness and blocking the activation of NF-κB pathway	In vivo: a model of mouse asthma (induced by OVA)	Thymol orally administered (4–16 mg/kg BW; acute, 24 hr) Control: normal control (no treatment) and dexamethasone (2 mg/kg)	Zhou et al. (2014)
Ablation of mast cell-associated skininflammation	Inhibition of passive cutaneous anaphylaxis Promotion of an activation-induced apoptotic death of mast cells, and mobilization of calcium, probably mediated by TRPA1	In vivo: a mast cell-dependent passive cutaneous anaphylaxis model and C57BL/6, BALB/c and HDC−/− (deficient in histamine) mice	In vivo: topical thymol (10 μl, 200 μM–20 mM and 20 μM–20 mM) In vitro: 0–3,000 mM depending on the assay	Wechsler, Hsu, and Bryce (2014)
	Depletion of mast cells, which leaded to a suppression of IgE-dependent responses to antigen	In vitro: BMMCs	Control: vehicle	

(Continues)

TABLE 5 (Continued)

Bioactivity	Effect and mechanisms of action	Type of study	Studied compound/plant, dose and duration[a]	Ref.
Reduction of gingival inflammation	Reduction of the tissue lesion at histopathology Decreased myeloperoxidase activity production in gingival tissue	In vivo: acute phase of ligature-induced periodontitis model in rats	Nanostructured thymol gel 1.2 mg/g Control: saline-based gel (negative) and diethylammonium diclofenac gel 10 mg/g (positive)	Botelho et al. (2016)
Immunomodulation				
IgG modulation	Herb did not affect immune response factors such as IL-1β and plasmatic IgG	In vivo: weaned piglet Control: normal diet	An herbal product (containing cinnamon, thyme, and oregano extracts), (0.75% inclusion in the diet), 4 weeks	Namkung et al. (2004)
Phagocytic modulating activity	Inhibition of the phagocytic activity of thymol (72%) and of red thyme (38%)	In vitro: inhibitory activity of thymol and red thyme containing 50% of thymol on phagocytosis by human neutrophils	Thymol at 56 μg/ml and red thyme at 47 μg/ml Control: LPS (1 mg/ml)	Pérez-Rosés, Risco, Vila, Peñalver, and Cañigueral (2015)
Modulation of heterophils/lymphocytes ratio	Significant increase in red blood cell, hemoglobin, white blood cell, and hematocrit values in broilers	In vivo: broiler chicks	100 and 200 ppm thyme EO added to the standard diet, 42 days Control: standard diet	Al-Kassie (2009)
Improvement of immune response	Increasing hypersensitivity response, total and IgG anti-sheep red blood cell titers, and decreasing heterophils/lymphocytes ratio compared with the control group.	In vivo: broiler chickens	Thymol + carvacrol (0, 60, 100, and 200 mg/kg of diet) Control group: 0	Hashemipour et al. (2013)
Analgesic activity				
Analgesic activity	Inhibition of prostaglandin biosynthesis by thymol (87.5%)	In vitro: using prostaglandin-synthesizing cyclooxygenase system from sheep seminal vesicles	Thymol (37 mM) Control: indomethacin	Wagner and Wierer (1986)
Anticarcinogenesis activity				
Citotoxicity effects on cancer cells	Induction of cell cycle arrest at sub G0/G1 phase and apoptotic cell death based on genomic DNA fragmentation patter Significant increase in ROS activity, depolarization of mitochondrial membrane potential, and mitochondrial H_2O_2 production Translocation of apoptosis inducing factor from mitochondria to cytosol and to nucleus (caspase independent apoptosis)	In vitro: using HL-60 (acute promyelotic leukemia) cells and normal human PBMC	Thymol (5–100 μM) Control: camptothecin at 50 mM	Deb et al. (2011)

Note. BMMCs = bone marrow mononuclear cells; COX = cytochrome C oxidase; DPPH = 2,2-diphenyl-1-picrylhydrazyl; EO = essential oil; GPx = glutathione peroxidase; HFD = high-fat diet; IL = interleukin; iNOS = inducible nitric oxide synthase; LPS = lipopolysaccharide; OVA = ovalbumin; PBMC = peripheral blood mononuclear cell; PMN = polymorphonuclear neutrophil; TNF = tumor necrosis factor; SOD = superoxide dismutase; TBARS = Thiobarbituric acid reactive substance; ROS = Reactive oxygen species.

[a]Dose and duration for in vivo studies.

3.4 | Antimicrobial and antiseptic properties

Thymol and thyme have a wide antimicrobial spectrum, including Gram-positive and Gram-negative bacteria (Al-Bayati, 2008; Nikolić et al., 2014). These include foodborne bacteria such as *Salmonella*, *Escherichia*, *Pseudomonas*, *Listeria*, and *Bacillus* species (Burt, 2004; Koraichi Saad et al., 2011) and some pathogens implicated in respiratory tract infections (Houdkova et al., 2017; Inouye et al., 2001; Table 4). In particular, the antibacterial activity of thyme essential oils and their major constituents, including thymol, was studied in vitro against pathogens related to diseases of respiratory system and in the gaseous state: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *Staphylococcus aureus*. The results indicated a higher potency of these essential oils (with a minimal inhibitory dose of 3.13–6.25 mg/L air) than those from other plants. Moreover, the antibacterial action was most effective at high

TABLE 6 Examples of studies of thymol and thyme in farm animals

Bioactivity	Effect and mechanisms of action	Animal	Studied compound/plant, dose, and duration[c]	Reference
Performance enhancement. Others: modulation of antioxidant enzyme activities[a] and digestive enzyme activities[b]	Decrease of feed intake, with a highest body weight gain and feed efficiency at the major concentration Others: increase of SOD and GPx activities and decrease of malondialdehyde level in some experiments; reduction of total saturated fatty acids, and increase of total polyunsaturated fatty acids; increase of intestinal and pancreatic trypsin, lipase, and protease activities[d] (24-days-old animals)	Broiler chickens	Thymol + carvacrol (0, 60, 100, and 200 mg/kg of diet) Control group: standard diet	Hashemipour et al. (2013)
Growth performance	No clear effect of thyme on animal performance parameters	Broiler chickens	Thyme (leaves and flowers without stems; 1.4% EO, 58% thymol; 0.1–1%, *w*/w, in the diet), 35 days Control: standard diet	Haselmeyer, Zentek, and Chizzola (2015)
Growth promoter	Higher feed intake, body weight gain, and feed conversion ratio than control. Reduction of serum cholesterol	Broiler chicks	100 and 200 ppm thyme EO added to the standard diet, 42 days Control: standard diet	Al-Kassie (2009)

Note. EO = essential oil; GPx = glutathione peroxidase; SOD = superoxide dismutase.

[a]Modulation of the activity of antioxidant enzymes, which also can be considered as an antioxidant mechanism of thymol.

[b]Properties of thymol also related to the digestive system.

[c]Dose and duration for in vivo studies.

vapor concentration applied for a short time (Inouye et al., 2001). Alternatively, another study suggested that thymol possessed moderate antibacterial activity against *H. influenzae*, *S. aureus*, *and S. pneumoniae*, in both vapor (minimal inhibitory concentration, MIC, values 128 μg/ml) and liquid phases (MIC values, 256 μg/ml). Carvacrol and cinnamaldehyde showed similar MIC values, whereas the controls (amoxicillin, ampicillin, and oxacillin) showed lower values in the vapor phase (0.125–1 μg/ml; Houdkova et al., 2017).

Another example is the fungicide effect in vitro of *Thymus* species rich in thymol on the yeast *Candida albicans* (Giordani et al., 2008), for example, *Thymus numidicus* (66.3–57.2% of thymol) and *Thymus ciliates* (60.5% of thymol) with MIC (80%) values ranged from 0.0005 to 1.6690 μg/ml. Because of the existence of both a single-celled form and a hyphal form, *C. albicans* is an unusual yeast. This property, the ability to transform from a cellular form to a hyphal form, is major part of *C. albicans* attack process. Researchers have demonstrated that thymol hinders this process (Shareck & Belhumeur, 2011). Moreover, certain combinations of thymol and eugenol (main component of clove oil) led to a synergistic effect against *C. albicans* in vitro (Braga, Alfieri, et al., 2007; Braga, Dal Sasso, Culici, & Alfieri, 2007). Thymol also inhibits other fungus, *Aspergillus*. A recent study shows that reactive oxygen species involves the fungicidal actions of thymol against the spores of *Aspergillus flavus* via the induction of nitric oxide (Shen et al., 2016). In addition, thymol improved the action of drugs used to treat aspergillosis and *Cryptococcus* infections because of its fungicidal activity showed in vitro (Faria et al., 2011).

3.5 | Respiratory system

It has been suggested that thymol has strong antiseptic characteristics, which can be very useful in relieving intestinal problems and respiratory infections. When it comes to lungs, it is a great expectorant. It helps ease the cough and sore throat and break down the mucus, thereby clearing the airways. Thyme, known for its expectorant specifications and antispasmodic abilities, is used as herbal medicine for cough. It can be used to treat bronchitis, colds, asthma, and other upper respiratory infections (Inouye et al., 2001; Kohlert et al., 2002). Throughout Europe, a tea made of thyme has been used for centuries to treat whooping cough, and several thyme extracts are currently used as mucolytic and expectorant and to treat respiratory tract diseases (European Medicines Agency, 2013; Table 1).

As commented before, the antimicrobial properties of thymol against pathogens of the respiratory system have been suggested by several studies. Some of them also suggest that besides a systematic antibiotic treatment, an inhalation therapy is an alternative way for the treatment of respiratory bacterial diseases. Nevertheless, it requires further studies to establish the effective dosage of thymol, thyme, or thymol-based extracts in clinical studies.

In 2013, the European Medicines Agency published a detailed assessment report on *T. vulgaris*, including nonclinical and clinical data of thyme extracts. Although the therapeutic significance could not be estimated based on these studies, they supported the traditional use of thyme against respiratory tract disorders. Among them, an ethanolic extract of thyme, containing 0.072% and 0.005% of thymol and

carvacrol, respectively, was tested at concentrations ranged from 0.2% to 2.0% (v/v) on isolated guinea pig trachea, a pharmacological model for the study of bronchospasmolytics (Meister et al., 1999). Their findings suggested a marked dose-dependent antispasmodic activity. Begrow et al. (2010) compared different thyme preparations, with a thymol content ranged from <0.005% to 0.15%, in order to evaluate their antispasmodic effect on smooth muscles of the trachea and the ileum, as well as on the ciliary activity (respiratory clearance). Their results showed that thymol and carvacrol contributed to the activity of the studied extracts. Moreover, thymol could interact with α-, α_2- and β-receptors of smooth muscles as shown in in vitro experiments with circular smooth-muscle strips (Beer, Lukanov, & Sagorchev, 2007). Another study suggested that the relaxing effect of thyme on rat trachea tissue could depend at least partly on the interaction of thyme constituents with β_2-receptors. The studied extract also improved the mucociliary clearance of mouse trachea in vivo after an intragastric dosage of 0.4 and 4 ml/kg body weight, that is, 0.13 and 1.3 mg/kg body weight of thymol. (Wienkötter, Begrow, Kinzinger, Schierstedt, & Verspohl, 2007).

Concerning clinical studies, the combination of thyme and primrose, which contains saponins with expectorant and secretolytic activity, was used to alleviate cough and dyspnea and to shorten the length of the disease. Its effectiveness was comparable with synthetic ambroxol (Schönknecht, Krauss, Jambor, & Fal, 2016). In addition, cough was modulated by inhalation of a tussive aerosol in healthy volunteers after nasal treatments with thymol (0.025 ml, 10^{-3} M), which could be related to olfactory signaling mechanisms (Gavliakova et al., 2013).

In another context, *Z. multiflora* has shown protective effects on tracheal responsiveness (in sensitized guinea pigs; Boskabady, Jalali, Farkhondeh, & Byrami, 2014; Boskabady, Tabanfar, Gholamnezhad, & Sadeghnia, 2012) and against lung disorders in animal models (guinea pigs model of chronic obstructive pulmonary disease by exposing to cigarette smoke; Boskabady & Mahtaj, 2015; Gholami Mahtaj, Boskabady, & Mohamadian Roshan, 2015). Interestingly, *Z. multiflora* (5 and 10 mg·kg·day) was tested in veterans, 27–30 years after exposed to sulfur mustard, to evaluate the effects in lung function. Their findings showed reduction of inflammatory cells and oxidant biomarkers, increasing antioxidant biomarkers, and improvement of pulmonary function tests (Khazdair et al., 2018). This plant has also shown a possible therapeutic potential against asthma in a recent study in asthmatic patients (Alavinezhad et al., 2017; Table 5). Although some of these studies highlighted carvacrol as one active component, the contribution of thymol should not be ruled out because it is also present in relatively high amounts (see Section 3.4).

3.6 | Nervous system

Komaki et al. (2016) demonstrated in their results that oral administration of *T. vulgaris* extract may have an anxiolytic profile in rats. The presence of phenolic compounds and essential oil compounds in the extract of *T. vulgaris* reinforces the anxiolytic effects of this plant observed in this study. Moreover, Asadbegi et al. (2017) reported that thymol decreased the effects of amiloid β on memory and could be considered as neuroprotective.

3.7 | Cardiovascular system

Phenolic derivatives can help to improve lipid profiles, to prevent oxidation of cholesterol and plaque formation, and to reduce molecular damage. So thymol may be useful for reducing the risk of cardiovascular diseases. In fact, thyme has been used as an antihypertensive agent in the Mexican traditional medicine (Castillo-España et al., 2009). A recent study has shown that the administration of an aqueous extract of *T. vulgaris* (100 mg·kg·day, orally) to rats for eight consecutive weeks reduced the blood pressure. This effect was associated to marked improvements on aortic vascular damage and hypertension-related biochemical changes (Kensara et al., 2013). Nevertheless, the extract was not characterized.

Thymol (3 or 6 mg·kg·day, for 8 weeks) suppressed the progression of hyperlipidemia in high-fat-diet rabbits and atherosclerosis by reducing aortic intimal lipid lesion, lowering serum lipids, as well as inhibiting oxidative stress and inflammation (Yu et al., 2016). Moreover, in other study, thymol (14 mg/kg, twice per day) was administered orally to high fat diet-induced obese rats for 4 weeks (Haque, Ansari, Najmi, & Ahmad, 2014). This compound prevented obesity through several mechanisms, such as the attenuation of visceral fat accumulation, improvement of insulin and leptin sensitivity, enhancement of the antioxidant potential, and a lipid lowering effect.

3.8 | Anti-inflammatory activity

The anti-inflammatory activity of thymol has been demonstrated in vitro and in vivo in different cells and animal models (Table 5). The potential anti-inflammatory action of thymol has been shown in vitro via an inhibitory effect on the release of human neutrophil elastase (Braga et al., 2006). It also inhibited the production of tumor necrosis factor alpha and interleukin (IL)-6 in lipopolysaccharide-stimulated mouse mammary epithelial cells, suppressed the expression of inducible nitric oxide synthase and cytochrome C oxidase-2, blocked the phosphorylation of p38 mitogen-activated protein kinases, and among others effects (Liang et al., 2014). Other study has shown that extracts from three *Thymus* spp. (10.05–71.15% of thymol) significantly reduced the production and gene expression of the proinflammatory mediators tumor necrosis factor alpha, IL-1B, and IL-6 in oxidized low-density lipoproteins-stimulated THP-1-macrophages. This reduction was dose dependent and according to the abundance of thymol of each species (Ocaña & Reglero, 2012).

Fachini-Queiroz et al. (2012) have evaluated the effects of thyme essential oil and its isolated constituents, thymol and carvacrol, in the inflammatory response. In this way, their effects were studied in experimental models of ear edema and carrageenan-induced pleurisy, as well as chemotaxis in vitro. Their results showed that thyme has anti-inflammatory effects, whereas their isolated compounds showed antagonist effects. Thymol showed irritative effects that likely involved histamine, prostanoids, and other inflammatory mediators, whereas carvacrol had an inhibitory effect on leukocyte migration, contributing to the anti-inflammatory action of thyme. Nevertheless,

the tissue or cellular target may be considered. For example, the results of Riella et al. (2012) suggested that thymol exhibited anti-inflammatory activity and wound healing in a paw edema as well as peritonitis rodent models treated with thymol (10, 30, and 100 mg/kg). Using different in vitro and in vivo models, Wechsler et al. (2014) have also revealed that thymol promoted an activation-induced apoptotic death of mast cells, which led to a suppression of subsequent IgE-dependent responses to antigen. Thus, thymol could be used topically for the ablation of mast cell-associated skin inflammation disorders (Wechsler et al., 2014). In addition, the anti-inflammatory effect of a thymol gel from *Lippia sidoides* was evidenced in acute periodontitis in rats (Botelho et al., 2016).

3.9 | Antioxidant activity

Studies suggest that thymol, as other phenolic derivatives, possesses useful antioxidant properties and may become important in the search for "natural" replacements for "synthetic" antioxidant food additives (Aeschbach et al., 1994; Fachini-Queiroz et al., 2012; Sharifi-Rad, Varoni, et al., 2018). The antioxidant properties may be related to its phenolic structure, which may adsorb and neutralize free radicals and exhibit redox properties (Yu et al., 2016). This compound scavenges hydroxyl free radicals and produces phenoxyl radicals, major transient species (Nagoor Meeran et al., 2017), being more active than the synthetic antioxidant *terc*-butylated hydroxytoluene in vitro (Gavaric, Smole Mozina, Kladar, & Bozin, 2015). As an example, Gavaric et al. (2015) reported the following values for the IC_{50} of thyme essential oil (41.6% of thymol) and thymol: 0.2 and 28.82 μg/ml, respectively. In the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical-scavenging assay, the latter thyme essential oil and thymol were able to reduce the DPPH radical into DPPH-H, with IC_{50} values of 0.24 and 70.06 μg/ml, respectively, whereas that of butylated hydroxytoluene was 6.95 μg/ml. Compared with other terpenes, such as caryophyllene, limonene, linalool, menthone, pulegone, camphor, and menthol, thymol showed the highest antioxidant activity in the DPPH, the 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid, and the ferric reducing antioxidant power antioxidant methods in vitro (Salgado-Garciglia et al., 2016; Sharopov, Wink, & Setzer, 2015). Nevertheless, it should be noted that in the intestinal Caco-2 cells, thymol exerted prooxidant/antioxidant activities, but it seems to depend on the concentrations tested (Llana-Ruiz-Cabello et al., 2015).

Thymol also increases the activity of endogenous antioxidant enzymes, such as superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, and the level of other non-enzymatic antioxidants such as vitamin C, vitamin E, and reduced glutathione (Nagoor Meeran & Prince, 2012), and thereby the total antioxidant status in vivo (Youdim & Deans, 2000).

In addition, thymol may become an important antioxidant food supplement. In fact, some studies suggest that thymol may inhibit lipid peroxidation (Rhee et al., 1996) and the formation of oxidative deterioration compounds, such as peroxides and hexanal, as well as undesirable off-flavors (Quiroga, Asensio, & Nepote, 2015). Moreover, thymol may be used as an antioxidant active packaging material as demonstrated Ramos, Jiménez, Peltzer, and Garrigós (2014).

3.10 | Allergy and toxicity

The use of thyme oil may cause in allergic reactions, even when it is diluted. Some people who use it may experience dermatitis or inflammation of the skin (Nardelli, D'Hooghe, Drieghe, Dooms, & Goossens, 2009). People with allergies to Lamiaceae plants should also stay away from medicines, cosmetics, nutraceuticals, and functional foods based on thyme or their constituents (Basch, Ulbricht, Hammerness, Bevins, & Sollars, 2004). Other studies suggest that in cosmetics, although separate ingredients, including thymol, do not give rise to allergy reactions, their reaction products may generate new allergens (Smeenk, Kerckhoffs, & Schreurs, 1987).

In another context, thymol could attenuate allergic airway inflammation in ovalbumin-induced mouse asthma (Zhou et al., 2014). It also reduced IgE-dependent responses through promotion of activation-induced apoptotic cell death of mast cells. This effect was related to the potential of thyme to treat eczema and psoriasis (Wechsler et al., 2014).

Concerning the toxicity of thyme and thymol, although thyme has a generally recognized-as-safe 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 (Basch et al., 2004). The toxicity of thymol has been evaluated in vitro and in vivo.

Concerning in vitro studies, the cytotoxicity of thymol and other essential oils constituents is commonly evaluated using cell lines. As an example, the toxicological effect of thymol on the digestive tract was studied by several authors using the Caco-2 model. LLana-Ruiz-Cabello et al. found no cytotoxic effects for thymol at any of the concentrations (0–250 μM) and time of exposures (24 and 48 hr) used. On the contrary, ultrastructural changes, such as lipid degeneration, mitochondrial damage, and nucleolar segregation, were evidenced, suggesting certain cellular damage (Llana-Ruiz-Cabello, Gutiérrez-Praena, et al., 2014). The genotoxic effects of thymol were also evaluated in Caco-2 cells and the standard comet assay, revealing that thymol (0–250 μM) had any affects at time of exposures of 24 and 48 hr (Llana-Ruiz-Cabello, Maisanaba, et al., 2014). Slamenová, Horváthová, Sramková, and Marsálková (2007) investigated the cytotoxic, genotoxic, and DNA-protective effects of the long-term (24 hr) incubation of thymol in Caco-2 and HepG2 (human hepatoma) cells. They found a slight cytotoxic effect for thymol compared with carvacrol. In contrast, thymol did not induce DNA strand breaks in both cases and also protected the latter cells toward DNA strand breaks induced by hydrogen peroxide (Slamenová et al., 2007).

In an acute toxicity test in mice, the median lethal dose (LD50) of thymol was 1.35 g/kg when administered in a single oral dose, whereas the LD50 of the essential oil of thyme (containing, mainly, carvacrol, 45.5%; André et al., 2017) and *Thymus broussonetii* (36.7% of thymol; Elhabazi et al., 2012) were reported to be above 4.00 and 4.47 g/kg, respectively. In rats, the orally LD50 of thymol, thyme, and a thymol oil–water emulsion (10%) was 0.98 g/kg (Jenner, Hagan, Taylor, Cook, & Fitzhugh, 1964), 2.84 g/kg (Basch et al., 2004), and 2.46 g/kg, respectively (Gad, 2012). This fact indicates that *Thymus* plants' essential oils and thymol-based formulations are less toxic than thymol as such. Nevertheless, according to these studies, the toxicity of thymol and the essential oils of *Thymus* spp. are slightly low based

on Hodge and Sterner (1949) classification, whereas a recent report of EFSA suggested a moderate acute toxicity for thymol when administered by the oral route in rat, mouse, and guinea pig (LD50 0.98, 1.8,0 and 0.88 mg/kg, respectively; EFSA, 2012). Moreover, in a repeated-doses toxicity study, the latter thymol formulation (thymol oil–water emulsion) was administered at different doses (15.39, 30.78, and 61.55 mg/kg) during 28 days. Thymol did not induce any statistically significant changes in body weight gain or organs weight compared with control group, and no significant alteration was observed in hamatological and biochemical parameters as well as in histopathological analyses (Gad, 2012). In Europe, the use of thymol as pesticide has raised some concerns detailed by EFSA (2012) because of a lack of some toxicological data, for example, about reproductive toxicity. This fact has also been stated by European Medicines Agency (2013). In contrast, when it is used as veterinary medicinal products, there is no need to establish a maximum residue limit for thymol in foodstuffs of animal origin (European Commission, 2010); thymol is a naturally occurring compound, and the natural background exposure through food items for humans is probably higher.

Finally, Andersen (2006) concluded that thymol did not induce primary lung tumors in mice, caused no dermal irritation, and is not a significant sensitizing or photosensitizing agent. Moreover, thymol did not show any mutagenic activity (0–250 μM) in the Ames *Salmonella* test (Llana-Ruiz-Cabello, Gutiérrez-Praena, et al., 2014; Llana-Ruiz-Cabello, Maisanaba, et al., 2014).

3.11 | Others

Other health benefits of thymol are shown in Table 5, including anticarcinogenesis (Deb et al., 2011; Nikolić et al., 2014) and analgesic activities in vitro (Wagner & Wierer, 1986), as well as the modulation of the immune system in vitro and in vivo (Al-Kassie, 2009; Pérez-Rosés et al., 2015) by several mechanisms. Moreover, several researchers have revealed that thymol (alone or in combination with other herbal constituents) may improve animal (e.g., chickens) growth and performance in vivo together with other benefits (Al-Kassie, 2009; Hashemipour et al., 2013), but it seems to depend on the experimental conditions tested (Haselmeyer et al., 2015; Table 6). Therefore, these studies are still limited and encourage further investigations.

The use of some spices as digestive stimulants is common in traditional medicine (Platel & Srinivasan, 2004). Thymol and thyme supplemented in diets may also improve the digestibility of the nutrients and the activity of digestive enzymes (Hashemipour et al., 2013; Hernandez, Madrid, Garcia, Orengo, & Megias, 2004), as well as modulate gut microbiota (Namkung et al., 2004), reducing the impact of undesiderable bacteria in animals (Yin et al., 2017).

3.12 | Conclusions and future trends

Several scientific studies have evidenced that thymol (or thyme) may exert beneficial effects for the treatment of several disorders affecting the respiratory, cardiovascular, and nervous systems. This compound also exhibits antimicrobial, antioxidant, immunomodulatory, anti-inflammatory, and antispasmodic properties. Some of these bioactivities of thymol may be the basis of the formulation of new pharmacological active ingredients to be used in pharmaceutical and cosmeceutical products, functional foods, for food control, and animal production. For the later purposes, thyme is one of the most studied medicinal plants, because of its high content in thymol and ethnopharmacology relevance. Nevertheless, there are other natural sources of thymol, and they deserve further works. These studies should be complemented with characterization works due to the natural intraspecies variability of thymol and the occurrence of other bioactive compounds, such as carvacrol. Moreover, besides in vitro and in vivo studies, clinical studies should be reinforced, and the most effective way of administration of thymol-based products and the required dosage clearly demonstrated.

As noted before, the ethnopharmacology knowledge of thymol and plants containing thymol can be expanded to the food industry, not only as natural preservatives but also as bioactive components in functional foods. However, their direct use in foods may be limited by their aromatic properties and the interaction with various food constituents. So, encapsulation (see Zhang et al., 2014) may be a useful strategy to be further studied and widen the application of thymol and thymol-based ingredients. In another context, thymol may be used in production animals as an alternative to avoid synthetic preservatives/additives, satisfying new consumers preferences and concerns about animal welfare (see Sato et al., 2017), for example, to improve growth, performance, digestibility, and antioxidant status as well as against pathogenic bacteria. Even so, these reports are controversial (Wallace et al., 2010), being probably dependent on the diet formulation, dosage, and the environment.

Concerning allergenicity, it seems that thymol/thyme may act as allergen, but also it may attenuate allergic inflammation (only corroborated in vitro and in vivo). Moreover, as for drugs, further studies are required to evaluate the generation of new reaction products and degradants in thymol-derived products and to establish their concentration, potential allergenicity, and toxicity.

Finally, the human metabolism of thymol released sulfate and glucuronide metabolites. Moreover, other metabolites have been identified in rats. Concerning the distribution of thymol, it may reach different tissues at different levels. Moreover, thymol and its metabolites have also been detected in animal food products. However, it is not clear whether these metabolites are active, vehicles of thymol or simply inactive, neither for humans nor animals.

ACKNOWLEDGEMENT

The authors would like to thank Universidad de Jaén (postdoctoral grant funded by the "Acción 6 del Plan de Apoyo a la Investigación de la Universidad de Jaén, 2017-2019").

CONFLICT OF INTEREST

There is no conflict interest.

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How to cite this article: Salehi B, Mishra AP, Shukla I, et al. Thymol, thyme, and other plant sources: Health and potential uses. *Phytotherapy Research*. 2018;32:1688–1706. https://doi.org/10.1002/ptr.6109