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A Review of the Chemical Composition of Essential Oils of Thymus Species in Iran

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ABSTRACT

The genus Thymus from the Lamiaceae family has more than 300 species distributed worldwide, including in Europe and Asia. 18 Thymus species have been identified in Iran's flora, of which 4 are endemic to Iran. Thymus species are known as medicinal plants due to their biological and medicinal properties. Thyme has many biological activities, including antimicrobial, antioxidant and anti-inflammatory effects. Therefore, Thymus species interest many pharmaceutical, food and cosmetic industries. Throughout the evolution of plants, essential oils have played a crucial part in the direct and indirect defenses of plants against possible predators and pathogens, as well as in the processes of plant reproduction by attracting pollinators and disseminators to the seeds The present study was conducted to investigate the chemical composition of essential oils of Thymus species in Iran. The information and findings in this review were obtained from scientific databases and search engines, including Web of Knowledge, PubMed, ScienceDirect, Medline, Reaxys and Google Scholar. In this research, we investigated different species of Thymus collected wild and cultivated in different parts of Iran. The results showed that the main composition of thyme included thymol, carvacrol, geraniol, γ-terpinene and linalool. The conclusion of this review shows that plant compounds are a promising source of bioactive compounds that can be explored for development against diseases and complications associated with its chemical drugs.

Keywords: Thymus species, Chemical composition, Essential oils, Thymol, carvacrol, Antimicrobial activity

INTRODUCTION

Thymus belongs to the family Lamiaceae, subfamily Nepetoideae, tribe Mentheae, subtribe Menthinae and genus Thymus (Morales 1997, Pedersen 2000). There are 300–400 perennial aromatic, evergreen or semi-evergreen herbaceous plant species in this genus, along with several subspecies, variations, subvarieties, hybrids, and ecotypes. This genus is distributed worldwide, from North Africa, Europe and Asia (Stahl-Biskup 2002). Nevertheless, this genus' core region is located around the Mediterranean Sea. Due to their heliophylous nature, Thymus plants grow in climates with moderate to warm temperatures, well-drained to dry soils (usually they grow on rocks, stones, or sand), and sunny places (Ghasemi Pirbalouti, Emami Bistghani *et al.* 2015). Thymus genus is divided into 36 sub-species and eight sections by (Jalas 1971) and (Morales 1997) including Micantes, Masticina, Piperella, Teucrioides, Pseudothymbra, Thymus, Hyphodromi and Serpyllum. Due to the high population variability in terms of various morphological and micromorphological traits, as well as the composition of secondary compounds, there are significant difficulties in the taxonomical interpretation of the taxa belonging to the genus Thymus. This variability is caused by environmental factors and genetic variation due to frequent hybridization leading to variable chromosome number and expressed gynodioecy, a sexual polymorphism in which natural populations contain two types of plants-females and hermaphrodites. Which makes taxonomic studies in this genus very difficult, especially in some taxonomical groups (Thompson, Manicacci *et al.* 1998, Thompson, Chalchat *et al.* 2003, Dajić-Stevanović, Šoštarić et al. 2008). In Thymus, so far diploid chromosome numbers have been determined: 2n = 28 or 2n = 30. Thymus genus also shows chromosome numbers of a multiple of x = 14 or x = 15 (Stahl-Biskup 2002) Also, the number of chromosomes of Thymus species including 2n=24, 26, 28, 30, 32, 42, 48, 50, 52, 54, 56, 58, 60, 84 and 90 corresponding to the diploid, tetraploid and hexaploid levels have been reported. The primary number of x=15 with different ploidy levels is present in most species. Therefore, Thymus is a complex genus with a various range of chromosome numbers is request more research about this genus (Morales 1980).

Some authors believe the Latin name Thymus derives from the Greek word word "*thyo"* which means "perfume," while others think it derives from the Greek word word "*thymos"* (courage, strength). Thyme's strong preservation properties made it a popular choice among the Egyptians for embalming. Thyme was mainly used as a medicinal herb in the first century AD, according to Dioscorides' writing. It was regarded as an antidote in ancient Rome. Thyme consumption before or during meals offered protection from poisons. Its renown led to it being one of the plants that emperors loved. Later, in 1340, during the Black Death, it was used as the primary component in medical mixtures and ointments applied directly to the blistered skin (Stahl-Biskup 2002, Stahl-Biskup and Venskutonis 2012).

The biological and pharmacological properties of Thymus species have earned them the reputation of being medicinal plants. Thymus is a rich source of phytonutrients, essential minerals, and vitamins. These nutrients known the advantages of this plant by having a properties for being disease-preventing and health-improving. Vitamins A, B (primarily vitamin B6 pyridoxine), C, E, and K are particularly abundant in the Thymus. Additionally, it includes minerals including magnesium, calcium, manganese, potassium, and iron (Dauqan and Abdullah 2017). Thymus is widely used fresh and dried. In traditional medicine, leaves and flowering branches of Thymus species are used as powder, boiled or infused to treat various diseases such as antiseptic effects (antimicrobial, antifungal, antiviral, antibacterial, anthelmintic, insecticide, antiparasitic), respiratory diseases (anti-cough, whooping cough, cold, bronchitis, asthma, sore throat, expectorant), digestive diseases (diarrhea, nausea, flatulence, indigestion, stomach ache, hepatoprotective), skin diseases (treatment of wounds, prevent hair loss and acne outbreaks) and other diseases such as anti-spasmodic, antioxidant, anti-inflammatory, antirheumatic, antihypertensive, antihyperlipidemic, hypoglycemic, arthritis, colic, diuretic, enuresis in children, astringent, menstrual and menopausal problems, hangover, analgesic, strengthening memory and concentration as well as calming the nerves. Thymus oils and extracts today are widely used in the food sector for flavoring and food preservation, as well as in the medicinal, cosmetic, and perfume industries (Zargari 1990, Newall, Anderson *et al.* 1996, Duke 2002, Ardalani, Hadipanah *et al*. 2020). The present study was conducted to investigate the chemical composition of essential oils of Thymus species in different parts of Iran.

MATERIALS AND METHODS

The information and findings in this review were obtained from scientific databases and search engines, including Web of Knowledge, PubMed, ScienceDirect, Medline, Reaxys and Google Scholar.

Thymus, with the common Persian name of "Avishan or Azorbe", consists of 18 species that are found wild in many regions of Iran, including: *Thymus armeniacus* Klokov and Des.-Shost, *T. caramanicus* Jalas, *T. caucasicus* Willd, *T. daenensis* Celak, *T. eriocalyx* (Ronniger) Jalas, *T. fallax* Fisch.et C.A. Mey, *T. fedtschenkoi* Ronniger, *T. kotschyanus* Boiss. & Hohen, *T. lancifolius* Celak, *T. linearis* Benth, *T. migricus* Klokov & Desj.-Shost, *T. marandensis* Jamzad, *T. nummularius* M. Bieb, *T. persicus* (Ronniger ex Rech.f.) Jalas, *T. pubescens* Boiss. & Kotschy ex Celak, *T. transcaspicus* Klokov, *T. transcaucasicus* Ronniger, *T. trautvetteri* Klokov & Desj.-Shost (Jamzad 2009, Jamzad and Asadī 2012). Among them, 4 species include *Thymus persicus* with the Persian name (Avishan-e-Persian), *T. caramanicus* (Avishan-e-Kermani), *T. trautvetteri* (Avishan-e-Talashi) and *T. daenensis* (Avishan-e-denaee) with two subspecies *T. daenensis* subsp. *daenensis* and *T. daenensis* subsp. *lancifolius* are endemic to Iran (Mozaffarian 2008, Ghasemi Pirbalouti, Emami Bistghani *et al*. 2015).

In Tables 1 and 2, the scientific names of Thymus species, the amount of essential oil, chemical compounds, organs used, collection in wild and cultivated region have been investigated.

Thymus persicus (Avishan-e-Persian or Persian thyme) is well distinguished among other species of Thymus by having narrow linear leaves with long non-glandular hairs and short single-celled glandular hairs. This species grows in the provinces of Zanjan and West Azerbaijan (Takab) of Iran (Sefidkon and Askari 2002, Saroukolai, Moharramipour *et al*. 2010).

Thymus caramanicus (Avishan-e-Kermani or Kerman thyme), is a wooden plant, perennial and gray whose stems are woody at the base, wide on the ground or slightly bent. Depending on the climate of the growing region and the quality of the soil, its height will be between 25 and 50 cm, its flowering branches are 3-10 cm high, often with long hairs and almost wide. The leaves of this plant are small, ovoid, almost petiolate and more or less fleshy. The leaves are 6-9.5 mm long and 4-7.2 mm wide with a petiole 1-1.5 mm long, broad ovate or circular oval with a rounded base or a truncate head with an apex. Almost sharp tip, sometimes with short tip, usually with soft hairs (Mozaffarian 2008, Ghasemi Pirbalouti, Emami Bistghani *et al*. 2015).

Thymus trautvetteri (Avishan-e-Talashi) is a perennial plant with petiolate, oval, hairy leaves, leaf width more than 1.5 mm, calyx length 3-4 mm, cup, upper teeth 0.4-0.8 mm, the bract and calyx are green and the calyx is pale, and it is distributed in the provinces of East and West Azerbaijan (Mozaffarian 2008).

Thymus daenensis (Avishan-e-denaee or Denaian thyme) is herbaceous and perennial plant with a maximum height of 30 cm, with short and thick stems completely woody at the bottom. The leaves are opposite and small, oval or ovate, pointed, petioleless and rarely linear, the length of the leaf varies from 5.9 to 16 mm and the width varies from 4.2 to 4 mm. The leaves may be overlapped or shorter than the internodes, the flowers are white, purplish or purple, and are complex next to the leaves, the calyx is tubular to a cup, the teeth of which are about 0.5 mm long in the upper part. The calyx is red and the fruit is ovoid, light brown with a smooth surface. Its distribution in Iran is mainly in high altitude places in the high altitudes in Zagros Mountains range, Alborz Mountains, Tehran, Fars, Kerman, Qazvin, Hamedan, Isfahan and Ilam (Mozaffarian 2008, Golparvar, Ghasemi Pirbalouti *et al*. 2012, Ghasemi Pirbalouti, Emami Bistghani *et al*. 2015).

Table 1. Chemical composition of Thymus species wild growing in Iran

NO	Thymus species	Yields (EO) %	Main Components	Organ	Altitude (M)	Origin	Reference
1.	*Thymus caramanicus* Jalas. (Kerman thyme)	0.60	Carvacrol (49.29-61.05%), thymol (8.72-18.34%), *p*-Cymene (5.19-10.89%)	Aerial parts	2500-3000, 3000-3500	Kuhsha (Kerman Province)	(Ghasemi, Barani *et al*. 2013)
		0.86	Carvacrol (44.11-50.99%), thymol (18.78-19.29%)	Aerial parts	2000-2500	Bardsir (Kerman Province)	
		1.47	Carvacrol (62.37-66.88%), γ-terpinene (5.54-8.56%), thymol (3.21-7.55%)	Aerial parts	2500-3000, 3000-3500	Dehbakri (Kerman Province)	
		0.99	Carvacrol (85.94%), thymol (3.33%), *p*-Cymene (3.16%)	Leaves and flowers/ inflorescences	2100	Kashan (Isfahan Province)	(Safaei-Ghomi, Ebrahimabadi *et al*. 2009)
2.	*Thymus caucasicus* Willd	0.5	1,8-cineol (21.5%), thymol (12.6%), β-fenchyl alcohol	Aerial parts	1850–2300	Ardabil Province	(Asbaghian, Shafaghat *et al*. 2011)

			(8.7%)				
		-	α-Terpineol (8.48%), α-pipene (6.56%)	Aerial parts (full flowering stage)	2122	Asalem-Khalkhal road (Gilan Province)	(Rabiei, Rastjoo *et al*. 2019)
		-	α-pipene (16.99%), 1,8-cineol (13.19%), verbenone (6.58%)	Aerial parts (full flowering stage)	1943	Rostamabad (Gilan Province)	
		-	Octadecanoic acid (6.93%), Borneol-L (4.36%)	Aerial parts (full flowering stage)	2003	Masouleh, Dooley Chal (Gilan Province)	
3.	*Thymus daenensis* Celak. (Denaian thyme) (red thyme)	0.85	Thymol (33.96%), carvacrol (24.78%), *p*-Cymene (8.13%)	Aerial parts (full flowering stage)	2070	Shahrekord (Chaharmahal va Bakhtiari Province)	(Pirbalouti, Hashemi *et al*. 2013)
		-	γ-terpinene (42.35%), thymol (14.18%), α-thujene (10.74%)	Aerial parts	1998	Semirom (Isfahan Province)	(Golparvar, Gheisari *et al*. 2015)
		2.2 to 3.4	Thymol (71.9-73.9%), γ-terpinene (0.9-9.6%), *p*-Cymene (3.3-9%)	Aerial parts (before flowering, floral budding, full flowering, seed set stages)	1840-1850	Hamadan Province	(Mumivand, Shayganfar *et al*. 2021)
			Carvacrol (25.55%), thymol (20.79%), linalool (16.18 %)	Aerial parts	-	Kakan Yasouj (Kohgiluyeh and Boyer-Ahmad Province)	(Jaberi, Moein *et al*. 2015)
		2.53	Thymol (70.6%), γ-terpinene (8.8%), *p*-Cymene (6.1%)	Aerial parts (50% flowering stage)	2000-2300	Qorveh (Kurdistan Province)	(Hasani and Mirza 2018)
		2.0	Thymol (59.40%), carvacrol (7.12%), trans-caryophyllene (5.34%)	Aerial parts (full flowering stage)	-	Kashan (Isfahan Province)	(Mahboubi, Heidarytabar *et al*. 2017)
		2.2	Carvacrol (50.4%), thymol (17.7%), thymol methyl	Aerial parts (full flowering stage)	-	Shahrood (Semnan Province)	

		ether (4.41%)				
T. daenensis ssp. *daenensis*	2.13	Thymol (72.2%), carvacrol (9.2%)	Aerial parts (full flowering stage)	2000	Eghlid (Fars Province)	(Bahreininejad, Mirza *et al*. 2010)
	1.93	Carvacrol (58.9%), geraniol (16.1%)	Aerial parts (full flowering stage)	2500	Sourian (Fars Province)	
	1.4	Carvacrol (80.1%), thymol (3.8%)	Aerial parts (full flowering stage)	2280	Abadeh (Fars Province)	
	1.23	Geraniol (75.7%), geranyl acetate (8.8%)	Aerial parts (full flowering stage)	2170	Yasouj - Shiraz road (Fars Province)	
	2.15	Carvacrol (61.3%), thymol (13.1%)	Aerial parts (full flowering stage)	2190	Shiraz - Isfahan road (Fars Province)	
	1.55	Thymol (53.1%), carvacrol (8.8%)	Aerial parts (full flowering stage)	2570	Sisakht (Kohgiluyeh and Boyer-Ahmad Province)	
	1.35	Carvacrol (47.3%), thymol (12.7%)	Aerial parts (full flowering stage)	2200	Kakan (Kohgiluyeh and Boyer-Ahmad Province)	
	1.53	Thymol (53.9%), p-cymene (10.9%)	Aerial parts (full flowering stage)	2660	Yasouj - Sepidan road (Kohgiluyeh and Boyer-Ahmad Province)	
	1.0	Geraniol (65.6%), thymol (14.6%)	Aerial parts (full flowering stage)	2600	Sepidar (Kohgiluyeh and Boyer-Ahmad Province)	
	2.0	Caervacrol (12.38%), α-terpineol (13.18%), cis-sabinene hydrate (9.2%)	Leaves	1600-2200	Highland of Zagros Mountain (Lorestan Province)	(Sfaei-Ghomi, Meshkatalsadat *et al*. 2009)
	2.4	Thymol (74.7%), *p*-Cymene (6.5%), β-caryophyllene (3.8%)	Aerial parts (flowering stage)	-	Hamadan Province	(Nickavar, Mojab *et al*. 2005)
T. daenensis ssp. *lancifolius*	2.0	Carvacrol (52.3%), thymol	Aerial parts (flowering	-	Lorestan Province	(Amiri 2012)

			(16.4%), γ-terpinene (10.8%)	stage)			
4.	*Thymus eriocalyx* (Ronniger) Jalas.	1.5	Thymol (42.6%), carvacrol (32.3%), *p*-Cymene (4.1%)	Aerial parts (flowering stage)	-	Lorestan Province	
		1.3	Thymol (66.34%), 1-borneol (10.46%), carvacrol (7.5%)	Leaves	1600-2200	Highland of Zagros Mountain (Lorestan Province)	(Sfaei-Ghomi, Meshkatalsadat *et al*. 2009)
		1.79	Thymol (58.4%), linalool (7.3%)	Aerial parts (full flowering stage)	1850-1900	Kamyaran-Sanandaj Road (Kordestan Province)	(Sefidkon, Kalvandi *et al*. 2005)
		0.61	Linalool (60.4%), (E)-β-Ocimene (5.5%)	Aerial parts (full flowering stage)	1650-1750	Saghez (Kordestan Province)	
		1.42	Linalool (19%), thymol (14%)	Aerial parts (full flowering stage)	2010-2300	Songhor, Dalakhani Mountain (Kermansha h Province)	
		2.15	Thymol (40.5%), linalool (12.2%)	Aerial parts (full flowering stage)	2300-2500	Arak, Absar Mountain (MarKazi Province)	
		2.48	Geraniol (50.5%), geranyl acetate (26.6%), linalool (6.1%)	Aerial parts (full flowering stage)	1800-1850	Khan Ghormaz Mountain (Hamedan Province)	
5.	*Thymus fallax* Fisch.et C.A. Mey.	2.5	Carvacrol (69.2%), *p*-Cymene (15.4%), thymol (5.3%)	Aerial parts	3520	Alvand Mountains (Hamedan Province)	(Rustaiee, Sefidkon *et al*. 2011)
		2.62	α-terpineol (26.3%), geraniol (20.6%), 1,8-cineole (7.6%)	Aerial parts (50% flowering stage)	1750-1850	Saqez (Kurdistan Province)	(Hasani and Mirza 2018)
		1.16	Thymol (39.3%), *p*-Cymene (12.9%), γ-terpinene (11%)	Aerial parts (flowering stage)	2000	Zagheh (Lorestan Province)	(Mohammadian, Karamian *et al*. 2014)
		1.15	Thymol (29.7%), caryophyllene oxide (11.8%), bicyclogermacren e (8.9%)	Aerial parts (flowering stage)	1800	Alashtar (Lorestan Province)	
		1.56	Thymol (47.1%),	Aerial parts	2200	Razan	

			γ-terpinene (9.7%), *p*-Cymene (7.1%)	(flowering stage)		(Lorestan Province)	
		2.76	Thymol (48%), γ-terpinene (11.5%), *p*-Cymene (7%)	Aerial parts (flowering stage)	2500	Rhimeleh (Lorestan Province)	
6.	*Thymus fedtschenkoi* Ronniger. (Sweet thyme)	0.8	Thymol (50.61%), *p*-Cymene (7.69%), carvacrol (6.58%)	Aerial parts (full flowering stage)	-	Semnan Province	(Mahboubi, Heidarytabar *et al*. 2017)
		1.31	Thymol (62.1%), γ-terpinene (6.5%)	Aerial parts (50% flowering stage)	1650-1850	Saqez (Kurdistan Province)	(Hasani and Mirza 2018)
		-	Camphene (21.78%), α-terpineol (17.87%), linalool-L (6.66%)	Aerial parts (full flowering stage)	1546	Deylaman (Gilan Province)	(Rabiei, Rastjoo *et al*. 2019)
		-	Thymol (14.12%), α-terpineol (11.5%), eicosane (9.84%)	Aerial parts (full flowering stage)	509	Manjil, Aliabad (Gilan Province)	
		0.7 to 2.9	Linalool (45.5-83.1%), α-terpineol (1.0-7.6%), (E)-caryophyllene (0.9-36.2%)	Aerial parts (vegetative, floral budding, full flowering, seed set stages)	2430-2440	Arak (MarKazi Province)	(Mumivand, Shayganfar *et al*. 2021)
7.	*Thymus kotschyanus* Boiss. & Hohen.	2.11	Thymol (39.7%), γ-terpinene (11.4%), carvacrol (7.6%)	Aerial parts (flowering stage)	-	Lorestan Province	(Amiri 2012)
		0.9	Carvacrol (24.4%), *β*-caryophyllene (14.5%), γ-terpinene (12.4%)	Aerial parts	1850–2300	Ardabil Province	(Asbaghian, Shafaghat *et al*. 2011)
		0.28 to 2.1	Carvacrol (40.7-41.4%), thymol (19.5-26.9%), γ-terpinene (7.3-10.3%)	Aerial parts (before flowering and full flowering stage)	-	Sirachal (Mazandaran Province)	(Sefidkon and Askari 2002)
		1.05	1,8-cineole (24.1%), cis-sabinen hydrate (20.9%), α-terpinene	Aerial parts (50% flowering stage)	1900-2200	Saqez (Kurdistan Province)	(Hasani and Mirza 2018)

			(14.1%)				
		1.2	Thymol (38.6%), carvacrol (33.9%), γ-terpinene (8.2%)	Aerial parts (Stages flowering)	-	Hamadan Province	(Nickavar, Mojab *et al*. 2005)
		0.68	Thymol (39.8%), geraniol (14.4%), 1,8-cineol (5.2%)	Aerial parts (full flowering stage)	-	Semnan Province	(Mahboubi, Heidarytabar *et al*. 2017)
		1.0	Linalool (31.1%), carvacrol (14.3%), thymol (13.1%)	Aerial parts (full flowering stage)	-	Yazd Province	
		1.1	Thymol (61.2%), carvacrol (5.4%), *p*-Cymene (5.3%)	Aerial parts (full flowering stage)	-	Shahrood (Semnan Province)	
	T. kotschyanus var. *kotschyanus*	0.93	Thymol (89.08%), γ-terpinene (4.62%)	Aerial parts	1200	Firouzkouh Road, Gadouk (Tehran Province)	(Mazooji, Salimpur *et al*. 2012)
	T. kotschyanus var. *pseuderiophorus* Rech. f. p. p.	0.27 to 0.82	Carvacrol (69.5-71.3%), borneol (4.8-11.8%), *p*-Cymene (2.2-7.3%)	Leaves, stems, roots	-	Firoozkooh (Tehran Province)	(Aberoomand Azar, Saber-Tehrani *et al*. 2010)
8.	*Thymus lancifolius* Celak.	-	Carvacrol (25.55%), thymol (20.79%), linalool (16.8%)	Aerial parts	-	Moorgol Peak Yasouj (Kohgiluyeh and Boyer-Ahmad Province)	(Jaberi, Moein *et al*. 2015)
9.	*Thymus migricus* Klokov & Desj.-Shost. (Azerbaijan thyme)	1.1	Thymol (64.9%), γ-terpinene (9.3%)	Aerial parts (flowering stage)	1900	Heris (East Azerbaijan Province)	(Yavari, Nazeri *et al*. 2010)
		3.3	Thymol (72.5%), γ-terpinene (8.5%)	Aerial parts (flowering stage)	736	Jolfa (East Azerbaijan Province)	
		1.5	Thymol (55.6%), γ-terpinene (16.7%)	Aerial parts (flowering stage)	1800	Ghushchi (West Azerbaijan Province)	
		1.8	Thymol (70.5%), γ-terpinene (7.5%)	Aerial parts (flowering stage)	1330	Nazloo (West Azerbaijan Province)	
		1.4	Thymol (46.6%), γ-terpinene (6.2%)	Aerial parts (flowering stage)	1316	Band (West Azerbaijan Province)	
10.	*Thymus persicus* (Ronniger ex Rech.f.) Jalas.	-	Carvacrol (44.69%), thymol (11.05%),	Leaves and flowers	2200	Highland of Zagros Mountain	(Saroukolai, Moharramipour *et al*. 2010)

			terpinen-4-ol (8.12%)			(Lorestan Province)	
		026 to 0.43	Carvacrol (27.1-39.0%), geraniol (9.4-15.7%), thymol (6.5-11.9%)	Aerial parts (before flowering and full flowering stage)	-	Manehshan (Zanjan Province)	(Sefidkon and Askari 2002)
11.	*Thymus pubescens* Boiss. & Kotschy ex Celak.	0.68	Carvacrol (27.02%), thymol (26.58%), linalool (8.42%)	Aerial parts (full flowering stage)	-	Semnan Province	(Mahboubi, Heidarytabar *et al*. 2017)
		0.55 to 1.45	Carvacrol (48.8-64.8%), thymol (11.9-13.9%)	Aerial parts (before flowering and full flowering stage)	-	Firoozkooh (Tehran Province)	(Sefidkon and Askari 2002)
		1.3	Thymol (65.6%), *p*-Cymene (7.2%)	Aerial parts (flowering stage)	1621	Malekan (Egdelou) (East Azerbaijan Province)	(Imani, Haghighi *et al*. 2015)
		1.3	Thymol (57.8%), α-terpinyl acetate (9.4%)	Aerial parts (flowering stage)	1685	Kaleibar, Yuzband (East Azerbaijan Province)	
		0.6	Thymol (27.6%), carvacrol (25.4%), geraniol (13.6%)	Aerial parts (flowering stage)	2098	Maraghe, Kordedeh (East Azerbaijan Province)	
		0.3	Thymol (30.9%), thymyl acetate (13.5%), methyl ether thymol (10.6%)	Aerial parts (flowering stage)	2766	Sahand (East Azerbaijan Province)	
		1.2	Carvacrol (82.1%), γ-terpinene (6.2%)	Aerial parts (flowering stage)	1986	Mishoo Mountain (East Azerbaijan Province)	
		2.83	Linalool (28.3%), thymol (27.8%), geraniol (16.4%)	Aerial parts (50% flowering stage)	1950-2200	Bijar (Kurdistan Province)	(Hasani and Mirza 2018)
		-	α-Terpineol (24.11%), terpinene-4 (11.18%), linalool-L (8.87%)	Aerial parts (full flowering stage)	1651	Deylaman, Spili (Gilan Province)	(Rabiei, Rastjoo *et al*. 2019)
			α-Terpineol (18.21%),	Aerial parts (full	1396	Deylaman, Asiabar road	

		terpinene-4 (12.67%), linalool-L (9.13%)	flowering stage)		(Gilan Province)	
		Geraniol (11.5%), terpinene-4 (8.17%)	Aerial parts (full flowering stage)	1014	Lowshan, Jyrdeh road (Gilan Province)	
		α-Terpineol (22.13%), geraniol (13.23%), borneol-L (7.96%)	Aerial parts (full flowering stage)	996	Lowshan, Jyrdeh (Gilan Province)	
	1.3	Thymol (57.6%), γ-terpinene (12.9%)	Aerial parts (flowering stage)	1710	Bostan-Abad (East Azerbaijan Province)	(Yavari, Nazeri *et al.* 2011)
	2.2	Thymol (44.9%), geraniol (10.8%), γ-terpinene (10.3%)	Aerial parts (flowering stage)	1550	Yam (East Azerbaijan Province)	
12. *Thymus transcaspicus* Klokov. (Khorasan thyme)	-	Carvacrol (47.4%), borneol (7.1%)	Aerial parts (flowerheads and leaves)	2048	Reiin, Aladagh Mountain (North Khorasan Province)	(Tabrizi, Koocheki *et al.* 2010)
	-	Thymol (54.3%), carvacrol (8.4%)	Aerial parts (flowerheads and leaves)	2032	Pakotal, Aladagh Mountain (North Khorasan Province)	
	-	Thymol (45.4%), carvacrol (13.2%), α-terpinene (10.1%)	Aerial parts (flowerheads and leaves)	1800	Laeen Kohneh, Hezar-masjed Mountain (Razavi Khorasan Province)	
	2.3	Thymol (45%), carvacrol (13.3%), α-terpinene (9.8%)	Aerial parts (flowerheads and leaves)	2300	Tiwan, Hezar-masjed Mountain (Razavi Khorasan Province)	
13. *Thymus transcaucasicus* Ronniger.	1.51	Linalool (68.4%), geranyl acetate (4.6%)	Aerial parts (50% flowering stage)	1900-2400	Sanandaj (Kurdistan Province)	(Hasani and Mirza 2018)

14.	*Thymus trautvetteri* Klokov & Desj.-Shost.	-	Thymol (24.43%), borneol (11.36%), *p*-Cymene (10.09%)	Aerial parts	1950	Ardabil Province	(Shahnazi, Khalighi-Sigaroodi *et al*. 2007)

Table 2.Chemical composition of Thymus species cultivated in Iran

NO	Thymus species	Yields (EO) %	Main Components	Organ	Altitude (M)	Origin	Reference
1.	*Thymus armeniacus* Klokov and Des.-Shost.	1.16 to 1.18	γ-terpinene (16.65-23.58%), *p*-Cymene (6.70-16.56%), α-pinene (12.16-15.78%)	Aerial parts (50 and 100% blooming Stages)	-	Shahrekord (Chaharmahal va Bakhtiari Province)	(Yousefzadeh, Houshmand *et al*. 2022)
2.	*Thymus carnosus* Boiss.	0.66 to 0.86	Thymol (27.2- 36.1%), *p*-Cymene (21.3-26.2%), γ-terpinene (19.1- 19.6%)	Aerial parts (before flowering and full flowering stage)	-	National Botanical Garden of Iran	(Sefidkon and Askari 2002)
3.	*Thymus daenensis* Celak. (Denaian thyme)	1.16	Thymol (67.77%), carvacrol (6.73%), γ-terpinene (5.23%)	Aerial parts (full flowering stage)	2070	Shahrekord (Chaharmahal va Bakhtiari Province)	(Pirbalouti, Hashemi *et al*. 2013)
		1.01	Thymol (55.87%), γ-terpinene (10.41%), *p*-Cymene (8.63%)	Aerial parts (full flowering stage)	2297	Kiyar (Chaharmahal va Bakhtiari Province)	
		0.97	Thymol (70.33%), γ-terpinene (8.03%), *p*-Cymene (6.57%)	Aerial parts (full flowering stage)	1890	Saman (Chaharmahal va Bakhtiari Province)	
		0.97	Thymol (66.43%), *p*-Cymene (5.23%)	Aerial parts (full flowering stage)	1600	Flavarjan (Isfahan Province)	
		0.99 to 1.4	Thymol (49.86-84.1%), γ-terpinene (2.24-11.2%)	Aerial parts (before flowering, beginning of flowering, 50% flowering, full flowering,	1550	Khorasgan (Isfahan Province)	(Golparvar, Hadipanah *et al*. 2015)

				seed set stages)			
		0.45	Thymol (71.2%), γ-terpinene (8.81%), *p*-Cymene (3.8%)	Aerial parts (beginning of flowering stage)	1700	Estahban (Fars Province)	(Hadipanah and Khorami 2016)
4.	*Thymus eriocalyx*	1.2	Thymol (63.8 %), β-phellandrene (13.30%), *cis*-sabinene hydroxide (8.1 %)	Aerial parts	-	National Botanical Garden of Iran	(Rasooli, Rezaei *et al*. 2006)
5.	*Thymus kotschyanus* Boiss. & Hohen.		γ-terpinene (17.69-28.11%), thymol (11.41-15.73%), *p*-Cymene (4.18-17.78%),	Aerial parts (50 and 100% flowering Stages)	-	Shahrekord (Chaharmahal va Bakhtiari Province)	(Yousefzadeh, Houshmand *et al*. 2022)
6.	*Thymus serpyllum* L. (Wild thyme)	0.57 to 0.9	*p*-Cymene (20.7-21.1%), γ-terpinene (21.9-22.7%), thymol (18.7%)	Aerial parts (before flowering and full flowering stage)	-	National Botanical Garden of Iran	(Sefidkon and Askari 2002)
7.	*Thymus transcaspicus* Klokov. (Khorasan thyme)	1.06 to 1.53	Thymol (73.73-8026%), carvacrol (7.88-12.02%)	Aerial parts (beginning of flowering, 50% flowering, 100% flowering stages)	1050	Bojnord (North Khorasan Province)	(Garivani, Sharifiashoorabadi *et al*. 2014)
		3.7	Carvacrol (81.5%), *p*-Cymene (6.9%)	Aerial parts (50% flowering stage)	1210	Shahediyeh (Yazd Province)	(Zarezadeh, Mirhossaini *et al*. 2014)
8.	*Thymus transcaucasicus* Ronniger.	1.6	Thymol (53.7%), *p*-Cymene (11.7%), carvacrol (8.3%)	Aerial parts (50% flowering stage)	1210	Shahediyeh (Yazd Province)	
9.	*Thymus vulgaris* L. (Thyme or Garden thyme)	0.82	Thymol (43.0%), *p*-Cymene (14.73%), γ-terpinene (10.47%)	Aerial parts (full flowering stage)	2070	Shahrekord (Chaharmahal va Bakhtiari Province)	(Pirbalouti, Hashemi *et al*. 2013)
		0.81	Thymol (44.41%), *p*-Cymene (16.13%), γ-terpinene (10.53%)	Aerial parts (full flowering stage)	2297	Kiyar (Chaharmahal va Bakhtiari Province)	

		0.75	Thymol (35.51%), γ-terpinene (11.87%), *p*-Cymene (8.47%)	Aerial parts (full flowering stage)	1890	Saman (Chaharmahal va Bakhtiari Province)	
		1.1	Thymol (43.8%), *p*-Cymene (15.2%), germacrene-D (11.7%)	Aerial parts	1850–2300	Ardabil Province	(Asbaghian, Shafaghat *et al*. 2011)
		1.16 to 1.7	Thymol (68.71-78.24%), *p*-Cymene (5.03-8.55%), γ-terpinene (1.82-8.89%)	Aerial parts (beginning of flowering, 50% flowering, 100% flowering stages)	1050	Bojnord (North Khorasan Province)	(Garivani, Sharifiashoorabadi *et al*. 2014)
		0.17	Thymol (63.14%), *p*-Cymene (9.45%), γ-terpinene (8.67%)	Aerial parts (beginning of blooming stage)	1700	Estahban (Fars Province)	(Hadipanah and Khorami 2016)
		2.0	Thymol (43.3%), carvacrol (11.5%), *p*-Cymene (11.4%)	Aerial parts (full flowering stage)	-	Yazd province	(Mahboubi, Heidarytabar *et al.* 2017)
		2.3	Carvacrol (62.5%), *p*-Cymene (9%), α-copaene (6.0%)	Aerial parts (full flowering stage)	-	Shahrood (Semnan Province)	
		2.1	Thymol (74.5%), *p*-Cymene (7.5%), γ-terpinene (5.5%)	Aerial parts (full flowering stage)	-	Kashan (Isfahan Province)	
10.	*Thymus x-porlock*	1.0	β-phellandrene (38.7%), thymol (31.7%), *cis*-sabinene hydroxide (9.6%)	Aerial parts	-	National Botanical Garden of Iran	(Rasooli, Rezaei *et al*. 2006)
11.	*Thymus × citriodorus* (Pers.) Schreb. Hybrid between (*T. vulgaris × T. pulegioides*) (Lemon thyme)	1.45 to 2.21	Geraniol (54.2-72.5 %), geranial (3.2-11.9%)	Aerial parts (before flowering, beginning of flowering, full flowering, fruit set stages)	-	Tehran Province	(Omidbaigi, Fattahi *et al*. 2009)

GLANDULAR TRICHOMES

Numerous glandular hairs of various shapes and sizes, which contain volatile essential oils that evaporate when the glandular hairs are damaged, are characteristic of Thymus and other fragrant plants. These protuberances can take on a wide range of sizes and forms, with cellular composition varies substantially between species (Guesmi, Saidi *et al*. 2019). Most plant species have hair-like epidermal structures below and/or above ground. When present on the aerial parts, they are usually referred to as trichomes, which is derived from the Greek word "*trichos*", meaning hair. Trichomes can be made of one or more cells and are extensions of the epidermis that come from epidermal cells. They can be various shapes and sizes, from a few micrometres to several centimetres (Schuurink and Tissier 2020).

The Lamiaceae family uses different structures in their plant organs, like glandular trichomes, to biosynthesize and store their essential oils. Glandular trichomes consist of secretory cells covered by a subcuticular storage cavity where the essential oil accumulates (Turner, Gershenzon *et al*. 1999). As the biosynthetically active location of several significant natural compounds in various plant species, these glandular trichomes serve a crucial role in plant growth and development. They are able to synthesize, store, and/or secrete a variety of natural compounds (Majdi, Malekzadeh-Mashhady *et al*. 2017).

In general, glandular trichomes are multicellular and comprise a differentiated base (of one or more cells) that connects the stalk to the surrounding epidermal cells, a head or gland (unicellular or multicellular) that secretes specialised metabolites, and a stalk (unicellular or multicellular) that supports the head (Feng, Bartholomew *et al*. 2021). Thymus species have been shown to contain these types of cells. These basal cells have been seen to function differently than ordinary epidermis cells, acting as a glandular hair accessory and contributing to the secretion of volatile oils. The size, shape, distribution, vacuolization, the pericline walls plasmodesm density, of these cells probably contribute to collecting the photosynthesis products in the mesophyll and to their transport to the basal cells of the glandular hairs. Through the stalk cells, these products will then get to the glandular hair's head, where they work with the "enzymatic machine" of the secretory cells to contribute to the production of volatile oil (Boz, Burzo *et al*. 2014).

There are two types of glandular trichomes called peltate and capitate on the surface of aerial vegetative organs of Lamiaceae family members (Guesmi, Saidi *et al*. 2019). Peltate trichomes of the Lamiaceae are usually composed of several secretory head-cells (up to 16), a wide short stalk, and one basal epidermal cell. It has been demonstrated that the Lamiaceae's peltate glands are the primary location of monoterpene and sesquiterpene chemical biosynthesis (Dajić-Stevanović, Šoštarić *et al*. 2008). Volatile compounds are usually stored in a compartment within peltate trichomes that allows for their retention in a liquid form; they are only released when the trichomes are damaged. (e.g. upon herbivory). This region, which can be subcuticular and occurs in Lamiaceae between the secretory cells and the cuticle (Turner, Gershenzon *et al*. 2000). Whereas capitate trichomes typically consist of a multicellular stalk of variable cell number and length with a smaller unicellular head. Which are usually much smaller than peltate trichomes and have a limited storage capacity and secrete mainly a complex mixture of carbohydrates, lipids, proteins, non-volatile and frequently sticky resinous substances, such as acylsugars or certain diterpenoids (Werker 1993, Dajić-Stevanović, Šoštarić *et al*. 2008). Thymol and carvacrol are found in the aerial parts of Thymus, and it has been suggested that thymol is produced in the glandular secretory trichomes of the Thymus species and stored in the subcuticular space of the trichomes. Thymus monoterpenes, which are accumulated in essential oil glands on the surface of the leaves, are broken by contact of herbivores and rubbing the surface of the leaves (Majdi, Malekzadeh-Mashhady *et al*. 2017).

SYNTHESIS OF THYME MONOTERPENES

In higher plants, more than 23,000 terpene structures have been found (Pavela and Benelli 2016, Trindade, Pedro *et al*. 2018). The terpenes or isopropenoids are secondary metabolites present in essential oils. They come from the five-carbon atom compound isoprene or 2-methyl-1,3-butadiene. Hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), and tetraterpenes (C40) are the different types of terpenes based on the number of carbon atoms in each. Terpenoids can have cyclic or acyclic structures depending on how isoprenoid chain reactions affect them, such as through ring breaks or rearrangements, cyclization, reduction, oxidation. Monoterpenes and sesquiterpenes are the most common components of essential oils. Terpenes may present various organic functions, such as hydrocarbons, alcohols, ketones, ethers, esters, carboxylic acids and aldehydes (Chappell 1995, Dewick 2002).

Mevalonic acid (MAV), which is found in the cytosol and produces sesquiterpenes and triterpenes, and methylerythritol phosphate (MEP), which is found in the plastid and produces hemiterpenes, monoterpenes, diterpenes, and tetraterpenes, are the two pathways through which terpenoids are produced (Kuzuyama 2002). The biosynthetic pathway of thymol and carvacrol (phenolic monoterpenes) is condensed from a two-carbon unit of pyruvate with glycerol aldehyde 3-phosphate (C2) by the enzyme 1-deoxy-D-xylulose 5-phosphate synthase (DXS) it produces 1-deoxy- D-xylulose 5-phosphate (DXP) (C3), and DXP by the enzyme DXP reductoisomerase (1-deoxy-D-xylulose 5-phosphate reductoisomerase or DXR) it irreversibly produces (MEP). This step is described as the first committed step in the MEP pathway. Further on, it causes the synthesis of isopentenyl pyrophosphate (IPP) (Fig 1). In the synthesis path of thymol and carvacrol from the condensation of (C5) units (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP), which are derived from the MEP pathway. In most of the cases, the joining of two initial five-carbon compounds happens so that the head (DMAPP) is connected to the terminal tail (IPP) (head-to-tail connection) by the enzyme geranyl diphosphate synthase (GDS) and cause the synthesis of geranyl diphosphate (GDP) (Fig 2). GDP is the precursor of all monoterpenes. GDP then produces the α-terpinyl cation, a highly unstable intermediate that can be converted to specific monoterpenes by terpinene synthase (TPS) enzymes. Therefore, γ-terpinene and *p*-cymene are synthesized by the enzyme γ-terpinene synthase (Tps2) (Dudareva, Andersson *et al*. 2005, Lima, Schimmel *et al*. 2013, Tohidi, Rahimmalek *et al*. 2020, Kianersi, Pour-Aboughadareh *et al*. 2021).

γ-terpinene is oxidized by cytochrome P450 monooxygenases (P450s) of the CYP71D subfamily to produce unstable cyclohexadienol intermediates, which are then dehydrogenated by a short-chain dehydrogenase/reductase (SDR) to the corresponding ketones. The subsequent formation of the aromatic compounds occurs via keto–enol tautomerisms, and these are the precursors of the monoterpenes thymol and carvacrol. The formation of thymol and carvacrol is done through the hydroxylation of γ-terpinene at the 3- (to thymol) or 6- (to carvacrol) position. In the absence of the SDRs, only p-cymene was formed by rearrangement of the cyclohexadienol intermediates (Krause, Liao *et al*. 2021). Subsequently, γ-terpinene synthase which is a member of the monoterpene synthase family produces γ-terpinene through cyclization of GDP. Furthermore, enzymes such as CYP71D178, CYP71D180 and CYP71D181 belonging to the cytochrome P450 (CYP) monooxygenases are also involved in further modifications of γ-terpinene backbone to yield thymol and carvacrol. Thymol is exclusively produced via CYP71D178 while carvacrol is biosynthesized via CYP71D178, CYP71D 180 and CYP71D181 (Kianersi, Pour-Aboughadareh *et al*. 2021).

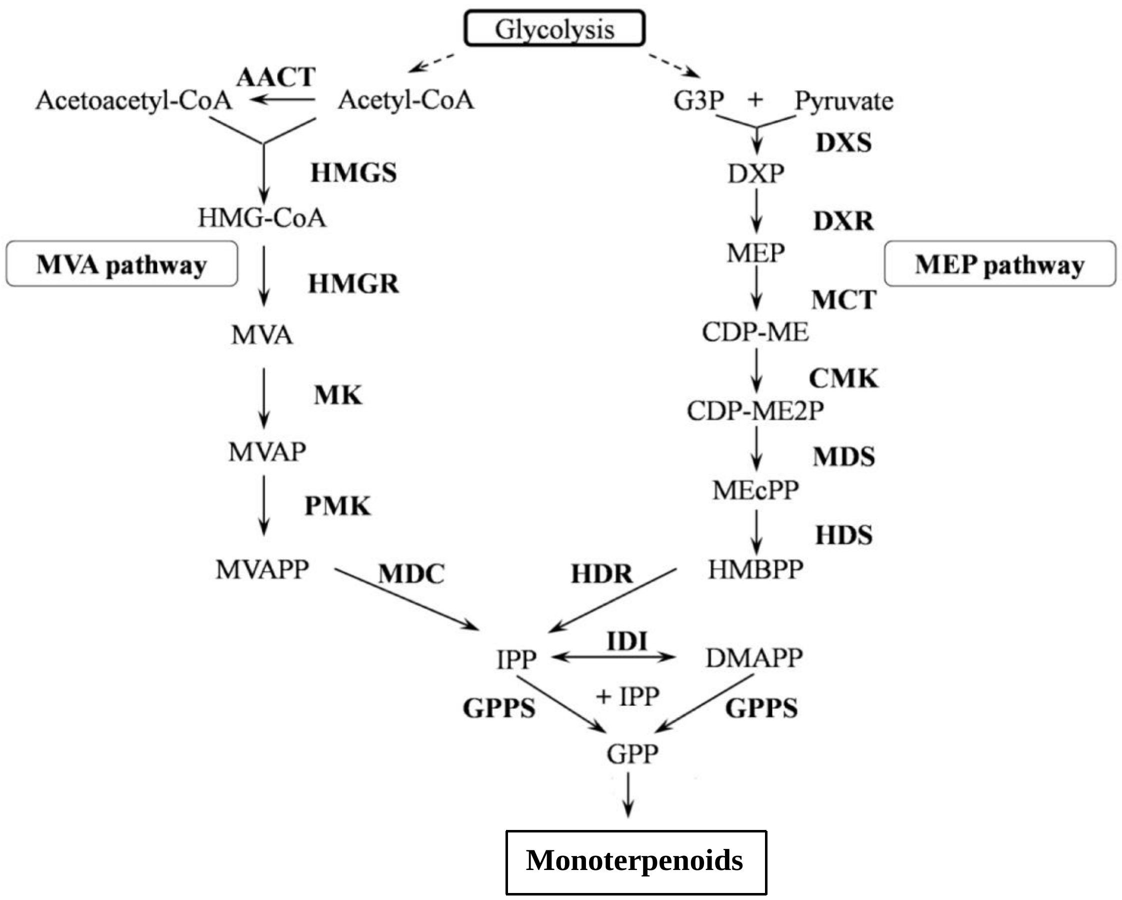

Figure 1. Biosynthesis of monoterpenoids; There are two biosynthetic pathways, the mevalonate (MVA) pathway and the MEP/ DOXP pathway

Abbreviations: 1-deoxy- D-xylulose 5-phosphate synthase (DXS), 1-deoxy-D-xylulose 5-phosphate (DXP), 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR), 2-C-methyl-D-erythritol 4-phosphate (MEP), mevalonic acid (MAV), 5-phosphomevalonate (MVAP), 5-diphosphomevalonate (MVAPP), dimethylallyl pyrophosphate (DMAPP), isopentenyl pyrophosphate (IPP), geranyl diphosphate (GDP) or geranyl pyrophosphate (GPP), 4-(cytidine 5'-diphospho)-2-C-methyl-D-erythritol (CDP-ME), 2-C-methyl-D-erythritol 2,4-cyclodiphosphate (MEcPP), 1-hydroxy-2-methyl-2-butenyl 4-diphosphate (HMBPP), 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGR), Mevalonate kinase (MK), Phosphomevalonate kinase (PMK), 4-hydroxy-3-methylbut-2-enyl diphosphate reductase (HDR), 4-hydroxy-3-methylbut-2-en-1-yl diphosphate synthase (HDS).

Typically, the ABC transporter carries out the transport of thyme monoterpenes (Lv, Li *et al*. 2016). Also, two P450s from the CYP76S and CYP736A subfamilies were found that catalyze the hydroxylation of thymol and carvacrol to thymohydroquinone when heterologously expressed in yeast and *Nicotiana benthamiana* (Krause, Liao *et al*. 2021). Thymus monoterpenes are classified into two groups: phenolic (thymol and carvacrol) and nonphenolic (geraniol, α-terpineol, linalool and *trans*-thujan-4-ol/terpinen-4-ol) (Thompson, Chalchat *et al*. 2003).

The amount of essential oil and essential oil compounds such as thymol and carvacrol are influenced by various factors such as plant species, cultivars, clones and ecotypes, geographical origin, weather conditions, geobotanical conditions (soil, light, humidity, altitude), cultivation method (planting time, planting density, fertilizers, pesticides), types of stress (salinity, heat, water, drought, ultraviolet radiation), time of plant collection, storage method of plant material (fresh, dry, etc), extraction method It depends on the essential oil (distillation, soaking, pressing, extraction with or without solvent), the age of the plant, wounds or herbivore and microbial attack, genetic changes, etc. For this reason, wild and cultivated plants of the same species, but from different contexts can express different features and chemical compositions (Hadipanah, Golparvar *et al*. 2011, Golparvar and Hadipanah 2013, Salehi, Golparvar *et al*. 2014, Golparvar, Hadipanah *et al*. 2015).

It was established that the production of phenolic compounds is higher in warmer and drier climatic zones while other, nonphenolic compounds usually accumulate in higher quantities in colder areas. Also, the amount of phenols (mainly thymol) is lower in winter (Loziene and Venskutonis 2005).

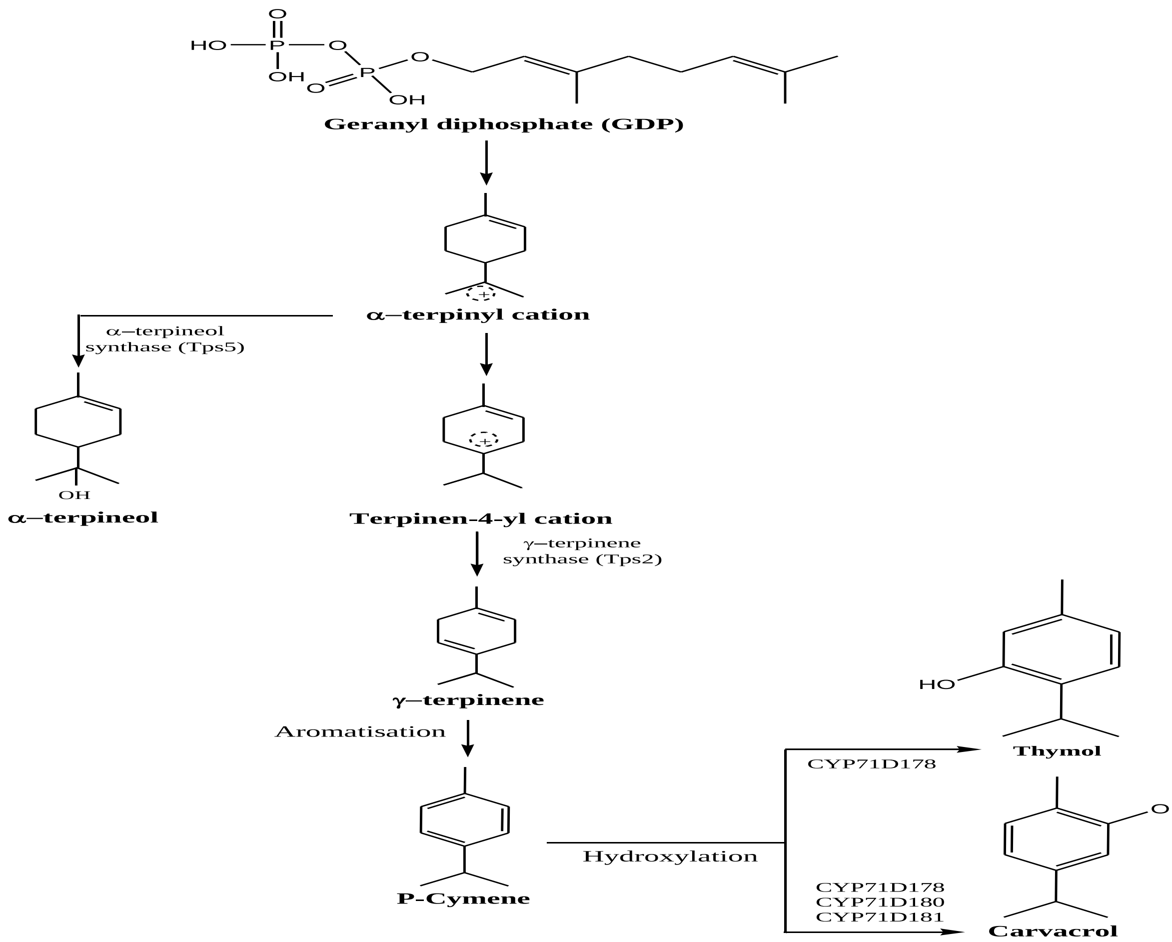

Figure 2. The biosynthetic chain of thymol and carvacrol production in Thymus.

CHEMICAL COMPOSITION OF ESSENTIAL OILS

Thymol ($C_{10}H_{14}O$) or 2-isopropyl-5-methylphenol, is a phenolic monoterpene in the form of relatively coarse and colorless prismatic crystals with a pleasant odor, melting at 50.5 to 51.5 and boiling at 233 degrees Celsius. The specific gravity of thymol is 0.972 to 0.979. Its refractive index is 1.523 at 20 °C. Thymol is completely volatile at 100 °C, and is also volatile in the presence of water vapor. Thymol is less soluble in water at neutral pH, but it is also soluble in some organic solvents and alcohols. It was in 1719 that thymol was isolated for the first time by the scientist Caspar Neumann. It was obtained in pure form by Lallemand in (1853). Later, between 1879 and 1880, Italian doctors discovered its anti-hookworm activity, when fighting the hookworm epidemic, a disease caused by a type of intestinal parasite (Anand and Sharma 1997, Salehi, Mishra *et al*. 2018, Escobar, Perez *et al*. 2020). Today it is known that thymol is a powerful antiseptic. It is also an isomer with carvacrol. In addition to Thymus species, thymol is found in other plants such as *Ocimum gratissimum* L., *Origanum* L., *Trachyspermum ammi* (L.), different species of the genus *Satureja* L. and *Monarda* L. (Lamiacaeae), *Carum copticum* L. and *Oliveria decumbens* Vent (Apiaceae), *Anemopsis californica* (Saururaceae) and species of Verbenaceae, Scrophulariaceae and Ranunculaceae. Thymol was globally recognized-as-safe food additive according to US Department of Food and Drug Administration (FDA). Nowadays, thymol is not only obtained on an industrial scale due to the large number of applications it has, but it is also a compound widely used in the synthesis of more complex molecules to improve their biological activity (Asadbegi, Yaghmaei *et al*. 2017, Akermi, Smaoui *et al*. 2022).

Carvacrol ($C_{10}H_{14}O$) or2-methyl-5-(1-methylethyl) phenol, is an oxygenated monoterpenoid and isomeric with thymol. The liquid state is colorless or yellowish and has a smell similar to thymol. It melts at a temperature of 0 to 1 °C and boils at a temperature of 236 to 237 °C. Its specific gravity is 0.9743 at 21 °C and 0.974 to 0.979 at 25 °C. Its refractive index is 1.5209 at 21 °C and 1.5210 to 1.5260 at 20 °C. Insoluble in water but soluble in alcohol and ether. Carvacrol is found in Thymus species and many aromatic plants such as *Satureja*, *Origanum* and *Thymbra* (Suntres, Coccimiglio *et al*. 2015, Sharifi-Rad, Varoni *et al*. 2018).

Geraniol ($C_{10}H_{18}O$) or 3,7-dimethylocta-trans-2,6-dien-1-ol, is an aliphatic monoterpene structure having a functional alcohol group in its organic composition. The product referred to as “geraniol” is a mixture of the two cis-trans isomers appropriately named geraniol (trans) and nerol (cis). Geraniol has a characteristic odor and flavor. This natural, organic acyclic compound is part of the constitution of various volatile oils, being a principal product in plants such as *Pelargonium*, *Cymbopogon* and *Rosa* (Chen and Viljoen 2010). The highest composition is found in several types of Thymus, including *Thymus* × *citriodorus*, *Thymus eriocalyx* and *Thymus pubescens*.

Eucalyptol ($C_{10}H_{18}O$) or 1,8-cineole, a cyclic ether monoterpene, with an ether bridge between C1 and C8, is the main compound of eucalyptus oil (*Eucalyptus globulus* and other species). 1,8-Cineol is as well component in numerous other essential oils, mainly in species of the genera Thymus, Achillea, and Artemisia (Juergens, Engelen *et al*. 2004).

γ-terpinene ($C_{10}H_{16}$) also known as p-mentha-1,4-diene, is a naturally occurring monoterpene hydrocarbon isolated from many plant sources, including *Origanum vulgare*, *Citrus limon* L, *Melaleuca alternifolia*, and *Eucalyptus obliqua*. This monoterpene is mainly used in food, cosmetic and pharmaceutical industries (Akermi, Smaoui *et al*. 2022).

Linalool ($C_{10}H_{18}O$) or 3,7-dimethyl-1,6-octadien-3-ol, is a naturally occurring acyclic monoterpenoid and tertiary alcohol which is commonly found as a major active component in the essential oil of several aromatic plant species principally in Lamiaceae and Lauraceae families, which are widely used in the food industry as an aromatic and preservative agent, in cosmetic as a fragrance and antiseptic constituent (Coelho, Gianesini *et al*. 2011).

OTHER *CHEMICAL* COMPOUNDS

Thymus species contain non-volatile compounds including non-flavonoid compounds (caffeic acid, rosmarinic acid, protocatechuic acid, ferulic acid, *p*-coumaric and tannin) and flavonoid compounds (luteolin, quercetin, apigenin, eriodictyol, naringenin, isosakuranetin, rutin, luteolin-O-glucoside, luteolin 7-O-glucoside, luteolin 7-O-glucuronide, quercetin-7-O-glucuronide and apigenin 7-Oglucoside). Also, salvianolic acids (salvianolic acid A isomer, salvianolic acid K and salvianolic acid A) are found in some types of Thymus (Dauqan and Abdullah 2017, Bekircan, Yaşar *et al*. 2018, Martins-Gomes, Taghouti *et al*. 2018).

ANTIMICROBIAL ACTIVITY

Thymus essential oil has antibacterial activity against gram positive bacteria (*Staphylococcus aureus*, *S. epidermidis*, *S. pseudintermedius*, *S. pneumonia*, *S. faecalis*, *Bacillus subtilis*, *B. cereus*) and gram negative (*Proteus mirabilis*, *Escherichia coli*, *Salmonella enterica* serovar Typhimurium, *S. enteritidis*, *Pseudomonas aeruginosa*, *Helicobacter pylori*). Anti-fungal activity against fungi (*Cladosporium herbarum*, *Alternaria infectoria*, *Trichophyton rubrum*, *Aspergillus ochraceus*, *A. flavus*, *A. niger*, *Alternaria alternata*, *Penicillium rubrum*, *Trichoderma viride*, *Candida albicans*), and anti-plant pathogens (*Colletotrichum acutatum*, *C. fragariae*, and *C. gloeosporioides*, *Botrytis cinerea*, *Rhizopus oryzae*, *Cryptococcus neoformans*) (Rasooli, Rezaei *et al*. 2006, Shahnazi, Khalighi-Sigaroodi *et al*. 2007, Asbaghian, Shafaghat *et al*. 2011, Ghasemi Pirbalouti, Emami Bistghani *et al*. 2015, Hadipanah and Khorami 2016, Mahboubi, Heidarytabar *et al*. 2017, Mumivand, Shayganfar *et al*. 2021).

Various chemical compounds of essential oil such as terpenes and aliphatic hydrocarbons (alcohols, aldehydes and ketones) have direct activity against many species of bacteria. The lipophilic character of their hydrocarbon skeleton and the hydrophilic character of their functional groups are of main importance in the antimicrobial action of essential oils components, and the importance of the hydroxyl group of phenolic structures has been confirmed (Mancini, Senatore *et al*. 2015). Lipophilic components of essential oils may change the lipid-protein interaction, and their direct interaction with hydrophobic parts of the protein is also possible. In addition to being able to connect to the lipids of bacterial cell membranes, monoterpenes' lipophilic components can also kill the bacteria by its morphological destruction (Gutierrez, Barry-Ryan *et al*. 2008).

The antibacterial activity of thyme essential oils have been the subject of several studies to focused the responsible compounds. Phenols appear to play a significant impact. These terpene phenols join to the amine and hydroxylamine groups of the proteins of the bacterial membrane altering their permeability and resulting in the death of the bacteria (Bounatirou, Smiti *et al*. 2007). The hydroxyl group on carvacrol and thymol depolarizes membrane potential (Ultee, Bennik *et al*. 2002). Due to their hydrophobic nature and the location of their phenolic hydroxyl group on the phenolic ring, carvacrol and thymol can disrupt the lipid bilayer of bacterial cytoplasmic membranes, resulting in a loss of integrity, an increase in fluidity and permeability, and the leakage of cellular material such as ions, ATP, and nucleic acids. Which can help them dissolve in the microbial membrane and damage them (Ultee, Kets *et al*. 1999, Sharifi-Rad, Varoni *et al*. 2018).

Due to lipopolysaccharides, which serve as a hydrophobic barrier, gram-positive bacteria are more likely to be sensitive to plant essential oils than gram-negative bacteria (Benameur, Gervasi *et al*. 2019). To combat gram-positive bacteria rather than gram-negative bacteria, carvacrol has a stronger antibacterial effect (Shen, Zhang *et al*. 2015). Thymol can alter the outer membrane, and carvacrol can destabilize the cytoplasmic membrane, act on proton exchange, and induce depletion of the ATP (adenosine triphosphate) pool, thereby reducing the pH gradient across the membrane and lead to cell death (Sarrazin, da Silva *et al*. 2015).

Thymol's high spectrum antibacterial activity, according to a study by (Boye, Addo *et al*. 2020), is attributable to the hydroxyl moiety on C1 of the monoterpene nucleus. A study by (Liu, Kang *et al*. 2021) confirmed that thymol has antibacterial activity against *P. aeruginosa by* affecting bacterial DNA’s normal function. It blocked gene expression processes by intercalation with bacterial DNA leading to bacterial death.

Carvacrol and thymol are both lipophilic substances with potent antifungal properties. They also damage the cell membrane, which affects the biosynthesis of ergosterol (Nobrega, Teixeira *et al*. 2016). Thymol, and carvacrol can change the cell membrane fluidity and permeability. Thymol can change the cell membrane in fungi such as *C. albicans* by affecting the function of cell membrane enzymes that catalyze the synthesis of cell wall polysaccharide compounds such as β-glucan and inhibit cell growth. Additionally, electron microscopy results showed that thymol and carvacrol change the envelope morphogenesis of *C. albicans* (Memar, Raei *et al*. 2017).

CONCLUSION

Thyme species are known as medicinal and aromatic plants due to their medicinal and biological properties. This review was focused on the chemical composition and antimicrobial properties of Iranian thyme species. The amount of essential oil and chemical compounds such as thymol and carvacrol can be due to genetic differences or environmental conditions of plant materials based on different geographical locations. Currently, Thymus species are of interest to many pharmaceutical, food and cosmetic industries.

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