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Thymelaea genus: Ethnopharmacology, Chemodiversity, and Bioactivities

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ABSTRACT

Thymelaea (F. *Thymelaeaceae*) is a large genus comprising around 30 species of evergreen and flowering plants. Most of them are native to the Mediterranean area. Despite its interesting chemical diversity and potent activities, there is still a lack of information about the characterization of its chemistry and mechanisms of action. This review aims to highlight the chemical and biological profiles of different *Thymelaea* species along with their Ethnopharmacology. In general, *Thymelaea* species possess potent anti-inflammatory, neuroprotective, antidiabetic, antihypertensive, and antioxidant activities. The pharmacology of the different plants is due to their remarkable active ingredients that vary from daphnane diterpenes, lignans, flavonoids, and phenolic acids to volatile oils. From ethnopharmacology to preclinical evidence, *Thymelaea* species demonstrated a unique chemical profile with potent bioactivities. However, until now, there is a lack of information about their toxicological and clinical controlled trials, and so this review may give attention to more clinical trials to be proceeded on *Thymelaea* species.

1. Introduction

Thymelaeaceae is a cosmopolitan family of flowering plants composed of 50 genera. One of its well-known genera is the *Thymelaea* genus, which consists of approximately 31 species of xerophyllous shrubs and herbs with very small leaves and yellowish or greenish flowers (Galicia-Herbada, 2006). Plants belonging to this genus commonly grow in the Mediterranean region (Boudjelal et al., 2013). The *Thymelaea* genus is very prominent for having distinctive active compounds such as daphnane terpenoids and lignans along with a various number of flavonoids, phenolic acids, and coumarins (Ghanem et al., 2014; Kabbaj et al., 2013; Kadri et al., 2011; Kerbab et al., 2015; Miyamae et al., 2009). *Thymelaea hirsuta* (L.) Endl., (Fig. 1), *Thymelaea microphyllag* Coss et Dur (Fig. 2) and *Thymelaea lythroides* Barratte & Murb (Fig. 3) are the most prominent species among the genus together with *Thymelaea linifolia* Andr., *Thymelaea nitida* (Vahl) Endl., *Thymelaea passerina* (L.) Coss. & Germ., *Thymelaea tinctoria* (Pourr.) Endl., and *Thymelaea tartonraira* (L.)

Abbreviations: COX, Cyclooxygenase enzyme; TNFα, Tumor necrosis factor-α; LPS, Lipopolysaccharide; IkB, kinase inhibitor; OGTT, Oral Glucose Tolerance Test; IVGTT, Intravenous Glucose Tolerance Test; STZ, Streptozotocin; NO, Nitric oxide; l-NAME, N^G-nitro-l-arginine methyl ester; HT-29, human colon cancer; MCF-7, human cells lines adenocarcinoma breast cancer; OVCAR, colon human cancer; CH_2Cl_2, Chloroform; MeOH, Methanol; DPPH, Diphenylpicrylhydrazyl; BHT, Butyl hydroxytoluene; ABTS, 2, 2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid); FRAP, Ferric reducing antioxidant power; LD_{50}, Lethal dose at 50%; IC_{50}, Inhibitory concentration at 50%

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Fig. 1. *Thymelaea hirsuta* (L.) Endl.

Fig. 2. *Thymelaea microphylla* Coss et Dur.

Fig. 3. *Thymelaea lythroides* Barratte & Murb.

All. These species proved to be potent as antitumor, anti-inflammatory, neuroprotective, antidiabetic, antihypertensive, and antioxidant agents (Azza et al., 2015; Berk et al., 2013; El Amrani et al., 2009; Túnez et al., 2010).

2. Taxonomy and geographic distribution

The *Thymelaea* genus can be classified as follows; Kingdom: Plants, Superdivision: Spermatophyta, Class: Magnoliopsida, Division: Magnoliophyta, Subclass: Rosidae, Order: Myrtales, and Family: Thymelaeaceae (Group, 1998).

The geographic distribution of the *Thymelaea* genus was described thoroughly by Galicia-Herbada (1995). The *Thymelaea* genus (90 % of the species) has a distinctive distribution around the Mediterranean region, mainly at the western Iberia peninsula, Balearic islands, and northwest Africa (Fig. 4), except for the annual *T. passerina* that may extend to the northeast and south (Galicia Herbada, 1995).

The evolutionary history of the *Thymelaea* genus was studied carefully by Galicia-Herbada (2006) through the estimation of ITS (rDNA) sequences. Phylogenetic analyses supported the monophyly of the genus *Thymelaea* and its parallel position with *Daphne* genus. The resulting phylogenetic hypothesis revealed that the *Thymelaea* genus practiced an early quick diversification. This diversification might be due to ontological, climatic, and geographical sources, or ITS (rDNA) substitution with other angiosperm groups, where the diversification firstly occurred in the upper Miocene in Eurasia especially in Iberia peninsula and North Africa (Galicia-Herbada, 2006).

The aim of this review paper is to provide a current state of knowledge concerning the traditional uses, phytochemistry, and pharmacology studies of the extracts and isolated compounds of the genus *Thymelaea.* To the best of our knowledge, there are no comprehensive reviews concerning medicinal *Thymelaea* plants.

3. Ethnopharmacological knowledge and toxicity

Species of this genus were extensively used as ethnomedicines, especially by the tribes and communities of Tunisia, Algeria, Morocco, and Palestine (Table 1) (Auda, 2011; Djeridane et al., 2006; Kabbaj et al., 2012; Said et al., 2002). *T. hirsuta* commonly known as “Methnane” in Morocco, Algeria, and Tunisia, was traditionally used for the treatment of hypertension, inflammation, dandruff, and respiratory system disorders (Jamila et al., 2014; Le Floc’h, 1983; Miara et al., 2019). *T. hirsuta* leaves and stems have been used along with olive oil to cure wounds, scabies and to feed the hair in Algeria (Benderradji et al., 2014; Rebbas et al., 2012), while a decoction of *T. hirsuta* has been used to treat diabetes, dandruff, migraine, and hair loss (Benderradji et al., 2014; El Amrani et al., 2010; Miara et al., 2019; Sarri et al., 2014). In Tunisia, *T. hirsuta* has been used as an antiseptic, anti-inflammatory, hypotensive and laxative (Barhoumi et al., 2019; Boukef et al., 1982; Le Floc’h, 1983; Najjaa et al., 2017). The plant was widely used in Moroccan traditional medicine, the aerial part was used as purgative and laxative (Bellakhdar, 1997; Bellakhdar et al., 1991) while the leaves and seeds were used as a remedy for diabetes (Alami et al., 2015; Yabrir et al., 2018). The leaves, seeds and stems also aided in respiratory and dental diseases (Jamila et al., 2014; Kharchoufa et al., 2018). In traditional Libyan medicine, *T. hirsuta* was taken as a vermifuge (Abugassa et al., 2012). In the middle east, it was used to treat asthma, coughing, and skin diseases (Borris et al., 1988; Friedman et al., 1986; Lev, 2002). The plant was also recommended as a remedy for hemorrhoids, stomach, intestine, and sexual diseases (Borris et al., 1988; Lev, 2002).

T. lythroides, an Ibero-endemic plant in Morocco, was popularly used to treat diabetes, uterus cancer, migraines, fever, inflammation, stomach pains, abscesses, cold and backache, rheumatism and prostate inflammation (Dohou et al., 2003; Gmira et al., 2007; Kabbaj et al., 2012; Miara et al., 2019). An infusion of the aerial part was used for the treatment of infertility, while the whole plant was used as a remedy for rheumatism and applied to swelling and fractures (Dohou et al., 2003). A tea prepared from *T. lythroides* aerial part, maintained anticancer properties (Kabbaj et al., 2012). *T. linifolia* was used as a remedy for constipation (Hind et al., 2017). Moreover, *T. microphylla* had valuable medicinal uses. The leaves possessed high antiparasitic properties and were used for hair care and hair loss, it was also used in the treatment of depression (Chermat et al., 2015). A decoction prepared from the aerial part possessed high antidiabetic

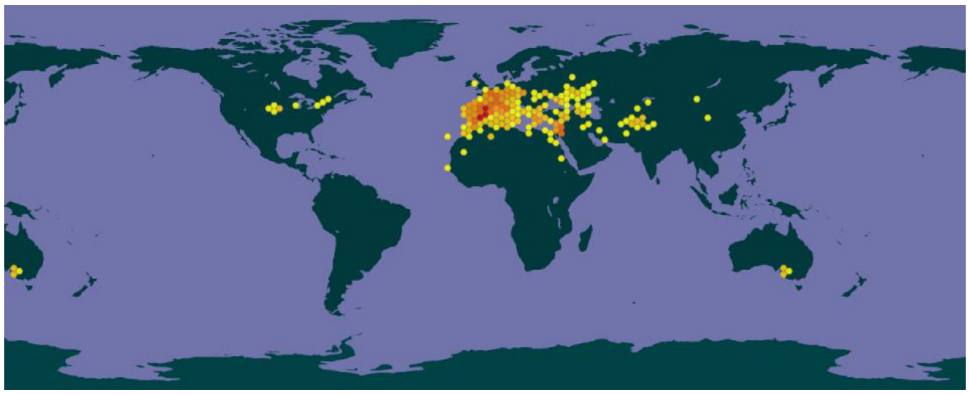

Fig. 4. Documented locations of different *Thymelaea* species based on data from GBIF (*Thymelaea* Mill in GBIF, 2019).

properties (Telli et al., 2016). An infusion of the dried aerial part was used in the treatment of hemorrhoidal crisis (Yabrir et al., 2018). The whole plant was used for curing a cold in the urinary tract (Mouhajir et al., 2001). *T. nitida* leaves have been used in the treatment of alopecia and helminthiasis (Chermat et al., 2015). *T. passerina* was used for curing various respiratory diseases (Arı et al., 2017). A decoction of *T. tartonraira* leaves was used in the treatment of diabetes (Tahraoui et al., 2007). *T. tinctoria* possessed high anti-inflammatory and antioxidant properties (Agelet et al., 2001). Although having excellent bioactivities, excess intake or high doses of *Thymelaea* was not free from side-effects (Bellakhdar et al., 1991; Bruneton, 1993; Charnot, 1945). *T. hirsuta* has been reported to be toxic to humans and animals (Azza et al., 2012; Bellakhdar et al., 1991; Berkiks et al., 2014; Brooks et al., 1990b; Bruneton, 1993; Charnot, 1945) such as headaches and hypersalivation (Bellakhdar et al., 1991). In over-dose, *T. hirsuta* has been associated with general weakness, pupil dilation and vomiting (Bellakhdar et al., 1991). Skin allergic reactions have also been reported after topical applications of *Thymelaea* (Brooks et al., 1990b).

4. Chemodiversity

Thymelaea plants contain various classes of compounds, including daphnane diterpenes, lignans, flavonoids, phenolic acids, and volatile oils. However, the chemical composition of the *Thymelaea genus* didn't receive enough attention and only limited information is available. *T. hirsuta, T. lythroides*, and *T. microphylla* were the most investigated species. Table 2 summarizes some of the major isolated and identified molecules from *Thymelaea species*.

4.1. Daphnane diterpenes and diterpenoids

Thymelaea plants are very specific for their content of daphnane diterpenes and diterpenoids (Fig. 5). In a study performed by Brooks et al. (1990), five daphnane diterpenes were isolated from the leaves and twigs of *T. hirsuta* including gnidicin (**1**), 12-*O*-heptadecenoyl ester (**2**), gniditrin (**3**), 12-O-benzoyl ester (**4**), 12-*O*-butenyl ester namely genkwadaphnin (**5**), 12-hydroxydaphnetoxin (**6**), and its triacetate derivative (**7**) (Brooks et al., 1990a). Moreover, two daphnane diterpenoids named hirseins A (**8**) and B (**9**) were isolated from *T. hirsuta* aerial parts (Miyamae et al., 2009).

4.2. Lignans

Lignans also are very prominent compounds in the different *Thymelaea* plants (Fig. 6). Chemical investigation of the hydro-alcoholic extract of the aerial parts of Algerian *T. microphylla* revealed the presence of three lignans namely; phyllyrin; syringaresinol-4-*O*-β-D-glucopyranoside (**10**) and lariciresinol-4"-*O*-β-D-glucopyranoside (**11**) (Kerbab et al., 2015). Moreover, three lignans namely pinoresinol (**12**), matairesinol (furofuran lignan) (**13**), and pregestane B (dibenzyl butanolide lignan) (**14**) were isolated and identified from the roots and the aerial parts of *T. microphylla* (Ghanem et al., 2014; Noman et al., 2017). On the other hand, δ-sesamin (**15**) was isolated from the aerial parts of the Moroccan *T. lythroides* (Kabbaj et al., 2013).

4.3. Flavonoids

A flavonoid glucoside (trans-tiliroside) was isolated from the aerial parts of the Moroccan *T. lythroides* (Kabbaj et al., 2013). While, Vicenin-2 was isolated from *T. hirsuta* leaves (Nawwar et al., 1977). On the other hand, chemical investigation of the hydro-alcoholic extract of the aerial parts of Algerian *T. microphylla,* revealed the presence of three flavonoids (yuankanin, kaempferol 3-O-(3",6"-di-*O*-[(*E*)-*p*-coumaroyl]- β -D-glucopyranoside), and stenopalustroside A) (Kerbab et al., 2015). Furthermore, the roots and the aerial parts of *T. microphylla* resulted in the presence of five biflavonoids (daphnodorin B, genkwanol A, neochamaejasmins (A and B), and stelleranol) (Ghanem et al., 2014). In addition, ladanein was identified as a flavone from the extract of leaves and flowers of *T. microphylla* (Kerbab et al., 2015). Recently, two biflavonoids were reported for the first time from *T. hirsuta* methanolic extract [3`-epi-dihydrodaphnodorin B and Wikstaiwanone B] (Fig. 7) (Badawy et al., 2019).

4.4. Phenolic compounds

A total of sixteen phenolic compounds were identified and characterized in the ethyl acetate extract of *T. hirsuta* using the Gas Chromatography-Mass Spectrometry (GC–MS). The identified compounds were named as 9,12-octadecadienoic acid (Z,Z), alpha-linolenic acid, benzoic acid, caffeic acid, ferulic acid, hydrocinnamic acid, m-hydroxybenzoic acid, *O*-coumaric acid, octadecanoic acid, o-hydroxybenzoic acid, p-coumaric acid, p-hydroxybenzoic acid, p-hydroxyphenylacetic acid, protocatechuic acid, and vanillic acid (Trigui et al., 2013). In other investigations, thirteen phenolic acids were identified from aerial parts of *T. hirsuta* from different Tunisian localities using several organic solvents. Chlorogenic acid, salvianolic acid B, baicalein, pinosylvin, and plumbagin were identified in the hexane extract; 7-hydroxy-6-methoxycoumarin, (z)-3-(3-ethoxy-4-hydroxy-phenyl)-2-phenyl-acrylic acid, cardamonin, 6-hydroxyflavone, and pinosylvin in the ethyl acetate extract; dihydromyricetin in the ethanol extract, while (-)-epicatechin and trans-cinnamic acid in the methanol extract (Yahyaoui et al., 2018). Moreover, chemical investigation of the hydro-alcoholic extract of the aerial parts of Algerian *T. microphylla* revealed the presence of three phenolic acid derivatives (chlorogenic acid butyl ester, protocatechuic acid, and ethyl gallate) (Kerbab et al., 2015). On the other hand, ethyl caffeate

Table 1
Some traditional uses of *Thymelaea* species in different regions

Species	Region (Local name)	Part	Preparation	Ethnomedical uses	Reference(s)
T. hirsuta	-	Leaves	-	Skin diseases, antihelmintic, hydragogue, cathartic, expectorant	(Ozturk et al., 2017)
	Algeria (Methnane, Metnan, Al metnen)		-	Anti-inflammatory	(Djeridane et al., 2006)
		Leaves	Infusion, Decoction	Dandruff	(Miara et al., 2019)
		Leaves, Stems	Mixed with olive oil	Wounds, scabies, and feed the hair	(Benderradji et al., 2014; Rebbas et al., 2012)
		Leaves	Decoction	Dandruff	(Benderradji et al., 2014)
		Aerial part	-	Female sterility	(Benarba et al., 2015)
			Infusion	Leishmanicidal, vermifuge, eczema	(Boudjelal et al., 2013)
			Decoction, Infusion	Migraine, hair loss	(Sarri et al., 2014)
			Decoction	Diabetes	(El Amrani et al., 2010)
			-	Cough, constipation	(Miara et al., 2013)
			Decoction, Infusion, Maceration	Eczema	(Sari et al., 2012)
		Roots, Seeds	Infusion	Cysts, sterility	(Ouelbani et al., 2016)
	Tunisia (Methnane)	-	-	Antiseptic, anti-inflammatory and for the treatment of hypertension	(Le Floc'h, 1983)
		-	External application	Antiseptic and anti-inflammatory agent and for the treatment of hypertension	(Najjaa et al., 2017)
		Leaves	-	Laxative	(Boukef et al., 1982)
		Stems	-	Treatment of infected pimples (boils) and sciatic nerve	(Barhoumi et al., 2019)
	Morocco (Methnane, Lmatnane, Mathnane, Ftitisa)	Leaves	Decoction, External application, Inhalation	Problems of the sphere buccodentaire, pathologies of the respiratory system	(Jamila et al., 2014)
		Seeds	Infusion	Diabetes	(Alami et al., 2015)
		Leaves, Stems	-	Diabetes, laxative, pathologies of the respiratory system, problems of the sphere buccodentaire	(Kharchoufa et al., 2018)
		Aerial part	-	Purgative	(Bellakhdar, 1997)
			-	Laxative, toxic	(Bellakhdar et al., 1991)
	Libya (Methnan)	-	-	Treatment of constipation and vermifuge	(Abugassa et al., 2012)
	Middle east (Metnan, Sparrow Wart)	-	-	Asthma	(Friedman et al., 1986)
		-	-	Stomach and intestine, internal diseases, hemorrhoids and sexual diseases, skin diseases	(Borris et al., 1988; Friedman et al., 1986)
		Leaves	-	Skin diseases, coughing and respiratory system	(Azaizeh et al., 1970)
			Cataplasm	Skin diseases	(Said et al., 2002)
	Palestine (Metnan)	-	-	Nervous diseases	(Auda, 2011)
T. linifolia	**Morocco** (Anawt)	Latex	Uncooked	Constipation	(Hind et al., 2017)
T. lythroides	**Morocco** (Ftiticha, Metnane, Mtnane)	Leaves	Infusion	Cold and backache	(Dohou et al., 2003)
			Powder in poultice	Migraines and fever	
			Powder	Cosmetology and for the care of hair	
			Poultices, drops of aqueous extract	Inflammations of the eyes	
			Infusion	Inflammation of the prostate, Diabetes, Stomach pains	
			Compresses	Abscesses	
		Flowers	Maceration in olive oil	Otitis	
		Leaves, Stems	Infusion	Bladder and kidney pain	(Dohou et al., 2003)
			Infusion	Bladder, kidney disease, cold, rheumatism and back pain	(Nguemfo et al., 2007)
		Leaves, Flowers	Infusion	Otitis, migraines, pains of the stomach, intestines, diabetes, rheumatism, inflammation of the prostate and uterus cancer	(Gmira et al., 2007)
		Aerial part	Decoction	Uterus cancer	(Kabbaj et al., 2012; Kabbaj, 2018)
			Infusion	Infertility	(Dohou et al., 2003)
			Fumigation, Cataplasm	Dermal fungi	(Dohou et al., 2003)
		Whole plant	Plaster (mixed with flour and crushed lentils)	Swelling and fractures	(Dohou et al., 2003)
			Powder and in the form of soup mixed with barley semolina	Rheumatism	(Dohou et al., 2003)

(*continued*)

Table 1 (*Continued*)

Species	Region (Local name)	Part	Preparation	Ethnomedical uses	Reference(s)
T. microphylla	**Morocco** (Metnan)	Whole plant		Cold in the urinary tract	(Mouhajir et al., 2001)
	Algeria (Methnan, Methnan, Elbahloul)	Aerial part	Decoction	Hemorrhoids	(Yabrir et al., 2018)
			Infusion	Diabetes	(Telli et al., 2016)
		Leaves	-	Hair care, hair loss, helminthiasis, depression	(Chermat et al., 2015)
T. nitida	**Algeria**	Leaves	-	Alopecia, helminthiasis	(Chermat et al., 2015)
T. passerina	**Turkey**	Aerial part	-	Respiratory, cold	(Arı et al., 2017)
T. tartonraira	**Morocco** (Talazazt)	Leaves	Decoction	Diabetes	(Tahraoui et al., 2007)
T. tinctoria	**-**	-	-	Antialgic, anti-inflammatory, antitoxic	(Agelet et al., 2001)
T. species	**Africa**	Bark	-	Alterative, Diuretic, sialagogue, stimulant	(Gathercoal et al., 1936; Thonner, 1962; Zohary, 1962)

Table 2
Chemical compounds isolated and identified from the *Thymelaea* genus

Type	Compound	Formula	Specific plant	Part	Extraction method	Reference(s)
Daphnane diterpenes	**Gnidicin** (12-O-Cinnamoyl-5-hydroxy-6,7-epoxy-resinifero-nol-9,13,14-orthobenzoate)	$C_{36}H_{36}O_{10}$	*T. hirsuta*	Leaves and twigs	Me2CO extract	(Brooks et al., 1990a)
	12-O-Heptaecenoyl-5-hydroxy-6,7-epoxy-resiniferonol-19,13,14-orthobenzoate	$C_{45}H_{62}O_{10}$	*T. hirsuta*	Leaves and twigs	Me2CO extract	(Brooks et al., 1990a)
	Gniditrin (12-O-n-Deca-2,4,6-trienoyl-5-hydroxy-6,7-epoxy-resiniferonol-9,13,14-orthobenzoate)	$C_{37}H_{42}O_{10}$	*T. hirsuta*	Leaves and twigs	Me2CO extract	(Brooks et al., 1990a)
	Genkwadaphnin (12-O-Benzoyl-5-hydroxy-6,7-epoxy-resinifer-onol-9,13,14-orthobenzoate)	$C_{34}H_{34}O_{10}$	*T. hirsuta*	Leaves and twigs	Me2CO extract	(Brooks et al., 1990a)
	12-O-Butenyl-5-hydroxy-6,7-epoxy-resinifer-onol-9,13,14-orthobenzoate	$C_{34}H_{34}O_{10}$	*T. hirsuta*	Leaves and twigs	Me2CO extract	(Brooks et al., 1990a)
Daphnane diterpenoids	**Hirsein A**	$C_{37}H_{44}O_{10}$	*T. hirsuta*	Aerial part	MeOH extract	(Miyamae et al., 2009)
	Hirsein B	$C_{39}H_{50}O_{11}$	*T. hirsuta*	Aerial part	MeOH extract	(Miyamae et al., 2009)
Flavonoids	**Vicenin-2** (4H-1-Benzopyran-4-one, 6,8-di-β-D-glucopyranosyl-5,7-dihydroxy-2-(4-hydroxyphenyl)-)	$C_{27}H_{30}O_{15}$	*T. hirsuta*	Leaves	Ethyl acetate extract	(Nawwar et al., 1977)
Phenolic compounds	**9,12-Octadecadienoic acid (Z,Z)**	$C_{18}H_{32}O_2$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Alpha-linolenic acid	$C_{18}H_{30}O_2$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Benzoic acid	$C_7H_6O_2$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Caffeic acid	$C_9H_8O_4$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Ferulic acid	$C_{10}H_{10}O_4$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Hydrocinnamic acid	$C_9H_{10}O_2$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***m*-Hydroxybenzoic acid**	$C_7H_6O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***o*-Coumaric acid**	$C_9H_8O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Octadecanoic acid	$C_{18}H_{36}O_2$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***o*-Hydroxybenzoic acid**	$C_7H_6O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***p*-Coumaric acid**	$C_9H_8O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***p*-Hydroxybenzoic acid**	$C_7H_6O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	***p*-Hydroxyphenylacetic acid**	$C_8H_8O_3$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Protocatechuic acid	$C_7H_6O_4$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Vanillic acid	$C_8H_8O_4$	*T. hirsuta*	Aerial part	Ethyl acetate extract	(Trigui et al., 2013)
	Chlorogenic acid	$C_{16}H_{18}O_9$	*T. hirsuta*	Aerial part	Hexane	(Yahyaoui et al., 2018)
	Salvianolic acid B	$C_{36}H_{30}O_{16}$	*T. hirsuta*	Aerial part	Hexane	(Yahyaoui et al., 2018)
	Baicalein	$C_{15}H_{10}O_5$	*T. hirsuta*	Aerial part	Hexane	(Yahyaoui et al., 2018)
	Pinosylvin	$C_{14}H_{12}O_2$	*T. hirsuta*	Aerial part	Hexane	(Yahyaoui et al., 2018)
	Plumbagin	$C_{11}H_8O_3$	*T. hirsuta*	Aerial part	Hexane	(Yahyaoui et al., 2018)
	7-Hydroxy-6-methoxycoumarin	$C_{10}H_8O_4$	*T. hirsuta*	Aerial part	Ethyl Acetate	(Yahyaoui et al., 2018)
	(z)-3-(3-ethoxy-4-hydroxy-phenyl)-2-phenyl-acrylic acid	$C_{17}H_{16}O_4$	*T. hirsuta*	Aerial part	Ethyl Acetate	(Yahyaoui et al., 2018)
	Cardamonin	$C_{16}H_{14}O_4$	*T. hirsuta*	Aerial part	Ethyl Acetate	(Yahyaoui et al., 2018)
	6-Hydroxyflavone	$C_{15}H_{10}O_3$	*T. hirsuta*	Aerial part	Ethyl Acetate	(Yahyaoui et al., 2018)
	Pinosylvin	$C_{14}H_{12}O_2$	*T. hirsuta*	Aerial part	Ethyl Acetate	(Yahyaoui et al., 2018)
	Dihydromyricetin	$C_{15}H_{12}O_8$	*T. hirsuta*	Aerial part	Ethanol	(Yahyaoui et al., 2018)
	(−)-Epicatechin	$C_{15}H_{14}O_6$	*T. hirsuta*	Aerial part	Methanol	(Yahyaoui et al., 2018)
	Trans-Cinnamic acid	$C_9H_8O_2$	*T. hirsuta*	Aerial part	Methanol	(Yahyaoui et al., 2018)

(*continued*)

Table 2 (*Continued*)

Type	Compound	Formula	Specific plant	Part	Extraction method	Reference(s)
Volatile oils	**1-Heptene**	C_7H_{14}	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Heptane	C_7H_{16}	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Hexamethylcyclotrisiloxane	$C_6H1_8O_3Si_3$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Iso menthone	$C_{10}H_{18}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Cyclohexaneethanol	$C_8H_{16}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	β-citronellol	$C_{10}H_{20}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Citronellyl formate	$C_{11}H_{20}O_2$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Citrol	$C_{10}H_{18}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Dodecamethyl-cyclohexasiloxane	$C_{12}H_{36}O_6Si_6$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-copaene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	β-Bourbonene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	trans-β-caryophyllene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-Muurolene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-Gurjunene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Germacrene-D	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-Humulene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-amorphene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	δ-selinene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Aromadendrene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	5-Methyl-2-N-methylphenyla-mino-2-thiazoline	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	δ-cadinene	$C_{15}H_{24}$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	α-agarofuran	$C_{15}H_{24}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	γ-Eudesmol	$C_{15}H_{26}O$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Cyclopentasiloxane, decamethyl	$C_{10}H_{30}O_5Si_5$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Neryl acetate	$C_{12}H_{20}O_2$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	linalyl acetate	$C_{12}H_{20}O_2$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Morphin silyliert	$C_{23}H_{35}NO_3Si_2$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Tetradecamethyl-heptasiloxane	$C_{14}H_{42}O_6Si_7$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
	Dodecamethyl-hexasiloxane	$C_{12}H_{38}O_5Si_6$	*T. hirsuta*	Aerial part	Hydrodistillation	(Kadri et al., 2011)
Depsipeptide	**Bassiatin** (2,5-Morpholinedione, 4-methyl-6-(1-methylethyl)-3-(phenylmethyl)-, (3S,6R)-)	$C_{15}H_{19}NO_3$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Coumarins	**Daphenone** (1-(4-Hydroxy-phenyl)-5-phenyl-2-penten-1-one)	$C_{17}H_{16}O_2$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
	Daphnelone	$C_{17}H_{18}O_2$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Dicoumarin	**Daphnoretin** (2H-1-Benzo-pyran-2-one, 7-hydroxy-6-methoxy-3-[(2-oxo-2H-1-ben-zopyran-7-yl)oxy]-)	$C_{19}H_{12}O_7$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Lignans	**δ-sesamin** (1,3-Benzodioxole, 5,5′-(tetrahydro-1H,3H-furo [3,4-c]furan-1,4-diyl)bis-, (1S,3aR,4S,6aR)-)	$C_{20}H_{18}O_6$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
	Wikstromol (2(3H)-Furanone, dihydro-3-hydroxy-3,4-bis[(4-hydroxy-3-methoxyphenyl) methyl]-, (3R,4R)-)	$C_{31}H_{30}O_{16}$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Flavonoid glucosides	**Trans-tiliroside** (Trans-tiliroside or kaempferol-3-O-β-D-(6″-E-p-coumaroyl)-glucopyranoside)	$C_{30}H_{26}O_{13}$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Dicoumarin glucosides	**Rutarensin** (2H-1-Benzopyran-2-one, 7-[[6-O-(4-carboxy-3-hydroxy-3-methyl-1-oxobu-tyl)-β-D-glucopyranosyl]oxy]-6-methoxy-3-[(2-oxo-2H-1-benzopyran-7-yl)oxy]-)	$C_{31}H_{30}O_{16}$	*T. lythroides*	Aerial part	Ethyl acetate extract	(Kabbaj et al., 2013)
Furofuran lignan	**Matairesinol** (2(3H)-Furanone, dihydro-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl]-, (3R,4R)-)	$C_{20}H_{22}O_6$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Noman et al., 2017)
Dibenzyl butanolide lignan	**Prestegane B** (2(3H)-Furanone, dihydro-3,4-bis[(3-hydroxy-4-methoxyphenyl)methyl]-, (3R,4R)-)	$C_{20}H_{22}O_6$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Noman et al., 2017)
Coumarin	**Umbelliferone** (2H-1-Benzo-pyran-2-one, 7-hydroxy-)	$C_9H_6O_3$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Noman et al., 2017)

(*continued*)

Table 2 (*Continued*)

Type	Compound	Formula	Specific plant	Part	Extraction method	Reference(s)
Dicoumarin	**Daphnoretin** (2H-1-Benzopyran-2-one, 7-hydroxy-6-methoxy-3-[(2-oxo-2H-1-benzopyran-7-yl)oxy]-)	$C_{19}H_{12}O_7$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Noman et al., 2017)
Spiro-γ-lactone glycoside	**Microphynolide A** (Spiro[furan-2(5H),3′(2′H)-furo[3,2-b] furan]-2′,5-dione, 6′-(acetyloxy)-3′a-(β-arabinopyranosyloxy)hexahydro-3-propyl-, (2S,3′aR,6′S,6′aR)-)	$C_{19}H_{26}O_{12}$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Ghanem et al., 2014)
	Microphynolide B (Spiro[furan-2(5H),3′(2′H)-furo[3,2-b] furan]-2′,5-dione, 3′a-(β-arabinopyranosyloxy)hexahydro-6′-hydroxy-3-propyl-, (2S,3′aR,6′S,6′aR)-)	$C_{17}H_{24}O_{11}$	*T. microphylla*	Aerial part	CHCl:MeOH 50% (v/v) extract	(Ghanem et al., 2014)
Benzimidazole derivative	**Microphybenzimidazole**	$C_{19}H_2O_7N_2Na$	*T. microphylla*	Aerial part	MeOH:H2O 70% (v/v) extract	(Noman et al., 2017)
Biflavonoids	**Neochamaejasmin A**	$C_{30}H_{22}O_{10}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
	Neochamaejasmin B ([3,3′-Bi-4H-1-benzopyran]-4,4′-dione, 2,2′,3,3′-tetrahydro-5,5′,7,7′-tetrahydroxy-2,2′-bis (4-hydroxyphenyl)-, (2R,2′S,3R,3′R)-rel-(+)-)	$C_{30}H_{22}O_{10}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
	Daphnodorin B (methanone, [(2R,3S)-3,4-dihydro-3,5-dihydroxy-2,8-bis(4-hydroxyphenyl)-2H-furo[2,3-h]-1-benzopyran-9-yl](2,4,6-trihydroxyphenyl)-)	$C_{30}H_{22}O_{10}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
	Genkwanol A (Spiro[benzofuran-2(3H),9′(8′H)-[2H]furo [2,3-h][1]benzopyran]-3-one, 3′,4′-dihydro-3′,4,5′,6-tetrahydroxy-2′,8′-bis(4-hydroxyphenyl)-, (2R, 2′R,3′S,8′R)-)	$C_{30}H_{22}O_{10}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
	Stelleranol (1H,5H,12H-Furo[3,4-b:2,3-h'] bis[1]benzopyran-1,5-dione, 4,4a,13,14-tetrahydro-4a,6,8,13-tetrahydroxy-4,12-bis(4-hydroxyphenyl)-, (12R,13R)-rel-(-)-)	$C_{30}H_{22}O_{11}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Lignans	**Pinoresinol** (phenol, 4,4′-[(1S,3aR,4S,6aR)-tetrahydro-1H,3H-furo[3,4-c]furan-1,4-diyl]bis[2-methoxy-)	$C_{20}H_{22}O_6$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Dicoumarin	**Daphnoretin** (2H-1-Benzopyran-2-one, 7-hydroxy-6-methoxy-3-[(2-oxo-2H-1-benzopyran-7-yl)oxy]-)	$C_{19}H_{12}O_7$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Furofuran lignan	**Matairesinol** (2(3H)-Furanone, dihydro-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl]-, (3R,4R)-)	$C_{20}H_{22}O_6$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Flavonoid glucoside	**Tiliroside** (4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[[6-O-[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-β-D-glucopyranosyl]oxy]-)	$C_{30}H_{26}O_{13}$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Sinapyl alcohol glucoside	**Syringin** (β-D-Glucopyranoside, 4-[(1E)-3-hydroxy-1-propen-1-yl]-2,6-dimethoxyphenyl)	$C_{17}H_{24}O_9$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Phytosterol	**β-sitosterol** (Stigmast-5-en-3-ol, (3β)-)	$C_{29}H_{50}O$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
	β-sitosterol-3-O-glucoside (β-D-Glucopyranoside, (3β)-stigmast-5-en-3-yl)	$C_{35}H_{60}O_6$	*T. microphylla*	Aerial part	Ethyl acetate extract	(Ghanem et al., 2014)
Caffeic acid ethyl ester	**Ethyl caffeate** (2-Propenoic acid, 3-(3,4-dihydroxyphenyl)-, ethyl ester, (2E)-)	$C_{11}H_{12}O_4$	*T. microphylla*	Leaves and flowers	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2016)

(*continued*)

Table 2 (*Continued*)

Type	Compound	Formula	Specific plant	Part	Extraction method	Reference(s)
Flavone	**Ladanein** (4H-1-Benzopyran-4-one, 5,6-dihydroxy-7-methoxy-2-(4-methoxy-phenyl)-)	$C_{17}H_{14}O_6$	*T. microphylla*	Leaves and flowers	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2016)
Monoterpene glucosides	**(3S,6R)-cis-linalool-3,7-oxide β-D-glucopyranoside** (β-D-Glucopyranoside, 1-[(2R,5R)-5-ethenyltetrahydro-5-methyl-2-furanyl]-1-methylethyl)	$C_{16}H_{28}O_7$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	3,7 dimethyl-1-octene-3,6,7-triol-6-O- β-D-glucopyranoside (β-D-Glucopyranoside, 4-hydroxy-1-(1-hydroxy-1-methylethyl)-4-methyl-5-hexen-1-yl)	$C_{16}H_{30}O_8$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Betulabuside B (β-D-Glucopyranoside, (2Z,6R)-6-hydroxy-2,6-dimethyl-2,7-octadien-1-yl)	$C_{16}H_{28}O_7$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Phenolic acid derivatives	**Chlorogenic acid butyl ester** (Cyclohexanecarboxylic acid, 3-[[(2E)-3-(3,4-dihydroxy-phenyl)-1-oxo-2-propen-1-yl] oxy]-1,4,5-trihydroxy-, butyl ester, (1S,3R,4R,5R)-)	$C_{20}H_{26}O_9$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Protocatechuic acid (Benzoic acid, 3,4-dihydroxy-)	$C_7H_6O_4$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Ethyl gallate (Benzoic acid, 3,4,5-trihydroxy-, ethyl ester)	$C_9H_{10}O_5$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Phenylpropanoid glucosides	**Coniferin** (β-Glucopyranoside, 4-(3-hydroxy-1-propen-1-yl)-2-methoxyphenyl)	$C_{16}H_{22}O_8$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v)	(Kerbab et al., 2015)
	Syringin (β-D-Glucopyranoside, 4-[(1E)-3-hydroxy-1-propen-1-yl]-2,6-dimethoxyphenyl)	$C_{17}H_{24}O_9$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Flavonoids	**Yuankanin** (4H-1-Benzopyran-4-one, 2-(4-hydroxyphenyl)-7-methoxy-5-[(6-O-β-D-xylo-pyranosyl-β-D-glucopyrano-syl)oxy]-)	$C_{27}H_{30}O_{14}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	K**aempferol 3-O-(3",6"-di-O-[(E)-p-coumaroyl]- β -D-glu-copyranoside)** (4H-1-Benzo-pyran-4-one, 3-[[3,6-bis-O-[(2E)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-β-D-glu-copyranosyl]oxy]-5,7-dihy-droxy-2-(4-hydroxyphenyl)-)	$C_{39}H_{32}O_{15}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Stenopalustroside A (4H-1-Ben-zopyran-4-one, 3-[[3,6-bis-O-[(2Z)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-β-D-glu-copyranosyl]oxy]-5,7-dihy-droxy-2-(4-hydroxyphenyl)-)	$C_{39}H_{32}O_{15}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Benzyl alcohol glucoside (β-D-Glucopyranoside, phenylmethyl)	$C_{13}H1_8O_6$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Ionol glucosides	**(E)-4-[3"-(β -D-glucopyranosy-loxy)butylidene]- 3,5,5-tri-methyl-2-cyclohexen-1-one** (2-Cyclohexen-1-one, 4-[3-(β-D-glucopyranosyloxy)buty-lidene]-3,5,5-trimethyl-, (4E)-)	$C_{19}H_{30}O_7$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v)	(Kerbab et al., 2015)
	3-oxo-α-ionol-9-O-β-D-gluco-pyr-anoside (2-Cyclohexen-1-one, 4-[(1E,3R)-3-(β-D-gluco-pyranosyloxy)-1-buten-1-yl]-3,5,5-trimethyl-, (4R)-)	$C_{19}H_{30}O_7$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v)	(Kerbab et al., 2015)
	Blumenol C-glucoside (2-Cyclo-hexen-1-one, 4-[(3R)-3-(β-D-glucopyranosyloxy)butyl]-3,5,5-trimethyl-, (4R)-)	$C_{19}H_{32}O_7$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Vomifoliol-9-O-β-D-glucopyra-noside (2-Cyclohexen-1-one,	$C_{19}H_{30}O_8$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)

(*continued*)

Table 2 (*Continued*)

Type	Compound	Formula	Specific plant	Part	Extraction method	Reference(s)
	4-[(1E,3R)-3-(β-D-glucopyranosyloxy)-1-buten-1-yl]-4-hydroxy-3,5,5-trimethyl-, (4S)-)					
Lignans	**Phyllyrin** (β-D-Glucopyranoside, 4-[(1S,3aR,4R,6aR)-4-(3,4-dimethoxyphenyl)tetrahydro-1H,3H-furo[3,4-c]furan-1-yl]-2-methoxyphenyl)	$C_{27}H_{34}O_{11}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Syringaresinol-4-O-β-D-glucopyranoside (β-D-Glucopyranoside, 2,6-dimethoxy-4-[(1R,3aS,4R,6aS)-tetrahydro-4-(4-hydroxy-3,5-dimethoxyphenyl)-1H,3H-furo[3,4-c]furan-1-yl]phenyl)	$C_{28}H_{36}O_{13}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
	Lariciresinol-4"-O-β-D-glucopyranoside (β-D-Glucopyranoside, 2-methoxy-4-[[(3R,4R,5S)-tetrahydro-5-(4-hydroxy-3-methoxyphenyl)-4-(hydroxymethyl)-3-furanyl]methyl]phenyl)	$C_{26}H_{34}O_{11}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Bis-coumarin	**Giraldoid A** ([8,8′-Bi-2H-1-benzopyran]-2,2′-dione, 7-(β-D-glucopyranosyloxy)-7′-hydroxy-)	$C_{24}H_{20}O_{11}$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Kerbab et al., 2015)
Phenolic acid derivatives	**Vanillin** (Benzaldehyde, 4-hydroxy-3-methoxy-)	$C_8H_8O_3$	*T. microphylla*	Aerial part	EtOH–H2O (70:30, v/v)	(Mekhelfi et al., 2014)
	(+)-syringaresinol (Phenol, 4,4′-[(1S,3aR,4S,6aR)-tetrahydro-1H,3H-furo[3,4-c]furan-1,4-diyl]bis[2,6-dimethoxy-)	$C_{22}H_{26}O_8$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
Dicoumarin	**Daphnoretin** (2H-1-Benzopyran-2-one, 7-hydroxy-6-methoxy-3-[(2-oxo-2H-1-benzopyran-7-yl)oxy]-)	$C_{19}H_{12}O_7$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
Phenolic acid derivatives	**(Z)-8-hydroxylinalool** (2,7-Octadiene-1,6-diol, 2,6-dimethyl-, (2Z)-)	$C_{10}H_{18}O_2$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
	Chrysoeriol (4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-)	$C_{16}H_{12}O_6$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
	Luteolin (4H-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-)	$C_{15}H_{10}O_6$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
Flavonoid glucoside	**Trans-tiliroside** (Trans-tiliroside or kaempferol-3-O-β-D-(6″-E-p-coumaroyl)-glucopyranoside)	$C_{30}H_{26}O_{13}$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
	Cis- tiliroside (4H-1-Benzopyran-4-one, 5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[[6-O-[(2Z)-3-(4-hydroxyphenyl)-1-oxo-2-propen-1-yl]-β-D-glucopyranosyl]oxy]-)	$C_{30}H_{26}O_{13}$	*T.microphylla*	Aerial part	EtOH–H2O (70:30, v/v) extract	(Mekhelfi et al., 2014)
Volatile oils	**D-menthone**	$C_{10}H_{18}O$	*T. microphylla*	Aerial part	Hydrodistillation	(Noman et al., 2015)
	2-Undecanone	$C_{11}H_{22}O$	*T. microphylla*	Aerial part	Hydrodistillation	(Noman et al., 2015)
	Pulegone	$C_{10}H_{16}O$	*T. microphylla*	Aerial part	Hydrodistillation	(Noman et al., 2015)
	Perillal	$C_{10}H_{14}O$	*T. microphylla*	Aerial part	Hydrodistillation	(Noman et al., 2015)

was identified from the extract of leaves and flowers of *T. microphylla* (Kerbab et al., 2015).

4.5. Sterols

The sterols composition of *T. hirsuta* investigated by Dohou et al. (2003), included cholesterol, campesterol, β–sitosterol, and β–stigmasterol (Dohou et al., 2003). Further, two phytosterols (β-sitosterol and β-sitosterol-3-O-glucoside) were identified in the roots and the aerial parts of *T. microphylla* (Ghanem et al., 2014).

4.6. Essential oils

Volatile oils are characteristic of *Thymelaea* plants; a total of 29 volatile compounds were identified in the aerial parts of *T. hirsuta* (Table 2). The volatile fraction was mainly composed of heptane (28.34%), followed by germacrene D (12.98%), γ-eudesmol (11.81%), citronellyl formate (9.98%), trans β-caryophyllene (3.25%) cyclopentasiloxane decamethyl (2.59%), δ-cadinene (2.55%), β-bourbonene (2.43%), citrol (1.87%), and α-amorphene (1.49%). Moreover, the volatile oil was highly dominated by sesquiterpenes proportion (40.73%) including 26.91% of sesquiterpenes hydrocarbons and 13.82% of

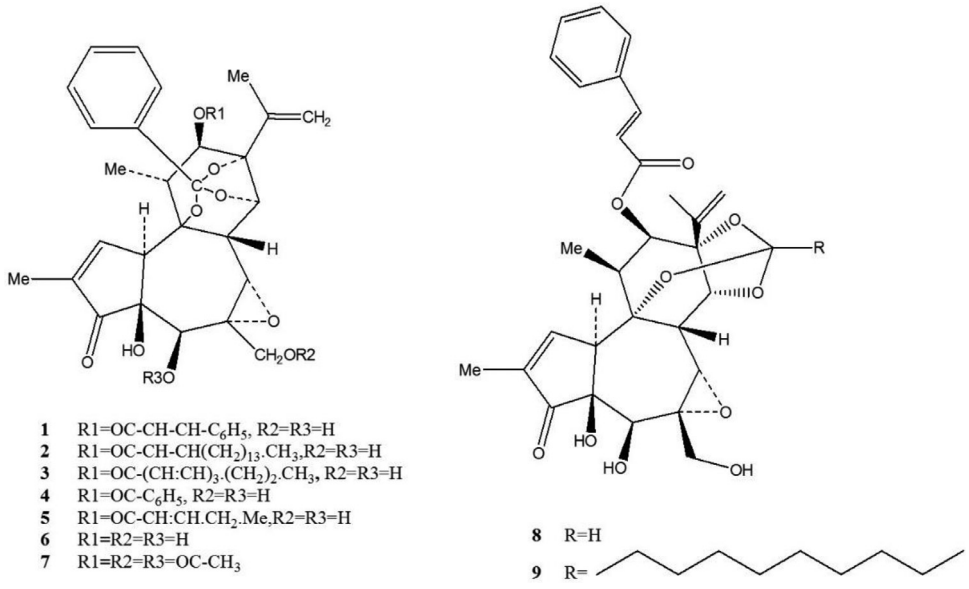

Fig. 5. Chemical structures of different daphnane diterpenes and diterpenoids isolated from the genus *Thymelaea*.

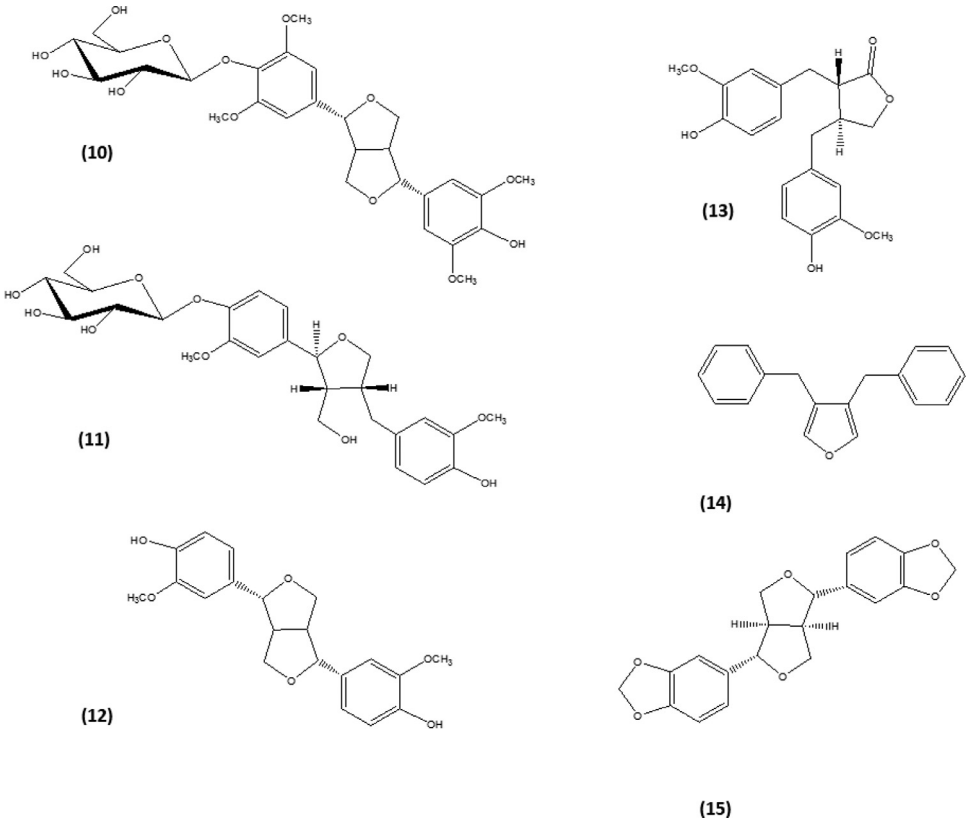

Fig. 6. Chemical structures of different lignans isolated from the genus *Thymelaea*.

oxygenated sesquiterpenes, while the oxygenated monoterpenes represented 13.26% of the total oil (Kadri et al., 2011). On the other hand, the chemical analysis of the essential oil from *T. microphylla* resulted in the presence of eleven volatile compounds dominated by D-menthone (41.86 %), followed by 2-undecanone (23.74 %), pulegone (11.94%), and perillal (9.34 %), respectively. The volatile composition was dominated by 67.84 % of the monoterpenes especially the oxygenated compounds (62.94% of total oil) (Labib et al., 2010).

4.7. Others

From the aerial parts of the Moroccan *T. lythroides,* six molecules were isolated and various classes of compounds were identified as depsipeptide (bassiatin), coumarin (daphenone, daphnelone), dicoumarin (daphnoretin), and dicoumarin glucoside (rutarensin) (Kabbaj et al., 2013). Moreover, chemical investigation of the hydro-alcoholic extract of the aerial parts of Algerian *T. microphylla* revealed

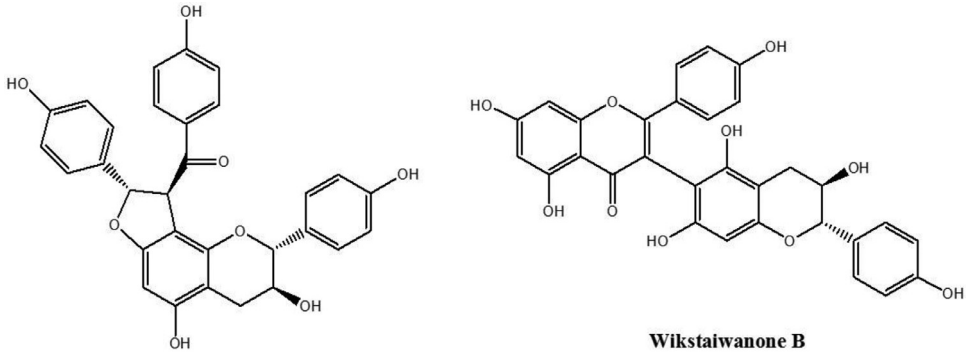

Fig. 7. Chemical structures of the two bioflavonoids were firstly isolated from *T. hirsuta.*

ten secondary metabolites, including three monoterpene glucosides ((3S,6R)-cis-linalool-3,7-oxide β-D-glucopyranoside; 3,7 dimethyl-1-octene-3,6,7-triol-6-O-β-D-glucopyranoside and betulabuside B), two phenylpropanoid glucosides (coniferin and syringin), one benzyl alcohol glucoside, and four ionol glucosides ((E)-4-[3"-(β -D-glucopyranosyloxy)butylidene]- 3,5,5-trimethyl-2-cyclohexen-1-one; 3-oxo-α-ionol-9-O-β-D-glucopyr-anoside; blumenol C-glucoside and vomifoliol-9-O-β-D-glucopyranoside) (Kerbab et al., 2015). Furthermore, the chemo-analysis of the roots and the aerial parts of *T. microphylla* resulted in the identification of two new spiro-γ-lactone glycosides (microphynolides (A and B) (Ghanem et al., 2014). Recently, microphybenzimidazole (a benzimidazole derivative) was isolated as a new compound from the extract of the aerial parts of *T. microphylla* (Noman et al., 2017). As well, 6` hydroxyldaphnoretin was isolated and identified as a new compound from the methanolic extract of *T. hirsuta* (Badawy et al., 2019). In another recent study, the organic extract of the aerial parts of *T. hirsuta* was investigated and different compounds of different classes were isolated and identified such as; triumbelletin (chromene), blumenol A (cyclohexanone), and 3-(4-hydroxy-phenyl)-acrylic acid methyl ester (acrylates) (Nocera et al., 2020).

5. *Thymelaea* genus bioactivities

Different *Thymelaea* species proved to have a valuable potential as antitumor, anti-inflammatory, neuroprotective, antidiabetic, antihypertensive, and antioxidant agents. The most promising activities were included in Table 3.

5.1. Anti-inflammatory and neuroprotective

The nonsteroidal anti-inflammatory drugs are a common treatment of inflammation and associated comorbidities (including affective and cognitive disorders) (Berk et al., 2013; Dantzer et al., 2011) through blocking the arachidonic acid by inhibiting the cyclooxygenase enzyme (COX-1 and/or COX-2), resulting from a reduction of the production of prostaglandin (Laflamme et al., 1999). Nevertheless, these drugs possessed a lot of problems (resistance and side effects); which prompted researchers to investigate other drug development pathways that exert an anti-inflammatory action; but, stripped of undesirable effects. Many studies have reported that polyphenols such as phenolic acids, flavonoids, and proanthocyanidins play a role as a protector against biotic and abiotic stresses. They reported that the polyphenol treatment inhibited the release of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α), IL-1b, and IL-6 induced by chronic and acute inflammation (Kawaguchi et al., 2011). The anti-inflammatory activity of polyphenols was mediated by mechanisms such as MAPKs (ERK and JNK) and NF-kB to decrease NO, COX-2, pro-inflammatory cytokines production (Túnez et al., 2010), and macrophages activation (Wu et al., 2018). The studies suggested that the anti-inflammatory impact of the *Thymelaea* genus was due to the polyphenol and flavonoids compounds, largely distributed in the family (Kristanti et al., 2018).

An *ex vivo* study showed that acetone extract of *T. microphylla* was able to inhibit COX 1 and 2 activities by decreasing the levels of prostaglandins, prostacyclins, and thromboxanes after LPS (lipopolysaccharide) stimulation in peripheral blood cells with IC_{50} = 15.12 μg/ml. *T. microphylla* extract also preserved endothelial cells vessel against the damage induced by TNF-α, in terms of leukocyte adhesion, and cell-released glutathione (GSH) content (Dehimi et al., 2016). As well, aqueous extract of *T. hirsuta* exhibited the same anti-inflammatory impact by reducing the leukocyte migration in carrageenan-induced paw edema model at 500 mg/ kg (Azza et al., 2015), as well as inhibiting adjuvant arthritis in Wistar rat models at 100 mg/kg. The mechanism proposed was that polyphenols exerted their anti-inflammatory activities by the transcriptional regulation of iNOS and TNF-α *via* a complex process involving several transcription factors, including NF-κB, AP-1, and various members of the family C/EBR, ATF/CREB, and STAT (Lowenstein et al., 1993). Furthermore, a study demonstrated that *T. lythroides* had a neuroprotective effect on microglia against neurotoxic circumstances caused by excessive NO production. Thus, *T. lythroides* strongly reduced NO generation in the hippocampus and prefrontal cortex-mediated by LPS, reduced lipid peroxidation and TNFα level after three months from LPS injection compared to the treated group by minocycline. *T. lythroides* was able to reduce the astrocyte activation during the neuroinflammation (Berkiks et al., 2018). Although the exact pro-inflammatory target of polyphenols was not well known in the *T. lythroides* case, it was very likely that they interfered with the NF-kB pathway and led to kinase inhibitor (IkB) phosphorylation. In the cell signalization, *in vivo* immune stimulation by LPS led to activate the TLR4 and so activated two signaling pathways: the canonical (or classical) and non-canonical (or alternative) pathways (Lu, 2008). *Thymelaea* species possessed inhibitory activity on inflammation through targeting many mechanisms; *via* the arachidonic pathway as *T. microphylla* or the MyD88 pathway for *T. lythroides.*

In the same study, *T. lythroides* presented a potential effect on depression and anxiety-like behavior related to inflammation. The authors demonstrated that the anti-inflammatory impact of *T. lythroides* prevented the pups injected by LPS to develop anxiety and depression-like behavior in adult age, speculating the neuroprotective effect of the plant. Usually, the changes in inflammatory markers exhibited an increase in brain cytokines release like TNFα, NO production, lipid peroxidation, and overactivation of microglial cells in the hippocampus. The inflammatory reaction could be accompanied by neuronal damage (Song et al., 2009) and their association with the

Table 3
Bioactivities of the genus *Thymelaea*

Plant species	Extract/ compound	*In vitro/ex vivo/in vivo*	Concentration/dose	Model	Effect	Reference
Anti-inflammatory and neuroprotective						
T. microphylla	Acetone extract	*Ex vivo*	IC_{50} 15.12 μg/mL	LPS-stimulated Peripheral blood samples	It showed a non-significant difference in COX 1 and 2 activities by decreasing the levels of prostaglandins, prostacyclins, and thromboxanes when compared to the aspirin group	(Dehimi et al., 2016)
T. hirsuta	Aqueous extract	*In vivo*	500 mg/kg	Carrageenan-induced rat paw edema model	It showed a 60% of inhibition of paw edema as compared to the drug, diclofenac (100 mg/kg) which showed a 40% of inhibition	(Azza et al., 2015)
T. hirsuta	Aqueous extract	*In vivo*	100 mg/kg	Complete Freund's adjuvant-induced arthritis model	It showed an 85% of inhibition of arthritis inflammation as compared to diclofenac (10 mg/kg; 72%)	(Azza et al., 2015)
T. lythroides	Methanolic extract	*In vivo*	200 mg/kg	LPS-stimulated neuroinflammation in adult rats	It showed a non-significant difference in reduction of NO, lipid peroxidation, and TNFα levels in the hippocampus and cortex when compared to the treated group by the drug minocycline	(Berkiks et al., 2018)
Antidiabetic and antihypertensive						
T. hirsuta	Aqueous extract	*In vivo*	250 mg/kg	Glucose-loaded rats	In the OGTT, a significant decrease of plasma glucose level at 2 h by 20.4% from the control group was observed. In the IVGTT, a significant inhibition (40.5%) of jejunal glucose absorption from the control group was observed	(Bnouham et al., 2007)
T. hirsuta	Aqueous extract	*In vivo*	250 mg/kg	Glucose-loaded and streptozotocin-induced diabetic rats	In the OGTT, the extract significantly reduced the fasting glucose level in glucose-hyperglycemic rats 60 min after oral glucose loading. In streptozotocin-induced diabetic rats, the extract also produced a significant reduction of plasma glucose levels when compared to the untreated group	(El Amrani et al., 2009)
T. hirsuta	Polyphenol-rich fraction	*In vivo*	80 mg/kg	STZ-induced diabetic and l-NAME-induced hypertensive rats.	The extract significantly increased the hepatic glycogen which reached 13.65 ± 1.84 mg/g tissue compared to the levels in untreated rats (6.34 ± 0.75 mg/ g tissue). It also significantly reduced the amount of glucose absorbed in situ perfused jejunum segments by 33.6% compared with the untreated group	(Bnouham et al., 2012)

(*continued*)

Table 3 (*Continued*)

Plant species	Extract/ compound	*In vitro/ex vivo/in vivo*	Concentration/dose	Model	Effect	Reference
T. microphylla	Aqueous extract	*In vivo*	250 mg/kg	Normal rats	The extract showed a very significant decrease in blood glucose level when compared with the control group, so the extract might have a hypoglycemic effect	(Dahamna et al., 2015)
Antitumor and cytotoxic						
T. hirsuta	Hexane and ethanol-water extracts	*In vitro*	Hexane (5 mg/mL) and ethanol-water (0.5 mg/mL) extracts	Human colon cancer cell lines (HT-29)	Hexane and ethanol-water extracts inhibited tumor growth significantly with a percent of inhibition of 58.19% and 65.54%, respectively, using MTT assay. This activity was supposed to be mediated by daphnane compounds	(Akrout et al., 2011)
T. hirsuta	Essential oil	*In vitro*	IC_{50}: 175 μg/mL	Human HeLa tumor cells	Essential oil of aerial parts of *T. hirsuta* exhibited a potent cytotoxic activity on human HeLa tumor cells, with a high IC_{50} value of 175 μg/mL using MTT assay	(Felhi et al., 2017)
T. microphylla	Compound: prestegane B	*In vitro*	IC_{50}: 62.5 μg/mL	Rat brain glioma cells (C6)	Prestegane B showed a selective antitumor activity against rat brain glioma cells (C6) using BrdU ELISA assay	(Noman et al., 2017)
T. hirsuta	Different compounds (6` hydroxyldaphnoretin, mithnin, docosylcoumarate, docosylcaffeate, daphnodorin B, 3`-epi-dihydrodaphnodorin B, and wikstaiwanone B)	*In vitro*	IC_{50}: docosylcoumarate = 51.52 μg/mL docosylcaffeate = 103.80 μg/mL hydroxyldaphnoretin = 1.33 μg/mL daphnodorin B = 24.71 μg/mL 3`-epi dihydrodaphnodorin B = 78.62 μg/mL wikstaiwanone B = 51.00 μg/mL mithnin = 80.11 μg/mL	HepG2 cancer cell lines	These isolated compounds showed a significant antiproliferative activity on HepG2 cells. They caused a significant decrease in the serum levels of AST, ALT, ALP, total bilirubin, GGT, and AFP. Also, a significant increase in *Bax* and *p53* expression was shown	(Badawy et al., 2019)
T. hirsuta	Daphnane diterpenoids as hirseins A and B	*In vitro*	Conc.:1 μM	B16 murine melanoma cells	These compounds showed a significant reduction in melanin content and cell viability from the control group	(Miyamae et al., 2009)
Antioxidant and antimicrobial						
T. hirsuta	The methanolic extract of the variety in Kasserine region	*In vitro*	IC_{50} in DPPH assay: 14.8 $\pm$ 0.35 mg/l IC_{50} in the $ABTS^{\cdot+}$ assay: 6.4 $\pm$ 0.43 mg/l	DPPH and $ABTS^{+}$ assays	The methanolic extract of *T. hirsuta* from the Kasserine region showed high antioxidant capacities due to their high phenolic and flavonoid contents	(Yahyaoui et al., 2018)
T. microphylla	Aqueous and ethanolic extracts	*In vitro*	IC_{50} of aqueous extract: 0.1 mg/mL IC_{50} of ethanolic extract: 0.2 mg/mL	DPPH radical scavenging assay	Aqueous and ethanolic extracts showed a good antioxidant activity	(Dahamna et al., 2015)

(*continued*)

Table 3 (*Continued*)

Plant species	Extract/ compound	*In vitro/ex vivo/in vivo*	Concentration/dose	Model	Effect	Reference
T. microphylla	Hydroalcoholic extract and fraction VI	*In vitro*	EC_{50} of the extract: 180.80 mg/mL EC_{50} of the fraction VI: 11.2 mg/mL	DPPH radical scavenging assay	Fraction VI showed a non-significant antioxidant activity (EC_{50}= 11.2 mg/mL) when compared to the standard a-tocopherol (EC_{50}= 10.1)	(Kerbab et al., 2015)
T. microphylla	Essential oil	*In vitro*	Conc.: 8 mg/mL	The disc diffusion method	The essential oil exhibited a strong antibacterial activity against *Staphylococcus blanc* using the disc diffusion method at 8 mg/mL	(Noman et al., 2015)
T. hirsuta	Ethyl acetate extract	*In vitro*	624 μg/mL	Agar-well diffusion assay	The ethyl acetate extract showed a drastic bactericidal effect after 5 min against *Staphylococcus aureus* and *Bacillus subtilis* as well as antifungal activities against *Alternaria alternate* and *Fusarium graminearum*	(Trigui et al., 2013)

onset of major depression in adulthood (Raison et al., 2006). Based on the studies, the TNFα could mediate LPS-induced indoleamine 2, 3-dioxygenase (IDO) activity *via* an IFNγ independent mechanism (O'connor et al., 2009). IDO is an extrahepatic enzyme that is present in macrophages and other cells that degrades the essential amino acid tryptophan along the kynurenine pathway representing a potential connection between activation of CNS innate immune cells and longer-lasting behavioral responses (Dantzer et al., 2011). This enzyme was induced by proinflammatory cytokines, mainly IFNγ (O'connor et al., 2009) and TNFα (Dantzer et al., 2011). When IDO was activated in conditions of chronic inflammation, its degree of activation was correlated to the intensity of depressive symptoms as observed in cancer patients chronically treated with IFNα. The administration of the cytokine-induced LPS and depressive-like behavior, as measured by increased immobility in the forced swim test and tail suspension test, decreased consumption of anhedonia, and suppression of sexual behavior (Túnez et al., 2010), which can be attenuated by chronic anti-inflammatory administration such as Minocycline or the medicinal plants. The chance that the *Thymelaea* genus had, as an anti-depression effect, was not surprising as the majority of the species among this family had potent anti-inflammatory and antioxidant impacts. The postnatal treatment by *T. lythroides* after the LPS immune stimulation prevented the rats in adult age to develop affective behavior disorders by protecting the pups from oxidative stress, and microglia activation (Berkiks et al., 2018).

5.2. Antidiabetic and antihypertensive

In a study performed by Bnouham et al. (2007), the aqueous extract of *T. hirsuta* growing in eastern Morocco was tested in rats by the Oral Glucose Tolerance Test (OGTT) and Intravenous Glucose Tolerance Test (IVGTT). In the OGTT, the rats received 250 mg/kg of the extract 30 min before glucose loading (1 g/kg), where it produced a significant decrease of plasma glucose level at 2 h by 20.4%, and 3 h by 16.4% after glucose loading. In the IVGTT the aqueous extract of *Thymelaea* produced a slight decrease of glycemia 60 min after glucose loading. The addition of *T. hirsuta* aqueous extract at a dose of 250 mg/kg, induced a significant inhibition (40.5%) of jejunal glucose absorption. Toxicity tests (high LD_{50} value) suggested no adverse effect of the use of the plant (Bnouham et al., 2007).

As well, the hypoglycemic effect of the aqueous extract of *T. hirsuta* was studied by El Amrani et al. in normal, glucose-hyperglycemic, and streptozotocin-induced diabetic rats (El Amrani et al., 2009). The aqueous decoction of the aerial parts of *T. hirsuta* L. was prepared according to the traditional Moroccan method (10 g powder + 100 ml water, boil for 10 min, cool for 15 min). Then the decoction was filtered and dried to be tested for antihyperglycemic effect at a dose of 250 mg/kg in rats. In normal rats, the extract produced a significant reduction in plasma glucose levels through the 1st to the 4th hour after administration. However, the effect was diminished after 6 h of administration. Concerning the OGTT, the extract could significantly reduce the fasting glucose level in glucose-hyperglycemic rats 60 min after oral glucose loading (2 g/kg). In streptozotocin-induced diabetic rats using 50 mg/kg b.wt. STZ, single oral administration of *T. hirsuta* also produced a reduction of plasma glucose levels which was significant at 60 min and went down after that. The aqueous extract of *T. hirsuta* possessed both hypoglycemic and antidiabetic effects in normoglycaemic, glucose-hyperglycaemic, and streptozotocin-induced diabetic rats. In a similar study, the aqueous extract of the aerial parts of *T. hirsuta* chronically administered in the drinking water at a level of 400 mg/L for 5 weeks to streptozotocin-induced diabetic rats, caused a 38.2% decrease in plasma glucose levels. Diabetes was induced in rats by administration of STZ intraperitoneally (i.p.) (90 mg/kg). In the oral glucose tolerance test, the oral administration of the water extract (150 mg/kg) of *T. hirsuta* 30 minutes before glucose (2 g/kg), had no significant effect. Glucose consumption by isolated rat hemidiaphragm in the presence of the aqueous extract was slightly increased when compared to control (Bnouham et al., 2010).

The aqueous extract of *T. microphylla* at a single oral dose of 250 mg/kg body weight in rats caused a very significant decrease in blood glucose level, so the extract might have a hypoglycemic effect (Dahamna et al., 2015).

Bnouham et al. (2012) proved the antidiabetic and antihypertensive activity of *T. hirsuta* in STZ-diabetic no-deficient hypertensive rats. The effects of administration of polyphenol-rich fraction from the aerial parts of *T. hirsuta* in a dose of 80 mg/kg per day (PRF-T) in the drinking water for 21 days, were evaluated in diabetic–hypertensive (DH) rats. Diabetes was induced by a single dose of STZ (90 mg/ kg, i.p.). Hypertension was induced in the same rats by administration of 30 mg/ kg per day orally of NO synthase inhibitor N^G-nitro-l-arginine methyl ester; l-NAME for 3 weeks. Administration of PRF-T together with L-NAME in rats prevented the rise in blood pressure. Administration of 2 mL/ kg per day of PRF-T to DH

rats significantly increased the hepatic glycogen which reached 13.65 ± 1.84 mg/g tissue compared to the levels in the untreated DH rats (6.34 ± 0.75 mg/ g tissue). Furthermore, PRF-T significantly reduced the amount of glucose absorbed in situ perfused jejunum segments by 33.6% compared with the untreated group (Bnouham et al., 2012).

5.3. Antitumor and cytotoxic

Few papers described a moderate to high antitumor and cytotoxic activity of the *Thymelaea* genus either by *in vitro* or *in vivo* assays. Akrout et al. (2011) investigated the antitumor growth inhibition on human colon cancer (HT-29) by extracts of *T. hirsuta* collected in southern Tunisia. This study showed that hexane and ethanol-water extracts inhibited tumor growth significantly with a percent of inhibition of 58.19% and 65.54%, respectively (Akrout et al., 2011). This activity could be mediated by compounds such as daphnanes, isolated from this plant (Abou–Karam et al., 1998; Brooks et al., 1990a; Kawano et al., 2007; Miyamae et al., 2009). Further, the study conducted by Felhi et al. (2017), showed that the cytotoxic activity of essential oil of aerial parts of *T. hirsuta* exhibited a potent cytotoxic activity on human HeLa tumor cells, with a high IC_{50} value of 175 μg/mL (Felhi et al., 2017). As well, Kawano et al. (2007) showed that *T. hirsuta* extract might have potent anti-melanogenesis effect through decreasing the synthesized melanin content in the murine melanoma B16 cells without cytotoxicity after 48 h of incubation (Kawano et al., 2007). This activity was mediated by ERK1/ 2 phosphorylation and inhibition of tyrosinase expression. The ERK1/ 2 phosphorylation is a target for a new melanogenesis anticancer therapies (Kim et al., 2018; Oh et al., 2018). Moreover, the antitumor effects of new compound microphybenzimidazole and two known compounds, prestegane B, and umbelliferone isolated from *T. microphylla,* were assayed. Indeed, the authors showed a selective antitumor activity of prestegane B and umbelliferone against rat brain glioma cells (C6) (Noman et al., 2017). Furthermore, the plant compound daphnoretin was moderately cytotoxic (IC_{50} = 21–114 mM) only in rapidly proliferating cultured mammalian cells, and also, inhibited the erb-b oncogene product, a tyrosine-specific protein kinase of human epidermal growth factor receptor (Abou–Karam et al., 1998). In another study, the aerial parts of *T. hirsuta*, harvested from four distinct localities of Tunisia, were tested against two human cell lines adenocarcinoma breast cancer (MCF-7) and colon human cancer (OVCAR) (Yahyaoui et al., 2018). On the MCF-7 cell line, the ethyl acetate extract of Kasserine and Fernana, produced inhibition of 53.00% ± 7.40 and 70.10% ± 2.80 respectively, while the methanol extract of the Chebba region exhibited the highest activity (62.70% ± 6.00 inhibition). The hexane extract of Kasserine and Fernane exhibited higher activity against OVCAR with 72.60 ± 4.10% and 63.30% ± 3.60 respectively. Also, a strong activity was recorded with a percent of inhibition of 70.80 ± 5.20% and 68.30 ± 2.30% for the ethyl acetate from Fernana and the ethanol extract from Chebba, respectively (Yahyaoui et al., 2018).

On the other hand, different compounds (6` hydroxyldaphnoretin, mithnin, docosylcoumarate, docosylcaffeate, daphnodorin B, 3`-epidihydrodaphnodorin B, and wikstaiwanone B) isolated and identified in the methanolic extract of *T. hirsuta*, showed a significant anti-proliferative activity on HepG2 cells. These compounds caused a significant decrease in the serum levels of AST, ALT, ALP, total bilirubin, GGT, and AFP. Also, a significant increase in *Bax* and *p53* expression was shown (Badawy et al., 2019).

Daphnane diterpenoids as hirseins A and B isolated from *T. hirsuta*, were tested against melanogenesis B16 Melanoma cells. The viability results suggested that the reduction in melanin content was most likely due to mechanisms that inhibited the synthesis or activity of melanogenesis enzymes rather than by cell death or cytotoxicity (Miyamae et al., 2009). Indeed, the *in vitro* antiproliferative activity of a subfraction of the CH_2Cl_2–MeOH extract of *T. microphylla* aerial parts and the major compound isolated from this fraction trans-tiliroside, proved moderate activity against human cervical cancer cells (HeLa) and rat brain tumor cells (C6) (Noman et al., 2015).

5.4. Antioxidant and antimicrobial

The antioxidant properties of the essential oil from T. hirsuta aerial parts were examined by Kadri et al. (2011). The authors determined the antioxidant activities using three methods: diphenylpicrylhydrazyl (DPPH) assay, carotene bleaching assay, and reducing power test, where the results were compared to the reference BHT (butyl hydroxytoluene). T. hirsuta essential oil possessed a good capacity to scavenge free radicals and to prevent lipid peroxidation, due to the presence of hydroxylated groups such as phenolic and terpenoid compounds in the chemical composition (Kadri et al., 2011). In another study, among all regions, the Kasserine region variety of T. hirsuta gave the most important antioxidant activity in both DPPH and ABTS assays. The antioxidant capacity of various extracts from the aerial parts of T. hirsuta, harvested from four distinct localities of Tunisia prepared by cold maceration, was investigated by DPPH and $ABTS^+$ assays. In the DPPH assay, the methanol extract possessed the highest activity with IC_{50} ranging from 14.8 ± 0.35 to 16.55 ± 0.44 mg/l, followed by ethanol extract (14.45 ± 0.957 to 37.9 ± 0.62 mg/l), and by acetate and hexane extracts with IC_{50} values superior or equal to 123 ± 8.4 mg/l. In the $ABTS^{\cdot+}$ assay, the methanolic extract exhibited the strongest activity (6.4 ± 0.43 to 22.23 ± 1.62 mg/l), followed by the ethanolic extract (18.43 ± 0.75 to 25.42 ± 0.40 mg/l) (Yahyaoui et al., 2018).

Furthermore, Amari et al. (2014) assessed the antioxidant activities of different aerial parts of T. hirsuta from the west of Algeria (leaf, flower, and stem). T. hirsuta extracts exhibited a concentration-dependent scavenging activity (flower>leaf>stem). Aerial parts of T. hirsuta were closely related to their phenolic hydroxyl groups, which donate hydrogen atoms and rapidly halt radical reactions by a radical scavenging mechanism (Amari et al., 2014).

Moreover, the aqueous extract of the dried aerial parts of T. microphylla showed strong scavenging activity with IC_{50} of 0.1 mg/ml; while the ethanolic extract had an IC_{50} of 0.2 mg/ml (Dahamna et al., 2015). Kerbab et al. (2015) also reported the free radical-scavenging activity of the hydroalcoholic extract and its fraction from T. microphylla. The extract demonstrated an EC_{50}= 180.80 mg/ml, and the fraction VI (EC_{50}= 11.2 mg/mL) compared to that of the well-known antioxidant, a-tocopherol (EC_{50}= 10.1mg/ml) (Kerbab et al., 2015).

Recently, methylene chloride–methanol (1:1) extract of the aerial parts of T. microphylla showed 72 % scavenging activity of DPPH which was more active than the standard vitamin C (Labib et al., 2010). Further, the air-dried aerial parts of T. hirsuta were extracted with solvents of increasing polarity viz. hexane, chloroform, ethyl acetate, acetone, ethanol, and water separately. Antioxidant activity of different extracts was evaluated using DPPH where acetone and ethyl acetate extracts had the highest activity, followed by water extract while the ethanol and chloroform extracts showed low activity. On the other hand, in the hydroxyl radical scavenging assay, the chloroform extract had the highest activity, followed by ethyl acetate and acetone extracts, while the ethanol showed lower activity (Trigui et al., 2013). Indeed, methanolic and aqueous extracts of leaves and stems from T. microphylla were assayed using FRAP and DPPH assays, where the authors reported a positive correlation between phenolic content and antioxidant activity comparable to previous work (Benhammou et al., 2009).

Concerning the antimicrobial activities, the aqueous and ethanol extracts of the dried aerial parts of T. microphylla showed no antibacterial activity against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Klebsiella oxytoca (Dahamna et al., 2015). On the other hand, the essential oil components of aerial parts of T. microphylla prepared at room temperature exhibited strong

antibacterial activity against Staphylococcus blanc using the disc diffusion method at 8 mg/mL (Noman et al., 2015). Further, the air-dried aerial parts of T. hirsuta were extracted with solvents of increasing polarity viz. hexane, chloroform, ethyl acetate, acetone, ethanol, and water separately at 30 ^{0}C for 24 h. The prepared extracts were tested using the agar-well diffusion assay (4 mg/well) against twenty microorganisms, food-borne bacteria, and spoilage fungi. Among the tested extracts, only the ethyl acetate extract showed antibacterial activity against Staphylococcus aureus and Bacillus subtilis as well as antifungal activities against Alternaria alternate and Fusarium graminearum. The ethyl acetate extract showed a drastic bactericidal effect after 5 min at a concentration of 624 μg/ml and good antifungal activity through a cellular target such as the pump H^+-ATPase (Trigui et al., 2013). Moreover, the antibacterial activity of the plant essential oil was studied using the disc diffusion method on five different bacterial strains. The plant exhibited high activity on B. subtillus, E. coli, E. faecalis bacteria and no effect against P. aureiginosa and S. aureus due to the developed resistance (Bounab et al., 2017).

6. Conclusion and recommendations

Herbal medicine is the most important type of complementary medicine. There are a lot of researches that have shown the role of many herbs in the treatment of different ailments such as inflammation, cancer, diabetes, and hypertension. In our review, we introduced the various bioactivities of the genus Thymelaea and their suggested mechanisms of action. The genus Thymelaea presented a valuable potential to prevent and treat various disorders, such as inflammation, cancer, and diabetes which have been evaluated in only experimental studies; but lacked the clinical data which is more reliable than others. The interesting chemodiversity of those plants can lead to the use of their potent bioactive compounds as drug candidates, performing their bioactivity through different mechanisms of action. This review correlated the bioactivity exhibited with the different active compounds in a dose-response mode underlying the supposed mechanism of action, giving recommended points of study for future clinical research.

On the other hand, few scientific reports explained the toxicity effects of Thymelaea extracts and their isolated active compounds, therefore, the evaluation of their safety should be considered as a future recommendation. Despite the promising biological activities of all Thymelaea species stated in this review, more studies are needed to determine which compounds are responsible for the extract's activity. In addition, it could be interesting to associate the phytotherapeutic potential of Thymelaea species with those of the clinical trials with a large number of participants and meta-analyses for the treatment of different ailments such as infection, inflammation, and neurodegenerative diseases to develop an effective, economical and safe therapeutic approach.

Declaration of Competing Interest

The authors declare no conflict of interests.

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