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CHEMO TAXONOMY OF SECONDARY METABOLITS OF *Vitex agnus-castus L*

Habbab Abdalah [1*], Nasser Belboukhari[1], Khaled Sekkoum[1], Yoshihiti Shonio[2]

[1] Bioactive Molecules and Chiral Separation Laboratory, Faculty of Exact Sciences, University TM Bechar, Istiklal street PO417 Bechar 08000, Algeria

[2] Natural product laboratory, Department of bioresource engineering, Faculty of agriculture, Yamagata University, Tokyo, Japan

Abstract

Plants and their active constituents play an important role in the prevention of a variety of ailments. *Vitex agnus-castus* L. was already in ancient medicinal art as an official medicinal plant.These species contain a variety of potentially bioactive molecules, such as iridoids, flavonoids, diterpenoids and essential oils. This review attempts to encompass the available literature on*Vitex agnus-castus* L. for giving an overview of the most widely studied of the known phytochemical constituents.

Key words**:** *Vitex agnus-castus L, phytoconstituents, essential oil.*

1. Introduction

Medicinal plants have been used by humanity for millennia **[1]**;their use is as old as humanity itself. The range of species used and their scope for healing is vast. Cures as yet undiscovered may exist in plants as yet undescribed. In 2008, it is estimated that the number of higher plant species used worldwide for medicinal purposes is more than 50,000. This equates to approximately 20% of the world's vascular flora and constitutes the biggest spectrum of biodiversity used by people for a specific purpose **[2]**.

Different aromatic plants are characterized by the biosynthesis of odorous molecules which constitute that are called essential oils (EO) known for a long time for their antiseptic and therapeutic activity in popular medicine. The chemical composition of essential oils is rather complex, the terpenic and aromatic compounds representing the principal constituents. The nature of the chemical function of the majority compound (phenol, alcohol, aldehyde, ketone ...) plays a preponderant role in the efficiency of their biological activities **[3]**.

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* Corresponding author.
E-mail: belboukhari.nasser@yahoo.fr (Habbab A.).
Address: University TM Bechar

The choice of plants to be study will be based on several criteria, with the aim of phytochemical and biological valorization of substances of vegetable origins. Among the most used criteria is that of their use in traditional medicine which values the experience accumulated by the autochtones. Another target is to consider the ecosystem in which the plants are growing.

As part of the research on medicinal plants of South-West Algerian, carried out by our laboratories (BMCSL and POSL), we have targeted the plant *Vitex agnus-castus* L of the Verbenaceae family for the purpose of phytochemical valorization of this species

2. *Vitex agnus-castus* L species

2.1.Botanical classification:

Vitex agnus-castus L. (Lamiaceae; formerly Verbenaceae) **[4]**is a botanical plant that has the following NationalOceanographic Data Center Taxonomic Code **[5-7]**:

Kingdom	Plantae
Phylum	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Under-class	Asteridae
Superorder	Lamianae
Order	Lamiales
Family	Verbenaceae
Under-family	Viticoideae
Genus	*Vitex* L
Species	*Vitex agnus-castus* L

2.2.Common names:

The species *Vitex agnus-castus* L has several common names such as **[7]**:

English: Chaste tree, Monk's pepper, Hemp tree and Wild lavender.

French: Gattilier commun, Poivre sauvage, Agneau chastre et Petit poivre.

Arabian: Hashishatabu-shih &Shajeratu-ar-ruh-bun.

2.3. Description:

A strongly aromatic shrub or low tree small tree 3 – 9 ft (~1 – 3 m) tall ofthe verbenaceae family. The leaves, 5-9, are digitate and velvetyand the underside is white-felted.Flowers are pale purple or violet, ininterrupted spikesproduce gray-brown fruits. The dry fruits are thesize of a black peppercorn, and these drupescontain four seeds **[8,9]**.

Fig. 1: The morphology of *Vitex agnus-castus* L (Hansel R et *al.* 1994)

Fig. 2: a) *Vitex agnus-castus* L (Fendi, Bechar, South-West Algerian) a.1) Seeds; a.2) Flowers; a.3) Leaves.

2.4.Distribution:

The plant grows in sandy (light) and loamy (medium) soils and in nutritionally poor soilcannot grow in the shade.The plantis now naturalized in most of the Eastern and Southern United States and in the tropics andwarm temperate regions **[10]**.There are approximately 380 species in the genus *Vitex* LINNE, which are found in thewarmer regions of both hemispheres. *Vitex agnus-castus* is native in the whole Mediterraneanregion up to the west of Asia and is found m dense stands m coastal areas and along rivers **[7]**.

In Algeria, this species finds an ultimate refuge in the wadis of Menou-aaraar and Kherrouaa in the heart of the Sahara (Gattilier or kherouaa) **[11]**.

2.5.Previous chemical studies:

The species *Vitex agnus-castus* L is rich in secondary metabolites; the main constituents include flavonoids, iridoids, diterpenoids, progestins, essential oils and ketosteroids **[12, 13]**.Total polyphenolic content forthe leaves (7.36% to 20%), flowers (9% to 10.64%) and fruits (6.92% to 24%) has beendetermined [14, 15]. The highest tannin content was foundin the leaves (0.68% to 3%); tannin content was similar in the flowers (0.24% to 2%) and fruits(0.24% to 1.6%) **[14]**.

2.5.1. Iridoids:

The iridoids are separated in three groups:iridoid glycosides, secoiridoid glycosides and non-glycosylated iridoids. Only iridoid glycosides are derived from *V. agnus-castus*. The iridoid glycosides were isolated from the leaves and fruits of the plant and includeAgnosid (0,7% in the leaves), Aucubin (0,3%) and unidentified glycosides constituted0,07% **[7, 16]**.The methanolic extract of the flowering stems of *Vitex agnus-castus* yielded three new iridoids:agnucastosideA, agnucastoside B and agnucastoside C in addition to four known iridoids (mussaenosidic acid and 6'-*O*-*p*-hydroxybenzoylmussaenosidic acid) and myzodendrone **[12, 17]**.

Table 1: Iridoids isolated from the species*Vitex agnus-castus* L.

Structure		Compound	References
1	**1a**	Aucubin	[12]
	1b	Agnusid	[12]
2	**2a**	Mussaenosidiqueacid	[12]
	2b	6'-*O*-*p*-hydroxybenzoylmussaenosidic acid	[12]
	2c	Agnucastoside A	[12]
	2d	Agnucastoside B	[12]
3		Agnucastoside C	[12]
4		Myzodendrone	[12]
5		Eurostoside	[7]

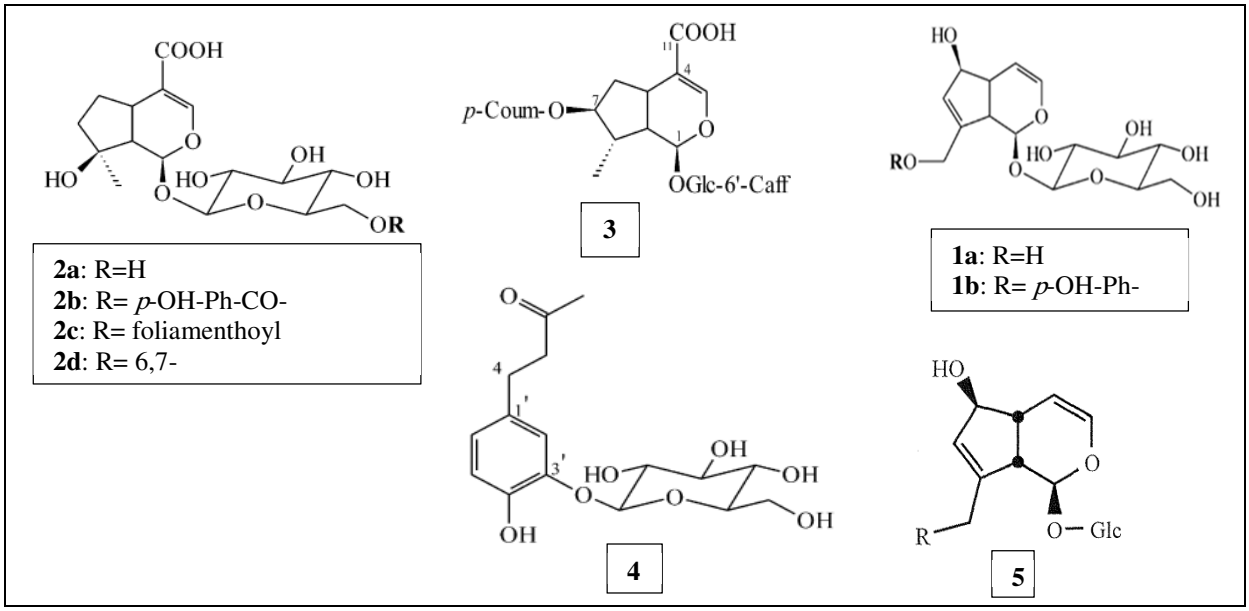


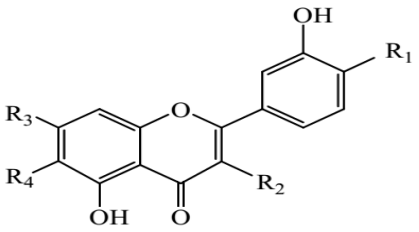
Fig. 3: Iridoids isolated structures of*Vitex agnus-castus* L species.

2.5.2.Flavonoids:

Flavonoids occur in all higher plants, but are missed in bacteria, algae,molds and the whole animal kingdom **[7]**.The flavonoid content has been determined inchaste tree leaves (1.0-2.7%), flowers(1.0-1.5%) and fruits (0.5-1.0%). Flavonoidsinclude flavonol derivatives of kaempferol,vitexin and quercetagetin, the major constituentbeing casticin. Four new flavonoids, luteolin6-C-(4"-methyl-6"-O-trans-caffeoylglucoside),luteolin 6-C-(6"-O-trans-caffeoylglucoside),luteolin 6-C-(2"-O-trans-caffeoylglucoside) andluteolin 7-O-(6"-p-benzoylglucoside,togetherwith four known ones 5,4'-dihydroxy-3,6,7,Y-tetra-methoxy flavone, luteolin, artemetin and isorhamnetin were isolated from the root barkof *Vitex agnus-castus* L **[14, 18]**.

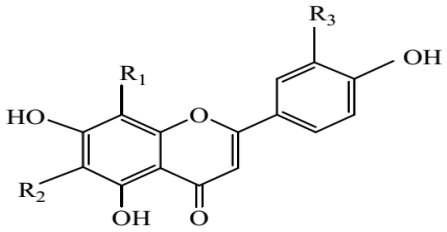
Table 2: Flavonoids isolated from the species *Vitex agnus-castus* L.

Structure		Compound	References
6	**6a**	Quercetagetin	[14, 18]
	6b	Casticin	[14, 18]
7		Vitexin	[14]
8		Kaempferol	[14]
9	**9a**	6 -C- (4"-methyl-6"-O-transcaffeoylglucoside) Lutéoline	[14, 19]
	9b	6- C- (6"-O-transcaffeoylglucoside) Luteolin	[14, 19]
	9c	6- C- (2"-*O*-transcaffeoylglucoside) Luteolin	[14, 19]
10	**10a**	7-*O*- (6"-*p*- benzoylglucoside) Luteolin	[14, 19]
	10b	5, 4'-dihydroxy-3,6, 7, 3'-tetramethoxyflavone	[14]
	10c	Artemetin	[14, 19]
	10d	Isorhamnetin	[14, 19]
11		Luteolin	[14, 19]

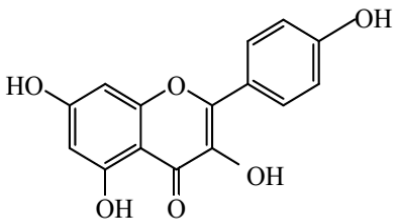


6a: R_1= OH; R_2= OH; R_3= OH; R_4= OH

6b: R_1= OCH_3; R_2= OCH_3; R_3= OCH_3; R_4= OCH_3



7 : R_1= C-glu ; R_2= H ; R_3= H



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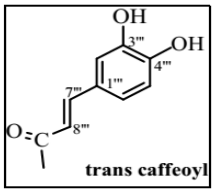
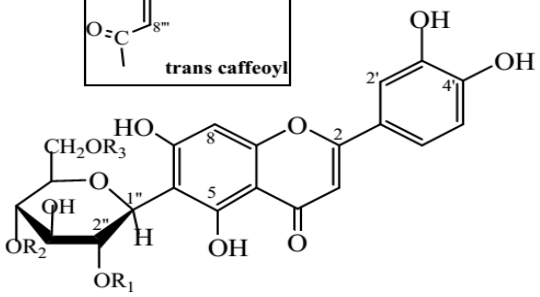
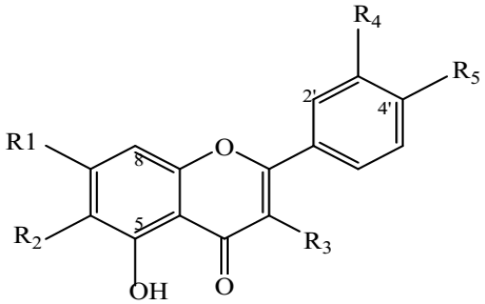




9a: R_1= H; R_2= OH; R_3= *trans*caffeoly

9b: R_1= H; R_2= H; R_3= *trans*caffeoly

9c: R_1= *trans*caffeoly; R_2= H; R_3= H



10a: R_1= *O*-Glu (6"-*p*-hydroxybenzoyl; R_2= H; R_3= H; R_4= OH; R_5= OH

10b: R_1= OCH_3; R_2= OCH_3; R_3= OCH_3; R_4= OCH_3; R_5= OH

10c: R_1= OCH_3; R_2= OCH_3; R_3= OCH_3; R_4= OCH_3; R_5= OCH_3

10d: R_1= OH; R_2= H; R_3= OH; R_4= OCH_3; R_5= OH

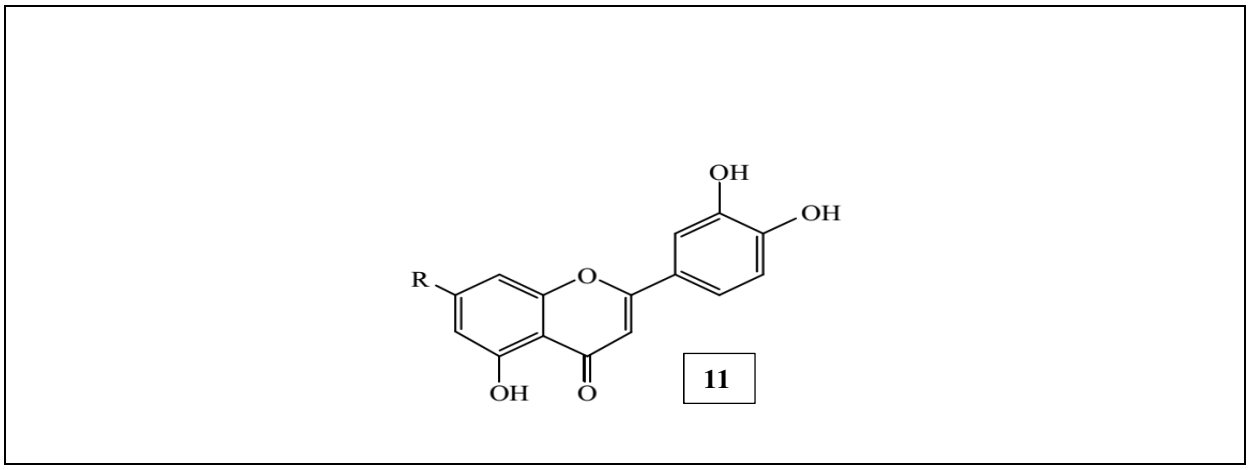


Fig. 4: Flavonoïdesisolated structuresfrom the species *Vitex agnus-castus* L.

2.5.3.Diterpenes:

There is some indication that the leaves and fruits of *Vitex agnus-castus* also contain diterpenoids and sesquiterpenoids besides monoterpenoids **[20]**. Two new halimane-type diterpenoids, viteagnusins A and B(**12** and**13**), and three new labdane-type diterpenoids, viteagnusins C, D, and E (**14, 15** and **16**), were isolated from the fruit of *Vitex agnus-castus* L. along with two known diterpenoids **[21]**. A new labdane-type diterpenoidglucoside and two new labdane-type diterpenoids were isolated from the fruit of *V. agnus-castus* L. along with 14 known compounds comprising seven labdane-type diterpenoids, one halimanee-type diterpenoid, two oleanane-type triterpenoids, two ursane-type triterpenoids, one aromadendrane-type sesquiterpenoid, and one flavonoid **[22]**. A novel labdanediterpene alkaloid, vitexlactam A was isolated as a prism from the n-hexane extract of the fruitsof *Vitex agnus-castus* through normal and reverse phase column chromatography **[23]**.

New labdane-type diterpenoid ,6β, 7β-diacetoxy-13-hydroxy-labda-8,14-diene, was isolated [24]. A new labdane-diterpene, viteagnusin I (**17**), was isolated from the fruits of *Vitex agnus-castus* L, and their structure characterized byspectroscopic methods (NMR and MS) **[25]**.

Table 3: Some diterpenes isolated from de species *Vitex agnus-castus* L.

Structure	Compound	References
12	Viteagnusin A	[21,22]
13	Viteagnusin B	[21,22]
14	Viteagnusin C	[21,22]
15	Viteagnusin D	[21,22]
16	Viteagnusin E	[21,22]
17	Viteagnusin I	[25]
18	Viteagnusin H	[25]

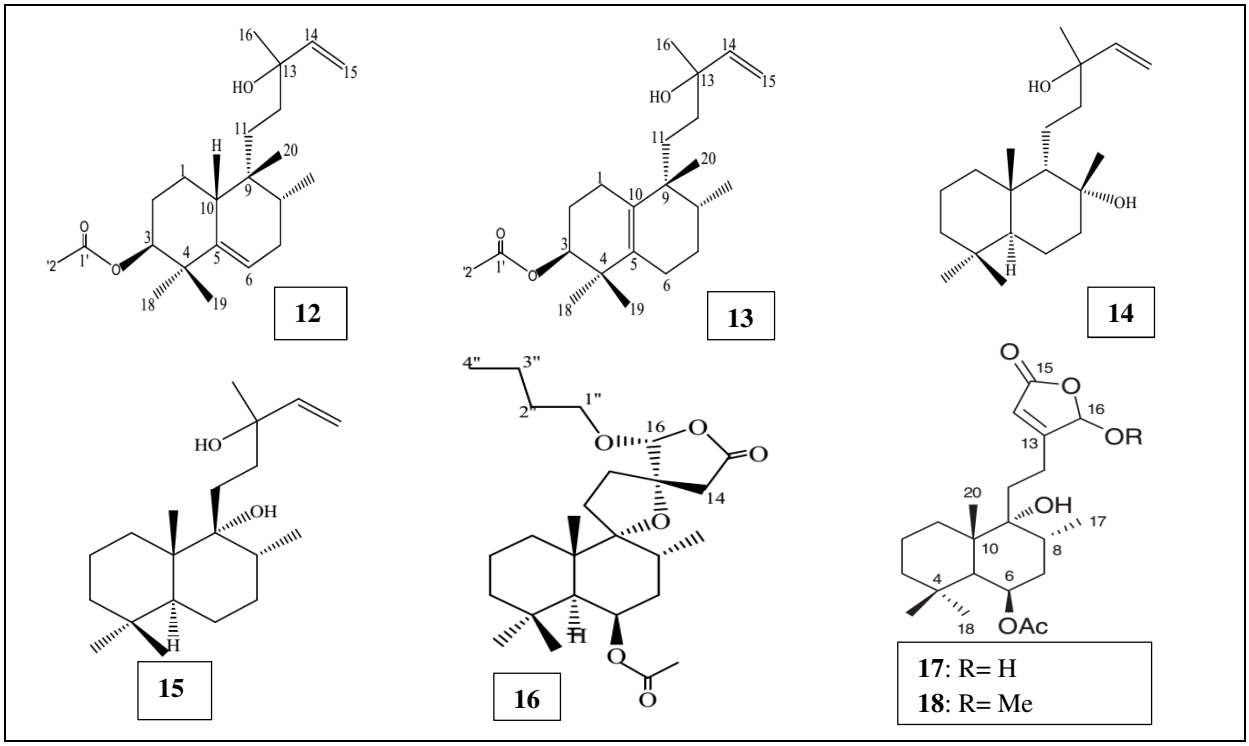


Fig. 5: Diterpenes isolated structures of *Vitex agnus-castus* L.

2.5.4.Essential oils :

The amount of the essential oil of *Vitex agnus-castus* differs from 0.023% to 2.8% inthe leaves, from 0.51 to 2.0% in the fruits and from 0.16 to 1.8% in the flowersaccording to different references **[7]**.

Mature and immature fruits of *Vitex agnus-castus* L. population were chosen to investigate different parameters such as comminution, maturity, distillation period and extraction method influencing the essential oil yield and composition. The effect of the comminution and the maturity of the plant material showed highly significant differences in yield and composition of the essential oils obtained, as well as the distillation duration from one to five hours and the method applied **[26]**.

Essential oils present in the *V. agnus-castus* L. mainly includes the following: monoterpenoids, 1,8-cineol, limes, linalool, terpinyl acetate, alphapinenes and beta along with sabinene, castine, myrcene, citronellol, cymene and camphene. Sesquiterpenoids such as caryophyllene, farnescene, cardinene and ledol also are present [14].The major constituent of the essential oil in the leavesand the fruits is 1,8-cineole. It often occurs together with limonene. Other dominateconstituents are bornyl acetate, β-caryophyllene and α-teipinyl acetate.The fruits also contain camphor, *p*-cymene, sabinene, E-β-farnesene, 4-terpineol, andgermacrene in higher concentration.As an exception Galletti et *al*.,had combined the extraction and the determination of the essential oil[20,27].They used pyrolysis gaschromatography coupled with mass spectrometry.

Several contents of the essential oil components obtained by different authors can be seen in Table 4.

Table 4: Amount and composition of the essential oils of different parts of *vitex agnus-castus* L.

References	**(Galletti et *al*., 1995)** [27]			**(Galletti et *al*., 1996)** [20]		**(Senatore et *al*., 1996)** [28]			**(Ghannadi et *al*., 2012)** [29]
Country	Italy			Italy		Italy			Iran
Part	Leaves (dried)	Fruits (dried)	Flowers (dried)	Seeds	Fruits (dried)	Inflorescences[c] (dried)	Leaves[c] (dried)	Fruits[d] (dried)	Seeds
Totalamount	TIC[a]	TIC[a]	TIC[a]	1% (v/w) TIC	0.51% (v/w) TIC[a]	1.4% (v/w) % of oil	0.8% (v/w) % of oil	1.8% (v/w) % of oil	1% (v/w) TIC
1,8-Cineole	27.9[b]	33.4[b]	15.8[b]	-	15.1[b]	14.1	15.6	20.6	-
Limonene				-		1.8	0.1	0.5	-
α-pinene	12.5	3.5	8.1	-	0.7	5.5	4.0	6.8	-
α-terpinyleacetat	2.7	7.7	1.6	11.6	17.1	0.2	0.3	0.1	11.6
α-thujene	0.6	0.1	-	-	-	0.2	0.2	trace	-
β-caryophyllene	4.4	4.8	16.8	5.8		9.7	8.9	9.3	5.8
β-farnesene	-	-	-	-	17.2	9.1	8.6	6.9	-
β-pinene	-	-	-	-	-	2.8	2.4	1.5	-
Caryophylleneoxid	0.3	0.1	0.6	24.9	-	0.7	0.5	2.5	24.9
Germacrene	0.1	8.1	1.4	-	11.2	-	-	-	-
Myrcene	0.7	0.5	0.6	-	0.1	-	-	-	-
p-cymene	0.2	trace	0.2	-	trace	0.2	trace	-	-
Sabinene	12.9	14.6	8.0	-	3.3	6.3	6.9	7.1	-

[a]TIC : % of the total ion chromatogram
[b]1,8-cineole et le limonene were detected together
[c] collected injuillet.
[d] collected in August.

References	**(M. G. B. Zogbi et *al*., 1999)** [30]			**(D. Stojkovic et *al*., 2011)** [31]		
Country	Brezil			Serbia		
Part	Leaves (Fresh)	Flowers (Fresh)	Fruits (Fresh)	Unripe fruit	ripe fruit	Leaves
Total amount	0.3% (v/w) % of the oil	0.2% (v/w) % of the oil	% of oil	%ID	%ID	%ID
1,8-Cineole	33.5	13.5	18.2	17.5	16.3	22.0
Limonene	-	-	-	5.3	6.8	4.8
α-pinene	-	-	-	12.2	9.4	9.4
α-terpinyleacetat	6.4	6.0	8.5	3.8	4.6	3.1
α-thujene	-	-	-	0.6	-	0.4
β-caryophyllene	2.8	8.2	5.3			
β-farnesene	0.3	1.0	0.4	7.5	9.3	9.4
β-pinene	-	0.6	1.0	1.2	0.9	1.0
Caryophyllèneoxid	0.8	1.1	0.8	3.8	4.6	2.2
Germacrene	-	-	-	-	-	-
Myrcene	2.7	1.7	-	1.9	1.9	1.3
p-cymene	-	-	-	4.2	2.3	3.0
Sabinene	18.5	5.7	7.7	17.8	13.4	2.3

%ID : Identification percentage

The possibility of existence of severalchemotypes of*V. agnus-castus* L. related to geographical origin has been discussed [20, 28 et 32].

In 1995, in the essential oils obtained from *V. agnus-castus* L, 50 compounds were identified by PY/CPG/SM[27].The main component of the essential oils of *V. agnus-castus* L, 1,8-cineole, was present at a level of 15,8% in the inflorescences, 27,9% in the leaves, and 33,4% in the seeds.In the sesquiterpene fraction, the main constituent, trans-β-farnesene, was present at level ranging from 3.2 to 17.6% depending on the location in the plant [27].

With GC/MS, a total of 38 compounds(includingtwo coelutingpairs) were identified (95.8 and 66.1% in leaf and berry oil, respectively);6 compoundswere tentatively identifiedand 7 compounds remained unknown. All the unknown and tentatively identified compounds eluted in the finalpart ofthe chromatogramsand were particularly abundant in the berry oil. The main componentsof the essentialoil were 1,8-cineole, sabinene, α-pinene, β-famesene, β-caryophylleneand α-terpinenyl acetate. The relativeamounts of two main constituents namely sabinene and β-farnesene, versus l,8-cineole and the wholesesquiterpenicfraction in leaves were more comparable to the data reported in the literature for a Dalmatian *V. agnus-castus* than to the composition of an African sample. The seed essential oil of the present samples wascharacterized by a large content of sesquiterpenes, diterpenes and other unknown high-molecular-weightcompounds (62.1%) compared to the leaf oil (15.3%)[20].

Eighty-five (85) compounds were identified by GC-MS in essential oils of *V. agnus-castus* L. of southern Italy. The ratio of hydrocarbon:oxygen-containing components was nearly 1:l. 1.8-Cineole, α-terpineol,sabinene, β-caryophyllene, β-selineneand cis-β-farnesene were the main components in the oils [28].

In 2012, investigation was to determinewhether the seeds volatile oil of *V. agnus-castus*possess antibacterial activities againstsome common pathogen and food-borne bacterial pathogens. More than twentycompounds were identified in *V. agnus-castus* L. volatile oil, accounting for 97.5%.Caryophylle oxide (24.9%), n-hexadecane(12.5%) and α-terpenyl acetate (11.6%) were themain constituents of the volatile oil of *V. agnus-castus*[29].

The essential oils of fresh leaves, flowers and fruits of *Vitex agnus-castus* L., growing in northBrazil were identified by GC/MS. The mostabundant constituents found were 1,8-cineole, (E)-β-farnesene, sabinene, α-pinene, α-terpenyl acetate, β-caryophyllene and bicyclogermacrene[30].

A research group was investigated the chemical composition, antimicrobial activity of essential oils obtained from unripe fruits, ripe fruits and leavesof *Vitex agnus-castus* L. The main compounds in the oil of unripefruits were sabinene (17.8%) and 1,8-cineole (17.5%), while in the oil of the ripe fruits dominantcompounds were 1,8-cineole (16.3%) and sabinene (13.4%). The leaves oil contained an abundance of1,8-cineole (22.0%), as well. All of the oils tested were rich sources of α-pinene (12.2%, 9.4% and 9.4%,respectively) [31].

3. Conclusion:

The plant *Vitex agnus-castus* L is a shrub native to Mediterranean Europe grows in sandy soils that has been used since ancient Greek and Roman as an herb treatment for female reproductive problems. This species is rich in secondary metabolites; the main constituents are flavonoids, iridoids, diterpenoids, progestins and essential oils[12, 13].Several compounds isolated from the species *Vitex agnus-castus* L, among them Aucubine, Vitexine, Viteagnusine A[12, 14 et 21].

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