Botanical description, phytochemical constituents, ethnobotany, traditional medicinal use, and pharmacological activities of *Stachys lavandulifolia* Vahl.

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Abstract

Stachys lavandulifolia Vahl known as "mountain tea", is a perennial flowering plant belonging to the Lamiaceae family and is widespread in Iran, Armenia, Azerbaijan, Iraq, Turkey and Turkmenistan. *S. lavandulifolia* is widely used in traditional medicine for its analgesic, anti-inflammatory and anxiolytic properties. This plant has different chemical compounds classes including terpenoids, iridoids, flavonoids and phenylethanoids that have been isolated from the aerial parts of it. This review covers the plant botany, traditional medicinal uses and chemical composition of *S. lavandulifolia*, along with its biological and pharmacological activities including clinical trial data. The information of this review article was obtained from different scientific databases such as Google scholar, Science Direct, Hindawi, SID, Scopus, PubMed, and ACS as well as traditional Persian books. Pharmacological and clinical studies, especially Anxiolytic activity and anti-inflammatory on the plant are relatively low, so these studies are suggested in the future. Also, phytochemical investigation on root of the plant is necessary.

Keywords:

Stachys lavandulifolia, mountain tea, pharmacological activity, traditional medicine, Botanical description, phytochemical constituents.

Figure captions

Figure S1. Photograph of different samples of ***S. lavandulifolia*** by Khadivi-Khub *et al* (Khadivi-Khub et al. 2014).

Figure S2. The main chemical constituents of *S. lavandulifolia* oil (germacrene-D (**1**), β-phellandrene (**2**), α-pinene (**3**), β-pinene (**4**), myrcene (**5**), ocimene (**6**) and spathulenol (**7**)).

Figure S3. Iridoids isolated from the aerial parts of *S. lavandulifolia*, monomelittoside (**8**), melittoside (**9**), 5-allosyloxy-aucubin (**10**).

Figure S4. Flavonoids isolated from the aerial parts of *S. lavandulifolia*, pachypodol (**11**), chrysosplenetin (**12**), kumatakenin (**13**), velutin (**14**), penduletin (**15**), viscosine (**16**), chrysoeriol (**17**), hydroxygenkwanin (**18**) and apigenin (**19**).

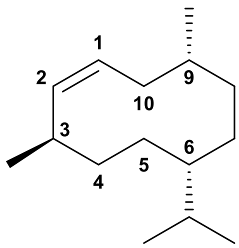
Figure S5. Flavonoid glycosides from the aerial parts of *S. lavandulifolia* include chrysoeriol-7-O-β-D glucopyranoside (**20**), apigenin-7-O-(6″- O-acetyl)-β-D-glucopyranoside (**21**), luteolin-7-O-β-D-glucopyranoside (**22**) and apigenin-7-O-β-Dglucopyranoside (**23**).

Figure S6. Phenylpropanoids isolated from the aerial parts of *S. lavandulifolia*, lavandulifolioside A (**24**), verbascoside (**25**), lavandulifolioside B (**26**), and leucosceptoside A (**27**).

Figure S7. Diterpenoids stachysolone (**28**) and labda-13-en-8,15-diol (**29**) obtained from the aerial parts of *S. lavandulifolia*.

Figure S1

Figure S2



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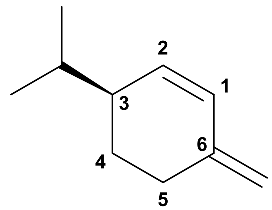

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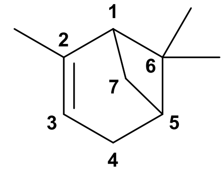

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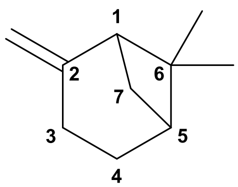

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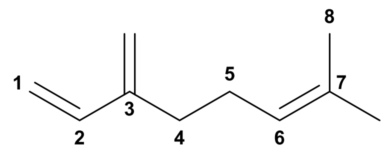

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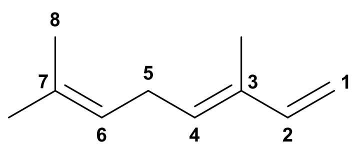

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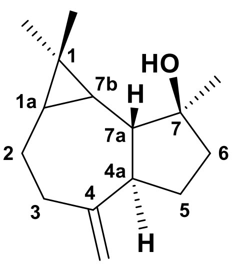

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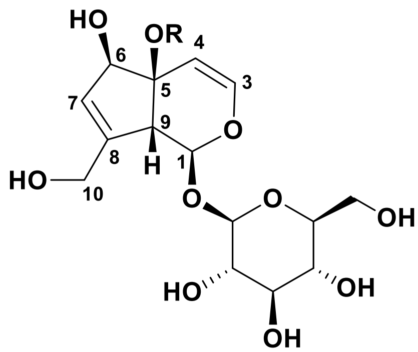
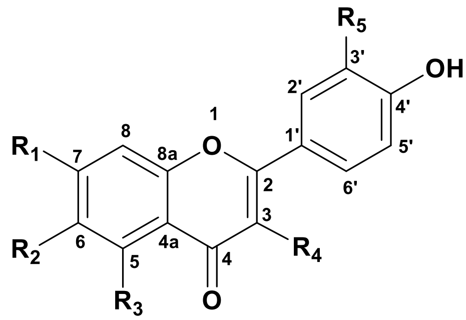
Figure S3



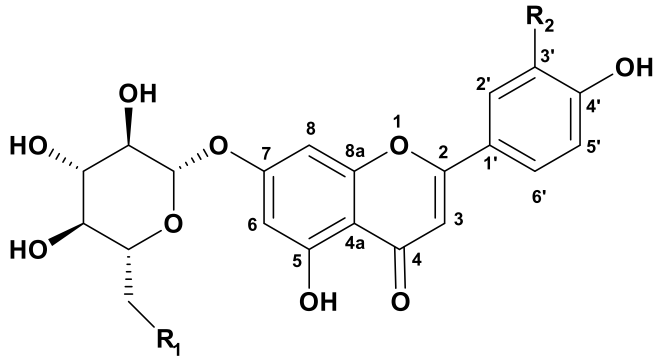
Comp	R
8	H
9	Beta glucose
10	Beta allose

Figure S4



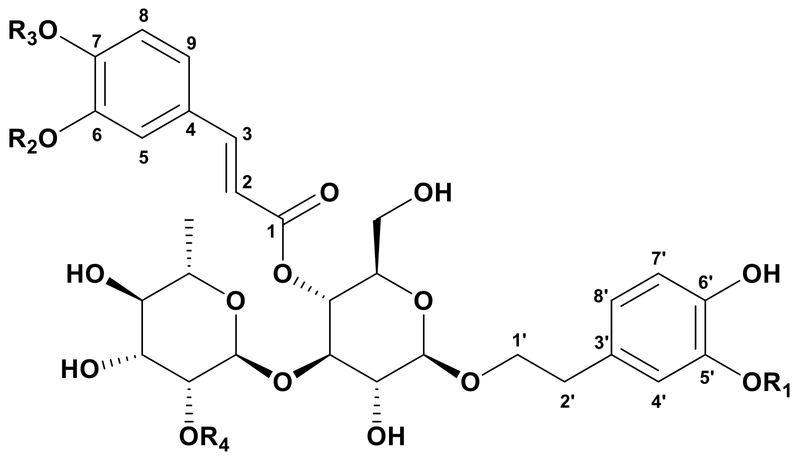
Comp	R_1	R_2	R_3	R_4	R_5
11	OMe	H	OH	OMe	OMe
12	OMe	H	OMe	OMe	OMe
13	OMe	H	OH	OMe	H
14	OMe	H	OH	H	OMe
15	OMe	OMe	OH	OMe	H
16	OH	OMe	OH	OMe	H
17	OH	H	OH	H	OMe
18	OH	H	OH	H	OH
19	OH	H	OH	H	H

Figure S5



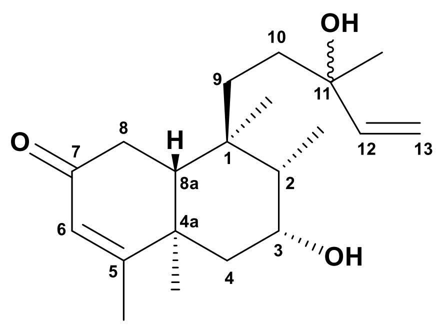
Comp	R_1	R_2
20	OH	OCH_3
21	$OCOCH_3$	H
22	OH	OH
23	H	OH

Figure S6



Comp	R_1	R_2	R_3	R_4
24	H	H	H	Beta-D-arabinopyranosyl
25	H	H	H	H
26	Me	Me	Me	Beta-D-arabinopyranosyl
27	H	Me	H	H

Figure S7



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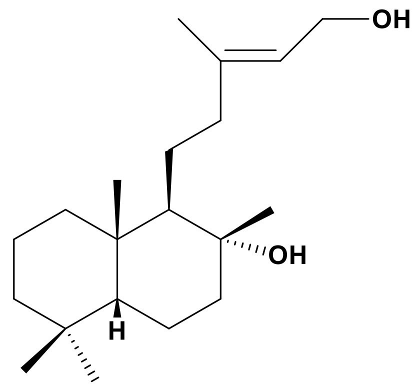

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Table captions:

Table S1. Chemical composition of the essential oil from aerial parts of *S. lavandulifolia* from different regions of Iran.
Table S2. The pharmacological profiles of *S. lavandulifolia* and its phytochemicals

Table S1

Compounds	**Formula**	**KI**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**	**S**	**T**	**U**	**V**	**W**	**X**
4-Hydroxy-4-methyl-2-pentanone	$C_6H_{12}O_2$	831												9												
α-Thujene	$C_{10}H_{16}$	924			16	24									13	24	26	32								
α-Pinene	$C_{10}H_{16}$	932	5				20	8	**14**	49	8	39	33	8					37				8			6
Benzaldehyde	C_7H_6O	952														6			3							
Sabinene	$C_{10}H_{16}$	969				3						3			4		5	2								
β-Pinene	$C_{10}H_{16}$	974					12	10	7	22		2	5		3		2									
cis-m-Mentha-2,8-diene	$C_{10}H_{16}$	983																					4		3	3
Myrcene	$C_{10}H_{16}$	988	4	4	4			9	5	2		10	42		16	4	7		6	6		5	6		3	
Decane	$C_{10}H_{22}$	1000																							6	
α-Phellandrene	$C_{10}H_{16}$	1002													7		3	14								
Carene <δ-3->	$C_{10}H_{16}$	1008	2																							
Limonene	$C_{10}H_{16}$	1024	15	5										2						8		3	24			
β-Phellandrene	$C_{10}H_{16}$	1025			14	28	5	13	6	12		18				38	18	2	12							
(Z)- β-Ocimene	$C_{10}H_{16}$	10			2		3	6	3							2					2					

		32																								
β-Ocimene	$C_{10}H_{16}$	1044										6														
Allo ocimene	$C_{10}H_{16}$	1128					2																			
cis-β-Terpineol	$C_{10}H_{18}O$	1140												2												
Terpinen-4-ol	$C_{10}H_{18}O$	1174																						2		
Thymol	$C_{10}H_{14}O$	1289									15															
(Z)-Hex-3-enyl tiglate		1319																			3	8			3	
α-Cubebene	$C_{15}H_{24}$	1345							2																	
α-Copaene	$C_{15}H_{24}$	1374	7	6.5			3	4		7	2									5	3	4.5	7	6	4	
β-Elemene	$C_{15}H_{24}$	1389									7	2.5													3	
Dihydro-alpha-ionone	$C_{13}H_{22}O$	1411																			3					
(E)-Caryophyllene	$C_{15}H_{24}$	1417		2																13	8	5			5	
β-Cedrene	C15H24	1419					3																			
β-Farnesene <(Z)>	$C_{15}H_{24}$	1440																2								

(E)-β-Farnesene	$C_{15}H_{24}$	1454					3	3													2					
Sesquisabinene	$C_{15}H_{24}$	1457																		3						
cis-Muurola-4(14),5-diene	$C_{15}H_{24}$	1465																							2	
γ-Gurjunene	$C_{15}H_{24}$	1475												3												
ar-Curcumene	$C_{15}H_{22}$	1479																			3	2				
α-Amorphene	$C_{15}H_{24}$	1483				3									6											
Germacrene D	$C_{15}H_{24}$	1484	14	9	11	3	5	13	9		16				6	3	7		7	13	19	8	7.5	12	8	
α-Zingiberene	$C_{15}H_{24}$	1493																			3				12	
Bicyclogermacrene	$C_{15}H_{24}$	1500	4.5	18			3	4	2						4	4		11		9	8	7	3			
γ -Cadinene	$C_{15}H_{24}$	1513					3				13															
Nootkatene	$C_{15}H_{22}$	1517																			2				2.0	
Δ-Cadinene	$C_{15}H_{24}$	1522	11	11	12	8			2											10	7	12	16	11	9	
Spathulenol	$C_{15}H_{24}O$	1577	4	10			7	2	3					3						3	11	8	2	7	4	
Caryophyllene oxide	$C_{15}H_{24}O$	15		2																	3			5		

		82																								
Globulol	$C_{15}H_{26}O$	1590												3												
1-*epi*-Cubenol	$C_{15}H_{26}O$	1627												3												
epi- α -Muurolol	$C_{15}H_{24}$	1640												3												
α-Muurolol	$C_{15}H_{26}O$	1644	3	6																8	4	4	1.5	4	2	
Guaia-3,10(14)-dien-11-ol	$C_{15}H_{24}O$	1676	2	2																3	3			3		
epi-α-Bisabolol	$C_{15}H_{26}O$	1683																			3			3		
α-Bisabolol	$C_{15}H_{26}O$	1685					3				2			3												
Eudesma-4(15),7-die*n*-1-β-ol	$C_{15}H_{24}O$	1687												3												
(2Z,6E)-Farnesol	$C_{15}H_{26}O$	1742																						3		
Phytol	$C_{20}H_{40}O$	1942									6															
Hexadecanoic acid	$C_{16}H_{32}O_2$	1959							14					5												
Linoleic acid	$C_{18}H_{32}O_2$	2132							3																	
Isocaryophyllene	$C_{15}H_{24}$								2																	
Pulegone	$C_{10}H_{16}O$																							6		

trans-Phytol	$C_{20}H_{40}O$							3																		
Tetradecanoic acid	$C_{14}H_{28}O_2$													4												
1,4-methano-1 H-indene					8	3									10		4									
Mint sulfid	$C_{15}H_{24}S$		2																						3	
Sigma-elemene	$C_{15}H_{24}$																				2					
1,6-Dodecatriene-7,11-dimethyl-3-methylene	$C_{15}H_{24}$										5															
2-Pentadecanone, 6,10,14-trimethyl	$C_{18}H_{36}O$										2															
sigma-Cadinene	$C_{15}H_{24}$							3						4												
α-Cadinol	$C_{15}H_{26}O$			2					3					4						2	2			3	3	
β-Terpinene	$C_{10}H_{16}$												12													
6,10,14-Trimethyl pentadecan-2-one	$C_{18}H_{36}O$													2												

A- Azarshahr [14, 29], **B**- Manbar [14, 29], **C**- Broujen [31], **D**- Gal-e-sang [31], **E**- Tehran, Abali [73], **F**- Fasham area near Tehran [37], **G**- central Alborz [35], **H**- (KamuMountain) Isfahan [38], **I**- western Isfahan [39], **J**- Khalkhal [40], **K**- Shahrood, Semnan province [41], **L**- Behshahr [43], **M**- Naghan [31], **N**- Sheyda [31], **O**- Faraydan [31], **P**- Kelishadrokh [31], **Q**- Frasan [31], **R**- Babanazar [14, 29], **S**- Zanjan [14, 29], **T**- Damerchi [14, 29], **U**- Saqez [14, 29], **V**- Ajabshir [14, 29], **W**- Gachsar [14, 29], **X**- Baderloo [29].

NB: Only compounds present in >2% have been shown in the table S1; The main compounds (>10% in content) have been bolded. KI:DB5 Adams.

Table S2

Activity	**Extract/compounds**	**The presumed mechanism of action**	**Tested living system/organ/cell**	**Result(s)**	**Reference(s)**
Toxicity on cancer cells	Chrysosplenetin	No data	MDA-MB-231 breast cancer cell	Having selective toxicity with selectivity indices of 2.70, in comparison with tamoxifen (selectivity index:2.45)	Delnavazi et al. 2018
	viscosine	No data	MDA-MB-231 breast cancer cell	Having selective toxicity with selectivity indices of 3.33, in comparison with tamoxifen (selectivity index:2.45)	Delnavazi et al. 2018
	kumatakenin	No data	MDA-MB-231 breast cancer cell	Having selective toxicity with selectivity indices of 2.59, in comparison with tamoxifen (selectivity index:2.45)	Delnavazi et al. 2018
	80% aq. Methanol extract	No data	HL-60 and MCF-7 cell lines	gaving IC50 values of 114 and 152 μg/mL against HL-60 and MCF-7 cell lines, respectively	Jassbi et al. 2014
	Ddichloromethane extract	No data	HL-60 and MCF-7 cell lines	gave IC50 values of 142 and 81 μg/mL against HL-60 human leukemia and MCF-7 breast cancer cell lines, respectively	Jassbi et al. 2014
anxiolytic effect	apigenin glycoside	No data	Albino rats	Apigenin 7-glucoside significantly decreased the percentage of head dips in EPM	Kumar and Bhat. 2014
	hydroalcoholic extract	No data	In vivo	The extract had anxiolytic effect with relatively lower sedative activity than diazepam.	Rabbani et al. 2004
Anti-inflammatory effect	ethyl acetate extract	lipid peroxidation inhibitor	In vitro assay	This extract inhibit lipid peroxidation with IC50 values of 32 μg/mL	Ghaffari et al. 2012
	methanol extract	lipid peroxidation inhibitor	In vitro assay	This extract inhibit lipid peroxidation with IC50 values of 65 μg/mL	Ghaffari et al. 2012
	hexane extract	lipid peroxidation inhibitor	In vitro assay	This extract inhibit lipid peroxidation with IC50 values of 64 μg/mL	Ghaffari et al. 2012
	(-)-α-bisabolol	Reducing TNF-α level	In vivo	This compound seems is related to anti-inflammatory effect of *S. lavandulifolia*	Barreto et al. 2016

Antioxidant activity	methanolic extract	Reducing free radicals	via a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (IC_{50}), ferric ion reducing antioxidant power (FRAP), and total antioxidant capacity (TAC)	The extract had the antioxidant activity	Rahimi Khoigani et al. 2017
Tyrosinase inhibitory activity	70% ethanol extract	Enzyme inhibitors	Tyrosinase was used as substrate	Tyrosinase was sensitive against the 70% ethanol extract with IC_{50} values of 33 µg/mL	Tundis et al. 2015
	Methanol extract	Enzyme inhibitors	Tyrosinase was used as substrate	Tyrosinase was sensitive against the methanol extract with IC_{50} values of 43 µg/mL	Tundis et al. 2015
	Acetoside compound	Enzyme inhibitors	Tyrosinase was used as substrate	This compound had tyrosinase inhibitory activity with an IC50 value of 13 µg/mL	Tundis et al. 2015
acetylcholinesterase (AChE) inhibitory activity	hexane and dichloromethane extracts	Enzyme inhibitors	Acetylcholinesterase was used as substrate	These extracts exhibited the highest inhibitory against AChE with an IC_{50} value of 14 µg/mL	Tundis et al. 2015
butyrylcholinesterase (BChE) inhibitory activity	hexane and dichloromethane extracts	Enzyme inhibitors	Butyrylcholinesterase was used as substrate	These extracts exhibited the highest inhibitory against AChE with an IC50 value of 144 µg/mL	Tundis et al. 2015
gastroprotective effects	Aqueous extract	No data	Male Wistar rats	This extract protected gastric mucosa from alcohol-induced gastric ulcers	Nabavizadeh 2011
Protective effect in gentamicin nephrotoxicity	Hydroethanolic extract		Male Wistar rats	The plant can be reduce gentamicin-induced nephrotoxicity	Feyzi et al. 2020

spasmolytic effect	Chloroform fraction	Inhibition of ileum contractility mainly via disturbing the calcium mobilization and partly by opioid receptors' activation	Male Wistar rats	The plant had activity with IC50 = 0.13 ± 0.02 mg/mL	Gharib-Naseri et al. 2011
Abortion	Hydroalcoholic extract	Decrease in progesterone levels	72 adult pregnant Wistar rats	Significant decrease in the estrogen and progesterone levels	Ahmadi moghaddam et al.2021
Antioxidant activity	Infusion from 3 g aerial parts on a daily basis	Increase in the total content of serum antioxidants and prevent cellular lipid peroxidation	Clinical trial on 26 healthy human subjects	Total blood antioxidants increased The lipid peroxidation reduced	Rahzani et al. 2013 .
Primary dysmenorrhea	Powdered aerial parts of the plant (capsule)	Inhibition of prostaglandin synthesis by cyclooxygenase 1 and 2 inhibition	Clinical trial on twenty-nine patients with primary dysmenorrhea	Reduce menstrual pain	Monji et al. 2018
Abnormal uterine bleeding	Brew of the dried aerial parts three times a day	Downregulation of estrogenic receptors	Clinical trial on 66 patients with Polycystic ovarian syndrome	Reduced abnormal uterine bleeding	Jalilian et al. 2013 .