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Ethnomedicinal Use, Phytochemistry, Pharmacology, and Toxicology of *Salvia verbenaca* L. : A Review

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Abstract: *Salvia verbenaca* L. is a Mediterranean medicinal plant used traditionally to treat several diseases such as burns, ocular wounds, contusion, stomach pain, eye diseases, dermal inflammation. This review highlighted previous reports, including the botanical, taxonomical, geographical distribution, traditional use, phytochemical, biological, and toxicological effects of *S. verbenaca*. The data were gathered from scientific databases PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, SpringerLink. The presented data on *S. verbenaca* were organized according to ethnomedicinal use, bioactive compounds, pharmacology, and toxicological investigation. Ethnobotanical studies reported that *many folk medicines use S. verbenaca*, especially against wounds, burns, and cicatrization. The phytochemical compounds in different parts of *S. verbenaca* belonged to different classes of chemical compounds, including terpenoids, flavonoids, phenolic acids, phenolic diterpenoids, and fatty acids. The extracts and essential oils from *S. verbenaca* have a wide variety of *in vitro* and *in vivo* pharmacological activities, i.e., antioxidant, antifungal, antidiabetic, anti-inflammatory, antitumor, antihemolytic, antihypertensive, antileishmanial, and immunomodulatory activities. This research suggests that the biological activities of *S. verbenaca* prove its traditional uses. However, in-depth investigations are required, such as pharmacokinetic, pharmacodynamic, and toxicological experiments, to prove the efficacy and safety of *S. verbenaca* extracts and essential oils and their bioactive compounds.

Keywords: *Salvia verbenaca*; traditional use; phytochemistry compounds; pharmacological properties.

1. Introduction

Salvia verbenaca L. belongs to the *Lamiaceae* family and the genus of *Salvia*. It is a perennial herbaceous plant [1] (10-30 cm in length) and is recognized by its strong pleasant smell and blue-lilac-colored flowers [2]. *S. verbenaca* is indigenous to the Mediterranean countries and the Canary Islands [3] and is distributed in the tropical region including Saudi Arabia [4], Central and South America, and Asia [5]. *S. verbenaca* know locally in Morocco

and Algeria as ‘‘Khayata’’, in Italy as ‘‘Erba del malocchio’’, in French as “Fausse verveine”, and in Spain as “Gallocresta” [6-8].

In traditional medicine, *S. verbenaca* is used against different illnesses, especially healing wounds in Morocco and Algeria [8-12]. It is also used to treat other diseases, including hypertension, constipation, muscle disorder, laryngitis, abscesses, contusion, stomach pain, eye diseases, dermal inflammatory, burns, ocular wounds [10, 13-18]. It is also used against respiratory diseases [19].

Many investigators reported the potential activity of *S. verbenaca* extracts and essential oils as antioxidant, antidiabetic, antibacterial, antifungal, antitumor, antihemolytic, antihypertensive, antileishmanial, and immunomodulatory activities [4, 20-23] (Figure 1). Furthermore, several studies investigated large variations according to geographical origin, diverse plant parts, genotype, and climate [2, 24-26], whereas there are scarcely those who reported the mechanistic investigations of these pharmacological effects. Phytochemical investigation of the extracts and essential oils from different parts of *S. verbenaca* showed the presence of numerous phytocompouds classes, including terpenoids, flavonoids, fatty acids, phenolic acids, phenolic diterpenoids, and carbonylic compounds [2,19,25].

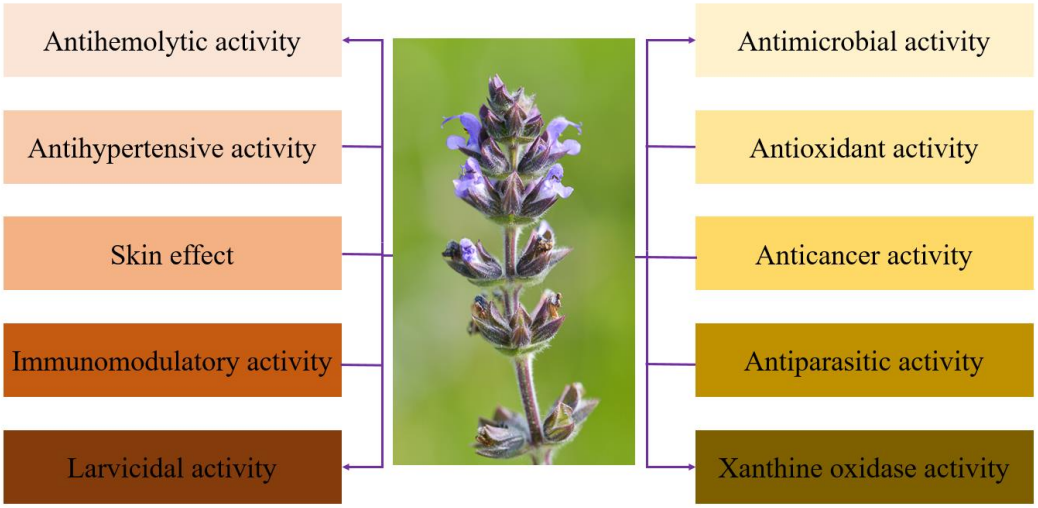


Figure 1. Pharmacological properties of *S. verbenaca*.

To the best of our knowledge, no review was published to critically summarized these results and suggested future clinical applications of this plant. Thus, this motivated us to write the current review, which highlighted *S. verbenaca* ethnomedicinal use, geographic distribution, taxonomy, phytochemical compounds, pharmacology activities, and toxicology effects.

2. Materials and Methods

The collected data of ethnomedicinal use, geographic distribution, taxonomy, phytochemical compounds, pharmacology activities, and toxicology effects of *S. verbenaca* was achieved from literature publication using various scientific search engines such as PubMed, Scopus, Web of Science, Google Scholar, ScienceDirect, SpringerLink, Scifnder, and Wiley Online to collected, analyzed, and summarized all published articles about this plant. In this research, several keywords were used such as ‘‘*S. verbenaca*’’, ‘‘ethnomedicinal of *S. verbenaca*’’, ‘‘*S. verbenaca* essentials oil’’, ‘‘antioxidant activity of *S. verbenaca*’’, ‘‘antidiabetic activity of *S. verbenaca*’’, ‘‘antibacterial activity of *S. verbenaca*’’, ‘‘antileishmanial activity of *S. verbenaca*’’. All published articles mentioning *S. verbenaca*

were cited in this bibliometric survey. To identify further relevant papers, reference lists of the retrieved papers were also examined. Dada was classified according to themes and organized into tables for their discussion. Concerning phytochemistry, chemical structures were drawn using ChemDraw Ultra 12.0 software.

3. Results and Discussion

3.1. Botanical description.

S. verbenaca is a perennial plant, 20-50 cm in height [27]. As depicted in figure 2, root is a woody rootstock. The leaves are simple, ovate to oblong-ovate (2-10 × 1.5-7 cm), margin deeply sinuate to unevenly dentate, and upper cauline leaves sessile [28]. The petiole is 1.2-8 cm long. Nutlet fruits contain 1-4 seeds [29]. There are obovate, elliptic, rare spherical, dorsal, and ventral side's convex, rare rooflike on the ventral side, base with round fall in hilum (2.1-2.4 × 1.6-1.9 mm) [30]. The inflorescence is verticillasters, each of which contains 4-10 flowers of about 1cm in length [28,29]. *S. verbenaca* flowering commences in mid-April and finishes towards the end of May [31]. The fruits mature about two weeks after the senescence of the flower. Each flower produces 0.6-1.5 µL of nectar per day [31]. The calyx, ± campanulate, is 5-12 mm in length with upper lip shortly 3-dentate. Corolla is 6-16 mm in length, lilac to purple, barely half as long as the calyx with a straight subfalcate upper lip, which is concave [28]. The plant cells are polyploid (2n = 6x = 42, 2n = 6x = 54, 2n = 6x = 60, 2n = 6x = 48, 2n = 8x = 64) [32].

Figure 2. *S. verbenaca*. (**A**) general aspect; (**B**) flowers [33]. Illustration by Marcelo Moreno, taken from O'Leary & Moroni (2016), courtesy: Instituto de Botánica Darwinion.

3.2. Taxonomy and geographic distribution.

S. verbenaca belongs to the family *Lamiaceae*, which contains 900 species worldwide, of which about 26 indigenous species are found in southern Africa [3]. *S. verbenaca* is indigenous to the Mediterranean countries and has been reported all around the Mediterranean basin: From Morocco to the Canaries, from Algeria, Tunisia, Libya, Egypt, Cyprus, Turkey to Transcaucasia, from South and West of Europe to the North of Great Britain. It has been naturalized in America, southern Africa, New Zealand, and Australia [34, 35]. *S. verbenaca* is widely distributed within the altitude range of 1-2500 m in Argentina [33], and 1-900 m in Turkey except for East and Southeast Anatolia [36]. This species has been subservient to human activity, and its current distribution results from this action [37].

3.3. Ethnobotanical use.

In several folk medicines around the world, different parts of *S. verbenaca* have been reported by ethnobotanical surveys to treat several disorders (Table 1). *S. verbenaca* has an antispasmodic, ophthalmic, antiseptic, anti-rheumatic, antiseptic, antipyrotic, antisudoral, astringent effect as well as it has been reported for preventing stomach pain, cough, hypertension, insomnia, and aerophagia [6-12,15,16,38-42]. The traditional use of *S. verbenaca* depends on the country traditional medicine. Table 1 listed the applications of *S. verbenaca* in traditional global systems.

In Morocco, healing wounds, abscesses, and burns by *S. verbenaca* have been described as their famous prescription. The most used part of the plant is the leaves which are used as a cataplasm in the different regions, including Zaer (Western of Morocco), province of Settat (Morocco), and the province of Gharb-Chrarda-Beni Hssen (Northwest of Morocco) [8,9,11,38,39]. In addition to their healing effect, Nassiri *et al.* (2016) reported the use of *S. verbenaca* to treat digestive, respiratory, dermatological, and rheumatic illness in Aguelmous (Khenifra Province, Morocco) [43]. El Abbouyi *et al.* (2014) investigated the use of medicinal plants to treat different diseases in the El Jadida region and reported that the leaves of this plant were used as a decoction to treat abdominal colics, cold, and fever [40]. In the same year, Akdime *et al.* (2014) studied an ethnobotanical in the Ain Leuh region (Middel-Atlas of Morocco) and showed that the whole plant of *S. verbenaca* is used as antispasmodic, aerophagia, cough, preservative of butter, stomach pain, digestive, cough, and cicatrization [13]. In the Gharb region, surveys carried by Bouayyadi *et al.* (2015) showed that leaves of *S. verbenaca* are used in decoction to treat stomach pains [8]. Recently, Salhi and coworkers (2019) identified the use of the leaves and whole plant of *S. verbenaca* to heal skin burns by occidental population (Rabat, Morocco) by sprinkling it directly on burns or by application of its maceration with olive oil [44].

In Algeria, *S. verbenaca* was recorded as a medicinal plant against several pathologies, including healing wounds and abscesses [10,12]. It is also used as stomachic, tonic, vulnerary, disinfectant, antispasmodic, antisudoral, astringent (diarrhea), carminative by using a decoction or an infusion of aerial parts [16].

In European countries, various form of *S. verbenaca* has been reported to treat specific diseases. Tisane flower, fresh fruits, and aerial part infusion of *S. verbenaca* have been reported to treat hypertension [15], foreign bodies in the eye [7], and respiratory affections [41], respectively. In the Italian pharmacopeia, the leaves of this plant were used as a decoction to treat cystic and septic diseases [6,42].

From this study, many disorders have been reported using different parts of *S. verbenaca* depending on the geographical region using ethnobotanical surveys. This lasts is the first step to identify the plant used for each disorder. It informs about the part use, the mode of preparation, etc. However, the lack of plant information given by researchers in many surveys was repeatedly remarked. This is the case of several researchers who reported the use of *S. verbenaca* in folk medicine without mentioning the part use, the mode of preparation, and the traditional use [45-52]. Thus, conserving traditional herbal remedies by the local population requires standardization of fiche ethnobotanical surveys.

Table 1. Traditional use of *S. verbenca.*

Used part	Mode of preparation	Traditional use	References
Whole plant	Not reported	Antispasmodic, aerophagia, cough, preservative of butter, stomach pain, digestive, cough, cicatrization	[42]
Aerial part	Decoction	Contusion, injury	[53]
Seed	Not reported	Wounds eyes	[54]
Leaf	Cataplasm	Wounds, drained abscesses, burns	[8,9]
Leaf	Decoction	Stomach	[8]
Leaf, flowered aerial part	Infusion	Respiratory affections	[41]
Leaf	Not reported	Wound healing, abscess, laryngitis	[10]
Leaf	Decoction, infusion	Abscesses, wounds	[14]
Leaf	Cataplasm, decoction	Abdominal colics, cold, fever, healing	[14]
Leaf	Not reported	Healing	[55]
Flower	Tisane	Antipyertensive	[15]
Leaf	Cataplasm	For curing cysts, pimples, wounds	[5,56]
Fruit (nuts)	Fresh	Foreign bodies in the eye	[7]
Aerial part, leaf	Infusion, decoction	Stomachic, tonic, vulnerary, disinfectant, antispasmodic, antisudoral, astringent, carminative	[16]
Leaf	Not reported	Wounds, astringent, diuretic, antiseptic	[57]
Essential oil, powder whole plant, leaves, fruit, flower, root, rods	Cutaneous	Healing wounds	[39]
Not reported	Not reported	Dermatological, digestives, respiratory, rheumatic	[43]
Leaf	Ointment	Antipyrotic	[58]
Leaf	Cataplasm	Wounds	[11]
Leaf	Powder, maceration	Burns	[44]
Whol plant	Powder	Burns	
Leaf	Decoction	Antiseptic	[42]
Leaf	Cataplasm	Healing wounds, anti-rheumatic	[38]
Not reported	Not reported	Indigestion, colds, hypertension, insomnia, anxiety, ophthalmic antiseptic, hypertensive, dermal anti-inflammatory washes, wax or oil anti-inflammatory ointment, vulnerary and anti-inflammatory plaster, snuff substitute, forage for rabbits	[17]
Leaf	Powder	Wounds	[12]
Leaf, seed	Not reported	Constipation, against sweat, sedative, eye diseases, dyspeptic, complaint	[18]
Leaf	Not reported	Respiratory	[59]

3.4. Phytochemistry.

Several investigators reported the chemical composition of extracts and essential oils of *S. verbenaca* growing in different parts of the world [25,26,60-66]. Table 2 summarized the plant organs, the country of origin, the class of bioactive compounds, and the most abundant compounds of *S. verbenaca* extracts and essential oils. Terpenoids, flavonoids, fatty acids, phenolic acids, and carbonylic compounds were the classes of bioactive compounds identified.

3.4.1. Terpenoids.

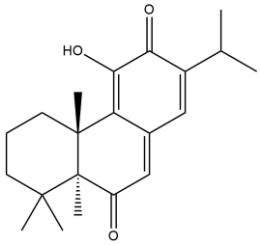
Various terpenoids were identified and characterized from *S. verbenaca* (Figure 3). In 1989, only one study identified the presence of terpenoids in roots. Sabri *et al.* (1989) isolated for the first time three terpenoids (Taxodione, horminone, and 613-hydroxy-7a-acetoxyroyleanone) from the petroleum ether extract of the roots of *S. verbenaca* [67].

Ben Taarid *et al.* (2010a) carried out a phytochemical investigation of the leaves, fruits, and stems essential oils. The authors revealed the presence of 13-*epi*-manool, and manool in leaves, β-caryophyllene, and caryophyllene oxide in fruits and camphor, and viridiflorol in stems [60]. The chemical composition of essential oils of *S. verbenaca* leaves (Irano-Turanian) was determined by gas chromatography-mass spectrometry (GC-MS). δ-Selinene was the main terpenoid, followed by germacrene D, β-caryophyllene [61]. The same investigators reported that essential oils of *S. verbenaca* flowers (from Iran-Turanian) contained several terpenoids especially sabinene, and *trans*-sabinene hydrate [61]. In a recent study, Mannu and coworkers (2020) investigated the geographical variation of the chemical composition of essential oils extracted from Italian *S. verbenaca* [68]. They studied the chemical composition of leaves and flowers of *S. verbenaca* in six different geographical areas of Sardinia (Italy) and found that monoterpenes and sesquiterpenes were predominant regarding the altitude level. Germacrene D (26.3%), (*E*)-β-caryophyllene (23.7%), terpinolene (11.9%), phytol (10.4%), α-humulene (4.6%) were the main simple identified from the Asinara island area. Whereas germacrene D (32.3%), (*E*)-β-caryophyllene (32.2%), and α-humulene (5.8%) were the main compounds identified from the Ala dei Sardi region. From this study, the authors showed that the essential oils profile significantly affected the site origin and the altitude for the four principal chemical groups identified.

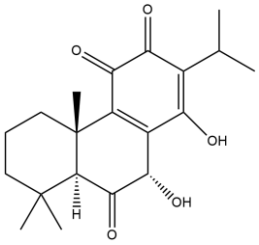
Two studies investigated the phytochemical characterization of essential oils in seeds of *S. verbenaca* [62,63]. They both revealed that camphor and caryophyllene oxide were the main volatile compounds. Other terpenoids were also revealed, such as tricyclene, and octane identified in seeds of *S. verbenaca* collected from Tunisia, and 13-*epi*-manool, and *α*-terpinyl acetate in seeds of *S. verbenaca* collected from Spain [62,63].

Al Howirine *et al.* (2002) identified sabinene, *δ*-cadinene, α-pinene, 4-terpeniol, and limonene as the main compounds of essential oils of *S. verbenaca* aerial part [26]. Four years later, the composition of the essential oil of the same part of *S. verbenaca* (Greece) using GC-MS was analyzed by Pitarokili *et al.* (2006) [64]. They reported the presence of several terpenoids, including β-phellandrene, β-caryophyllene, and methyl ester of 6-octadecenoic acid as the main compounds, whereas viridiflorol, camphene, methyl eugenol, and β-caryophyllene were the main compounds identified in the same part of *S. verbenaca* essential oils (Tunisia) [70]. β-Phellandrene is the main component of the essential oils obtained from *S. verbenaca* aerial part (Italy). Russo and co-workers (2015) revealed the presence of hexadecanoic acid as the main component from the essential oils obtained from *S. verbenaca* aerial part (Italy) [27]. In the same year, verbenacine and salvinine have been isolated and identified by Ahmed *et al.* (2004) from the acetate extract of *S. verbenaca* aerial part harvested from Saudi Arabia [65]. Aissaoui and investigators (2014) analyzed the essential oils of *S. verbenaca* (Algeria) and found that it was very rich in sesquiterpenes [70]. It was found that 1,10-di-epi-cubenol, epi-α-cadinol, β-caryophyllene, bicyclogermacrene, γ-cadinene, cis muurola-4(14),5-diene were the most abundant compound. However, the main compounds of *S. verbenaca* essential oils from the same country (Algeria) were different in another research elaborated by Belloum and

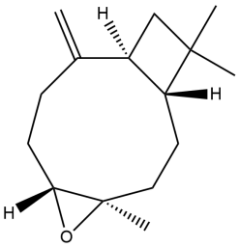
co-workers (2015) as they identified germacrene D, and α-copaene [71], while Al Jaber and co-workers (2015) reported a dominance of linalool, and (Z)-β-ocimene in *S. verbenaca* essential oils from Jordan [72]. In Tunisia, Ben Farhat *et al.* (2019) investigated the composition of aerial part essential oils of *S. verbenaca* using gas chromatography (GC) and GC-MS [24]. They revealed the dominance of 1,8-cineole followed by *p*-cymene, viridiflorol, and β-Caryophyllene. Furthermore, these authors reported that monoterpene hydrocarbons were predominated at the flowering stage while oxygenated sesquiterpenes were dominant at the early fruiting stage. In a very recent study, *cis*-muurola-3,5 diene, and γ-amorphene have been identified as the main compounds in essential oils of *S. verbenaca* aerial part from Algeria [66]. The aerial part of *S. verbenaca* contained a diversity and difference of bioactive constituents, which could be assigned to the detection method, the distillation method, the collection time, the collect site, and the phenophase.



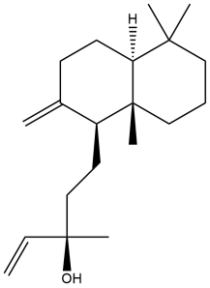
Taxodione



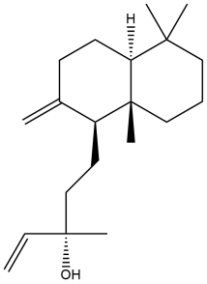
Horminone



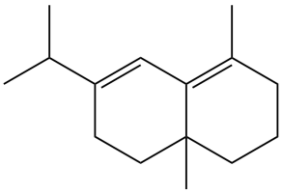
Caryophyllene oxide



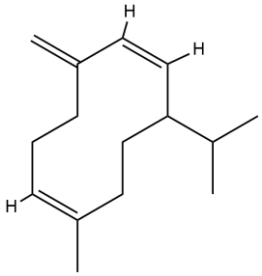
Manool



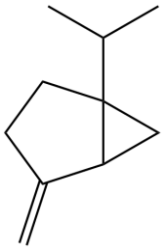
13-*epi*-manool



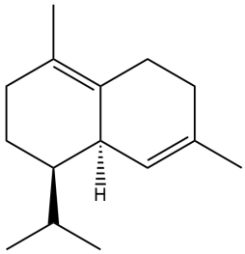
δ-Selinene



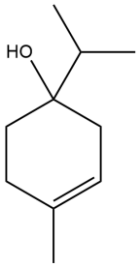
Germacrene D



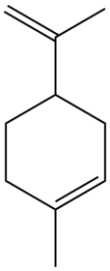
Sabinene



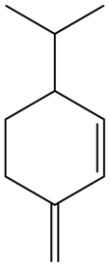
δ-Cadinene



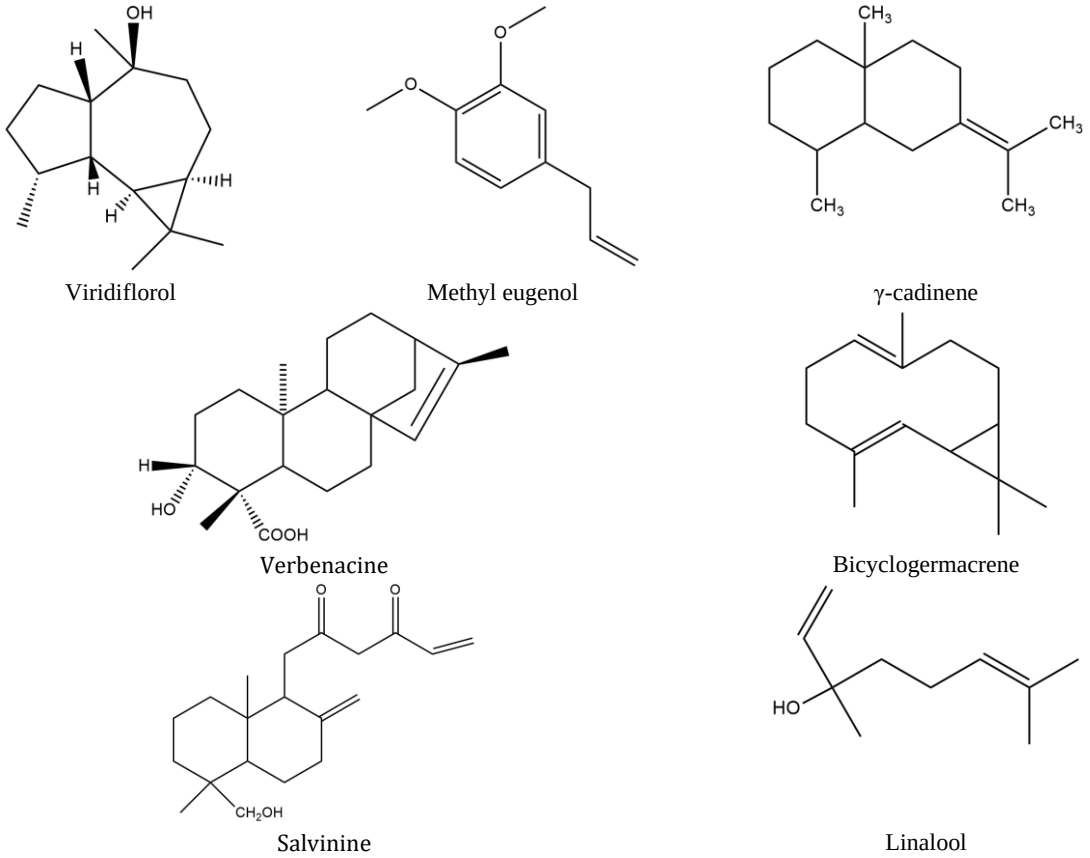
4-Terpineol



Limonene



β-Phellandrene



Viridiflorol | Methyl eugenol | γ-cadinene

Verbenacine | Bicyclogermacrene

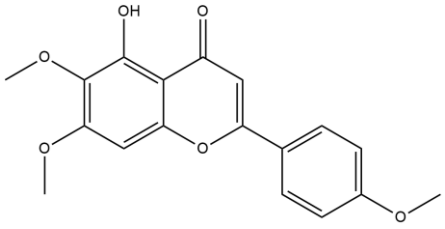
Salvinine | Linalool

Figure 3. Chemical structure of terpenoids identified in *S. verbenaca* essential oils and extracts.

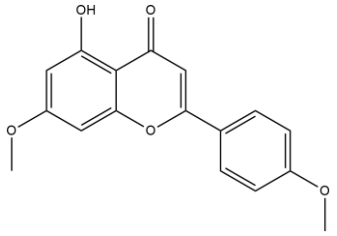
3.4.2. Flavonoids.

S. verbenaca was found to contain several flavonoids (Table 2, Figure 4). Camarasa *et al.* (1982) identified for the first time four flavonic aglycons (apigenin, luteolin, salvigenin, and 5-hydroxy-7,4'-dimethoxyflavone) from leaves of *S. verbenaca* harvested in Spain [73]. In 2005, Ahmed *et al.* (2005) isolated and identified three flavonoids (5-hydroxy-3,4',7-trimethoxyflavone, retusin, verbenacoside) from *S. verbenaca* aerial part collected in Saudi Arabia [4]. Using HPLC, Ben Farhat *et al.* (2013) identified and quantified in 2013 various flavonoids in methanolic extract of *S. verbenaca* aerial part growing wild in ten Tunisian locations and collected at the flowering time in March and April 2008 [1]. Naringenin was the main compound identified in all stations, followed by cirsiliol in Rass Zebib, Tunis, Bou Arada, Sers, and Hancha location and by hesperidin in Bir Mroua, Beja, and Touiref station. The same tool was used to analyze the flavonoids compounds of *S. verbenaca* aerial part in three phonological stages using the same extract [25]. Naringenin and cirsiliol were the main flavonoid chemical family identified at the flowering stage compared with the early fruiting and late fruiting stages. From this study, the authors showed the significant effect of phenophase influenced in chemical compounds. Thus, studying chemical compounds at different phenophase periods is a way to valorize plant medicinals.

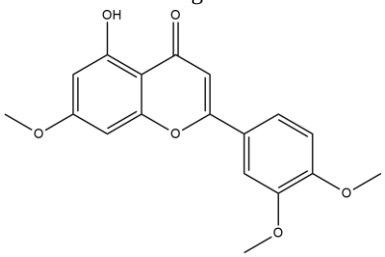
Apigenin | Luteolin



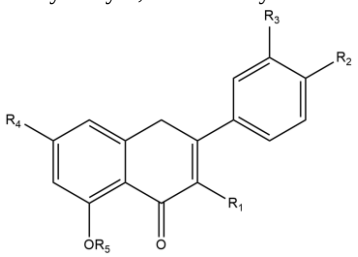
Salvigenin



5-hydroxy-7,4'-dimethoxyflavone

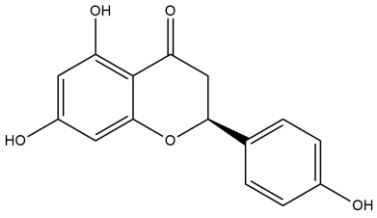


5-hydroxy-3,4',7-trimethoxyflavone

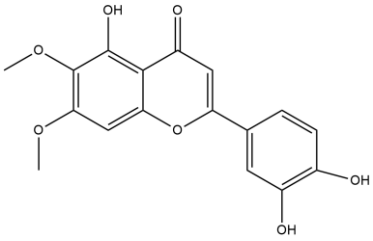


Retusin : R_1=R_2=R_3=R_4=OMe, R_5=H

Verbenacoside : R_1=R_3=R_4=H, R_2=OH, R_5= β-D-glucoside



Naringenin



Cirsiliol

Figure 4. Chemical structure of flavonoids identified in *S. verbenaca* essential oils and extracts.

3.4.3. Fatty acids.

Certain fatty acids were identified from *S. verbenaca* essential oils using GC-MS and GC-FID (gas chromatography equipped with a flame ionization detector) [60,19,74]. Canzoneri and coworkers (2011) investigated the fatty acids composition of the essential oils obtained from *S. verbenaca* aerial part (Sicily, Italy) using GC-MS [19]. The authors found that essential oils were dominated by hexadecanoic acid followed by (*Z*)-9-octadecenoic acid and ethyl hexadecanoate. Ben Taarid and coworkers (2010b) evaluated the fatty acids composition of *S. verbenaca*, seed oil from Tunisia, extracted with chloroform/methanol mixture (2:1, v/v), in three stations (Sabelet Ben Ammar, Somâa, and Sers) [60]. According to the plant region, linolenic acid and linoleic acid were the dominant compounds (45.89 mg/g and 27.39 mg/g, respectively) with no significant differences in most fatty acid proportions. In 2015, Ben Farhat and investigators (2015) analyzed the composition of fatty acids of *S. verbenaca* seed (from Tunisia) in different habitats [74]. They showed that the main unsaturated fatty acids were linolenic acid and linoleic acid with a value of 45.02%, and 23.36%, respectively. In addition, these two compounds were the main fatty acids identified in all stations [74]. These results confirmed that the distribution of fatty acids did not depend on the region.

3.4.4. Phenolic acids and phenolic diterpenoids.

Chromatography analysis of phytochemical compounds of *S. verbenaca* extract revealed the presence of phenolic acids and phenolic diterpenoids. The work of Ben Farhat *et al.* (2013) identified the composition of methanolic extracts of *S. verbenaca* aerial part from Tunisia growing in ten different habitats [1]. They found that rosmarinic acid was the main

phenolic acid of all analyzed samples (349.60 - 2560.37 µg/g), followed by *p*-Hydroxybenzoic acid (173.69 - 383.37 µg/g) and caffeic acid (30.79 - 231.37 µg/g). Methyl carnosate was the major phenolic diterpenoids identified in all extracts. Two years later, Ben Farhat (2015) studied the chemical compounds of the same extract in three different phenological stages [25]. Rosmarinic acid was the main phenolic acid identified in all phonological stages (649.26 - 544.51 µg/g) followed by *p*-hydroxybenzoic acid (83.62 - 47.27 µg/g) and caffeic acid (59.44 - 42.36 µg/g) in the early fruiting stage, and the late fruit stage. For phenolic diterpenoids, the major compounds were methyl carnosate and carnosic acid (821.45 - 919.82 µg/g, and 110.22 - 199.60 µg/g, respectively) (Figure 5, Table 2).

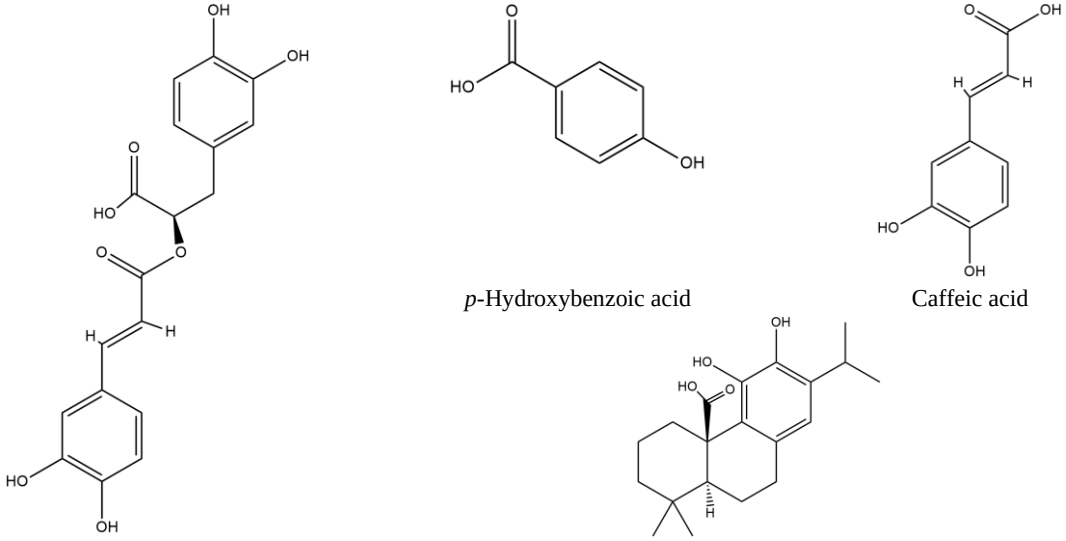


Figure 5. Chemical structure of phenolic acid and phenolic diterpenoids identified in *S. verbenaca* extracts.

3.4.5. Carbonylic compounds and hydrocarbons.

The chemical composition of the essential oil of *S. verbenaca* from Italy was completely distinct from other essential oils by their composition of carbonylic compounds and hydrocarbons.

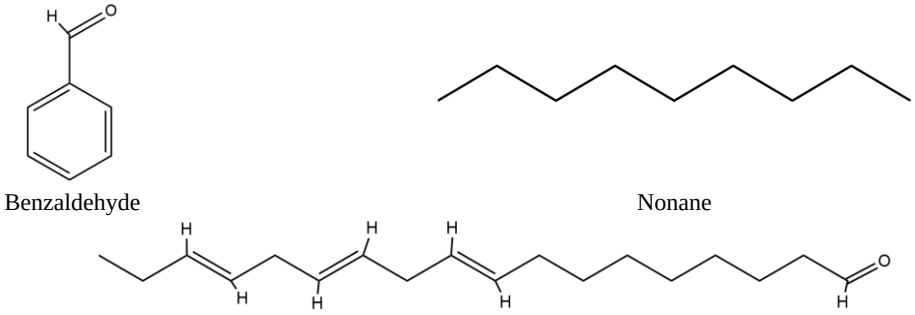


Figure 6. Chemical structure of carbonylic compounds and hydrocarbons identified in *S. verbenaca*.

Table 2. Phytochemistry of *S. verbenaca.*

Used part	Extracts/ essential oils	Compounds groups	Main compounds	References
Aerial part (Algeria)	Essential oils	Terpenoids	1,10-di-epi-cubenol (20.9%) epi-α-cadinol (11.6%) β-caryophyllene (11.33%) Bicyclogermacrene (10.9%) γ-Cadinene (7.9%) cis muurola-4(14),5-diene (7.8%)	[70]

Used part	Extracts/ essential oils	Compounds groups	Main compounds	References
Aerial part (Jordan)	Essential oils	Terpenoids	Linalool (61.32%) (Z)-β-Ocimene (4.03%) *E*-β-Ocimene (2.63%) Bicyclogermacrene (5.94%) Spathulenol (3.40%) β-Eudesmol (3.66%)	[71]
Leaves (Irano-Turanian)	Essential oils	Terpenoids	δ-Selinene (21.5%) Germacrene D (19.8%) *E*-Caryophyllene (11.4%) α-Copaene (9.6%) Sabinene (9.0%) Z-β-Ocimene (4.8%)	[61]
Flowers (Irano-Turanian)	Essential oils	Terpenoids	Sabinene (37.5%) *trans*-Sabinene hydrate (20.0%) Z-β-ocimene (9.9%) *E*-β-ocimene (8.9%) α-thujene (4.6%)	[61]
Aerial part (Saudi Arabia)	Methanol extract	Flavonoids	5-hydroxy-3,4',7-trimethoxyflavone Retusin Verbenacoside	[4]
Aerial part (Saudi Arabia)	Alcoholic extract	Terpenoids	Verbenacine Salvinine	[65]
Aerial parts (Algeria)	Essential oils	Terpenoids	Germacrene D (20.5%) α-Copaene (10.4%) β-Caryophyllene (3.8%) β-Phellandrene (3.8%) (E)-β-Farnesene (3.5%)	[71]
Aerial parts (Tunisia)	Methanolic extract	Phenolic acids	Caffeic acid (81.48 µg/g) Rosmarinic acid (1065.78 µg/g) *p*-Hydroxybenzoic acid (173.69 µg/g)	[1]
		Phenolic diterpenes	Carnosic acid (65.83 µg/g) methyl carnosate (286.37 µg/g)	
		Flavonoids	Hesperidin (39.37 µg/g) Naringenin (472.03 µg/g) Cirsiliol (75.44 µg/g)	
Seed (Tunisia)	Oil extract	Fatty acids	Oleic acid (16.45%) Linoleic acid (23.36%) Linolenic acid (45.02%)	[74]
Aerial parts (Tunisia)	Methanolic extract	Phenolic acids	Rosmarinic acid (544.51 µg/g) Caffeic acid (68.75 µg/g) *p*-Hydroxybenzoic acid (67.02 µg/g) Ferulic acid (32.46 µg/g)	[25]
		Phenolic diterpenes	Methyl carnosate (919.82 µg/g) Carnosic acid (110.22 µg/g)	
		Flavonoids	Naringenin (241.50 µg/g) Cirsiliol (71.57 µg/g) Cirsilineol (24.65 µg/g)	
Aerial parts (Tunisia)	Essential oil	Terpenoids	1,8-Cineole (9.7%) *p*-Cymene (8.4%) Viridiflorol (7.3%) β-Caryophyllene (5.3%) epi-13-Manool (4.7%)	[24]
Seed (Spain)	Essential oil	Terpenoids	Camphor (38.94%) Caryophyllene oxide (7.28%) 13-epi-Manool (5.61%) *α*-Terpinyl acetate (4.77%)	[63]
Leaf (Tunisia)	Essential oil	Terpenoids	*epi*-13-manool (13.7%) Manool (11.0%) Caryophyllene oxide (3.9%)	[60]

Used part	Extracts/ essential oils	Compounds groups	Main compounds	References
			Camphor (3.9%)	
Fruit (Tunisia)	Essential oil	Terpenoids	β-Caryophyllene (23.1%) Caryophyllene oxide (15.9%) Camphene (6.5%) α-Humulene (5.6%) Viridiflorol (4.3%)	
Stem (Tunisia)	Essential oil	Terpenoids	Camphor (10.9%) Viridiflorol (10.3%) Terpinolene (6.6%) Methyl eugenol (6.1%) α-Pinene (5.9%)	
Seed (Tunisia)	Essential oil	Terpenoids	Camphor (33.83%) Caryophyllene oxide (10.11%) Tricyclène (5.54%) Octane (4.78%)	[62]
		Fatty acids	Linolenic acid (45.89 mg/g) Linoleic acid (27.39 mg/g) Oleic acid (14.67 mg/g)	
Aerial part (Tunisia)	Essential oil	Terpenoids	Viridiflorol (21.8%) Camphene (17.6%) Methyl eugenol (9.4%) β-caryophyllene (7.1%)	[69]
Aerial part (Italy)	Essential oil	Hydrocarbons	Nonane (1.2%) Tricosane (0.9%)	[19]
		Carbonylic compounds	Benzaldehyde (7.3%) 9,12,15-Octadecatrienal (2.9%) (*E*)-β-Ionone (1.9%) (*E*)-2-Hexenal (1.5%) Phenyl acetaldehyde (1.5%)	
		Terpenoids	β-Phellandrene (5.9%) Limonene (2.0%) Caryophyllene oxide (1.9%) (*E*)-Caryophyllene (1.2%) Linalool (0.7%)	
		Fatty acids	Hexadecanoic acid (23.1%) (*Z*)-9-Octadecenoic acid (11.1%) Ethyl hexadecanoate (2.6%)	
Aerial part (Saudi Arabia)	Essential oil	Terpenoids	Sabinene (16.0%) *δ*-cadinene (7.9%) alpha-Pinene (7.3%) 4-Terpeniol (7.4%) Limonene (6.7%)	[26]
Aerial part (Algeria)	Essential oil	Terpenoids	*cis*-Muurola-3,5 diene (14.6%) γ-amorphene (10.5%) Bicyclogermacrene (6.8%) γ-cadinene (4.8%) 2,3-dehydro-1,4-cineol (3.7%)	[66]
Aerial part (Greece)	Essential oil	Terpenoids	β-Phellandrene (30.3%) (*E*)-Caryophyllene (16.1%) Methyl ester of 6-octadecenoic acid (15.0%)	[64]
Aerial part (Italy)	Essential oil	Terpenoids	Hexadecanoic acid (23.1%) (Z)-9-Octadecenoic acid (11.1%) Benzaldehyde (7.3%)	[27]
Flowers, leaves (Italy)	Essential oil	Terpenoids	Terpinolene (11.9%) (E)-β-caryophyllene (23.7%) Germacrene D (26.3%) Phytol (10.4%) α-humulene (4.6%)	[68]

Benzaldehyde and 9,12,15-Octadecatrienal were the main carbonylic compounds identified in *S. verbenaca* essential oils (7.3% and 2.9%), while nonane was the main hydrocarbons with the value of 1.2% [19] (Figure 6, Table 2).

3.5. Pharmacological investigation.

3.5.1. Antibacterial activity.

Several studies reported the antibacterial efficacy of different extracts and essential oils from different plant parts of *S. verbenaca* [21,26,19,75-79]. As reported, the antibacterial activity of the essential oils and extracts from different parts of *S. verbenaca*, type of extract, type of antibacterial assay, tested strains, and mains results are summarized in Table 3.

Al Howirine (2002) studied the antibacterial effect of essential oils obtained from the aerial parts of this plant from Saudi Arabia against five strains [26]. They showed a similar antibacterial effect of tested oil against *Bacillus subtilis* (MIC = 2.0 mg/mL), *Staphylococcus aureus* (MIC = 2.0 mg/mL), and *Mycobacterium smegmatis* (MIC = 3.0 mg/mL) while no effect has been reported for *Escherichia coli*, and *Pseudomonas aeruginosa*. Canzoneri *et al.* (2011) also investigated the antibacterial activity of *S. verbenaca* essential oils from aerial parts (Sicily, Italia) using the dilution method against Gram-negative and Gram-positive bacteria [19]. The authors reported that essential oils were not active against Gram- bacteria (MIC > 100 μg/mL), while it exhibited a good antimicrobial effect against *B. subtilis*, and *Staphylococcus epidermidis* (MIC = 50 μg/mL, for both strains).

Researchers reported the effect of organic extract of *S. verbenaca* against Gram- and Gram+ bacteria. The antibacterial activity of leaves methanolic extract of *S. verbenaca* from Tunisia was tested using the agar diffusion method [75]. According to this study, the MICs varied from 500 to 1000 μg/mL, and the extracts seemed to be selective. Leaves methanolic extracts exhibited the same potent antibacterial against *S. epidermidis, Staphylococcus cohnii, Corynebacterium gr. C, Corynebacterium gr. D2, Micrococcus sedentarius*, and *Corynebacterium xerosis*, while less activity was obtained for *Micrococcus luteus, Staphylococcus intermedius, Pseudomonas cepacia*, and *P. aeruginosa* (MIC > 1000 μg/mL). In 2007, Kamatou *et al.* (2007) evaluated *in vitro* the antibacterial effects of methanol:chloroform of *S. verbenaca* aerial parts using microdilution assay against *E. coli, K. pneumonia, B. cereus*, and *S. aureus* [76]. From this study, the authors demonstrated that *K. pneumonia* and *B. cereus* (MIC = 2 mg/mL) were the most sensitive bacteria in 1:1 dilution. In another study, Sarac et Ugur (2007) reported the growth inhibitory effect of ethanol extract of this plant (Mugla, Turkey) on various pathogenic bacteria with inhibition zones ranged between 9-11 mm [77].

The antibacterial activity of ethyl acetate extract of *S. verbenaca* from the southern part of Al Karak governorate (Jordan) and Bordj-Bou-Arerridj region (Algeria) was tested using agar and disc diffusion methods [21,78]. Al-Zereini (2017) evaluated the effect of ethyl acetate extract of *S. verbenaca* leaves (Jordan) [78]. At 100 mg/mL, the extract exhibited low inhibitory zones of 9.3 ± 0.6 mm and 7.1 ± 1.2 mm for *Bacillus brevis*, and *B. subtilis*, respectively. The same extract of *S. verbenaca* from aerial part growth in Algeria was investigated against eight microorganisms in the next year. The authors studied the effect of two different concentrations (100 mg/ml and 200 mg/ml) and indicated a proportional effect of *S. verbenaca* ethyl acetate extract concentration. At 200 mg/mL, the inhibitory zone varied

between 13 and 16 mm, with a large inhibitory zone was reported against *S. aureus* (16 mm) [21].

Kabouche and Kabouche (2008) investigated the antibacterial activity of root acetone extract at 128 mg/mL against several strains [79]. The results indicated that *B. subtilis* (28 mm, MIC = 4 µg/mL), *S. aureus* (26 mm, MIC = 16 µg/mL), and *Streptoccocus hemolytic* (22 mm, MIC = 6 µg/mL) were extremely sensitive to the concentration of 128 mg/mL while a week antibacterial effect was reported for *E. coli*, *K. pneumonia*, *P. mirabilis*, and *S. hemolytic*.

All these researches reported that *S. verbenaca* presented an important antibacterial effect with a variation of the results depend on different factors including extract used, localization of plant, period of collect, used part, extraction methods, the experimental used as well as bioactive compounds present in the plant [80]. However, the mechanism by with extracts and essential oils exhibited their effect was not fully understood. Indeed, different researchers reported that bioactive molecules such as flavonoids have the ability to form complexes with extracellular and solubles protein as well as the cell wall [75]. Naringenin, a flavonoid belonging to the flavanones subclass, showed an important antibacterial activity by decreasing biofilm formation and decreasing fatty acid secretion [81]. Moreover, modifying cell morphology and gene expression, increasing cell permeability, and inhibiting the quorum-sensing system are also mechanisms of pathways by which molecules exert their effects on bacteria [20,82,83]. Furthermore, the synergistic effects of the major and the minor phenolic compounds should be taken into consideration

Table 3. Antibacterial activity of *S. verbenaca*.

Part used	Extract tested	Method used	Tested strains	Keys results	References
Leaves	Ethyl acetate (100mg/ml)	Agar diffusion method	*Bacillus brevis* ATCC 9999	Φ = 9.3 ± 0.6 mm	[78]
			Bacillus subtilis ATCC 6633	Φ = 7.1 ± 1.2 mm	
Aerial part	Ethyl acetate (100mg/ml)	Disc diffusion method	*Escherichia coli* ATCC 25922	Φ = 11 mm	[21]
			Pseudomonas aeruginosa ATCC 27853	Φ = 12 mm	
			Staphylococcus aureus ATCC 52952	Φ = 12 mm	
			Bacillus cereus ATCC 10876	Φ = 13 mm	
			P. mirabilis ATCC 35659	Φ = 13 mm	
			Enterococcus faecalis ATCC 49452	Φ = 12 mm	
			Citrobacter freundii ATCC 8090	Φ = 12 mm	
			Acenetobacter baumanii ATCC 19306	Φ = 10 mm	
Aerial parts	Essential oil -	Broth dilution method	*Staphylococcus aureus*	MIC = 100 µg/mL	[19]
			Streptococcus faecalis	MIC = 100 µg/mL	
			Bacillus subtilis	MIC = 50 µg/mL	
			Staphylococcus epidermidis	MIC = 50 µg/mL	
Aerial parts	Essential oil -	-	*Bacillus subtilis*	MIC = 2.0 mg/mL	[26]
			Staphylococcus aureus	MIC = 2.0 mg/mL	
			Mycobacterium smegmatis	MIC = 3.0 mg/mL	
Root	Acetone extract (128 mg/ml)	-	*Bacillus subtilis*	Φ = 28 mm MIC = 4 µg/mL	[79]
			Escherichia coli	Φ = 14 mm MIC = 128 µg/mL	
			Klebsiella pneumonia	Φ = 12 mm MIC > 128 µg/mL	
			Proteus mirabilis	Φ = 8 mm MIC > 128 µg/mL	
			Staphylococcus aureus	Φ = 26 mm	

Part used	Extract tested	Method used	Tested strains	Keys results	References
				MIC = 16 µg/mL	
			Streptoccocus hemolitic	Φ = 22 mm MIC = 6 µg/mL	
Aerial parts	Methanol: chloroform (1:1) extracts	Micro-dilution	*E. coli* ATCC 8739	MIC = 8 mg/mL	[76]
			K. pneumoniae NCTC 9633	MIC = 2 mg/mL	
			B. cereus ATCC 11778	MIC = 2 mg/mL	
			S. aureus ATCC 25923	MIC = 3 mg/mL	
-	Ethanol extract	Disk diffusion method	*B. subtilis* ATCC 6633	Φ = 9 mm	[77]
			S. aureus ATCC 25923	Φ = 11 mm	
			S. aureus MU 38	Φ = 9 mm	
			S. aureus MU 44	Φ = 10 mm	
			S. epidermidis MU 30	Φ = 9 mm	
Leaves	Methanolic extract	Agar diffusion method	*Staphylococcus epidermidis* (L1S2)	MIC = 500 µg/mL	[75]
			Staphylococcus cohnii (L6S3)	MIC = 500 µg/mL	
			Corynebacterium gr. B (L16C3)	MIC > 1000 µg/mL	
			Corynebacterium gr. C (L3C3)	MIC = 500 µg/mL	
			Corynebacterium gr. D2 (L19C1)	MIC = 500 µg/mL	
			Micrococcus sedentarius (L7B5)	MIC = 500 µg/mL	
			Acinetobacter sp. (LH5DC1)	MIC = 700 µg/mL	
			Moraxella sp. (LH7SV1)	MIC > 1000 µg/mL	
			Alcaligenes sp. (LH4TV1)	MIC > 1000 µg/mL	
			Staphylococcus xylosus (IP8166)	MIC > 1000 µg/mL	
			Corynebacterium xerosis (IP5216)	MIC = 500 µg/mL	
			Micrococcus luteus (L1C5)	MIC > 1000 µg/mL	
			Staphylococcus intermedius (IP8160)	MIC > 1000 µg/mL	
			Pseudomonas cepacia (V6108)	MIC > 1000 µg/mL	
			Pseudomonas aeruginosa (V5791)	MIC > 1000 µg/mL	

Φ : Zone of inhibition, MIC: Minimum Inhibitory Concentration.

3.5.2. Antifungal activity.

The antifungal activity of *S. verbenaca* essential oils and the methanolic extract was elaborated by two studies [26,75] (Table 4). The essential oil extracted from aerial parts of *S. verbenaca*, rich in sabinene and δ-cadinene, was studied against *Candida albicans*. The essential oil was active against this strain with a MIC value of 2.0 mg/mL [26].

Salah *et al.* (2006) investigated the antifungal effect of methanolic extract of this plant from Tunisia against *Trichophyton mentagrophytes* var. mentagrophytes, *Trichophyton mentagrophytes* var. interdigitale, *Trichophyton rubrum, Trichophyton soudanense, Microsporum canis, Microsporum gypseum, Epidermophyton floccosum, Aspergillus fumigatus, Scopulariopsis brevicaulis, Scytalidium dimidiatum, C. albicans*, and *Cryptococcus neoformans* [75]. This study was realized using the agar incorporation method and evaluated using two methods: by calculating the percentage inhibition (%I) and determining the MIC. Variable antifungal activity has been reported of the tested methanolic extract (0-100% for %I, and 500 to > 1000 µg/mL for MIC). The most sensitive strain was observed for dermatophytes *T. rubrum, T. soudanense*, and *M. canis* with an inhibition growth of 100% and MIC values of 500 µg/mL while hyphamycets (*A. fumigatus, S. brevicaulis*) and pathogenic yeasts (*C. albicans*, and *C. neoformans*) were resistance for this extract. The potent antifungal properties of essential oil and extracts of *S. verbenaca* highlighted that several bioactive compounds could

be further isolated, tested, and developed into antifungal drugs. However, further, *in vivo* preclinical tests should be conducted to ensure the safety and efficacy of these essential oils, extracts, and bioactive compounds.

Table 4. Antifungal activity of *S. verbenaca*.

Part used	Extract tested	Method used	Tested strains	Keys results	References
Aerial parts	Essential oil	-	*Candida albicans*	MIC = 2.0 mg/mL	[26]
-	Methanolic extract	Agar incorporation method	*Trichophyton mentagrophytes* var. mentagrophytes	I = 13 % MIC = 900 µg/mL	[75]
			Trichophyton mentagrophytes var. interdigitale	I = 10 % MIC = 950 µg/mL	
			Trichophyton rubrum	I = 100 % MIC = 500 µg/mL	
			Trichophyton soudanense	I = 100 % MIC = 500 µg/mL	
			Microsporum canis	I = 100 % MIC = 500 µg/mL	
			Microsporum gypseum	I = 17 % MIC = 900 µg/mL	
			Epidermophyton floccosum	I = 24 % MIC = 850 µg/mL	
			Aspergillus fumigatus	I = 0 % MIC > 1000 µg/mL	
			Scopulariopsis brevicaulis	I = 0 % MIC > 1000 µg/mL	
			Scytalidium dimidiatum	I = 7.5 % MIC > 1000 µg/mL	
			Candida albicans	I = 0 % MIC > 1000 µg/mL	
			Cryptococcus neoformans	I = 0 % MIC > 1000 µg/mL	

I: Percentage inhibition, MIC: Minimum Inhibitory Concentration.

3.5.3. Antioxidant activity.

Several studies revealed that Salvia species have an interesting potential for antioxidant activity, which made them one of the interesting sources of natural antioxidants that could provide a chemical basis in the food and pharmaceutical field [84,85]. The *in vitro* antioxidant activity of *S. verbenaca* extracts was studied by many researchers [21,25,76,87-90] (Table 5). In a study conducted by Salah and co-workers (2006), the methanolic extracts of *S. verbenaca* aerial part from Tunisia were tested for their antioxidant effect using DPPH and ABTS assays [76]. The methanolic extract showed a potent antioxidant effect with values of IC50 = 86.9 µg/mL, IC50 = 777.3 µg/mL at 5 min, IC50 = 499.5 µg/mL at 20 min, in DPPH, and ABTS, respectively. In the same year, another study investigated the antioxidant effect of *S. verbenaca* hydormethanolic extract towards linoleic acids, linolenic acids, and low-density lipoproteins (LDL) peroxidation. At 100 µg/mL, this extract showed significant inhibition of oxygen consumption, conjugated dienes (CD) formation of LDL peroxidation, and thiobarbituric acid reactive substances (TBARS) (92%, 92%, and 93%, respectively), which was correlated with phenolic compounds present in *S. verbenaca* extract [86]. In 2008, the antioxidant activity of the methanol extract of Turkish *S. virgata*, *S. staminea*, and *S.verbenaca* was investigated using DPPH and β-carotene assays by Tepe (2008) [87]. It showed that the extract from *S. verbenaca* exerted the most important antioxidant activity with an IC50 value of 14.30 ± 1.42 µg/mg, and

inhibition of 77.03 ± 0.42 % in DPPH and β-Carotene test, respectively. Ben Farhat *et al.* (2013) tested the antioxidant activity of the methanolic extract of Tunisian *S. verbenaca* collected from ten different habitats using DPPH, ABTS, and FRAP assays [88]. The methanolic extract from *S. verbenaca* collected from Bir Mroua showed interesting antioxidant effect (IC50 = 205.27 ± 0.29 µM TE/mg for ABTS assay and IC50 = 159.25 ± 2.89 mM Fe(II)/mg for FRAP assay) compared with *S. verbenaca* collected from Enfida (IC50 =165.28 ± 10.80 µM TE/mg for ABTS assay and IC50 = 106.50 ± 2.20 mM Fe(II)/mg for FRAP assay) while, using DPPH assay, the antioxidant effect of *S. verbenaca* harvested from Enfida was IC50 = 36.28 ±0.01 µg/mL compared with the methanolic extract collected from Bir Mroua (IC50 = 23.00 ± 0.46 µg/mL). Furthermore, the authors reported that the antioxidant effect was significantly correlated with the presence of polyphenolic compounds, especially with rosmarinic acid. A significant correlation with DPPH and FRAP was attributed to naringin and with ABTS to gallic acid [88]. A recent study demonstrated that the plant's habitat or origin could impact the biological activities and plant composition and the altitude since the main four chemicals that they identified were affected [68]. The same group conducted by Ben Farhat and co-workers (2015) evaluated the Tunisian *S. verbenaca* methanolic extracts in three phenological stages for their antiradical effect [25]. This antiradical effect was studied using numerous methods such as DPPH, ABTS, and FRAP assays. The authors showed that this extract has a potent antioxidant effect at the early fruiting period (49.22 µg/mL, 146.86 µM TE/mg, and 188.93 mM Fe(II)/mg for DPPH, ABTS, and FRAP, respectively) and evidenced the significant effect of phenophase on antioxidant activity. Nassar *et al.* (2015) investigated the antioxidant effect of *S. verbenaca* (Algeria) n-BuOH extract using DPPH assay and showed an IC50 = 47,50 µg/mL [23]. In another study, the supercritical carbon dioxide extract, ethanol extract, and aqueous extract of *S. verbenaca* were tested for *their in vitro* antioxidant activity by Šulniūtė *et al.* (2016) using ABTS, and ORAC (Oxygen radical absorbance capacity) assays [89]. The aqueous extract showed potent antiradical activity compared with ethanol extract (IC50 = 69.6 ± 1.4 µmol TE/g vs. IC50 = 1742 ± 2.3 µmol TE/g for ABTS assay and IC50 = 626 ± 34.2 µmol TE/g vs. IC50 = 4121 ± 300.7 µmol TE/g for ORAC assay). Belkhiri *et al.* (2017) evaluated the antioxidant effect of ethyl acetate extract, chloroform extract, aqueous extract, and crude extract of *S. verbenaca* aerial part (Algeria) using ferrous iron chelating assay and DPPH free radical scavenging [21]. The ethyl acetate extract was the most active extract in reducing power assay (EC50 = 0.0047 ± 0.000 mg/ml) and in DPPH radical scavenging assay (IC50 = 0.0086 ± 0.000 mg/ml). Recently, the aqueous extract and the methanolic extract of aerial parts of *S. verbenaca* from Algeria have been investigated for their *in vitro* antioxidant properties using DPPH radical scavenging, ABTS radical scavenging, alkaline DMSO superoxide radical scavenging, β-carotene bleaching assays. From this study, all extracts showed a comparison with butylhydroxytoluene (BHT) as a positive control. Recently, Nassar and coworkers (2020) investigated *in vitro* the protective activities of the methanolic extract from *S. verbenaca* root against oxidative stress induced by H_2O_2 by measuring the intracellular ROS level using the 2,7-dichlorodihydrofluorescien diacetate (H2DCFDA) assay [90]. At 10 µg/L, the methanolic extract with H_2O_2 showed a significant decrease in the intracellular ROS level. In 2021, Righi *et al.* (2021) investigated the antioxidant effect of hydromethanolic extract of *S. verbenaca* (Algeria) using DPPH, AAPH, iron chelating, and FRAP assays and showed an IC_{50} = 7.6 ± 0.6 µg/mL, IC_{50} = 111.1 ± 8 µg/mL, IC_{50} = 189.2 ± 7.9 µg/mL, and 4.3 ± 0.1 mmol FeSO4 Eq./g, respectively [91]. Diterpenoids and rosmarinic acid were the most characterized compounds of *Salvia* species, and they were

confirmed to be the actors in many biological activities, especially the antioxidant effect. It was shown that *S. verbenaca* methanolic extract had the highest level of rosmarinic acid (29.30 ± 0.24 µg/mg) compared to *S. virgate* and *S. staminea* [79,85,92]. Indeed, several *in vitro* investigations illustrated the correlation between phenolic compounds and antioxidant activities and with the synergy effect with other compounds [93,94].

Table 5. Antioxidant activity of *S. verbenaca*.

Use part	Extracts	Used method	Key results	References
Aerial parts	Ethyl acetate extract	Ferrous iron-chelating assay, and DPPH free radical scavenging, respectively	EC_{50} = 0.0047 ± 0.000 mg/mL IC_{50} = 0.0086 ± 0.000 mg/mL	[21]
	Chloroform extract		EC_{50} = 0.453 ± 0.0006 mg/mL IC_{50} = 0.0725 mg/mL	
	Aqueous extract		EC_{50} = 0.0455 ± 0.000 mg/mL IC_{50} = 0.0389 mg/mL	
	Crude extract		EC_{50} = 0.0178 ± 0.000 mg/mL IC_{50} = 0.0336 mg/mL	
Aerial parts	Methanolic extracts	DPPH	IC_{50} = 23.00 ± 0.46 µg/mL	[88]
		ABTS	IC_{50} = 205.27 ± 0.29 µM TE/mg	
		FRAP	IC_{50} = 159.25 ± 2.89 µM Fe(II)/mg	
Aerial parts	Methanolic extract	DPPH	IC_{50} = 107.71 ± 4.18 µg/mL for flowering stage IC_{50} = 49.22 ± 1.10 µg/mL for early fruiting stage IC_{50} = 69.66 ± 2.35 µg/mL for late fruiting stage	[25]
		ABTS	IC_{50} = 102.37±2.04 µM TE/mg for flowering stage IC_{50} = 146.86±5.44 µM TE/mg for early fruiting stage IC_{50} = 116.80±4.70 µM TE/mg for late fruiting stage	
		FRAP	IC_{50} = 106.00±5.29 mM Fe(II)/mg for flowering stage IC_{50} = 188.93±8.86 mM Fe(II)/mg for early fruiting stage IC_{50} = 127.33±2.42 mM Fe(II)/mg for late fruiting stage	
Aerial parts	Hydromethanolic extract	Conjugated dienes (CD) formation	Inhibition = 92%	[86]
		Oxygen consumption	Inhibition = 92%	
		Thiobarbituric acid reactive substances (TBARS)	Inhibition = 93%	
Aerial parts	Methanol extract	ABTS radical scavenging	IC_{50} = 19.96 ± 1.03 µg/mL	[95]
		Alkaline DMSO superoxide radical scavenging	IC_{50} = 07.77 ± 1.00 µg/mL	
		β-carotene bleaching	I= 82.58 ± 2.39 %	
		DPPH	IC_{50} = 24.36 ± 1.13 µg/mL	

Use part	Extracts	Used method	Key results	References
	Aqueous exract	ABTS radical scavenging	IC_{50} = 36.86 ± 1.03 µg/mL	
		Alkaline DMSO superoxide radical scavenging	IC_{50} = 18.78 ± 1.11 µg/mL	
		β-carotene bleaching	I= 96.12 ± 2.48 %	
		DPPH	IC_{50} = 27.26 ± 1.05 µg/mL	
Aerial parts	n-BuOH extract	DPPH	IC_{50} = 47,50 µg/mL	[23]
Root	Methanol extract	2,7-Dichlorodihydrofluorescien diacetate (H2DCFDA) assay	I > 150 % at 10 µg/mL	[90]
Aerial parts	Hydromethanol extract	DPPH	IC_{50} = 7.6 ± 0.6 µg/mL	[91]
		AAPH	IC_{50} = 111.1 ± 8 µg/mL	
		Iron chelating	IC_{50} = 189.2 ± 7.9 µg/mL	
		FRAP	4.3 ± 0.1 mmol FeSO4 Eq./g	
Aerial parts	Methanol extract	DPPH	IC_{50} = 86.9 µg/mL	[75]
		ABTS	IC_{50} = 777.3 µg/mL at 5 min IC_{50} = 499.5 µg/mL at 20 min	
Not mentionned	Supercritical carbon dioxide extract	ABTS	-	[99]
		ORAC	IC_{50} = 1142 ± 38.7 µmol TE/g	
	Ethanol extract	ABTS	IC_{50} = 1742 ± 2.3 µmol TE/g	
		ORAC	IC_{50} = 4121 ± 300.7 µmol TE/g	
	Aqueous extract	ABTS	IC_{50} = 69.6 ± 1.4 µmol TE/g	
		ORAC	IC_{50} = 626 ± 34.2 µmol TE/g	
Not mentionned	Methanol extract	DPPH	IC_{50} = 14.30 ± 1.42 µg/mg	[87]
		β-Carotene	Inhibition = 77.03 ± 0.42 %	

3.5.4. Anticancer activity.

The anticancer activity of essential oils and different extracts of *S. verbenaca* was conducted against several cancer cells using different methods [20,78,96,97]. Table 6 summarized all research that evaluated the cytotoxicity effect of *S. verbenaca,* including the part used, the extract tested, the method used, and the main results.

Organic extracts of different parts from *S. verbenaca* against anticancer cells were widely evaluated. Badisa *et al.* (2005) evaluated the anticancer activity of the aerial parts of *S. verbenaca* methanolic extract (Greece) at different concentrations (10-100 µg/mL) against four human cell lines, namely human colon adenocarcinoma (HCA), human hepatoblastoma (HepG2), human breast cancer cells (MCF-7), and human pancreatic carcinoma (HPC) using brine shrimp lethality assay [96]. The result showed that this extract exhibited a lethal concentration LC_{50} > 75 µg/mL in all cell lines tested. At the same time, there was a low cytotoxic effect of this extract against normal mouse adipose areolar cell line (NCTC clone 929) with 12% of death at 0.1 mg/mL. Furthermore, the same extract was investigated *in vivo* for cytotoxic activity against brine shrimps and found to be highly active with ED_{50} < 300 µg/mL. Leaves methanolic extracts of this plant collected from Riyadh (Kingdom of Saudi Arabia) showed the highest activity against Vero cells (CC_{50} = 73.65 µg/mL) compared with human larynx cancer cells (HEp-2 cells) (CC_{50} = 114.36 µg/mL) [97]. In 2018, the anticancer activity of three organic extracts of *S. verbenaca* aerial parts from Ain Aouda (Rabat, Morocco)

was investigated. Hexane, ethyl acetate, and n-butanol extracts were evaluated *in vitro* against Human Embryonal Rhabdomyosarcoma cancerous cell lines (RD) and Monkey kidney cancerous cell lines (Vero) using MTT assay [20]. These authors reported that all extracts exhibited a weak cytotoxicity activity (IC_{50} > 500 µg/mL) except for ethyl acetate extract, which presented an IC_{50} value of 223.63 ± 1.61 µg/mL. Moreover, ethyl acetate extract of *S. verbenaca* leaves (from Jordan) showed the highest activity against MDA MB-231 breast cancer cells with an IC_{50} = 41.3 ± 4.8 µg/mL using a low concentration of ethyl acetate extract (10-100 µg/mL) [78]. The variability of the phytochemical composition of each extract could be the main cause of the different cytotoxicity observed.

Few studies investigated the anticancer activity of *S. verbenaca* essential oils. Russo *et al.* (2015) studied *in vitro* antitumor effect of essential oils of *S. verbenaca* aerial parts collected from Sicily (Italia) with those cultivated in the Botanical Gardens of Palermo [27]. The cytotoxic activity was carried out on human melanoma cells (M14) using the MTT assay. The essential oil exhibited a potent antiproliferative effect of both *S. verbenaca* wild and cultivated with an IC_{50} value of 12.2 ± 0.4 µg/mL, and 8.1 ± 0.6 µg/mL, respectively. The slight variation observed in the same species is due to localization growth, climate, light, nutrient variability, and seasons resulting in the chemical variation of the essential oil [95]. In this study, the authors reported that sesquiterpene compounds possess an anticancer potential by caspase-3 activity [65]. Furthermore, essential oil from *S. verbenaca* cultivated presents a high concentration of carvacrol. This phenolic compound inhibited the growth of melanoma cells [27] and has been reported recently for its action in the different molecular mechanisms through the alteration of soluble factors and the inhibition of protein expressions (PI3K/p-AKT) [98,99]. The essential oil of *S. verbenaca* exhibited a potent *in vitro* anticancer activity, which can be possible to use in the pharmaceutical industry. However, this effect should be in-depth validated *in vivo* to exploit the mechanistic pathways and the bioactive compounds responsible for the action.

Table 6. Anticancer activity of *S. verbenaca.*

Part used	Extract tested	Methods used	Tested strains	Keys results	References
Leaves	Ethyl acetate	-	MDA MB-231	IC_{50} = 41.3 ± 4.8 µg/mL	[78]
Aerial parts	Methanol extract	Shrimps assay	Brine shrimps larvae	ED_{50} < 300 µg/mL	[96]
		-	HCA	LC_{50} > 75 µg/mL	
			HepG2	LC_{50} > 75 µg/mL	
			MCF-7	LC_{50} > 75 µg/mL	
			HPC	LC_{50} > 75 µg/mL	
Aerial parts	Hexane	MTT assay	RD	IC_{50} = 474.62 ± 1.31 µg/mL	[20]
			Vero	IC_{50} > 500 µg/mL	
	Ethyl acetate		RD	IC_{50} > 500 µg/mL	
			Vero	IC_{50} = 223.63 ± 1.61 µg/mL	
	n-butanol		RD	IC_{50} > 500 µg/mL	
			Vero	IC_{50} > 500 µg/mL	
Leaves	Methanol extract	CTB assay	Vero	CC_{50} = 73.65 µg/mL	[97]
			HEp-2	CC_{50} = 114.36 µg/mL	
Aerial parts	Essential oil (0.25%)	MTT assay	M14	IC_{50} = 12.2 ± 0.4 µg/mL for *S. verbenaca* wild IC_{50} = 8.1 ± 0.6 µg/mL for *S. verbenaca* cultivate	[27]

3.5.5. Antileishmanial activity.

As reported by World Health Organization, more than 20 protozoan species of the genus *Leishmania* caused leishmaniasis. The bite of infected sandflies transmits this disease. Cutaneous and visceral leishmaniasis, forms of this disease, is the most serious form, leading to death if untreated [100]. Due to the increase of the resistance of parasites against current

therapies and the lack of vaccines against *Leishmania* spp., the researchers are particularly interested in developing urgent new treatments [101]. Natural products from medicinal plants showed an interesting antileishmanial property and present potential leads in treating this disease [102]. In 2016, three solvent partitions (methanol, n-hexane, and dichloromethane) of *S. verbenaca* were tested by Et-Touys and coworkers (2016) against three promastigote forms *Leishmania major, Leishmania tropica,* and *Leishmania infantum* [103]. The dichloromethane partition showed better activity with IC_{50} values ranging from 24.56 to 33.77 µg/mL. The n-hexane extract showed the most active effect against *Leishmania infantum* (IC_{50} = 14.11 µg/mL), whereas lower activity against *Leishmania major,* and *Leishmania tropica* has been observed (IC_{50} = 155.43 µg/mL, and IC_{50} = 148.23 µg/mL, respectively). The methanolic extract did not exhibit antileishmanial activity against any of the tested parasites. From this study, the authors suggested that extracts act through walls and membrane disruption by the lipophilic compounds [103].

3.5.6. Antidiabetic activity.

The antidiabetic effect of *S. verbenaca* was reported for the first time by Mamach and coworkers (2020) [96]. One promising strategy to reduce glucose absorption is by inhibiting enzymes implicated in intestinal hydrocarbons catabolism, such as α-amylase and α-glucosidase. In a recent study, Mamach *et al.* (2020) evaluated the inhibitory effect of *S. verbenaca* (Algeria) aqueous and methanolic extracts against α-amylase and α-glucosidase enzymes. They showed that the methanolic extracts of *S. verbenaca* (aerial part) inhibited α-amylase and α-glucosidase (IC_{50} = 101.30 µg/mL, and IC_{50} = 150.5 µg/mL, respectively), while the aqueous extract was no active against α-amylase and inhibited α-glucosidase with an IC_{50} > 300 µg/mL [95]. In this study, the authors suggested that phenols such as caffeic acid, curcumin, hesperetin, cyanidin, naringenin, and quercetin can inhibit the α-amylase and α-glucosidase enzyme.

3.5.7. Anti-inflammatory activity.

Bioactive compounds have an anti-inflammatory effect by inhibiting the release of lysosomal enzymes and stabilizing the lysosomal membranes. In this context, Righi and coworkers (2021) tested *ex vivo* the capacity of hydromethanolic extract of *S. verbenaca* to protect the cell membrane of mice erythrocytes from hypotonic and heat-induced hemolysis [91]. At 400 µg/mL, the hydromethanolic extract exerted relevant protection of erythrocytes against hemolysis induced by heat and hypotonic conditions, with a maximum inhibition percentage of 78% and 69%, respectively. Furthermore, this extract has the ability to inhibit erythrocytes' hemolysis with an IC_{50} value of 30 µg/mL. In this study, the authors suggested that some compounds in *S. verbenaca* bonded to the erythrocyte's membranes with subsequent alteration of the surface charges of the cells [91]. They also investigated *in vivo* the anti-inflammatory effect of *S. verbenaca* hydromethanolic extract using xylene-induced ear edema as an acute inflammation model. Using the hydromethanol extract at different concentrations (200-600 mg/kg bw), the ear weight caused by xylene has been reduced with maximal percentage reaching 50% of inhibition at the highest dose (600 mg/kg bw). The authors suggested that the anti-edematogenic effect attributed to phenolic compounds and triterpenoids present in *S. verbenaca,* mainly rosmarinic acid, caffeoylmalic acid, and luteolin [91]. Rosmarinic acid modulated inflammation by inhibition of neutrophil infiltration and regulation

of ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (vascular cell adhesion molecule 1), and cyclooxygenase-2 [108], while luteolin may also inhibit TNF-induced proinflammatory gene expression in murine intestinal epithelial cells [105].

3.5.8. Antihemolytic activity.

Recent research reported the protective biochemical function of extracts from aromatic and medicinal plants on free radicals and their mechanism of action [106]. *S. verbenaca* aerial part extracts were evaluated for their protection capacity on red blood cells (RBCs) against oxidative damage induced by 2,2,-azobis (2-amidinopropane) dihydrochloride (AAPH). Ethyl acetate extract exhibited the most antihemolytic effect (HT_{50} = 165 min). *S. verbenaca* aerial part extracts significantly protected the erythrocyte membrane from hemolysis in a time-dependent manner through the involvement of the phytochemicals. The authors of this study suggested that phytochemicals in *S. verbenaca* trapped the peroxyl radicals in the aqueous phase before they attack the erythrocyte membrane's lipid molecules, thus protecting against lipid peroxidation. Thus, the free radical chain reaction is broken and subsequent oxidative hemolysis is inhibited [21].

3.5.9. Antihypertensive activity.

In 2005, Ahmed and coworkers (2005) isolated three flavonoids from *S. verbenaca*, namely 5-hydroxy-3,4',7-trimethoxyflavone, retusin, and verbenacoside, and investigated their antihypertensive activity in normotensive albino rats [4]. At a dose of 3.3 mg/kg, 5-hydroxy-3, 4′, 7-trimethydoxyflavone, and verbenacoside showed the most potent effect in decreasing the blood pressure with a value of 30.0 mmHg, and 13.2 mmHg, respectively and in decreasing in heart rate with a value of 28.5% and 15.4%, respectively. This indicated that the lowering of blood pressure was due to a decrease in heart rate produced by vasodilatation. Likewise, the alcoholic extract of *S. verbenaca* (0.5 mg/kg) displayed an important decrease in blood pressure (36.2 mmHg), and an 18.8% decrease in heart rate. However, the compounds extracted from *S. verbenaca* were found to play a major part in lowering blood pressure as well as heart rate [4].

3.5.10. Skin effect.

The use of herbal medicines is in growing demand. *S. verbenaca* is widely used in traditional medicine [107] and has been reported to have many pharmacological properties and beneficial effects on human health [26,86]. In 1998, Bellakhdar (1998) reported that the leaves of *S. verbenaca* are traditionally applied in poultices on wounds and emptied abscesses to facilitate their healing [108]. After twenty years, the first preclinical test of *S. verbenaca* was evaluated in their skin effect. Acute dermal toxicity and sub-chronic dermal toxicity of *S. verbenaca* aerial parts were explored on mice through a single application of extracts at 2000 mg/kg. Hexane, ethyl acetate, and n-butanol extracts did not show any toxic symptoms and not affected their appetite and general behavior, indicating that their metabolism was not affected by the treatment of the extract [20].

3.5.11. Immunomodulatory activity.

Numerous *in vitro* studies reported that natural antioxidants from plants such as polyphenols play an important role in the protection of cells from oxidative damage and

consequently induce immunostimulatory effects [109]. *S. verbenaca* can be used as a potential source of useful drugs due to its richness with flavonoids and tannins [110]. According to Nassar *et al.* (2015), the immunomodulatory effects of the crude extracts from the aerial parts of *S. verbenaca* proved an immune-stimulatory effect on the reticuloendothelial system [23]. The phagocytic index was increased significantly in animals injected with *S. verbenaca* extracts at doses of 200 mg/kg ($\alpha = 0.095 \pm 1.71$) compared to the control group. The clearance rate of carbon was faster, and the corrected phagocytic index was increased with *S. verbenaca.*

3.5.12. Larvicidal activity.

Synthetic insecticides are today at the fore of mosquito control agents. However, they produce an environmentally ill effect. Besides that, most mosquito species are becoming physiologically resistant and develop high levels of resistance to synthetic control agents [111,112]. Plants crude extracts and their compounds display novel insecticidal constituents and provide potential alternatives for the use of synthetic chemical products. According to Pavela (2008), methyl alcohol extracts of *S. verbenaca* stem showed important larvicidal activity against the fourth larval instar of the mosquito *Culex quinquefasciatus* Say (Diptera: Culicidae) after 24 h of exposure with the plant extracts in a maximal dose of 500 ppm. Methyl alcohol extract exhibited larvicidal activity with 90% mortality and LD_{50} value of 311 ppm [113].

3.5.13. Xanthine oxidase activity.

Using the colorimetric method, Belkhiri and coworkers (2017) evaluated the activity of xanthine oxidase of ethyl acetate, crud, chloroform, and aqueous extracts of *S. verbenaca* aerial parts collected from Algeria. They investigated xanthine oxidase inhibitory activity by measuring uric acid production at 295 nm. The chloroform extract showed significantly the highest activity followed by ethyl acetate, crud, and aqueous extracts with an IC_{50} values of 0.009 mg/ml, 0.017 mg/ml, 0.052 mg/ml, and 0.98 mg/mL, respectively [21]. From this research, the authors suggested that this activity is related to the presence of flavonoids in *S. verbenaca* aerial part extracts and their structural differences. The unsaturation in the C ring and the free hydroxyl group at C-7 enhanced the activity.

3.5.14. Toxicological investigation.

S. verbenaca was widely tested for several pharmacological properties and beneficial effects. However, few studies evaluated its toxicity. Guaouguaou and coworkers (2018) were the first to assess the toxicological effect of *S. verbenaca* [20]. They investigated *in vivo* the acute and subchronic toxicological effects of *S. verbenaca* extracts (hexane, ethyl acetate, and n-butanol extracts) collected from Ain Aouda (Rabat, Morocco). They observed that the oral administration of all extracts, at a dose of 2000 mg/kg b.w, did not cause mice mortality within 72 h and during the 14 days of observation. This indicated that the eventual harmful effects of the investigated extracts are greater than the single high dose recommended by OECD guidelines-423. Two years later, Nassar and investigators (2020) evaluated the cytotoxicity activity of methanolic extract of *S. verbenaca* (Algeria) on human monocytic leukemia cells (THP-1) using thiazolyl blue tetrazolium bromide (MTT) assay [90]. At less than 500 µg/ml, the methanolic extract exhibited a non-cytotoxic effect on the cell viability of THP-1 cells, while 500 µg/ml and 1000 µg/ml decreased significantly in the cell viability of THP-1 cells.

Recently, Righi and coworkers (2021) investigated the toxicity of hydromethanolic extract of *S. verbenaca* aerial parts (Algeria) on *Artemia salina* larvae [91]. The result revealed that the hydromethanolic extract exhibited a mortality rate of *A. salina* larvae in a dose-dependent manner. The mortality rate was 17% at 1 µg/mL, and 100% at 500 µg/mL with LC_{50} value of 30 ± 5.4 µg/ml. At the same time, the same group of research assessed *in vivo* acute and subacute oral toxicity of hydromethanol extract of *S. verbenaca* (Algeria). They evaluated the acute toxicity of the hydromethanol extract of *S. verbenaca* in mice by orally administering a unique limit dose of 2000 mg/kg body weight for 14 days and the subacute toxicity in mice by administering a daily oral dose of 200, 400, and 800 mg/kg bw during 21 days. They found that the treatment by gavage did not cause any deaths or side effects. From these data, it can be concluded that the toxicological effect of *S. verbenaca* is scarcely explored. Thus, further preclinical tests are necessary for a safe dose.

Table 7. Other activities of *S. verbenaca.*

Activities	Use part	Extracts	Experimental approach	Key results	References
Antihemolytic activity	Aerial parts	Ethyl acetate extract	Oxidative hemolysis induced by 2,2,-azobis (2-amidinopropane) dihydrochloride	HT_{50} = 165 min	[21]
		Crud extract		HT_{50} = 125.17 min	
		Chloroform extract		HT_{50} = 111.50 min	
		Aqueous extract		HT_{50} = 111.50 min	
Antihypertensive activity	Aerial parts	Alcoholic extract (0.5 mg/kg)	Normotensive Wistar albino rats (NTR)	Decease in BP = 36.2 mmHg 18.8 % decrease in HR	[4]
		5-hydroxy-3, 4', 7-trimethoxyflavone (3.3 mg/kg)		Decease in BP = 30.0 mmHg 28.5 % decrease in HR	
		Verbenacoside (3.3 mg/kg)		Decease in BP = 13.2 mmHg 15.4 % decrease in HR	
Antileishmanial activity	Whole plant	Methanol extract	MTT assays against *Leishmania infantum* (MHOM/MA/1998/LVTA) *Leishmania tropica* (MHOM/MA/2010/LCTIOK-4) *Leishmania major* (MHOM/MA/2009/LCER19-09).	IC_{50} > 1000 for *L. major* IC_{50} = 850.76 for *L. tropica* IC_{50} > 1000 for *L. infantum*	[22]
		Hexane extract		IC_{50} = 155.43 for *L. major* IC_{50} = 148.23 for *L. tropica* IC_{50} = 14.11 for *L. infantum*	
		Dichloromethane extract		IC_{50} = 24.56 for *L. major* IC_{50} = 33.77 for *L. tropica* IC_{50} = 31.57 for *L. infantum*	
Antidiabetic effect	Aerial parts	Methanol extract	α-amylase inhibition activity	IC_{50} = 101.30 ± 0.08 µg/ml	[95]
			α-glucosidase inhibition activity	IC_{50} = 150.5 ± 1.40 µg/ml	
		Aqueous extract	α-amylase inhibition activity	Non-active	
			α-glucosidase inhibition activity	IC_{50} > 300 µg/ml	
Anti-inflammatory effect	Aerial parts	Hydromethanol extract	*Ex vivo* membrane stabilization	IC_{50} = 111 µg/ml	[91]

Activities	Use part	Extracts	Experimental approach	Key results	References
			In vivo xylene induced ear edema	Reduced 50% of xylene induced ear edema at 600 mg/kg bw.	
Larvicidal activity	Stem	Methyl alcohol extract	Against fourth larval instar of *Culex quinquefasciatus* after 24 h of exposure and maximal dose 500 ppm	90.0 % Mortality LD_{50} = 311 LD_{90} > 500	[113]
Skin effect	Aerial parts	Hexane, Ethyl acetate, n-butanol extracts	Acute dermal toxicity test and Sub-chronic dermal toxicity	not show any toxic symptoms, changes in behaviour or mortality at the used dose of 2000 mg kg^{-1} b.w.	[20]
Immunomodulatory activity	Aerial parts	n-BuOH extract	*In vivo* phagocytic index using the carbon clearance rate test	α = 0,095 ± 1,71	[23]
Toxicity	Aerial parts	Hexane, Ethyl acetate, n-butanol extracts	*In vivo* acute and subacute oral toxicity	All extracts with not cause mice mortality within 72 h and during the 14 d of observation at the used dose of 2000 mg kg^{-1} b.w.	[20]
	Root	Methanol extract	*In vitro* on human monocytic leukemia cells (THP-1) using MTT assay	70% of cell death at 1000 µg/mL	[90]
	Aerial parts	Hydromethanol extract	Larvicidal effect on *Artemia salina* larvae	LC_{50} = 30 ± 5.4 µg/mL	[91]
			In vivo acute and subacute oral toxicity	Did not exhibit any acute/subacute toxicity effect on mice.	
Xanthine oxidase activity		Chloroform extract	Colorimetric method	IC_{50} = 0.0088 ± 0.000 mg/mL	[21]
		Crud extract		IC_{50} = 0.0520 ± 0.0030 mg/mL	
		Ethyl acetate extract		IC_{50} = 0.0165 ± 0.0010 mg/mL	
		Aqueous extract		IC_{50} = 0.9800 ± 0.0040 mg/mL	

3.5.15. Other properties.

In addition to their pharmacological effects, several authors reported different investigations of *S. verbenaca*, including preventing self-fertilization, fruit and seeds production, production of phytomass, soil adaptation, a correlation between the classical taxonomy and chemical taxonomy, phytoremediation, insecticide agent, and allelopathic effects on plant development.

Navarro and collaborators investigated the dichogamy of *S. verbenaca* for preventing self-fertilization based on the quantification of temporal variability in pollen germinability and the length of the period of stigma receptivity. From this study, the authors reported that the occurrence or non-occurrence of selfing in protandrous species was more dependent on pollen germination patterns than the temporal separation of the stamen dehiscence and stylar elongation phases [114]. One year later, the same authors investigated the cause of variation in fruit and seed production of this plant and reported that neither fruit set nor seed/ovule ratio varied significantly among inflorescences [115]. These findings suggested that the pattern of inflorescence variation in mean single-seed weight was attributed to a gradual increase in the non-self-pollen receipt as the flowering season progressed.

In 2002, Castro *et al.* (2002) studied the use of *S. verbenaca* in urban green spaces after their seed broadcast at the following densities: 20 000, 15 000, 10 000, and 5 000 viable seeds/m^2. The result showed that between 5 000 and 10 000 $m^{2,}$ the densities of seeding could be more advantageous [116].

To identify their landscape potential in low-maintenance conditions, Bretzel and coworkers (2009) evaluated the ecological characteristics and the cultivation needs of *S. verbenaca* and found that the plant height of *S. verbenaca* was not affected by soil characteristics (68 cm in non-cultivated soil vs.78 cm in soil from the mixture of a non-cultivated and regularly fertilized soil) [117]. In addition, this plant showed a higher production of biomass in non-cultivated soil (172 g DM/m) compared with the mixture soil (149 g DM/m), suggesting their adaptation to infertile soils. In another study, Fisheretal *et al.* (2016) investigated the efficacy conditions for seed germination of three-month-old and nine years old seeds of *S. verbenaca* and showed that germination of the three-month-old seed was significantly less than nine-year-old seed (41% vs. 7.4%, respectively) [118]. Recently, the optimum conditions for germination of two varieties of *S. verbenaca* (*S. verbenaca* var. *verbenaca* and *S. verbenaca* var. *vernalis*) were conducted by Javaid and coworkers (2018) [119]. The result showed that both varieties germinated strongly at neutral pH. Their germination rate was significantly inhibited by complete darkness. In contrast, *S. verbenaca* var. *vernalis* showed slightly more tolerance to reduced moisture availability, moderate to strong salinity, and burial depth, compared to *S. verbenaca var. verbenaca*.

Furthermore, the correlation between the classical taxonomy and chemical taxonomy in *Salvia* sp. L. was conducted by Naküboúlu (2002) [120]. The coefficient of similarity and the matching coefficient of *S. verbenaca* and *S. virgate* reported a value of 0.66 and 0.87, respectively, which showed clearly the degrees of these species' relativity. The authors of this study suggested that chemotaxonomy can be used in the taxonomy of *Salvia* species. In addition, Ifrim investigated the differences in ornamentation and mucilage production in *Salvia* nutlets and reported that seeds of *S. verbenaca* presented a reticulate surface and produced mucilage when they are in contact with water [121]. The authors suggested that the surface of the nutlets in *Salvia* highlights characters that may be used to clarify some taxonomic aspects at the species level.

The potential of *Salvia verbenaca* for phytoremediation of trace metals from soil contaminated with copper mine tailings treated with technosol and compost was conducted by Novo and coworkers (2013) [122]. *Salvia verbenaca* had the ability to tolerate trace metals and effectively respond to the subsequent oxidative stress towards Cd.

In 2014, Fatiha *et al.* (2014) tested the insecticide effect of *S. verbenaca* essential oil *in vitro* (at 10, 20, and 30 µl) on different biological parameters of *Callosobruchus chinensis* L. such as fertility, longevity, and fecundity, under controlled temperature and relative humidity (28°C and 75%) [123]. The essential oil did not affect *Cicer arietinum* L. germination, while at 30 µl, it caused a significant reduction in longevity (2.8, and 4.6 days for males and females, respectively) and inhibition of oviposition (0% compared with 39.8% in the control group).

Another study reported the allelopathic effects of the essential oils of *S. verbenaca* on plant development [118]. The authors tested the allelopathic effect of *S. verbenaca* essential oils *in vitro* on the germination of *L. sativa*. The results showed that essential oil had a strong inhibitory effect (1.00 ± 0.50 mm) on radical growth compared with those treated with the leachate (1.29 ± 0.27 mm) [118].

4. Conclusions and Future Perspective

This bibliometric survey reported a review of *S. verbenaca* regarding their ethnomedicinal use, geographic distribution, taxonomy, bioactive compounds, pharmacological activities, and toxicological evidence. The phytochemical analysis conducted by several research groups showed that this plant contains different bioactive compounds, especially terpenoids in the essential oils of this plant. Terpenoids were dominated by hexadecanoic acid, β-phellandrene, β-caryophyllene, camphor, sabinene, germacrene D. Its flavonoids and phenolic acids were naringenin, and rosmarinic acid as the main compounds, respectively. However, there is a lack of research on flavonoids and phenolic acids in flowers, seeds, roots, and fruits. Thus, investigation of these chemical classes in these parts should be explored using different analytical tools such as HPLC, GC-MS, and LC-MS. Furthermore, *in vitro* and *in vivo* pharmacological effects of *S. verbenaca* extracts and essential oils possessed several biological effects, including antioxidant, antidiabetic, antibacterial, antifungal, antitumor, antihemolytic, antihypertensive, antileishmanial, and immunomodulatory activities. However, elaborating the pharmacokinetic and pharmacodynamic studies is necessary to prove these compounds' molecular effects on human health. Moreover, little literature data are available on the toxicological of *S. verbenaca*. Therefore, to determine the safety of this plant, further toxicological studies are necessary.

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Conflicts of Interest

The authors declare no conflict of interest.

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