

White Sage (*Salvia apiana*)—a Ritual and Medicinal Plant of the Chaparral: Plant Characteristics in Comparison with Other *Salvia* Species

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ABSTRACT

Salvia apiana, commonly known as white sage, is an aromatic evergreen subshrub of the chaparral, commonly found in coastal plains in California and Baja California. It has been traditionally used by the Chumash people as a ritual and medicinal plant and used as a calmative, a diuretic, and a remedy for the common cold. However, until recently, relatively little has been known about the composition and biological activity of white sage. Phytochemical studies on *S. apiana* revealed the presence of substantial amounts of essential oil, accompanied by a variety of triterpenes, C23 terpenoids, diterpenes, and flavonoids. Extracts of the plant have been shown to exhibit antioxidative, antimicrobial, and cytotoxic effects. The influence of white sage constituents on the nervous system, including GABA, opioid, and cannabinoid receptors, has also been documented. The review aimed to compile information on the taxonomy, botany, chemical composition, and biological activities of *S. apiana*. White sage was compared with other representatives of the genus in terms of chemical composition. The differences and similarities between *S. apiana* and other sage species were noted and discussed in the context of their therapeutic applications. Reports on ethnomedicinal uses of white sage were confronted with reports on chemistry, bioactivity, and bioavailability of *S. apiana* constituents. Finally, a critical assessment of the available data was made and perspectives for the use of white sage preparations in modern phytomedicine were discussed.

ABBREVIATIONS

CB	cannabinoid
GABA	gamma-aminobutyric acid
LPS	lipopolysaccharides
TRPA1	transient receptor potential cation channel subfamily A member 1
TRPM8	transient receptor potential cation channel subfamily M member 8

Introduction

The genus *Salvia*, one of the largest members of the Lamiaceae family, is distributed in various regions throughout the world. Central America and, in particular, Mexico are hotspots of sage biodiversity with ca. 300 from ca. 900 *Salvia* species [1]. One important and characteristic sage species of southwestern North America, used as both sacred and therapeutic plant, is *Salvia apiana* Jeps., commonly known as white sage or bee sage. It has been used for food, medicine, and religious practices by the Chumash Indians of southern California, who called it *khapshikh* [2] or *xapcix* [3]. Due to the largely unwritten nature of American Indian cultures, herb healing was based on oral tradition, and it is impossible to determine when they recognized the therapeutic poten-

tial of *S. apiana*. However, by the time it was discovered by Western medicine it had already been well-grounded in Indian native healing practices [4].

This paper aimed to review the available data on *S. apiana* including its taxonomy, botany, chemical composition, and biological activity, as well as its traditional use in American Indian medical practices, to evaluate the potential use of this plant in modern medicine. This paper was based on the relevant literature gathered from the existing scientific databases, including Scopus, Google Scholar, PubMed, and The Biodiversity Heritage Library. The following terms were adopted as the search items: “*Salvia apiana*”, “white sage”, or “bee sage” (search in the title, abstract, and keywords). Moreover, sources like plant guides, books, master’s and Ph.D. theses, and government reports were used. The data search included all years up to the present. Molecular formulas and molar masses of compounds presented in figures were calculated using ACD/ChemSketch software (Advanced Chemistry Development, Toronto, Canada). The ethnopharmacological aspects of white sage usage were discussed in the context of the results of contemporary studies on the plant’s chemistry, as well as the biological activity and bioavailability of its components. From a broader perspective, *S. apiana* was also compared with other sage species in terms of the content of major bioactive metabolites, including essential oil constituents, diterpenes, and triterpenes. Based on the compiled data, we attempted to critically evaluate the potential of *S. apiana* for modern medicine, and confront its therapeutic value with other representatives of the genus.

Taxonomy

Salvia apiana Jeps. (also known as *Salvia californica* Jeps., *Ramona polystachya* (Benth.) Greene, *Audibertiella polystachya* (Benth.) Briq., *Audibertia polystachya* (Benth.) belongs to the family Lamiaceae, subfamily Nepetoideae, tribe Salviae, genus *Salvia* [5], section *Audibertia* Benth. The section *Audibertia* Benth. with sister section *Echinosphece* Benth. is specific for California’s and Baja California’s flora [1, 6]. The taxonomy of *S. apiana* has a long and dynamic history. For botanists coming into California from Europe or eastern North America, difficulties with the proper identification of the genus were due to the weak exploration of the American continent and the limited experience with the morphology and the habitat of American kinds of sage [7].

No written records document possible knowledge of *S. apiana* in pre-Columbian America. *S. apiana* was first recognized as *Audibertia polystachya* by George Bentham, based upon a specimen collected in California by David Douglas, and described in his *Labiatarum Genera et Species* [8].

Another botanist who investigated the *Salvia* genus, including nomenclatural issues of *S. apiana*, was John Briquet. Based on corolla analyses that revealed details that were not noticed by Bentham, he proposed a new taxonomic name for *S. apiana*, namely: *Audibertiella polystachya*. This is consistent with the original idea of Bentham [9].

Edward Greene, a pioneer taxonomist of California flora, in his papers [7] considered the *Audibertia* section as a part of the *Salvia* genus based on both the habitat and the floral structure. How-

ever, he made an exception for *S. apiana* because of its unique inflorescence and corolla, considering them as noncongeneric with other shrubs. He thus proposed a new name for the plant: *Ramona polystachya*.

The taxonomy of *S. apiana* was redefined by Willis Jepson [10], one of the most recognized botanists of California flora, who started his botanical research under the leadership of Edward Greene. He examined earlier studies of *S. apiana* and presented his proposal for its taxonomical position. He described the genus *Audibertia* as congeneric with *Salvia* and transferred *Ramona polystachya* Greene to *Salvia*, initially naming it *Salvia californica*. After finding that this name had been taken, he changed it to *Salvia apiana*, the name still accepted by botanists today [11]. *S. californica* is currently not a legitimate name in botanical nomenclature and is only of historical significance.

Subsequent revisions to *S. apiana* taxonomy came in 1927 from Philip Munz, who distinguished 2 varieties of the species: *S. apiana* var. *typica* (also known as var. *apiana*) and *S. apiana* var. *compacta*. The basis for the distinction was the difference in inflorescence morphology. Panicles in *S. apiana* var. *typica* are open and well-branched, while in *S. apiana* var. *compacta*, they are condensed and spicate. Moreover, these 2 varieties occupy different habitats—coastal slopes and edges of the desert, respectively [12].

Recent phylogenetic studies based on molecular data indicate that genus *Salvia* is polyphyletic and represented by 4 distinct evolutionary lineages [13–15]. The current state of knowledge is not sufficient to determine the route of phylogenetic origin that would account for the observed distribution of the genus *Salvia* into the New World. The probable diversification time of the *Salvia* genus from other Salviinae was early Oligocene [16] and the jump dispersal from Southwest Asia to the New World in the late Oligocene has given rise to subgenera *Audibertia* and *Calosphece* [17]. Nevertheless, the putative origin of the section *Audibertia* is the Mediterranean area. *Audibertia* pollen fossils from Alaska, dated to the Upper Miocene, indicate the Bering Land Bridge as the most probable route of dispersal [6, 18]. It is also proposed that the 2 sections, *Audibertia* Benth. and *Echinosphece* Benth., should be separated as individual genus *Ramona* Greene [6].

Botany

S. apiana is a highly aromatic, evergreen, perennial herb or subshrub, which grows 1–3 m tall [11]. It forms rounded shrubs, woody at the base with rod-shaped erected branches coated with a tomentose layer. The root system is branched and fibrous, penetrating as much as 1.5 m deep. The plant produces 4–8 cm long pale-green leaves that persist throughout the year. They consist of petioles and widely lanceolate blades with crenulate margins. The base tapered leaves are covered with dense hairs and oil glands that give them a silvery sheen [19]. This important bee-food plant has white to pale lavender flowers, surrounded by 5.0–7.5 mm long calyx, whitened with very tiny appressed hairs. Its corolla conformation and pollination mechanism deviate from the ones typical in the Lamiaceae family and are in a class by themselves in the genus [20]. The corolla consists of 2 lips. The upper one is reduced, whereas the lower, cushion-shaped corolla lip is huge and

obstructs the entrance to the corolla chamber. Two long (14–17 mm) erected stamens, each with 2 pollen sacks, and a pistil's style (13–15 mm) are exerted over the flower tube. Such construction of the flower is an adaptation for pollination by large insects like carpenter bees and bumblebees [20, 21]. Flowering time is April to August. The fruit is a shiny, light brown, rectangular narrow in cross-section, 5–3 mm nutlet [11]. The plant has $2n = 30$ chromosomes [22].

The details in the morphology of the inflorescence differentiate *S. apiana* populations located in the coastal slopes and the edge of deserts. *S. apiana* var. *compacta*, found on the edge of deserts, has open and well-branched panicles, while *S. apiana* var. *typica* forms condensed and spicate panicles [12, 23].

The chaparral and desert sage communities in California Floristic Province are represented by 19 species of *Salvia*, members of sections *Audibertia* and *Echinosphece*. Hybrids between *S. apiana* and other native sages with the same number of chromosomes and structurally similar genomes (e.g., *Salvia mellifera* Greene, *Salvia munzii* Epl., *Salvia leucophylla* Greene, *Salvia clevelandii* [Grey] Greene, *Salvia eremostachya* Jeps., *Salvia pachyphylla* Epl. Ex Munz., and *Salvia vaseyi* [Porter] Parish) are possible but restricted mainly by ecological, seasonal, mechanical, and ethological isolation of autochthonous species. Hybridizations between *S. apiana* and *S. mellifera* are particularly common, but the fertility of the resulting plants is reduced [20, 24–26].

Ecology and Cultivation

S. apiana (white sage) is a notable species of the coastal sage formation of the Californian and Baja California chaparral, the coastal sage scrub, and the upper edges of desert scrub. However, it extends even further, including as far as the yellow-pine forest. It often neighbors species like *S. mellifera* (black sage), *Eriogonum fasciculatum* (California buckwheat), *Artemisia californica* (California sage-brush), and *S. leucophylla* (purple sage) [24, 27]. Its preferred habitat is in the drier sites of coastal slopes below 1500 m with sandy and rocky soils [19]. *S. apiana* is resistant to drought; in the area of its occurrence, there are high summer temperatures and annual precipitation between 250–450 mm [28]. During the dry season, its leaves often become folded and are held vertically, probably as an adaptation to avoid overheating. Observations made in chaparral have shown that the white sage is better adjusted to water shortage than other evergreen shrubs (e.g., *S. mellifera*) [20]. Because of specific environmental requirements, *S. apiana* occurs in ecosystems between Santa Barbara County, California south to the middle of Baja California and the Colorado Desert.

The peculiar structure of the *S. apiana* flower reflects its atypical pollination mechanism: unlike other *Salvia* species, it has adapted to be pollinated by large insects. Co-evolution with *Xylocopa* bees, whose shape and size ensure the highest possible pollination efficiency, is considered to be the most probable reason for the unusual morphology of *S. apiana*'s flower. Effective pollination by honeybees is also possible since they visit the flowers of white sage in great numbers [21].

The coastal sage community is one of the areas most susceptible to frequent wildfires, historically every 20–150 y [28].

S. apiana is well adapted to recurring fires, and its recovery is possible thanks to sprouting from distinct basal burls [19, 29]. There was a custom among the Cahilla and Chumash to periodically burn grasslands, plains, and chaparral covered with sage shrubs to promote the next season's growth [3]. It is worth noting that *S. apiana* can be successfully used for renewing and restoring degraded, damaged, or destroyed areas [30].

A progressive decline of white sage populations has been observed. The California floristic province is a Mediterranean-type climate area where 1315 of 4976 native plant species (26.4%) are endemic [28]. The introduction of foreign and invasive species, the increase of fire frequency, the expansion of urban areas, and the overharvesting of the plant for spiritual ceremonies are considered to be the main factors responsible for the decline of the species. Although *S. apiana* is currently not a threatened plant, the restricted distribution range in the California Floristic Provinces puts it at high risk of rapid decline or extinction [21, 28]. Uncontrolled harvesting without necessary permits is a major issue, only exacerbated by the growing commercialization of white sage in recent years. *S. apiana* is widely advertised and sold as a ceremonial plant. However, the harvesting practices employed are often illegal despite the claims by the distributors that the material has been obtained sustainably. Cases were reported of illegal harvesting of substantial amounts of white sage from protected areas [31].

Although threatened by overexploitation, white sage can be cultivated, and nursery stocks can be established from seeds or cuttings [19]. As of 2020, there were over 40 nurseries in California that carry *S. apiana* [32]. So far, no formal industry of white sage has been established; however, there seems to be a huge potential for sustainable production of white sage raw material for medicinal purposes. If responded properly, the increasing demand for sage material can give rise to a profitable industry without negatively affecting natural resources. A good example of an industry that transitioned from being based solely on the harvesting of wild plants to developed farm cultivation is South Africa's honeybush production [33]. *Cyclopia* plants used to manufacture the honeybush tea belong to fynbos shrublands, which are South Africa's counterpart of Californian chaparral. Similar to white sage, *Cyclopia* spp are endemic and thus vulnerable to overexploitation and habitat loss. The growing demand for honeybush, mainly for international markets, necessitated the development of a sustainable industry that now provides the bulk of raw materials of high quality [33].

Studies concerning endemic plants can also be aided by cell culture techniques. For instance, *in vitro* cultures of the aforementioned *Cyclopia* plants have been used to produce compounds of interest [34, 35] and to develop micropropagation protocols [36]. Such techniques, enabling efficient propagation and production of bioactive metabolites independently of natural resources, have also been applied to different sage species: examples include *in vitro* cultures of *S. officinalis* and *S. miltiorrhiza* which have been examined for the biosynthesis of salvia-specific diterpenes and phenolic acids [37].

Ethnomedicinal Uses

Native American medicine and religion are strongly connected. Phytotherapy is a coherent part of the spiritual healing system rather than a standalone treatment method. This system includes not only herbal treatment elements accepted by Western medicine but also prayers, shamanistic practices, and other ways of spiritual healing. From this point of view, the application of particular herbs for a medical purpose involves not only giving a drug to the patient but also sacral action conducted by the healer (medicine man, as called by Native Americans) [38]. One of the plants with a long tradition of medical use is *S. apiana*, which has significant religious meaning to Californian Native American tribes. White sage is deeply rooted in tribal culture as an apotropaic herb. It is believed to have a great power of cleansing the spirit, restoring its balance, drawing a blessing upon people, or even carrying the prayers to God. The illness itself is considered as an imbalance or impurity in the sick person's soul, so the core of the healing process is restoring the balance and driving the impurities away. White sage is used for healing due to its valuable properties. It is possibly the reason for its major role in Native American healing (and, consequently, in religion) [4, 39].

S. apiana is used both as a herbal drug itself and as an addition to other herbal compositions; it is believed to exert a magnifying effect on other herbs' properties [40]. It is used as a calmative and analgesic agent in native medicine. Other observed effects of its use are decreased sweating, salivation, and milk secretions and reduced mucous secretions of the sinuses, throat, and lungs [30]. Drinking cold water with pounded leaves could induce vomiting [2]. Antimicrobial activity also was reported [30]. As for the healing methods of a spiritual nature, the preferred ways of application include smudging or sucking the plant to bless or cleanse the spirit. The treatment methods involving less religious aspects include drinking infusions, tinctures, and macerations, as well as rubbing into the skin [41].

Ethnomedicinal uses of *S. apiana* include the social initiation ceremony of 8-yr-old Chumash children. The addition of white sage leaves to a decoction of *Datura meteloides*, containing tropane alkaloids, enhanced the effects of the potion, referring to white sage's ability to purify the mind and spirit [39]. *S. apiana* seeds or infusions and tinctures of leaves were taken orally to cure cough due to its diuretic and diaphoretic activity [30]. Infusion of *S. apiana* roots was taken orally by women during the postpartum period to facilitate passage of the afterbirth and to promote healing [42]. Moreover, Chumash women take the infusion for menstrual problems, like hypermenorrhea, and during weaning to decrease lactation [30].

Also, *S. apiana* is applied as an eye treatment. The method is to put on a few *Salvia* seeds to the eyes during sleep. While moving under the eyelids, mucilage obtained from the seeds collects all pollutants from the eyeballs. Removing them in the morning leaves the eyes purified [30]. Fresh leaves of *S. apiana* are placed on the head to get relief from headaches [2].

S. apiana plays a major role in the life of California Native American tribes, as it is not only used for healing and religious rituals but is also a part of their diet. White sage and 3 other sage shrubs: *S. mellifera*, *S. columbariae*, and *S. leucophylla* are the source of

seeds that are called "chia". Chia seeds are prepared by toasting and pounding in a mortar and are eaten mixed with water as a gruel or as cakes. Young shoots of *S. apiana* are also eaten by Native American Indian tribes. White sage seeds contain about 8% water, 10% protein, 12% fat, and 65% carbohydrate and as such were an important source of food for California Native Americans [3]. Today, *S. apiana* seeds have lost their importance due to the high popularity of *S. columbariae* Benth. chia seeds with their higher nutritional value [2, 3, 43]. Apart from the medical and nutritional use of *S. apiana*, California Native Americans also use white sage as a cosmetic and shampoo [30, 44].

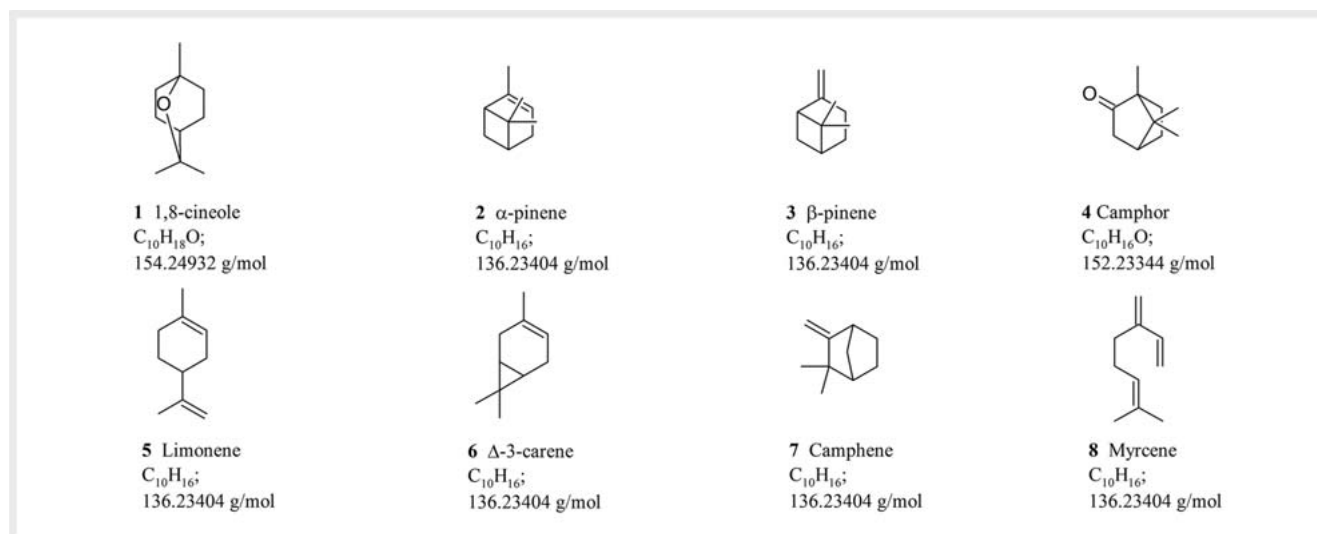
Chemical Composition

Similar to other *Salvia* species, the main components of *S. apiana* are terpenoids, (represented by monoterpenes, diterpenes, C23 terpenoids, and triterpenes), as well as flavonoids and phenolic acids. In the current work, the data concerning *S. apiana* chemistry was compiled. For compounds that are present in the plant in known quantities, the quantitative data were compared with other representatives of the genus. The purpose was to find differences and similarities between white sage and other sage species and discuss them in the context of the therapeutic uses of the plant.

Essential Oil

There is only a limited number of reports concerning white sage phytochemistry, and the studies conducted so far have been focused mainly on determining the essential oil content of the plant. The first investigation of terpene content using gas chromatography-flame ionization detector (GC/FID) in fresh leaves of *S. apiana* revealed the presence of 6 compounds: α -pinene, camphene, β -pinene, dipentene, cineole, and camphor [45]. The GC/FID, together with GC/MS analysis showed the presence of 14 constituents, which accounted for 97.76% of the total essential oil obtained through steam distillation of the entire plant. 1,8-cineole (1), constituting 60.65% of the oil, was the major component [46]. Takeoka et al. [47] identified 84 compounds that comprise 95.1% of the volatile fraction. In all cases, essential oil was primarily composed of 1,8-cineole (26,1–71,1%), α -pinene (2) (5.1–10.14%), β -pinene (3) (3.8–10.68%), camphor (4) (2.1–21.7%), limonene (5) (1.5–3.5%), δ -3-carene (6) (1.3–6.3%), camphene (7) (0.4–5.5%), and myrcene (8) (0.5–3.2%). The structures of volatiles present in *S. apiana* are presented in ► Fig. 1.

Various studies have demonstrated that quantitative differences in essential oil content are common in *Salvia* species and depend on environmental conditions, harvesting time, and geographic and climatic factors [48, 49]. In *S. apiana*, age-dependent variations were not reported, but some variability in the composition of the volatile fraction between day and night was described [50]. Moreover, the differences in terpene content between the subspecies of *S. apiana* were observed. *S. apiana* var. *compacta* contains a notably higher amount of β -pinene and lower concentration of cineole than *S. apiana* var. *apiana* [51]. The data concerning the composition of *S. apiana* essential oil was summarized in ► Table 1.



► **Fig. 1** Structures of major components of *S. apiana* essential oil.

► **Table 1** Composition of *S. apiana* essential oil (the amounts of individual terpenoids expressed as a percentage of the total volatile fraction).

Main components of essential oil	Raw material	Collection place and time	Method of isolation and analysis	Ref.
Cineole (1), camphor (4), α-pinene (2), β-pinene (3), camphene (7) ^a	Fresh leaves	Data not specified	Extraction with anhydrous ethyl ether for 48 h; GC/FID	[45]
Camphor (4) (44.6%), 1,8-cineole (1) (33.1%), β-pinene (3) (6.3%), α-pinene (2) (5.8%), camphene (7) (5.5%), limonene (5) (2.7%) ^b	Leaves	Botanical Gardens, University of California, Los Angeles	Extraction with anhydrous ethyl ether; GC	[51]
Camphor (4) (46.9%), 1,8-cineole (1) (26.4%), β-pinene (3) (7.5%), α-pinene (2) (5.3%), camphene (7) (5.5%), limonene (5) (2.7%) ^c				
1,8-cineole (1) (60.7%), β-pinene (3) (10.7%), α-pinene (2) (10.1%), δ-3-carene (6) (3.2%), camphor (4) (2.7%)	Branches and leaves	Data not specified	Steam distillation; GC/FID and GC/MS	[46]
1,8-cineole (1) (71.6%), β-pinene (3) (9.1%), α-pinene (2) (9.0%), limonene (5) (2.0%), camphor (4) (2.1%), δ-3-carene (6) (1.3%)	Entire plant	Data not specified	Steam distillation; GC/FID and GC/MS	[123]
1,8-cineole (1) (34.5%), camphor (4) (21.7%), β-pinene (3) (7.4%), α-pinene (2) (6.4%), δ-3-carene (6) (6.3%), camphene (7) (3.9%), myrcene (8) (3.2%)	Fresh aerial parts of the plant	Davis Botanical Gardens, University of California; June 2007	Extraction with diethyl ether followed by high vacuum distillation with a solvent-assisted flavor evaporation apparatus; GC/FID and GC/MS	[47]
1,8-cineole (1) (71.1%), α-pinene (2) (5.1%), camphor (4) (4.4%), β-pinene (3) (3.8%), δ-3-carene (6) (2.4%), limonene (5) (1.5%), myrcene (8) (1.2%)	Dried aerial parts of the plant	The South Mississippi Branch Experiment Station in Poplarville, Mississippi, USA; February and March 2010	Hydrodistillation for 3 h using a Clevenger-type apparatus; GC/MS	[54]

^a confirmed presence, quantitative data not available; ^b composition of essential oil of *S. apiana* var. *apiana*; ^c composition of essential oil of *S. apiana* var. *compacta*

In ► **Table 2**, *S. apiana* was compared with other *Salvia* species in terms of essential oil content and its composition. The compilation reveals white sage to be exceptionally rich in essential oils: the content reported by Dentali [44] was 3.8%, which is even

higher than in *S. officinalis* (up to 3.7%) [52, 53]. If confirmed, this would place *S. apiana* in the first place in terms of essential oil content within the genus *Salvia*. However, the data regarding volatiles yield in white sage has to be confirmed, and further studies are

► **Table 2** Comparison of essential oil composition in different sage species. Only major compounds are included (i.e., exceeding 3% content in at least 1 of the considered species).

Compound [% in oil]	<i>Salvia apiana</i> Jeps.	<i>Salvia officinalis</i> L.		<i>Salvia sclarea</i> L.	<i>Salvia lavandulaefolia</i> Vahl.	<i>Salvia hispanica</i> L.	<i>Salvia melifera</i> Greene	<i>Salvia miltiorrhiza</i> Bunge	<i>Salvia rosmarinus</i> Schleiden (<i>Rosmarinus officinalis</i> L.)
		α -thujone/camphor chemotype ²	1,8-cineole/camphor chemotype ²						
Oil yield [%]	0.6–3.8	1.2–3.7 ^g		0.3–2.5 ^{m,n}	0.9–2.7 ^q	0.05 ^r	0.68 ^t	1.47 ^w	1.1–1.9 ^x
δ -Amorphene						3.1 ^r			
Aromadendrene oxide-(1)								8.3 ^w	
Aromadendrene oxide-(2)								3.4 ^w	
Bicyclogermacrene	0.1 ^a			1.2–8.7 ^{m,o}					
Borneol	0.2 ^{a,c,e}	0.2–11.8 ^{f,g,h,i,k}	5.6 ⁱ	0.1 ^m	1.6–4.3 ^q	0.2 ^r		0.24 ^w	0.46–5.1 ^{x,y,z}
Bornyl acetate	0.0–0.2 ^{a,e}	0.05–7.8 ^{f,g,h,i,k}	1.8 ⁱ	T ⁿ	T–0.6 ^q		0.5 ^t	2.5 ^w	0.1–3.5 ^{x,z}
α -Cadinol						1.7 ^r	1.9 ^t	7.3 ^w	
Camphene (7)	0.4–5.5 ^{a,b,c,d,e}	0.1–9.7 ^{f,g,h,i,k}	5.5 ⁱ	T ⁿ	2.7–5.8 ^q	T–0.01 ^s	0.6 ^t		0.3–12.0 ^{x,y}
Camphor (4)	2.1–21.7 ^{a,b,c,d,e}	0.15–36.5 ^{f,g,h,i,k}	18.6 ⁱ		6.1–9.4 ^q	T–0.27 ^s	12.2 ^t		5.0–24.1 ^{x,y,z}
Δ -3-Carene (6)	1.3–6.3 ^{a,b,c,d}		3.0 ^j		0.1 ^q	0.2 ^r			
β -Caryophyllene (trans-Caryophyllene)	1.0–1.7 ^{abc}	0.2–8.7 ^{f,g,h,i,k}	3.8 ⁱ	1.2–17.2 ^{m,n,o,p}	4.0–8.5 ^q	13.3–35.7 ^s	0.9 ^t	4.7 ^w	3.3 ^x
(Z)-Caryophyllene						11.5 ^r			
(E)-Caryophyllene						10.6 ^r			
Caryophyllene oxide		0.0–4.3 ^{f,g,h,i,k}	0.0 ^j	0.2–10.4 ^{m,n,o}	0.1–1.2 ^q	2.7 ^r	1.4 ^t	2.6 ^w	0.94 ^x
1,8-Cineole (1)	26.4–71.7 ^{a,b,c,d,e}	1.2–19.6 ^{f,g,h,i,k}	20.8 ⁱ	T–0.1 ^{m,n}	21.4–33.8 ^q	T–0.47 ^s	39.8 ^t	1.3 ^w	16.0–38.0 ^{x,y,z}
α -Copaene	0.1–0.2 ^{ac}	T–0.5 ^{h,i}		1.0–6.7 ^{m,o}	0.0–T ^q	0.7 ^r		0.8 ^w	
p-Cymene	T ^l –3.1 ^{ab,c,d}	0.1–3.6 ^{f,g,h,i,k}	0.73 ^j	0.5 ^m	0.0–T ^q		0.5 ^t		0.8–2.5 ^z
α -Eudesmol				0.2–0.5 ^{m,n}		3.8 ^r			
Ferruginol								35.2 ^u	
Geraniol				6.5 ⁿ	0.0–0.1 ^q		0.1 ^t		
Geranyl acetate				3.5–7.5 ^{m,n,p}					
Germacrene D	0.2 ^a			11.4–20.8 ^{m,o}	0.0–T ^q		0.1 ^t	0.15–6.82 ^{u,w}	
Globulul						12.7–23.4 ^s	1.8 ^t		
α -Gurjunene	0.1 ^a					3.1 ^r			continued

▶ Table 2 Continued

Oil yield [%] Compound [% in oil]	<i>Salvia apiana</i> Jeps.	<i>Salvia officinalis</i> L.		<i>Salvia sclarea</i> L.	<i>Salvia lavandulaefolia</i> Vahl.	<i>Salvia hispanica</i> L.	<i>Salvia melifera</i> Greene	<i>Salvia miltiorrhiza</i> Bunge	<i>Salvia rosmarinus</i> Schleiden (<i>Rosmarinus officinalis</i> L.)
		α -thujone/camphor chemotype ²	1,8-cineole/camphor chemotype ²						
Humulane-1, 6-dien-3-ol	0.6–3.8	1.2–3.7 ^g		0.3–2.5 ^{m,n}	0.9–2.7 ^q	0.05 ^r	0.68 ^t	1.47 ^w	1.1–1.9 ^x
α -Humulene	0.1 ^{a,c}	0.18–16.7 ^{f,g,h,i,k}	6.0 ⁱ	0.1–1.0 ^{m,n,o}		2.9–6.1 ^{t,s}	0.2 ^t	14.1 ^u	0.54 ^x
Humulene epoxide I		0.0–3.5 ^{f,g,k}							
Humulene epoxide II		0.5–3.2 ^{f,g,h}				0.4 ^r		3.1 ^w	0.06 ^x
Isoborneol									5.6 ^x
7-Isopropyl-1, 1,4a-trimethyl-1, 2, 3, 4, 4a, 9, 10, 10a-octahydrophenanthrene								12.3 ^u	
Limonene (5)	1.5–3.5 ^{a,d,c,e}	1.4–3.4 ^{f,g,i}	7.5 ⁱ	0.15–2.1 ^{m,n,o}	5.6–10.4 ^q	T–0.05 ^s	2.2 ^t		0.26–5.0 ^{y,z}
Linalool	0.2–0.22 ^{a,b,c}			12.5–38.0 ^{m,n,p}	0.0–T ^q	0.33–1.0 ^r		1.5 ^w	3.7 ^x
Linalyl acetate				3.6–39.2 ^{m,p}		2.0 ^r			
Manool		0.4–15.9 ^{f,g,h}		0.2–2.5 ^{m,n}				0.93 ^w	
γ -Murolene	0.1 ^a	0.0–0.7 ^{g,h,i}	0.0 ⁱ	T ⁿ		4.4–17.5 ^s	0.1 ^t		
Myrcene (8)	0.5–3.2 ^{a,b,c,d}	0.0–4.2 ^{f,g,h,i,k}		0.25–0.7 ^{m,n}	T–10.0 ^q	0.09–1.4 ^r	2.0 ^t		0.11–5.0 ^{x,z}
1-Naphthalenopropanol, alpha.-ethenyldecahydralpha., 5, 8a-tetramethyl-2-Methylene-, [1S-[1.alpha.(R), 4a.beta, 8a.alpha.]								17.37 ^u	
Nerol				1.1–5.5 ^{m,n}	0.0–T ^q				
Neryl acetate				1.9–5.2 ^{m,n}		0.6 ^r			
1-Octen-3-ol								5.9 ^w	
α -Pinene (2)	5.1–10.1 ^{a,b,c,d,e}	T–6.4 ^{f,g,h,i,k}	4.0 ⁱ	0.1–0.49 ^{m,n,o}	10.5–17.5 ^q	T–0.72 ^s	9.2 ^t		1.4–26.0 ^{x,y,z}
β -Pinene (3)	3.8–10.6 ^{a,b,c,d,e}	0.0–13.1 ^{f,g,h,i,k}	6.1 ⁱ	0.1 ^{m,n}	6.0–17.3 ^q	2.5–15.1 ^s			0.42–9.0 ^{x,y,z}
Sciareol				1.2–5.2 ^{m,n}					
β -Selinene				0.2 ^m	1.5–4.1 ^q	2.0 ^r			
Spathulenol		0.0–0.2 ^k		0.2–9.9 ^{m,n,o}	0.0–1.0 ^q	0.7–2.2 ^{t,s}		0.18 ^w	continued

▶ **Table 2** Continued

Oil yield [%] Compound [% in oil]	<i>Salvia apiana</i> Jeps.	<i>Salvia officinalis</i> L.		<i>Salvia sclarea</i> L.	<i>Salvia lavandulaefolia</i> Vahl.	<i>Salvia hispanica</i> L.	<i>Salvia mellifera</i> Greene	<i>Salvia miltiorrhiza</i> Bunge	<i>Salvia rosmarinus</i> Schleiden (<i>Rosmarinus officinalis</i> L.)
		α -thujone/camphor chemotype ²	1,8-cineole/camphor chemotype ²						
	0.6–3.8	1.2–3.7^g		0.3–2.5^{m,n}	0.9–2.7^q	0.05^r	0.68^t	1.47^w	1.1–1.9^x
γ -Terpinene	0.4–0.5 ^{ac}	0.0–2.9 ^{f,g,h,i,k}	1.0 ⁱ	0.3 ^m	2.1–7.0 ^q		2.0 ^t	0.14 ^w	0.15 ^x
α -Terpineol	T–0.47 ^{ab,c}	0.0–2.3 ^{f,g,h,i,k}		5.5–15.1 ^{m,n}	0.3–0.4 ^q	0.2 ^r	0.7 ^t	0.91 ^w	1.0–6.4 ^{x,z}
<i>Cis</i> -Thujone (β -thujone)		1.33–29.3 ^{f,g,h,i,k}	1.0 ⁱ	0.5 ^m	0.0–T ^q		0.2 ^t		
<i>Trans</i> -Thujone (α -thujone)		1.5–27.1 ^{f,g,h,k}	4.5 ⁱ	0.4 ^m	0.0–T ^q			0.49	
Tridecyl acrylate									5.5 ^x
Verbenone									0.4–18.8 ^{x,z}
Viridiflorol		1.7–15.7 ^{f,g,h,i,k}	0.0 ⁱ			0.7 ^r			0.08 ^x

¹ Traces; ² Division into chemotypes in accordance with Graft and co-workers [124]; ^a Fresh leaves and flowering tops; extraction with diethyl ether followed by high vacuum distillation with a solvent-assisted flavor evaporation apparatus; GC/FID and GC/MS [47]; ^b Branches and leaves; steam distillation; GC/FID and GC/MS [46]; ^c Dried aerial parts; hydrodistillation with a Clevenger-type apparatus; GC/FID and GC/MS [54]; ^d Entire plant; steam distillation; analyzed with GC/FID and GC/MS [123]; ^e Dried leaves; extraction in anhydrous ethyl ether; GC [51]; ^f Fresh leaves; hydrodistillation with a Clevenger-type apparatus; GC/FID and GC/MS [125]; ^g Dried distal parts of leafy shoots; hydrodistillation with a Clevenger-type apparatus; GC/FID and GC/MS [126]; ^h Dried leaves; hydrodistillation, using n-hexane as collecting solvent; GC/FID and GC/MS [127]; ⁱ Tops of plant; steam distillation with a Clevenger apparatus; GC [128]; ^k Dried herb; hydrodistillation with a Clevenger-type apparatus and xylene as collecting solvent; GC/FID [55]; ^m Dried aerial parts; hydrodistillation with a Clevenger-type apparatus; GC/MS [129]; ⁿ Fresh leaves and flowers; steam distillation; GC/MS [130]; ^o Dried leaves; hydrodistillation; GC/FID [132]; ^p Leaves; hydrodistillation; GC/MS [131]; ^q Dried aerial parts; steam distillation; GC/MS [133]; ^r Aerial parts; hydrodistillation; GC/MS [134]; ^s Dried leaves; steam distillation with a Clevenger-type apparatus; GC/MS [135]; ^t Dried aerial parts; hydrodistillation; GC/MS [136]; ^u Dried aerial parts; hydrodistillation with a Clevenger-type apparatus; GC/MS [137]; ^w Fresh leaves; hydrodistillation with a modified simultaneous distillation extraction apparatus; GC/MS [138]; ^x Fresh leaves; hydrodistillation; GC/MS [139]; ^y Fresh leaves; solvent-free microwave extraction; GC/MS [140]; ^z Composition of Spanish, Morocco and Tunisia rosemary essential oil (European Pharmacopoeia 2005) [141]

necessary to assess intraspecies variation in this regard. One must be aware that essentially only single reports are available on the essential oil content of *S. apiana* [44, 54] whereas *S. officinalis* has been extensively studied in this aspect [53]. The study by Ali et al. [54] showed that essential oil yield in *S. apiana* (0.6%) is 2.5 times higher than in *S. officinalis* (0.24%). However, the reported values do not seem to be representative since common sage typically contains higher amounts of oil, and 1.0% (v/w) is the lower limit set in European Pharmacopoeia [55].

In terms of essential oil composition, *S. apiana* bears resemblance to *S. lavandulaefolia*, *S. rosmarinus*, and the cineole chemotypes of *S. officinalis*. All these plants are characterized with high contents of 1,8-cineole and camphor in varying proportions (► **Table 2**). Apparently, there are no major essential oil constituents differentiating white sage from other representatives of the genus (for detailed information concerning minor constituents of the oil, please refer to supplementary **Table 15**). It is worth noting that the essential oil of *S. apiana* does not contain the neurotoxic thujone [54], the presence of which limits the daily intake of leaf preparations of *S. officinalis* [56]. According to EMA, the daily exposure to thujone must not exceed 6.0 mg. At recommended doses, *S. officinalis* preparations are considered safe even for long-term use; however, chemotypes with low-thujone content should be preferred in therapy [57]. Given this, *S. apiana* appears to have a wider safety margin than thujone chemotypes of common sage. Overdose of common sage preparations, corresponding to over 15 g of leaves, was reported to cause tachycardia and epileptic seizures. This applied in particular to the isolated essential oil of *S. officinalis*, which was shown to exhibit convulsant properties. Cases of children who experienced seizures after ingesting sage oil were described [57]. On the other hand, the main component of white sage oil, 1,8-cineole, is regarded as safe in amounts usually used in phytotherapy. However, exposure to camphor can still cause toxic effects, especially in children [46, 58]. Given the above, recommendations discouraging the use of common sage in children and adolescents [57] seem to be valid also for *S. apiana*, even if there is no apparent risk of inducing epileptic seizures.

Diterpenoids

A distinctive feature of several American *Salvia* species is the presence of clerodane-type diterpenoids in the aerial part of the plant or the whole plant [59]. However, in *S. apiana*, the diterpenoid fraction (► **Fig. 2**) is represented by abietane derivatives [60]. Dentali [44] confirmed the presence of carnosic acid (9) and 16-hydroxycarnosic acid (10) in the acid fraction of methylene chloride extract of the herb. Moreover, in the aerial part of the plant, the following diterpenoids were identified: salvicanol (11), 16-hydroxyrosmanol (12), 16-hydroxycarnosol (13), 16-hydroxy-7-methoxyrosmanol (14), rosmanol (15), and 7-epirosmanol (16) [61]. Gonzalez et al. [62] found other compounds of this group in the roots of white sage: 6,7-didehydroferruginol (17), 6,7-didehydrosempervirolo (18), 16-hydroxy-6,7-didehydroferruginol (19), 11,12,16-trihydroxy-20(10→5)abeo-abieta-1(10),6,8,11,13-pentaene (20), 16-hydroxyroleanone (21), 6-deoxy-5,6-didehydrolanugon Q (22), ferruginol (23), miltiodiol (24), cryptotanshi-

none (25), and lanugon Q (26). Besides the above compounds, the presence of carnosol (27) was confirmed in the plant [63]. Also, Srivedavyasari et al. [64] reported the presence of sageone (28) and rosmadial (29) in an aqueous ethanolic extract from *S. apiana* herb. The quantitative data concerning *S. apiana* diterpenoids are scarce; so far, only carnosic acid has been quantified at 21.8 mg/g dry weight [63].

Triterpenoids

Besides essential oil, *S. apiana* was shown to contain triterpenoids such as α -amyrin (30), oleanolic acid (31), and ursolic acid (32) (► **Fig. 3**), which were isolated from a hexane extract of the aerial parts of the plant [65]. Oleanolic and ursolic acid are common triterpenoids, found in almost all *Salvia* species [59,66]. Another compound of this group is uvaol (33), found in the ethanolic extract of *S. apiana* [64]. So far, no quantitative data on these constituents are available.

C23 Terpenoids

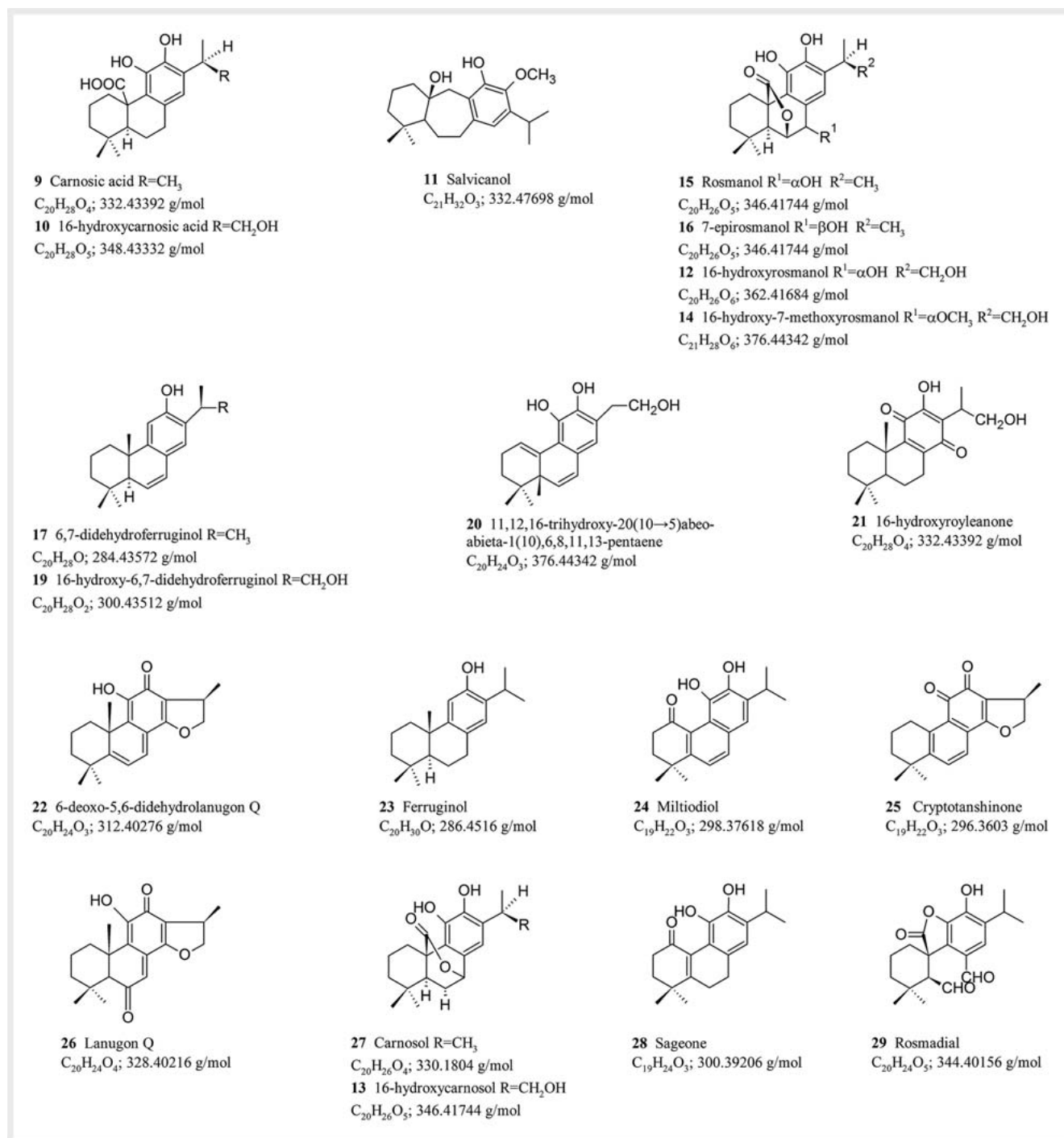
C23 terpenoids were isolated by Luis et al. from acetonetic extract of aerial parts of *S. apiana* [61,67] and named hassananes and apiananes: 13,14-dioxo-11-hydroxy-7-methoxy-hassane-8,11,15-trien-(22,6)-olide (34), 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide (35), and 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide (36) (► **Fig. 4**). The initially proposed structures of hassananes [67], based on spectroscopic methods, were revised by Yang et al. (37) [68] through chemical structure analysis of these novel compounds and similar C23 terpenoids przewalskins A and B. The revised structures of hassananes were confirmed by Zhang et al. [69] (► **Fig. 4**). No quantitative data concerning C23 terpenoids of white sage are available.

Flavonoids and Phenolic Acids

The aerial parts of the *Salvia* species contain several polar constituents, including flavonoids such as flavones, flavonols, and their glycosides [70]. These are accompanied by rosmarinic acid (38) [71, 72] and quinic acid (39) [72], which are common constituents of the plants from the mint family.

The data concerning flavonoid constituents in white sage are scarce. The presence of 2 flavonoids, cirsimaritin (40) and salvigenin (41), has been documented in ethanolic extracts of *S. apiana* [64]. Moreover, the decoction from aerial parts of the plant was shown to contain hesperidin (42) and quercetin-O-hexoside (► **Fig. 5**) [72]. However, none of these compounds have been quantitatively analyzed. So far, quantitative data are available only for rosmarinic acid, which was determined in methanol extracts (ca. 1.1 mg/ml) [71] and white sage decoction (57 mg per g of the extract) [72].

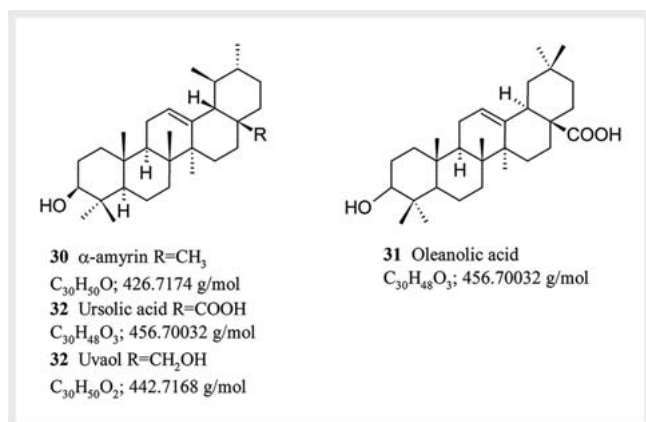
The nonvolatile constituents of *S. apiana* were listed in ► **Table 3**. A substantial number of secondary metabolites have been identified and isolated from the plant, however, the quantitative studies are scarce and limited to major abietane diterpenes (i.e., carnosic acid and carnosol) and rosmarinic acid. The results of these analyses are summarized in ► **Table 4** and confronted with quan-



► **Fig. 2** Structures of diterpenoids isolated from *S. apiana*.

titative data available for 2 widely used plants of the *Salvia* genus: *S. officinalis* and *S. rosmarinus*. It has to be emphasized that the compiled values are difficult to compare because of different types of plant material (leaves vs. whole aerial parts, fresh vs. dried), extraction methodologies, as well as differences in data presentation (mg/g DW, mg/g of extract, or mg/ml of extract). In this regard, comparative studies can provide reliable data since the same extraction and analytical methodology is applied to dif-

ferent plant materials. Unfortunately, only one such work is available: in the study by Abreu et al. [63], *S. apiana* was shown to contain the highest amounts (21.8 mg/g DW) of carnosic acid out of 60 investigated sage species. The second was the common sage, with a carnosic acid content of 14.6 mg/g DW. The same study showed that the content of carnosol in *S. apiana* and *S. officinalis* was 0.3 and 0.4 mg/g DW, respectively. The work did not include *S. rosmarinus*, however, other studies indicate its diterpene con-



► **Fig. 3** Structures of triterpenoids isolated from *S. apiana*.

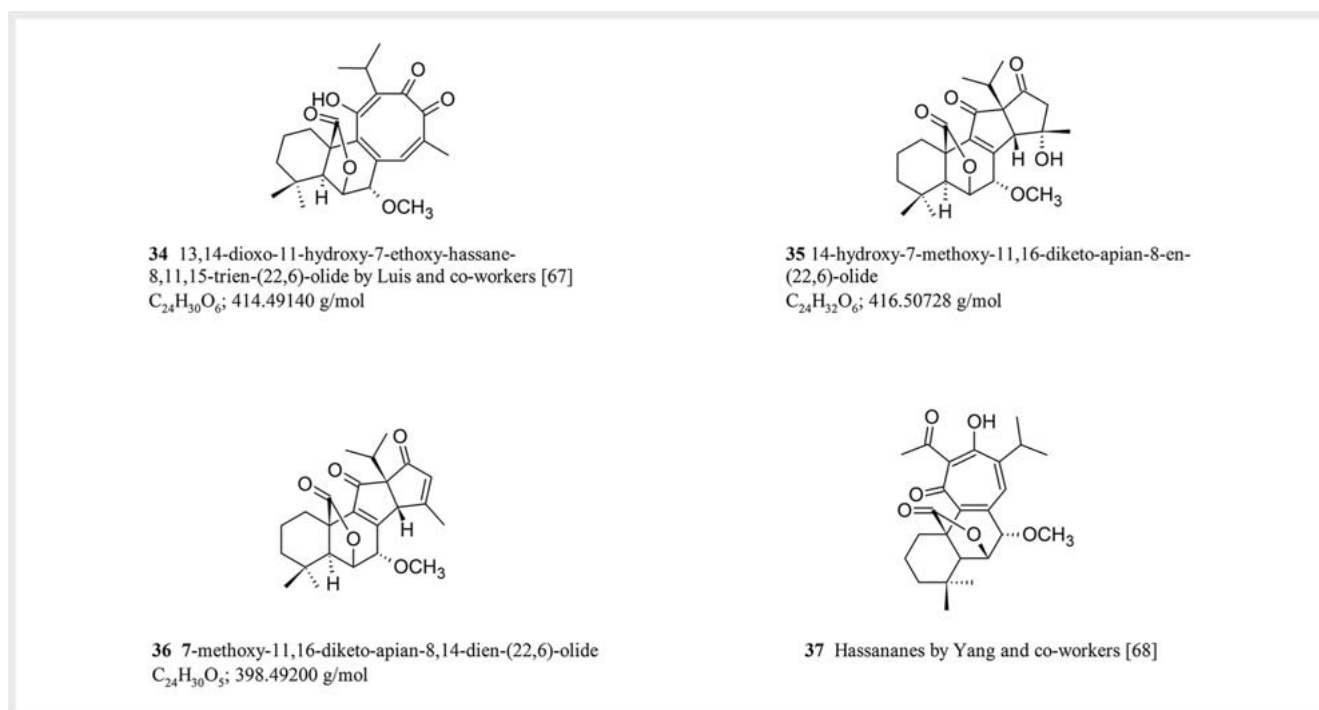
tent can be even higher. For instance, the concentration of carnolic acid determined by Hidalgo et al. [73] ranged from 31.1 to 73.5 mg/g DW. As mentioned earlier, *S. apiana* extracts were shown to contain rosmarinic acid (► **Table 4**), however, the reported values only refer to its content in white sage extracts. According to Vulganova et al. [71], rosmarinic acid concentration in *S. apiana* extracts (1.1 mg/ml) was higher than in *S. officinalis*, but no specific values were provided for the latter. Besides, the cited work is the only one dealing with total phenolic and total flavonoid contents of *S. apiana* and other sage species. In comparison to *S. officinalis*, total phenolic and total flavonoid contents of white sage were 1.3–1.6-fold and 1.3–2.0-fold higher, respectively [71].

Biological Activities

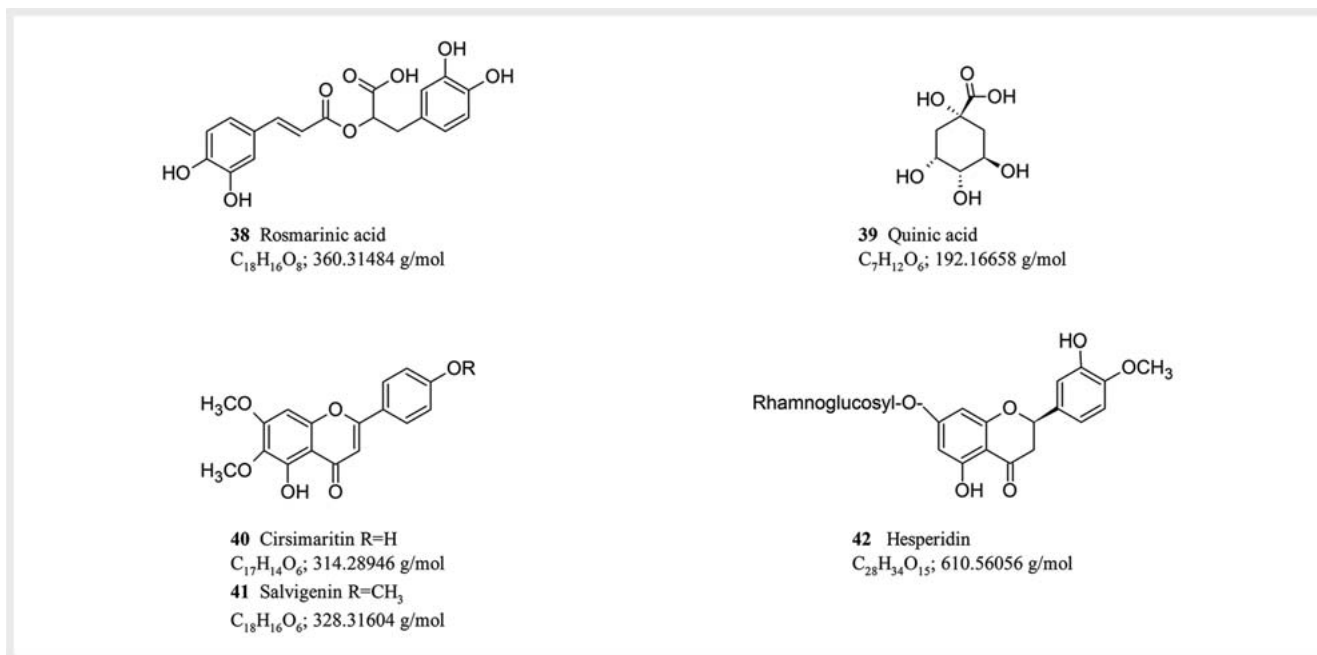
As mentioned earlier, *S. apiana* is well-known among Native American tribes for its medicinal properties. Collected from the wild, it has been used mainly as an antimicrobial, calmative, and diuretic agent, as well as a cold remedy [2, 30]. In the current work, the results of studies on the biological activity of white sage were reviewed, in an attempt to determine to what extent, the empirical knowledge of Native American and the traditional usage were confirmed by modern research. The results of the studies revealing new activities and potential fields of application of *S. apiana*, like cytotoxic properties and cancer treatment, were also critically reviewed [74–76].

Antimicrobial and Anti-inflammatory Activities

S. apiana extracts were investigated by several bioassays to confirm their antimicrobial properties, in accordance with the traditional use of this plant. However, only tentative *in vitro* bioassays have so far been performed. The most in-depth experiment was conducted by Dentali [44] who characterized dichloromethane extract from white sage to identify bioactive compounds using the agar dilution-streak test. Firstly, screening bioassays of 20 herbal remedies of Southwestern US revealed *S. apiana* to be the only plant in this study that completely inhibited the growth of all 4 tested pathogens: *Staphylococcus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae*, and *Candida albicans*. Further analysis of white sage extracts revealed that its antibacterial and antifungal activity resulted from the presence of carnolic acid and 16-hydroxycarnolic acid. The tests excluded antimicrobial activity of essential oil and ursolic acid [44]. Unfortunately, quantitative results



► **Fig. 4** Structures of C23 terpenoids isolated from *S. apiana*.



► **Fig. 5** Structures of flavonoids and phenolic acids isolated from *S. apiana*.

of growth inhibition (the MIC values) are not provided by the author, so it is not possible to confirm these findings and compare the results with other papers. If confirmed, the above-mentioned antimicrobial effects could be indeed therapeutically relevant. Following the respiratory pathogenesis, *K. pneumoniae* and *S. aureus* are microorganisms able to develop respiratory disorders such as pneumonia [77, 78]. However, the agar dilution-streak method investigates antimicrobial activity against bacteria in the planktonic mode of growth. Given this, the prediction of therapeutic outcome basing on an *in vivo* test can be of limited value as *S. aureus* can colonize the nasopharyngeal mucosa as a biofilm [79, 80]. *S. aureus* is the most frequent microbe found in biofilm-associated infections [81, 82].

It is noteworthy that carnosic acid and the related abietane-type diterpenoid, carnosol, were found to be responsible for antibacterial activity against oral pathogens *Streptococcus mutans*, *S. salivarius*, *S. sobrinus*, *S. mitis*, *S. sanguinis*, and *Enterococcus faecalis* during the bioassay-guided fractionation of *R. officinalis* leaf extracts [83]. Carnosic acid and other phenolic diterpenoids, identified in dichloromethane extract, also are present in water and alcoholic extracts of aerial parts of *S. apiana* (► **Table 4**). Pharmacokinetic studies of carnosic acid and carnosol from rosemary extract using the rat *in vivo* model give insight into the bioavailability of these compounds. Carnosic acid is absorbed into the bloodstream after oral administration and is present in its free form in plasma. Administration of ca. 40 mg of carnosic acid in rosemary extract (ca. 100 mg) resulted in plasma concentration at the level of 2–30 µM. The concentrations measured in the small and large intestine were up to several hundred µg/g, and the levels recorded in the liver were 1–15 µg/g [84]. Also, the main elimination route is the fecal route [85]. Carnosic acid was found in relatively high concentrations of over 1% in *S. apiana* extracts (► **Table 4**). How-

ever, neither bioavailability nor active concentrations from human studies are available, so it is not clear if achieved systemic concentrations of carnosic acid could show significant antimicrobial effect. Besides being used in digestive therapies, white sage was employed for gargling in sore throats. Carnosic acid inhibited clinical isolates of *S. aureus* methicillin-resistant and *E. faecalis* gentamicin and streptomycin-resistant bacteria with MIC and MBC values 60 µg/ml. Another main phenolic compound in the extract, rosmarinic acid, was inactive against these bacterial strains even at a high concentration of 480 µg/ml [86]. Also, in this study, carnosic acid showed antibacterial activity against the Gram-negative multidrug-resistant bacteria *Escherichia coli*, *Proteus mirabilis*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Morganella morganii*, and *Providencia stuartii*, and its MIC values are at a level of 120 to 240 µg/ml. The results suggest that topically applied water extracts of *S. apiana* can exert antimicrobial activity because of a high content of carnosic acid.

► **Table 5** intends to succinctly collate the available quantitative data on the antimicrobial activity of *S. apiana* extracts. Afonso et al. [72] investigated the antibacterial activity of *S. apiana* leaves decoction against *S. aureus*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, and *Salmonella typhimurium* using the broth microdilution method. The highest activity was observed for *S. epidermidis* with an MIC value of 0.34 mg/ml and *S. aureus* with an MIC value of 0.69 mg/ml. The MBC value was 0.69 mg/ml for both *S. epidermidis* and *S. aureus*. As suggested by van Vuuren et al. [87], noteworthy antimicrobial activity of crude extract of medicinal plants is ascribed for concentrations less than or equal to 160 µg/ml. Since the MIC concentration of *S. apiana* decoction towards *S. epidermidis* was over 2-times higher than the aforementioned value, its effectiveness against said pathogen is doubtful.

► **Table 3** Nonvolatile constituents found in *S. apiana* extracts.

Type of secondary metabolite	Solvent for extraction	Metabolites	Ref.
Root extracts			
Diterpene	Acetone	Cryptotanshinone (25) Lanugon Q (26) Salvicanol (11) 6,7-didehydroferruginol (17) 6,7-didehydrosemperviol (18) 16-hydroxy-6,7-didehydroferruginol (19) 11,12,16-trihydroxy-20(10 → 5)abeo-abieta-1(10),6,8,11,13-pentaene (20) 16-hydroxyroyleanone (21) 6-deoxo-5,6-didehydrolanugon Q (22) Ferruginol (23) Miltiodiol (24)	[62]
Leaf extracts			
Triterpene	Hexane	α-amyrin (30) Oleanolic acid (31) Ursolic acid (32)	[65]
Diterpene	Methanol	Carnosic acid (9) Carnosol (27)	[63]
	Dichloromethane	Carnosic acid (9) 16-hydroxycarnosic acid (10)	[44, 142]
Tocopherols	Methanol	α-tocopherol	[63]
Aerial parts extracts			
Triterpene	Ethanol	Oleanolic acid (31) Ursolic acid (32) Uvaol (33)	[64, 116]
Diterpene	Acetone	16-hydroxycarnosic acid (10) Salvicanol (11) Rosmanol (15) 7-epirosmanol (16) 16-hydroxycarnosol (13) 16-hydroxyrosmanol (12) 16-hydroxy-7-methoxyrosmanol (14)	[61, 67]
	Ethanol	Sageone (28) Carnosol (27) 16-hydroxycarnosol (13) Rosmadial (29)	[64, 116]
	Water (decoction)	Rosmanol (15) Sageone derivative (28) Hydroxycarnosic acid (10) Carnosol (27) Carnosic acid (9)	[72]
C23 terpenoids	Acetone	13,14-dioxo-11-hydroxy-7-methoxy-hassane-8,11,15-trien-(22,6)-olide (34) 14-hydroxy-7-methoxy-11,16-diketo-apian-8-en-(22,6)-olide (35) 7-methoxy-11,16-diketo-apian-8,14-dien-(22,6)-olide (36)	[61, 67]
Phenolic acids	Water (decoction)	Rosmarinic acid (38) Quinic acid (39)	[72]
	Methanol	Rosmarinic acid (38)	[71]
Flavonoids	Ethanol	Cirsimaritin (40) Salvigenin (41)	[64, 116]
	Water (decoction)	Hesperidin (42) Quercetin-O-hexoside Cirsimaritin (40)	[72]

► **Table 4** Content of carnosic acid, camosol, and rosmarinic acid in *S. apiana*, *S. officinalis*, and *S. rosmarinus* (*Rosmarinus officinalis*).

	<i>S. apiana</i> Jeps.			<i>S. officinalis</i> L.			<i>S. rosmarinus</i> Schleiden		
	material/extract type	concentration	Ref.	material/extract type	concentration	Ref.	material/extract type	concentration	Ref.
Carnosic acid (9)	Aerial parts/decoction	14.3 mg/g extract	[72]	Fresh leaves/acetic	12.40 mg/g extract	[143]	Leaves/supercritical CO ₂ extraction	31.1–73.5 mg/g DW	[73]
	Leaves/methanolic	21.8 mg/g DW	[63]	Leaves/methanolic	14.6 mg/g DW	[63]	Leaves/75% dichloro-methane + 25% ethanol	3.4–17.7 mg/g fresh leaves	[144]
				Postdistilled aerial parts/methanolic	746.43–3109.28 µg/g DW	[145]	Fresh leaves; dried leaves/acetic	22.79 mg/g extract; 42.05 mg/g extract	[143]
Carnosol (27)				Leaves/supercritical CO ₂ extraction	0.29–120.0 µg/g extract	[146]	Leaves/hexane and ethyl acetate	177.3 mg/g dry extract	[147]
				Leaves/hexane and ethyl acetate	42.9 mg/g dry extract	[147]			
	Aerial parts/decoction	17.3 mg/g extract	[72]	Fresh leaves/acetic	1.66 mg/g extract	[143]	Fresh leaves; dried leaves/acetic	2.38 mg/g extract; 3.87 mg/g extract	[143]
	Leaves/methanolic	0.3 mg/g DW	[63]	Leaves/methanolic	0.4 mg/g DW	[63]	Leaves/hexane and ethyl acetate	21.5 mg/g dry extract	[147]
				Postdistilled aerial parts/methanolic	2535.11–5541.11 µg/g DW	[145]			
Rosmarinic acid (38)				Leaves/supercritical CO ₂ extraction	0.46–65.5 µg/g extract	[146]			
				Leaves/hexane and ethyl acetate	31.1 mg/g dry extract	[147]			
	Leaves/methanolic	1120 µg/ml extract	[71]	Postdistilled aerial parts/methanolic	8195.80 to 9731.15 µg/g DW	[145]	Leaves/ethanolic 70%	48.09 µg/g	[148]
	Aerial parts/decoction	56.8 mg/g extract	[72]	Leaves/ethanolic 30%	8.5–14.1 mg/g	[149]	Leaves/ethanolic 30%	10.0–11.0 mg/g	[149]
				Leaves/ethanolic 80%	19.5 mg/g DW	[150]	Leaf/methanolic	4040.00 mg/100 g extract	[151]
			Leaves/ethanolic 30%	3634.12 mg/100 g DW	[152]	Leaves/hexane and ethyl acetate	10.0 mg/g dry extract	[147]	
			Leaves/hexane and ethyl acetate	11.6 mg/g dry extract	[147]				

► **Table 5** Antimicrobial bioassays performed on *S. apiana* extracts.

Strain	Type of extract; test conc. [mg/ml]	Positive control/ test conc.	Zone diam. in agar diffusion test [mm]		MIC and MBC values in agar dilution test [mg/ml]		Ref.
			Extract	Control	Extract	Control	
<i>S. aureus</i>	Hexanic 27; 13.5; 6.8; 3.4 [mg/ml]	NP	10.0–24.0	–			[90]
<i>S. pyogenes</i>	Hexanic 27; 13.5; 6.8; 3.4 [mg/ml]	NP	28.0–40.0	–			[90]
<i>E. faecalis</i>	Hexanic 27; 13.5; 6.8; 3.4 [mg/ml]	NP	9.0–17.0	–			[90]
<i>C. albicans</i>	Hexanic 27; 13.5; 6.8; 3.4 [mg/ml]	NP	8.0–13.0	–			[90]
<i>S. aureus</i>	Decoction	Nisin			MIC 0.69; MBC 0.69	> 0.63; > 0.63	[72]
<i>S. epidermidis</i>	Decoction	Nisin			MIC 0.34; MBC 0.69	> 0.63; > 0.63	[72]
<i>S. typhimurium</i>	Decoction	Nisin			MIC 2.75; MBC 2.75	> 0.5; > 0.5	[72]
<i>E. coli</i>	Decoction	Nisin			MIC 2.75; MBC 2.75	> 0.5; > 1.0	[72]
<i>P. aeruginosa</i>	Decoction	Nisin			MIC 2.75; MBC 2.75	> 1.0; > 1.0	[72]

NP: not provided

Allison et al. [88] reported inhibition of growth of a Δ tolC mutant strain of the bacterium *E. coli* by dichloromethane fraction of methanol extract from leaves and stems of white sage in concentration 100 μ g/ml. Unfortunately, the study should be considered as an initial screening since no phytochemical analysis of the obtained extract was performed.

Dentali [44] excluded antimicrobial activity of *S. apiana* essential oil, which was tested in a concentration of 1000 μ g/ml in agar dilution-streak test. According to the criteria described by van Vuuren et al., [87], an essential oil cannot be considered as a noteworthy antimicrobial agent if its active concentration value exceeds 1000 μ g/ml. In such a case, therapeutic doses necessary to achieve contact inhibition may result in dangerously high systemic concentrations and possible toxic effects. Antimicrobial activity *in vivo* of essential oils should be considered mainly for topical therapies since MIC concentrations cannot be realistically achieved in the plasma [89].

The majority of studies on the antimicrobial activity of *S. apiana* were conducted using extracts from aerial parts of the plant; however, there is one report dedicated to the evaluation of the antibacterial activity of a hexane extract of roots in concentrations of 27, 13.5, 6.8, and 3.4 mg/ml using agar disk-diffusion method [90]. All concentrations of the extract significantly inhibited the growth of bacteria, depending on the applied dose: *S. aureus* (inhibition zone in the range of 10 to 24 mm), *Streptococcus pyogenes* (inhibition zone in the range of 28 to 40 mm), *E. faecalis* (inhibition zone in the range of 9 to 17 mm), and fungi *C. albicans* (inhibition zone in the range of 8 to 13 mm). No growth inhibition was revealed for *E. coli* and *Candida tropicalis*.

The folkloric use of aromatic plants as anti-infective agents may be associated with the antimodulatory effects of essential oils [91–93]. Most reports on the traditional use of *S. apiana* mentions using water for extract preparation. This can be done by macerating fresh leaves in water (a few leaves per 1 liter) [39,41] or by preparing an infusion (tea) from white sage [4,30]. Essential oil can be administered as an infusion; however, during its preparation, part of volatile compounds will be lost. For instance, rosemary infusions contain only 19.6% of the initial essential oil (1.84% v/w in leaves and 0.36% oil yield in infusion). The major compounds of essential oil in leaves were 1,8-cineole (41.6%), camphor (17.0%), α -pinene (9.9%), α -terpineol (4.9%), and borneol (4.8%), whereas volatiles present in the infusion included 1,8-cineole (42.4%), camphor (31.4%), α -terpineol (8.6%), and borneol (8.3%) [94]. Radulescu et al. [95] presented the composition of volatile compounds in the infusion from *S. officinalis* leaves. The essential oil of leaves, obtained using Clevenger-type apparatus, consisted mainly of thujone (α and β ; 27.36%), camphor (11.25%), 1-octen-3-ol (8.5%), and 1,8-cineole (6.72%). The losses of volatile compounds in *S. officinalis* infusions were most evident for monoterpene hydrocarbons like ocimene and camphene, which were not found in this delivery form. The volatile fraction of common sage infusion contained mainly thujone (α and β ; 32.85%), camphor (24.94%), and 1,8-cineole (16.16%). As mentioned earlier, the composition of *S. apiana* essential oils (► **Table 2**) is similar to rosemary and common sage. Since 1,8-cineole was found in infusions from *S. rosmarinus* and *S. officinalis*, it can be assumed that it is probably present also in an *S. apiana* infusion. If this were to be confirmed experimentally, it would be

important from a therapeutic standpoint. It is worth noticing that 1,8-cineol has good bioavailability after oral administration, and about 20% of an oral dose reaches the peripheral airways [96, 97]. *In vivo* and *in vitro* studies have confirmed that 1,8-cineole has a potential therapeutic role in inflammatory-based respiratory diseases [96, 97]. Its mechanism of action is based on inhibition of cytokine production: tumor necrosis factor TNF α , interleukin-1b, leukotriene B4, thromboxane B2, IL-8, and IL-5, as well as inhibition of arachidonic acid metabolism [98–101]. Further studies revealed that 1,8-cineole reduces pro-inflammatory NF- κ B-activity [102] and inhibits the expression of the mucin genes MUC2 and MUC19 [103]. 1,8-cineole possibly exhibits antiviral activity due to the increase of antiviral transcription factor interferon regulatory factor 3 activity [102]. The anti-inflammatory capabilities of 1,8-cineole were studied also in various multi-center, double-blinded, and randomized trials in humans with acute and chronic respiratory conditions like asthma or rhinosinusitis. The results revealed a promising efficacy profile and safety, with few side effects reported when consuming therapeutic doses of 1,8-cineole [96]. In Germany, 1,8-cineol has been registered as a drug Sole-dum forte[®] (200 mg dose). The daily recommended dose of the drug is 400–800 mg.

The anti-inflammatory activity of *S. apiana* decoction and its potency to counteract NO radical was evaluated in the lipopolysaccharide LPS-activated RAW264.7 macrophage model. The ability to modulate inflammatory reactions was about one-third of that of dexamethasone [72].

To sum up, studies on antibacterial and immunomodulatory activity of *S. apiana* preparations may provide some explanation of therapeutic effects observed by the Chumash in infections like cold and sore throats [30]. The presence of volatile compounds may be vital especially because ethnopharmacological reports warned against treating white sage leaves with boiling water in order not to lose the effect [4]. Also, experiments linked the presence of diterpenes, which are abundant in *S. apiana* (► Table 4), with the antimicrobial activity of the extracts. The studies were conducted with the use of panels of clinically relevant bacterial strains, and the results generally support the topical use of *S. apiana* extracts for the treatment of infections. This is not the case in all of the studies, however, since MIC values reported in some of them are not considered noteworthy according to the proposed criteria. The systemic antibacterial effects of white sage have not been confirmed and are unlikely, given the doses that would be required to achieve necessary concentrations. Also, it has to be noted that the majority of the studies conducted thus far should be considered preliminary. Their limitations include the use of extracts with unknown composition, the absence of positive controls, no MIC or IC50 values, and the absence of cytotoxicity studies involving reference cell lines that would enable evaluation of the specificity of antimicrobial actions.

GABA-ergic Activity

A number of studies investigated the influence of sage constituents on the GABA-ergic system. Among these, abietane diterpenes have been the most extensively studied; however, experiments involving flavonoids and volatile compounds have also

been conducted. The results of selected studies from this field are presented in ► Table 6.

Carnosic acid and carnosol have been shown to enhance the function of ionotropic GABA receptors by inhibiting the binding of antagonists to its chloride channel site [104–106]. More recently, the GABA-ergic activity of carnosol was confirmed by Khan et al. [107]; however, the results suggest that the compound acts via the benzodiazepine site of the receptor. This observation is in agreement with other studies that demonstrated that related diterpenes like 7-methoxyrosmanol, rosmanol, and miltirone also bind to GABA receptors at the benzodiazepine site [108–110]. Apart from diterpenes, flavonoids and volatile compounds found in *S. apiana* have also been shown to exhibit GABA-ergic and anxiolytic effects (► Table 6).

The above-described activities of *S. apiana* constituents might explain the use of white sage as a calmative agent in folk medicine. However, the plausibility of the proposed mechanism needs to be verified. In particular, one must consider the bioavailability of potentially active constituents. The pharmacokinetics of carnosic acid in humans have not been studied so far, however, its bioavailability in rats is ca. 40% [85]. The results of animal experiments [84] indicate that after ingestion, the concentration of carnosic acid in brain tissue can reach 1.5–1.9 μ g/g (roughly equal to 4.5–5.7 μ M), which is lower as compared to effective levels reported in most of the receptor studies (► Table 6). Moreover, it has to be noted that Zucker rats involved in the study were fed a diet supplemented with 0.5% enriched rosemary extract containing ca. 40% carnosic acid for over 2 months [84]. At the assumed 15–25 g daily food intake in rats, this corresponds to a daily dose of 30–50 mg of carnosic acid. Given the above, it seems unlikely that carnosic acid is the sole constituent responsible for the putative psychoactive properties of *S. apiana*, even with its high content of over 20 mg/g. However, the observed effects might be the result of the synergistic action of white sage diterpenes and different constituents. Recent studies indicate that 1,8-cineole, which is present in substantial quantities in *S. apiana* essential oil, exerts anxiolytic and antidepressant effects in rats [111] and mice [112]. The results of both studies suggest that 1,8-cineole may act at the benzodiazepine site of GABA receptors. This phenomenon is certainly worth further investigation, especially given that 1,8-cineole has been shown to have good bioavailability and is capable of crossing the blood-brain barrier [113, 114]. Nevertheless, it has to be stated that 1,8-cineole has so far not been reported to exhibit sedative properties in humans, and no such effect has been observed even after the intake of high doses (200 mg 3 times daily) of pure compound [96].

Summing up, the available data indicate that studies concerning the GABA-ergic activity of *S. apiana* are certainly worth further attention. Given the availability of constituents exhibiting said activity, the biological effects cannot be definitively excluded. However, one must note that this statement is based on an extrapolation of activities reported *in vitro* for specific constituents of the plant. Further studies are necessary to determine whether this translates to clinical effects.

► **Table 6** Selected studies concerning GABA-ergic activity of white sage constituents

Investigated compounds	Experimental model	Results	Ref.
Carnosic acid, carnosol (abietane diterpenes)	<i>In vitro</i> : isolated Wistar rat cortex membranes; inhibition of binding of radiolabeled ligands to different sites of GABA receptors	Inhibition of binding of tert-butylbicyclophosphorothionate to chloride channel site of the receptor (IC ₅₀ values for carnosic acid and carnosol: 33 and 57 μM, respectively); no effect on muscimol and diazepam binding	[106]
7-Methoxyrosmanol (abietane diterpene), cirsimaritin (flavonoid)	<i>In vitro</i> : crude synaptic tissue membranes isolated from post-mortem human frontal cortex; inhibition of binding of radiolabeled flumazenil to benzodiazepine site of GABA receptors	Competitive inhibition of flumazenil binding (IC ₅₀ values for 7-methoxyrosmanol and cirsimaritin: 350 and 7.2 μM, respectively)	[109]
Carnosol (abietane diterpene)	<i>In vitro</i> : <i>Xenopus</i> oocytes expressing recombinant GABA receptors; electrophysiological studies	Positive modulation of GABA receptor at 1–10–30–100–300 μM, effect attenuated by flumazenil indicating binding at benzodiazepine site	[107]
Carnosol (abietane diterpene)	<i>In vivo</i> : male Swiss mice; elevated plus maze and light-dark box test	Anxiolytic effect at 10–100 mg/kg dose	[107]
Carnosol, rosmanol (abietane diterpenes), salvigenin, cirsimaritin (flavonoids)	<i>In vitro</i> : <i>Xenopus</i> oocytes expressing recombinant GABA receptors; electrophysiological studies	Carnosol (100–300–1000 μM): found to act as a non-competitive GABA blocker at high GABA doses; slight positive modulation at low GABA doses Rosmanol (100 μM): flumazenil-independent inhibition of GABA currents at high GABA doses; positive modulation at low GABA doses, inhibited by flumazenil Salvigenin (100 μM): flumazenil-independent inhibition of GABA currents at high GABA doses; positive modulation at low GABA doses, inhibited by flumazenil Cirsimaritin (100 μM): inhibition of GABA currents at high GABA doses; flumazenil-independent positive modulation at low GABA doses	[110]
1,8-Cineole (monoterpene)	<i>In vivo</i> : male Sprague-Dawley rats; elevated plus maze	Anxiolytic effect at 1 mg/kg (intraperitoneal route), diminished by flumazenil	[111]
1,8-Cineole (monoterpene)	<i>In vivo</i> : male ddY mice; light-dark box test, marble-burying test	Anxiolytic effect at 4 × 10 ⁻⁴ mg/400 μl (inhalation), reversed by flumazenil	[112]

Analgesic Activity

Besides being used as a calmative, white sage has been reported to possess analgesic properties. With this in mind, the role of the cannabinoid and opioid system in the antinociceptive effects of ethanolic extract of *S. apiana* was investigated. The crude extract of the plant was shown to exhibit moderate activity towards CB1. Further isolation and analysis of the compounds in that fraction showed the diterpene sageone to be active toward CB1 and CB2 (73 and 78% displacement at 33 μM, respectively) and moderately active towards the μ-opioid receptor (55% displacement at 33 μM) [64]. The reported values were higher (in the case of CBs) or lower (for μ-opioid receptor) as compared to positive controls. The reported activity on opioid receptors is not typical for abietane-type terpenoids present in plants from the genus *Salvia*. So far, the best-known nonalkaloid modulators of opioid receptors are neoclerodane diterpenes from *Salvia divinorum*, which act mostly as κ-opioid receptor agonists [76, 115]. As opposed to other sage species found in the Americas, clerodane-type diterpenes were not identified in *S. apiana* aerial parts [59]. Another white sage constituent that showed moderate inhibition of the μ-opioid receptor was the triterpene uvaol [64, 116]. Since neither the exact content nor bioavailability of sageone and uvaol are known, it is

not possible to tell whether they actually contribute to analgesic effects of the plant. The reported activity needs to be confirmed and validated using other *in vitro* and *in vivo* models.

Besides di- and triterpenoids, the pain-relieving activity of *S. apiana* can be possibly attributed to the composition of the essential oil and its high level of 1,8-cineole, which inhibits the formation of prostaglandins and cytokines [117] and has TRPM8-activating and TRPA1-inhibiting abilities [118]. As a small lipophilic molecule, 1,8-cineole is absorbed by inhalation or ingestion, and can easily cross the blood-brain barrier [113, 114].

Antioxidant Activity

Antioxidant activity of *S. apiana* decoction was confirmed by Afonso et al. [72] using 4 methods: DPPH, ferric reducing power assay, thiobarbituric acid reactive substances, and bleaching of β-carotene. Likewise, in the DPPH scavenging test, ABTS radical cation assay, FRAP method, and reducing power assay, methanolic extract of *S. apiana* has been reported to have the ability to change the oxidation status [71]. Quantitative results of antioxidant assays are presented in ► **Table 7**.

Antioxidant capacity and ability to scavenge free radicals are most likely associated with the presence of phenolic components,

► **Table 7** Antioxidant bioassays performed on *S. apiana* extracts.

Test of antioxidant activity	Type of extract	Positive control	Antioxidant activity [µg/ml]	Antioxidant activity of positive control [µg/ml]	Ref.
DPPH ^a	Decoction	Ascorbic acid	13.3 ^b	6.7	[72]
FRAP ^c	Decoction	BHA ^d	55.0 ^b	16.1	[72]
TBARS ^e	Decoction	Trolox	2.79 ^b	23.0	[72]
BCBA ^f	Decoction	Trolox	41.2 ^b	41.7	[72]
DPPH	Methanolic	Trolox	2935.57 ^g	NA	[71]
ABTS	Methanolic	Trolox	1710.91 ^g	NA	[71]
FRAP	Methanolic	Trolox	1959.39 ^g	NA	[71]
RP ⁱ	Methanolic	Trolox	4669.13 ^g	NA	[71]

NA: not available; ^a DPPH: 1,1-Diphenyl-2-picryl-hydrazyl (DPPH) scavenging test; ^b expressed as the sample concentration providing 50% of antioxidant activity; ^c FRAP: ferric reducing antioxidant power assay; ^d BHA: 2,6-di-tert-butyl-4-methylphenol; ^e TBARS: thiobarbituric acid reactive substances assay; ^f BCBA: β -Carotene bleaching assay; ^g expressed as micrograms of Trolox equivalent; ^h ABTS: 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate) radical scavenging assay; ⁱ RP: reducing power method

such as rosmarinic acid and phenolic diterpenoids. Among the latter are carnosic acid, carnosol, rosmanol, hydroxycarnosic acid, and a derivative of sageone. Methanolic extracts of *S. apiana* leaves are rich in polyphenols. Total phenolic contents of the investigated plant are about 1.3–1.6-fold higher than in *S. officinalis* and 2.5-fold higher than in *S. divinorum* methanolic extract. Also, *S. apiana* was confirmed to be the richest source of flavonoid compounds among these species, as its total flavonoid content was about 1.3–2.0-fold and 6.6-fold higher than in *S. officinalis* and *S. divinorum*, respectively [71]. Interestingly, the described differences did not directly translate to the results of antioxidant activity studies. *S. apiana* and *S. officinalis* yielded comparable results in terms of antioxidant activity determined by DPPH and ABTS assays; however, *S. apiana* performed better in FRAP and RP (reducing power) method. Also, both species had stronger antioxidant activity as compared to *S. divinorum* (3- to over 10-fold difference, depending on the test used). Rosmarinic acid was the dominant secondary metabolite in all sage extracts examined in the study. The highest content of this compound was detected in white sage extract (1120 µg/ml), higher than in *S. officinalis* and *S. divinorum* [71]. In decoction, rosmarinic acid concentration was 56.8 mg per g of the extract [72].

It has to be emphasized that promising results obtained using *in vitro* bioassays of antioxidant capacity cannot be a predictor of its ability to reduce oxidative stress in *in vivo* free-radical diseases. Numerous studies indicate that bioavailable concentrations of phenolic compounds of plant origin are too low to exhibit antioxidant effects *in vivo* [119]. Nevertheless, a polyphenol-rich diet has beneficial effects on health and diseases associated with free-radical pathological mechanisms, like diabetes, obesity, cancer, cardiovascular, and neurodegenerative diseases. Their mode of action may be related to mediation of interactions with specific proteins central to intracellular signaling cascades, modification of the expression and activity of key proteins, modulation by epigenetics modifications, or impact on the gut microbiota [120]. Vulganova et al. [71] reported the significant inhibitory activity

of methanolic extract of dried leaves of *S. apiana* against 4 selected serine proteinases: trypsin, thrombin, urokinase, and plasmin. These proteinases are responsible for the pathological mechanisms of some diseases (e.g., cancer and viral infections).

Cytotoxic and Antitumor Activity

Recent *in vitro* studies show that *S. apiana* methanolic and water extracts exhibit cytotoxic effects on cancer cell lines. So far, no studies indicate that white sage would have chemopreventive activity, and only the chemotherapeutic antitumor effect was investigated for the plant. The results of the tests conducted on drug-sensitive parental CCRF-CEM leukemia cells and their multidrug-resistant P-glycoprotein-overexpressing subline CEM/ADR5000 confirmed the cytotoxic activity of the methanol extract of *S. apiana* [74]. A decoction of white sage exhibited significant, tumor-selective cytotoxic effects against tumor cell lines: hepatocellular carcinoma HepG2, cervical carcinoma HeLa, and breast carcinoma MCF-7 [72]. Quantitative data of conducted experiments are presented in ► **Table 8**.

Besides therapeutically-relevant effects, it was shown that the essential oil of the plant inhibits the growth of *Cucumis sativa* and *Avena* seedling roots. Growth inhibition was induced by the presence of terpenes and the highest cytotoxic effect was observed during the exposition of the seedlings to camphor and cineole. The weakest effect was observed during the treatment of seedlings with α -pinene and β -pinene [45, 121].

Both methanolic and water extracts of *S. apiana* contain carnosic acid and carnosol. These 2 compounds were identified in supercritical *Rosmarinus officinalis* extracts as the key components responsible for its antitumor effects, demonstrated using colon and pancreatic cancer cell lines, as well as by *in vivo* experiments. In this study, carnosic acid inhibited tumor cell viability in a dose-dependent manner, and carnosol significantly enhanced the antitumor activity of carnosic acid [122]. The relatively good bioavailability of carnosic acid [84] and its high content in *S. apiana* ex-

► **Table 8** Cytotoxic bioassays performed on *S. apiana* extracts.

Cell model	Type of extract	Positive control/ test conc.	Cytotoxic activity (IC ₅₀) [µg/ml]	Cytotoxic activity of posi- tive control (IC ₅₀) [µg/ml]	Ref.
CCRF-CEM	Methanolic	NP	7.17	NP	[74]
CEM/ADR5000	Methanolic	NP	9.91	NP	[74]
HepG2	Decoction	Ellipticine	40.9	1.0	[72]
HeLa	Decoction	Ellipticine	57.3	2.0	[72]
MCF-7	Decoction	Ellipticine	60.2	1.0	[72]
NCI-H460	Decoction	Ellipticine	254.7	1.0	[72]
PLP2	Decoction	Ellipticine	361.7	3.0	[72]

NP: not provided

tracts suggests the potential anti-tumor activity of this plant. Moreover, according to the study on rosemary [122], not only carnosic acid and carnosol but also other components like volatile compounds are involved in antitumor activity of the plant. Thus, white sage extracts may be a good candidate for further research aimed at examining the effective doses in animal models.

Conclusions and Future Prospects

In the current work, the information concerning botany, chemistry, biological activity, and possible therapeutic use of *S. apiana* (white sage) was compiled. Given the available data, the following conclusions can be made:

- *S. apiana* is rich in essential oil and abietane-type diterpenes. The reported contents of these constituents are comparable or higher than in common sage. Studies also revealed the presence of rosmarinic acid; however, its content in white sage cannot be reliably compared with other representatives of the genus. The composition of essential oil is similar to *S. lavandulaefolia*, *S. rosmarinus*, and cineole chemotypes of *S. officinalis* whose notable characteristic is the lack of neurotoxic thujone. This feature of white sage is clearly beneficial in terms of safety of use. Phytochemical studies revealed the presence of species-specific C23 terpenoids hassananes and apiananes; however, their exact contents were not reported and it is not known whether they contribute to the biological effects of the plant. Given the above, future studies should focus on more detailed quantitative analyses that would include major compounds typical for the *Salvia* genus, as well as unique constituents of white sage. Moreover, the chemical variability of the plant depending on the time and place of harvesting needs to be assessed.
- Studies on antimicrobial and anti-inflammatory activity of white sage generally support its topical use as an anti-infective agent, which is similar to the traditional use of other representatives of the genus, such as common sage (*S. officinalis*). Some results link the above effects with the presence of diterpenoids and 1,8-cineole, which is in agreement with phytochemical studies demonstrating the high content of these

compounds in *S. apiana*. However, these reports do not definitely prove the clinical efficacy of the plant extracts. Some of the results indicate that the effective concentrations reported cannot be considered therapeutically noteworthy. Also, there are several limitations of the conducted studies including the use of nonstandardized extracts or extracts prepared using biologically incompatible solvents such as hexane. Other limitations include lack of positive controls, IC₅₀ or MIC values, and parallel cytotoxicity studies. Given this, more state-of-the-art studies are needed if the plant is to be included in modern phytotherapy.

- Several *in vitro* and animal studies demonstrated that selected compounds present in *S. apiana*, including monoterpenes, diterpenes, and flavonoids, exhibit GABA-ergic properties. Given the results of bioavailability studies, the calmative effects reported in traditional medicine cannot be completely excluded. However, none of the studies in this field have been conducted with the use of white sage extracts, and the above assumption is based solely on the reported effects of single compounds. Moreover, it must be confronted with the fact that other sage species with similar compositions (such as *S. officinalis*) are not traditionally used as calmative agents. Thus, conducting experiments using *S. apiana* extracts is crucial to exclude or confirm its calmative action.
- Biological activity studies concerning the analgesic activity of *S. apiana* constituents have been performed. Selected diterpenes and triterpenes present in the plant were shown to bind to CB and opioid receptors *in vitro*, which is in agreement with the traditional use of white sage. However, given the lack of data on the exact contents and bioavailability of these constituents, the reports should be considered preliminary.
- Antioxidant activity studies on *S. apiana* have so far been limited to simple *in vitro* tests whose results likely do not translate to *in vivo* effects. However, this is a common issue that does not refer specifically to studies on white sage. Comparative experiments in this field demonstrated that the antioxidant activity of white sage is similar to common sage. These studies reflect the high phenolic content of both plants.

- Studies concerning the cytotoxic and antitumor activity of the plant are limited to *in vitro* assays. These experiments showed that white sage extracts are active against different cancer cell lines, albeit at concentrations noticeably higher as compared to positive controls. Literature data indicate that the observed effects may result from the high diterpenoid content of *S. apiana* extracts. However, none of the studies indicate that white sage contains compounds with exceptionally high cytotoxic properties.
- Limited availability and threats of overexploitation of *S. apiana* populations is an important issue. If white sage is to be used and investigated more extensively, sustainable and standardized cultivation practices have to be employed to provide a sufficient amount of raw material. On the positive side, the plant can be successfully propagated by seeds or cuttings, and farm cultivation can be established.

Summing up, the results of contemporary studies on white sage suggest that at least some of the therapeutic effects claimed in Native American phytotherapy may be plausible, and the plant has great potential for practical application in modern phytomedicine. However, as compared to other sage species, the reports concerning the chemistry and biological activity of *S. apiana* are scarce, and further studies are required to confirm its therapeutic value. Given the similarities to the common sage in terms of major constituents, white sage can likely find the same use but research concerning other activities is so far preliminary.

Supporting Information

The detailed composition of essential oils in different sage species is provided as Supporting information.

Contributors' Statement

Data collection: A. Krol, A. Kokotkiewicz; design of the study: A. Krol, A. Kokotkiewicz, M. Luczkiewicz; analysis and interpretation of the study: A. Krol, A. Kokotkiewicz, M. Luczkiewicz; preparing a first version of the manuscript: A. Krol, A. Kokotkiewicz, M. Luczkiewicz; critical revision of the manuscript: M. Luczkiewicz. All authors read and approved the manuscript in its final form.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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