Published in final edited form as:

Nat Prod Res. 2017 September ; 31(17): 2058–2061. doi:10.1080/14786419.2016.1269096.

Phytochemical and biological evaluation of *Salvia apiana*

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Abstract

Salvia apiana (white sage, Lamiaceae family) plant is native to southern California and parts of Mexico. Some Native American tribes local to this region consider *S. apiana* to be sacred and burn the leaves as incense for purification ceremonies. The plant has been used to treat sore throats, coughs, chest colds, upper respiratory infections and poison oak rashes. The aqueous ethanolic extract of *S. apiana* showed moderate CB1 activity (58.3% displacement). Chromatographic purification of the ethanolic extract on silica gel column led to isolation of nine compounds: rosmadial (I), carnosol (II), 16-hydroxycarnosol (III), sageone (IV), cirsimaritin (V), salvigenin (VI), oleanolic acid (VII), 3 β ,28-dihydroxy-urs-12-ene (VIII), and ursolic acid (IX). The structures of the isolated compounds were determined by their 1D, 2D NMR and MS spectral data. All the fractions and isolated compounds were tested for cannabinoid and opioid receptor binding.

Graphical abstract

Keywords

Salvia apiana; isolation; cannabinoid receptor; opioid receptor

1. Introduction

The genus *Salvia* L. (Lamiaceae) contains more than 1000 species of herbs, subshrubs and shrubs with many of the species commonly used in cosmetics and in local folk medical

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Disclosure statement

No potential conflict of interest was reported by the authors.

Supplemental data for this article can be accessed at <http://dx.doi.org/10.1080/14786419.2016.1269096>.

practices (Walker et al. 2004). Some of the species possess antimicrobial, antimalarial, anti-oxidant and antiproliferative activities (Loizzo et al. 2014; Russo et al. 2015; Jassbi et al. 2016; Moridi Farimani & Abbas-Mohammadi 2016). *Salvia apiana*, commonly known as white sage, can be found scattered throughout southwestern North America, with the highest concentration in Southern California (Borek et al. 2006). Natives to the Southern California region have been known to use the leaves in traditional Chumash healing involves prayer, relaxation and natural plant-based remedies to cure a variety of ailments (Takeoka et al. 2010). In this practice, white sage is infused into water in order to relax the patient (Luis, Lahlou, Andrés, Sood, et al. 1996). The plant is used for diaphoretic and diuretic effects (Dentali & Hoffmann 1990). Previous to our research, several compounds including flavonoids, mono-, sesqui-, di- and tri terpenes, have been already identified and/or isolated from *S. apiana* (Pettit et al. 1966; González et al. 1992; Luis, Lahlou, & Andrés 1996; Luis, Lahlou, Andrés, Sood, et al. 1996; Dentali & Hoffmann 1990; Borek et al. 2006; Abreu et al. 2008; Takeoka et al. 2010). However, this plant has not been studied for cannabinoid or opioid receptors activity.

Based on the native uses and previous research, we were interested in isolating compounds from *S. apiana* that could have a significant effect on cannabinoid (CB₁ and CB₂) and opioid (mu, delta and kappa) receptors as ethanolic extract showed moderate activity (58.3% displacement) in CB₁ receptor.

2. Results and discussion

Ethanolic extract of areal parts of *S. apiana* was subjected to phytochemical investigation which led to the isolation of nine (**I–IX**) compounds (Figure 1). The isolated compounds were identified by their NMR and MS spectral analysis as four diterpenes: rosmadial (**I**) (Nakatani & Inatani 1983), carnosol (**II**) (Abreu et al. 2008), 16-hydroxycarnosol (**III**) (Luis, Lahlou, Andrés, Sood, et al. 1996), sageone (**IV**) (Tada et al. 1994); two flavonoids: cirsimaritin (**V**) (Wang et al. 2004), salvigenin (**VI**) (Ayatollahii et al. 2009); and three triterpenes: oleanolic acid (**VII**) (Pettit et al. 1966; Martins et al. 2013), uvaol (3 β ,28-dihydroxy-urs-12-ene) (**VIII**) (Lee et al. 2013), ursolic acid (**IX**) (Pettit et al. 1966; Silva et al. 2008).

The affinity of the total extracts and isolated compounds towards cannabinoid and opioid receptors were carried out using the following controls: AM251 (1.25 nM, for CB₁ assay), AM630 (10 nM, for CB₂) and Naloxone (20 nM, for opioid receptors). The results were given in Table 1.

3. Conclusion

S. apiana extract showed 58.3% displacement of the CB₁ receptor, indicating high potential for the presence of active compounds. Bioassay guided fractionation and purification yielded nine compounds (**I–IX**), four of them were diterpenes, two were flavones, and three were triterpenes. Compounds **I**, **IV**, **V**, **VI**, and **VIII**, were isolated for the first time from *S. apiana*. Compound **IV** showed moderate CB₁, CB₂ and μ -opioid activities (CB₁-40.0,

CB2-50.8, μ -31.1% displacement), while compound **VIII** showed moderate μ -opioid activity (μ -45.6% displacement) only.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank Ms. Janet Lambert and Mr. Samuel Hans for cannabinoid and opioid receptor assay results.

Funding

The project was supported by the National Institute of General Medical Sciences [grant number P20GM104932] and in part by NCNPR.

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Figure 1.
Isolated compounds structures (**I–IX**).

Table 1

Bioassay results of active compounds.

Code	Concentration	% Displacement				
		CB1	CB2	Delta	Kappa	Mu
Extract	10 µg/mL	58.3	22.2	14.7	15.4	10.0
Sageone (IV)	10 µM	40.0	50.8	1.2	18.7	31.1
	33 µM	72.5	79.8	14.4	36.1	54.7
Uvaol (VIII)	10 µM	–	13.8	29.9	6.1	45.6
Control		46.1	25.9	31.0	74.9	83.4