THE CHEMICAL AND BIOLOGICAL ROLE OF PIMARANES AND LABDANES FROM MEXICAN *SALVIA* SPECIES

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ABSTRACT

The genus *Salvia* (Lamiaceae) is widely distributed in Mexico with approximately 300 species. Aerial parts, leaves, and branches of sages are prepared as infusions or decoctions in traditional Mexican medicine to treat conditions such as dysentery, diarrhea, gastritis, stomach-ache, headache, sore throat, cough, bronchitis, fever, diabetes, epilepsy, nerves, insomnia, anxiety, among other ailments. The aim of this review was to compile and resume relevant information from literature regarding the chemical constituents of the pimarane and labdane type isolated from Mexican salvias and their biological activities covering the period from 1986 to 2022. A total of 31 compounds of these types were registered with 24 pimaranes and 7 labdanes. It was noticed that scientific evidence of the participation in the medicinal effects of *Salvia* species has not yet been reported for most of these diterpenoids. However, those described as bioactive have shown antibacterial, anticancer, anti-inflammatory, antihypotensive, antimutagenic, and antidiabetic properties. The present review provides information on the chemical and biological properties of pimaranes and labdanes from Mexican *Salvia* species suggesting their potential to become an option of treatment for diabetes and cancer, among other common diseases of Mexican population and of all the world. Nevertheless, further research is encouraged to demonstrate the benefits of these chemical constituents for health.

Key words: Bioactive compound, Labdanes, Pimaranes, Diterpenes, Lamiaceae, *Salvia*

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RESUMEN

El género *Salvia* (Lamiaceae) está ampliamente distribuido en México con aproximadamente 300 especies. Las partes aéreas, hojas y ramas de salvias son preparadas como infusiones o decocciones y se utilizan en la medicina tradicional mexicana para tratar padecimientos como disentería, diarrea, gastritis, dolor de estómago, dolor de cabeza, dolor de garganta, tos, bronquitis, fiebre, diabetes, epilepsia, nervios, insomnio, ansiedad, entre otras enfermedades. El objetivo de esta revisión fue compilar y resumir información de la literatura acerca de los constituyentes químicos de tipo pimarano y labdano aislados de salvias mexicanas cubriendo el periodo de 1986 a 2022, incluyendo aquellas con actividad biológica. Un total de 31 compuestos de este tipo fueron registrados como 24 pimaranos y 7 labdanos. La evidencia de la participación de estos diterpenoides en los efectos medicinales de las especies de *Salvia* aún no ha sido reportada para la mayoría de estos metabolitos. Sin embargo, los que se han descrito como bioactivos demostraron presentar propiedades antibacterianas, anticancerígenas, antiinflamatorias, antihipotensivas, antimutagénicas y antidiabéticas. La presente revisión proporciona información sobre la importancia química y biológica de los pimaranos y labdanos de salvias mexicanas sugiriendo a estos constituyentes como posibles alternativas para el tratamiento de la diabetes y el cáncer, entre otras enfermedades que son comunes en México y en todo el mundo. No obstante, más investigación es requerida para demostrar los beneficios de estos componentes químicos para la salud.
Palabras clave: Compuestos bioactivos, Labdanos, Pimaranos, Diterpenos, Lamiaceae, *Salvia*.

INTRODUCTION

Mexico is a vast source of ethnobotanical knowledge, since it encompasses a great diversity of medicinal plant species (ca. 4,000 spp.; Ramamoorthy & Elliot, 1993). This diversity has motivated various investigations of herbal medicine with the purpose of endorsing its traditional use. However, finding effective and safe molecules with pharmacological activity that can tackle health problems faced by the world population remains a challenge.

The genus *Salvia,* from the mint family (Lamiaceae), has around 1,000 species worldwide (Etminan *et al.,* 2018). These species are divided into ten clades, nine of them currently considered formally as subgenera (Drew *et al.,* 2017). Mexico is one of the most important centres of diversification of the genus, harbouring ca. 306 species of sages, 75.6% endemic to the country (Martínez-Gordillo *et al.,* 2013; 2017). These species mainly belong to the subgenus *Calosphace* (288 spp.), followed by subgenus *Audibertia* (13 spp.) and clade *Heterosphace* (5 spp.). Regarding the diversity of salvias in Mexico, the most species-rich states are Oaxaca (98 species), Jalisco (91), Guerrero (82), Puebla (79), Michoacán (68) (Martínez-Gordillo *et al.*, 2017). The species of this genus are herbs and shrubs that thrive mainly in temperate forests (e.g., conifer and oak forests and cloud forests), but they can also be found in deciduous and sub-deciduous forests and in arid zones (Espejo & Ramamoorthy, 1993).

Ethnobotanical studies in Mexico have reported that in the traditional medicine, the aerial parts of the sages are prepared as an infusion or decoction to treat ailments of the gastrointestinal system such as dysentery, diarrhea, bile, gastritis, and stomach pain (Domínguez-Vázquez & Cas-

tro-Ramírez, 2002; Jenks & Seung-Chul, 2013; De La Cruz-Jiménez *et al.,* 2014; Ortiz-Mendoza *et al.,* 2022). Additionally, the infusions are also used to relieve ear, head, and throat pain. Regarding the central nervous system, the decoctions have been reported to be useful against epilepsy, "nervios" or anxiety and insomnia (Jenks & Seung-Chul, 2013; Casselman *et al.,* 2014), fever and other conditions such as cough and bronchitis (Ortiz-Mendoza *et al.,* 2022).

Phytochemical and pharmacological studies to identify, characterise, and isolate the compounds responsible for the biological activity of various species of *Salvia* have allowed to recognize several molecules that belong to document chemical groups such as monoterpenes, sesquiterpenes, diterpenes, triterpenes and phenolic compounds (Ortiz-Mendoza *et al.,* 2022). Although in this genus the diterpenes with abietane and clerodane-type skeleton structures have been highlighted for being the most abundant and diverse of the identified compounds (Rodríguez-Hahn, *et al.,* 1995, Jenks & Seung-Chul, 2013; Esquivel, 2008; Esquivel et al, 2017; Fragoso-Serrano *et al.,* 2019), other constituents that are less abundant (e.g., pimaranes and labdanes) are also important, because their presence allows characterization of these species as well. Pimaranes are tricycle diterpenes with different stereochemistry features and are biosynthetically related to labdane terpenoids (Isca *et al.,* 2020). The phytochemical and biological evaluation, and the impact on health benefits of these constituents are not yet described. This review focuses on compiling and integrating scientific information of the studies focused on the phytochemical and biological activity of the groups of pimaranes and labdanes in species of *Salvia,* which will allow to recognize their existing contributions and to promote their research, identification, isolation and biological characterization.

The Mexican species of subgenera *Audibertia* and *Calosphace* considered for this review were verified following the checklists of Martínez-Gordillo *et al.,* (2017) and González-Gallegos *et al.,* (2020). The ethnopharmacology and phytochemistry studies were searched in scientific databases of several platforms and editorials such as Google, Google Scholar, PubMed, Elsevier, Science Direct, Springer, Willey, Taylor & Francis, ACS, and RSC, using keywords like *Salvia* and more specific terms such as epithets (e.g., *Salvia adenophora, S. semiatrata, S. urica,* etc.). This review includes literature from 1986 to 2022. All the literature found in databases was classified, systematised, organised, and finally summarised in Table 1. To avoid duplication of information regarding the use of names other than chemical compounds, the digital databases of the National Institute of Standards and Technology (NIST), of the National Center for Biotechnology Information (NCBI) were used, which allowed us to verify synonyms in chemical nomenclature or the trivial names of molecules.

Chemical compounds isolated as pimarane or labdane from *Salvia* species

Terpenes are ubiquitous natural products generated by two well-established biosynthetic pathways: the mevalonate pathway and the more recently discovered 1-deoxyxylulose-5-phosphate pathway (Reveglia *et al.,* 2018). Of the variety of compounds that have been isolated and characterised in species of the genus *Salvia*, most of the diterpenes that have been described belong to species of subgenus *Calosphace* (Ortiz-Mendoza *et al.,* 2022). Among the nature of the different chemical groups identified in Mexican species of *Calosphace*, ca. 450 compounds have been characterised. According to their structures, these compounds are classified into four main subgroups (i.e., mono-, di-, sesqui- and triterpenoids). However, the pimaranes and labdanes are the least abundant of all the diterpenoids (Fig. 1).

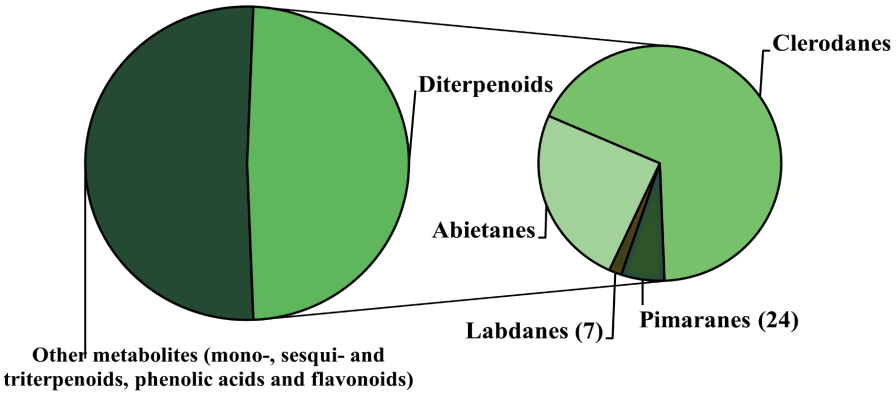


Figure 1. Secondary metabolites in Mexican species of *Salvia* specifying the number of constituents that have been characterised per group.

Only nine species of Mexican sages have been reported to synthesise labdanes (LB) and pimaranes (PM). Eight of these species belong to subgenus *Calosphace* and one to subgenus *Audibertia*, and they are integrated in this review as 24 PM (7%) and 7 LB (2%) as follows: *S. cinnabarina* (4 LB & 3 PM), *S. elegans* (1 LB & 3 PM), *S. dugesii* (1 LB & 2 PM), *S. parryi* (7 PM), *S. microphylla* (5 PM), *S. greggii* (4 PM), *S. leucantha* (1 LB & 1 PM), *S. mellifera* (2 PM), *S. fulgens* (1 PM) (Table 1, Figure 2). It is important to mention that four pimaranes are found in more than one *Salvia* species.

It is worth noting that eight of these species, all belonging to subgenus *Calosphace*, are widely distributed (*S. cinnabarina*, *S. elegans*, *S. leucantha, S. tiliifolia, S. mexicana, S. hispanica, S. coccinea* and *S. microphylla*) and therefore inhabit different microenvironments. Additionally, three of them share both types of diterpenes, suggesting that greater diversity of metabolites can contribute to their ability to adapt to different ecological conditions and increase their dispersal ability.

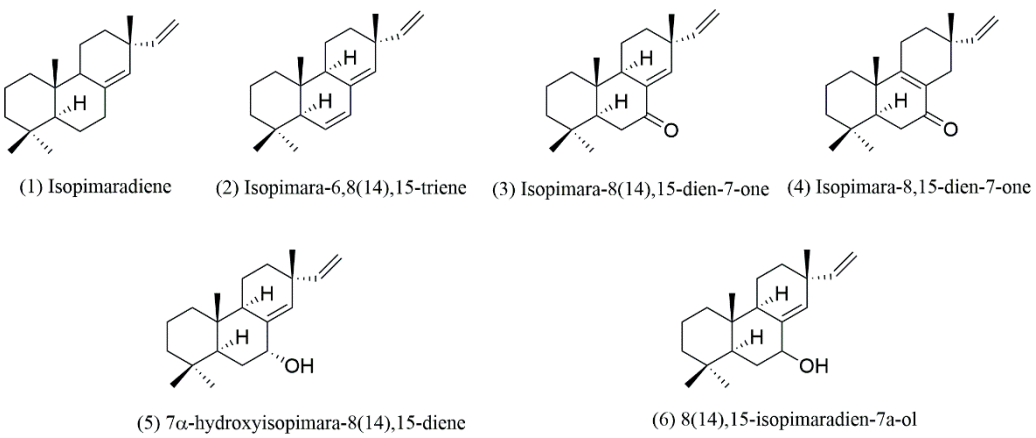
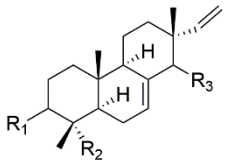
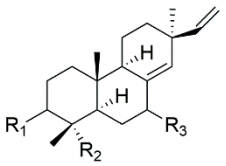


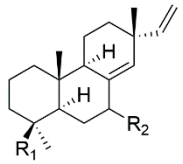
Figure 2. Chemical structure describing the pimaranes and labdane-type skeletons and derivatives found in Mexican species of *Salvia*.



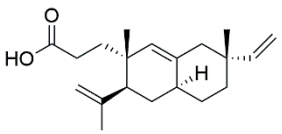
(7) Isopimaric acid: R_1=R_3= H, R_2= COOH
(8) Isopimara-7,15-dien-3-one: R_1= O, R_2= CH_3, R_3= H
(9) Isopimara-7,15-dien-3β-ol: R_1=OH, R_2=CH_3, R_3=H
(10) 3β-hydroxy-isopimaric acid: R_1= OH, R_2=COOH, R_3= H
(11) 14α-hydroxyisopimaric acid: R_1=H, R_2=COOH, R_3=OH
(12) 14α, 18-dihydroxy-7,15-isopimaradiene: R_1= H, R_2= CH_2OH, R_3=OH
(13) 14α-hydroxyisopimara-7,15-diene: R_1=H, R_2= CH_3, R_3= OH



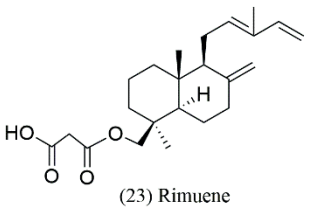
(14) Pimaradiene: R_1= R_3= H, R_2= CH_3
(15) Pimara-7,15-dien-3-one: R_1= O, R_2=CH_3, R_3=H
(16) Pimara-7,15-dien-3-ol: R_1= OH, R_2=CH_3, R_3= H
(17) Pimaradiene-7α,18-diol: R_1= H, R_2=CH_2OH, R_3= OH



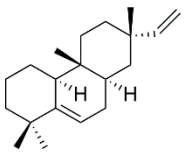
(18) Sandaracopimaradiene: R_1=CH_3, R_2=H
(19) Sandaracopimaric acid: R_1= COOH, R_2= H
(20) 7α-hydroxy-sandaracopimaric acid : R_1= COOH, R_2=OH
(21) 7α-acetoxy-sandaracopimaric acid: R_1=COOH, R_2= OAc



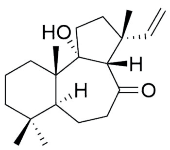
(22) 3,4-secoisopimar-4(18),7,15-trien-3-oic acid



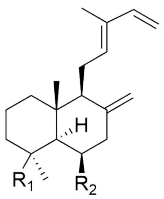
(23) Rimuene



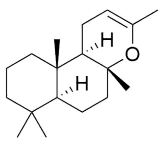
24 (Parryin)



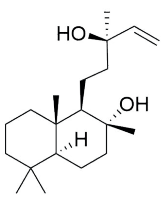
(25) Malonylcommunol



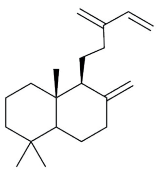
(26) 6β-hydroxy-trans-communic acid: R_1= COOH, R_2= OH
(27) Trans-communic acid: R_1= COOH, R_2= H
(28) Trans-communol: R_1= CH_2OH, R_2= H



(29) Sclareol oxide



(30) Sclareol



(31) Sclarene

Figure 2. Chemical structure describing the pimaranes and labdane-type skeletons and derivatives found in Mexican species of *Salvia* (Continuation).

BIOLOGICAL ACTIVITIES

Pimaranes and labdane-type diterpenes found in Mexican sages have been scarcely explored for biological activity. However, these kinds of metabolites have been identified and explored for their biological activities in other plant species (see Table 1).

The pimarane, isopimarane, and ent-pimarane-type diterpenes are associated to a wide range of biological activities including antimicrobial, antifungal, antiviral, cytotoxicity, antispasmodic and relaxant effects (Reveglia *et al.,* 2018). Similarly, the labdane-type diterpenes possess biological activities such as antibacterial, antifungal, antiprotozoal, enzyme inducing, anti-inflammatory activities and modulation of immune cell functions, in cancer and in cardiovascular disorders (Singh *et al.,* 1999).

Pimaranes are tricycle diterpenes with different stereochemistry features and are biosynthetically related to labdane terpenoids (Isca *et al.,* 2020). The presence of both types has been identified in Mexican species of *Salvia*, being the pimaranes more representative than labdanes, since 24 molecules were found in contrast to 7 cases, respectively.

The diversity of terpenoid compounds produced by plants plays an important role in mediating various plant-herbivore, plant-pollinator, and plant-pathogen interactions, where a single amino acid mutation can switch levopimaradiene/abietadiene synthase to produce isopimaradiene or sandaracopimaradiene (Keeling *et al.,* 2008). Derivatives found in the species of *Salvia* so far lack scientific evidence on their biological activity are included in Table 1.

Diterpenoids, especially of the isopimarane type have been reported in specific taxa such as those from the genus *Kaempferia* (Zingiberaceae), which are plants widely used in traditional medicine worldwide (Elshamy *et al.,* 2019).

Salvia cinnabarina (subgenus *Calosphace*) is one of the most studied species, and pimaranes and labdane-type constituents have been isolated from it. This species is recognized as a medicinal plant in Chiapas and Oaxaca, where it is used for pain relief in rheumatism as an antispasmodic (Ortiz-Mendoza *et al.,* 2022). From this species, the leaf exudate of populations collected in Puebla was investigated, leading to the isolation of a 3,4-seco-isopimarane diterpenoid whose structure and relative stereochemistry was established as 3,4-seco-isopimara-4(18),7,15-trien-3-oic acid as possible responsible of the antispasmodic in *in vitro* assays (Romussi *et al.,* 2001). This compound has also been identified in *S. elegans,* which is closely related to *S. cinnabarina* (Martínez-Gordillo *et al.,* 2013; Fragoso-Martínez *et al.,* 2018). In addition, two new labdane-type diterpenoids—malonylcommunol and 6β-hydroxy-trans-communic acid—were evaluated in yeast α-glucosidases to demonstrate a concentration-dependent inhibition together to two already known labdane diterpenoids, trans-communic acid and trans-communol (Bustos-Brito *et al.,* 2020). Antimutagenic activity was reported for a pimarane diterpene isolated from this species and named 3,4-secoisopimar-4(18),7,15-trien-3-oic acid. It is suggested that the antimutagenic mechanism of action of this compound is through the alteration of cell permeability, which blocks the mutagen adsorption across the bacterial membrane, or by chemical or enzymatic inhibition of the mutagens (Di Sotto *et al.,* 2009). Dose-response hypotensive action was reported for the natural diterpene 3,4-seicosopimar-4(18),7,15-triene-3-oic acid isolated from *S. cinnabarina* by an independent nitric oxide mechanism of action (Alfieri *et al.,* 2007). Whereas NO production was observed when this constituent inhibited rat bladder contractility (Capasso *et al.,* 2004), as well as spasmolytic activity by several neurotransmission systems mechanisms of action (Romussi *et al.,* 2001).

Table 1. Pimaranes and labdane-type diterpenes found in Mexican species of *Salvia* and their biological activities

	Compound identified	*Salvia* species	Biological activity	Reference
		Pimaranes		
1	Isopimaradiene	*S. mellifera*	n.d.	Luis *et al.,* 1993
2	Isopimara-6,8(14),15-triene	*S. parryi*	n.d.	Guajardo *et al.,* 1997
3	Isopimara-8(14),15-dien-7-one	*S. parryi*	n.d.	Guajardo *et al.,* 1997
4	Isopimara-8,15-dien-7-one	*S. parryi*	n.d.	Guajardo *et al.,* 1997
5	7α-hydroxyisopimara-8(14),15-diene	*S. parryi*	n.d.	Guajardo *et al.,* 1997
6	8(14),15-isopimaradien-7α-ol	*S. mellifera*	n.d.	Luis *et al.,* 1993
7	Isopimaric acid	*S. gregii*	Activity against *Staphylococcus aureus* multidrug-resistant (MIC 32-64 μg/mL). Inhibitory effects Epstein-Barr virus (IC_{50} =352 mol ratio/ TPA)	Smith *et al.,* 2005, Tanaka *et al.,* 2008
8	Isopimara-7,15-dien-3-one	*S. cinnabarina*	n.d.	Bustos-Brito *et al.,* 2020
9	Isopimara-7,15-dien-3β-ol	*S. cinnabarina*	n.d.	Busto-Brito *et al.,* 2020
10	3β-hydroxy-isopimaric acid	*S. gregii*	n.d.	Bruno *et al.,* 1986
11	14α-hydroxyisopimaric acid	*S. microphylla*/*S. gregii*	n.d.	Bruno *et al.,* 1986; Luis *et al.,* 1993
12	14α, 18-dihydroxy-7,15-isopimaradiene	*S. gregii*/*S. microphylla*	n.d.	Bruno *et al.,* 1986; Luis *et al.,* 1993
13	14α-hydroxyisopimara-7,15-diene	*S. parryi*	n.d.	Guajardo *et al.,* 1997
14	Pimaradiene	*S. leucantha*	n.d.	Upadhyaya *et al.,* 2013
15	Pimara-7,15-dien-3-one	*S. elegans*	n.d.	Mathew & Thoppil, 2011
16	Pimara-7,15-dien-3-ol	*S. elegans*	n.d.	Mathew & Thoppil, 2011
17	Pimaradiene-7α,18-diol	*S. microphylla*	n.d.	Luis *et al.,* 1993
18	Sandaracopimaradiene	*S. dugesii*/*S. parryi*	Nitric oxide inhibitory activity (IC_{50} =18.6 μM)	Calderón-Oropeza *et al.,* 2021; Guajardo *et al.,* 1997; Tungcharoen *et al.,* 2020

Table 1. Continuation

	Compound identified	*Salvia* species	Biological activity	Reference
19	Sandaracopimaric acid	*S. fulgens*	Relaxation of pulmonary artery via P13K/Akt-eNOS	Gao *et al.,* 2014
20	7α-hydroxy-sandaracopimaric acid	*S. microphylla*	n.d.	Luis *et al.,* 1993
21	7α-acetoxy-sandaracopimaric acid	*S. microphylla*	n.d.	Luis *et al.,* 1993
22	3,4-secoisopimar-4(18),7,15-trien-3-oic acid	*S. cinnabarina*/*S. elegans*	Hypotensive effect (30 mg/kg, i.v.), in male Wistar rats. Spasmolytic activity on acetylcholine-induced contractions in the isolated guinea-pig ileum (IC_{50}= 1.5 μg/mL). Antimutagenic activity, Ames 'test on *S. typhimurium* TA98 and TA100 and on *E. coli* (92.2% against 2-aminoanthracene).	Romussi *et al.,* 2000; Alfieri *et al.,* 2007; Di Sotto *et al.,* 2009
23	Rimuene	*S. dugesii*	n.d.	Calderón-Oropeza *et al.,* 2021
24	Parryin	*S. parryi*	n.d.	Guajardo *et al.,* 1997
		Labdanes		
25	Malonylcommunol	*S. cinnabarina*	α-glucosidase inhibitor in yeast (IC_{50} =20.96 μM)	Bustos-Brito *et al.,* 2020
26	6β-hydroxy-trans-communic acid	*S. cinnabarina*	Anti-inflammatory in edema induced by TPA (21.72% inhibition at 1.0 μmol/ear). The α-glucosidase inhibitor in yeast (IC_{50} =43.74 μM)	Bustos-Brito *et al.,* 2020
27	Trans-communic acid	*S. cinnabarina*	Anti-inflammatory in edema induced by TPA (9.09% inhibition at 1.0 μmol/ear). The α-glucosidase inhibitor in yeast (IC_{50} =45.15 μM)	Bustos-Brito *et al.,* 2020
28	Trans-communol	*S. cinnabarina*	n.d.	Bustos-Brito *et al.,* 2020
29	Sclareol oxide	*S. dugesii*	n.d.	Calderón-Oropeza *et al.,* 2021
30	Sclareol	*S. elegans*	Anti-cancer, anti-inflammatory, anti-hypertensive, and anti-diabetic effects.	Zhou *et al.,* 2020
31	Sclarene	*S. leucantha*	n.d.	Villalta *et al.,* 2021

n.d. no data

Salvia elegans, *S. greggii*, and *S. officinalis* L. prepared as decoction were reported to possess benefits against metabolic diseases because of their α-glucosidase, α-amylase, and pancreatic lipase activities, as well as antioxidant properties. However, these effects were only associated with possible involvement of phenolic acids (Pereira *et al.,* 2018). It should be interesting to investigate the role of possible labdanes and pimaranes found in this species but not yet explored for their biological activity.

Sandaracopimaradiene and rimuene, two pimaranes already reported in *Kaempferia galanga* (Zingiberaceae) describing anti-inflammatory activity (Tungcharoen *et al.,* 2020) and as a useful treatment against polycystic ovary syndrome in *Thuja occidentalis* were identified in *S. dugessi* (Cupressaceae; Küpeli-Akkol *et al.,* 2015).

No specific activities have been described for pimarane-type diterpenes isolated of *S. parryi*. However, some of their constituents in other species have been considered to possess antimicrobial activity (Porto *et al.,* 2009) and vascular relaxation (Hipólito *et al.,* 2009). The sclarene identified in *S. leucantha* has been described among the constituents in the immunostimulant effects of frankincense oil (Mikhaeil *et al.,* 2003), as well as antibacterial activity isolated from *Nicotiana glutinosa* (Solanaceae; Popova *et al.,* 2019). Whereas, the sclareol characterised in *S. elegans* has been reported to possess antimicrobial but also proapoptotic activity (Wang *et al.,* 2015).

The resistance that microorganisms have developed against various drugs has led to the search for new sources of antimicrobials and anti-inflammatories, which also have fewer side effects. Among the compounds explored are diterpenes of the pimarane and labdane type, for example, isopimarane isolated from *Aeollanthus rydingianus* van Jaarsv & A.E.van Wyk (Lamiaceae) has been tested. This compound has proven to be effective on strains of *S. aureus* and *E. faecalis*, *E. faecium*, *E. flavescens,* and *E. hirae* (Isca *et al.,* 2020). Labdanes of *Vitex negundo* L. (Lamiaceae) are effective on *E. coli* and *S. aureus* strains (Sichaem *et al.,* 2021).

In conclusion, few studies have been done by analysing the biological properties of pimarane- and labdane-type diterpenes in salvias. Although they were found to be less abundant metabolites of this genus, they are also scarcely examined to investigate their value for biological activities. Nevertheless, scientific evidence found in literature suggests their involvement in diseases of major importance around the world. Since according to reports of WHO in 2022, cardiovascular diseases, diabetes, and cancer as non-communicable diseases now outnumber infectious diseases as the "top killers globally". Therefore, it is of great relevance to look for health alternatives, where *Salvia* species might be a source of new drugs for effective and safety therapy.

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AUTHOR CONTRIBUTIONS

Aguirre-Hernández, Martínez-Gordillo, and González-Trujano participated in the conceptualization, investigation, supervision, and writhing original draft preparation. Ortiz-Mendoza participated in the compilation, systematization, and elaboration of the tables to resume information of the labdanes and pimaranes in Mexican *Salvia* species. Fragoso-Martínez and Basurto-Peña participated in the investigation of literature information. Ortiz-Mendoza, Dorazco-González, and Bazany-Rodríguez contributed with the chemical information

of labdanes and pimaranes. All authors have read and agreed to the final version of the manuscript. This paper was taken in part from the Ph.D. of the Student Nancy Ortiz-Mendoza.

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