# Bioactive Triterpenoids from *Salvia* Species[⊥]

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*Salvia* species are important medicinal and culinary plants, and they have been the subject of numerous chemical and biological studies. The bioactive triterpenoids of *Salvia* species, reported in the literature to date, are reviewed. About 200 triterpenoids, almost 80 of which are new, isolated, and characterized from about 100 *Salvia* species, are presented herein. In addition to the diverse biological activities of the pure triterpenoids, studies on biological activity of extracts of *Salvia* species are also described.

## Introduction

The Lamiaceae (Labiatae) family comprises 200 genera and 3000 species. One of the largest genera of the family, *Salvia* L., is represented by over 900 species[1] and is widely distributed in various regions of the world, namely, the Mediterranean area, South Africa, Central and South America, and Southeast Asia. The plants are typically 30−150 cm tall, herbaceous or suffruticose, and perennial, rarely biennial, or annual, with attractive flowers in various colors.[2] The name *Salvia* comes from the Latin word "salvare", which means "to heal". *Salvia* species have been used since ancient times for more than sixty different ailments ranging from aches to epilepsy, and mainly to treat colds, bronchitis, tuberculosis, hemorrhage, and menstrual disorders.[3,4] Sage (*Salvia officinalis* L.) is used extensively as a household remedy in Europe for several purposes, including to relieve inflammation of the oral cavity and throat when used as a mouthwash or gargle.[4] German health authorities have also approved its external use for digestive upset and excessive perspiration.[3,4] Sage is also used to preserve foods, especially meat and cheese, due to its antioxidant properties, as well as being employed as a spice for flavoring.[5]

The main secondary metabolite constituents of *Salvia* species are terpenoids and flavonoids. The aerial parts of these plants contain flavonoids, triterpenoids, and monoterpenes, particularly in the flowers and leaves, while diterpenoids are found mostly in the roots. However, a literature survey indicates that some American *Salvia* species also contain diterpenoids in the aerial parts, and in certain *Salvia* species, triterpenoids and flavones are present in the roots.

In this review article, the triterpenoid constituents and the biological activities of both representative extracts and these compounds in all of the *Salvia* plants investigated to date are reported. Although the yields of the triterpenoid constituents are fairly high in most *Salvia* species, so far the plants have been investigated in more detail for their diterpenoids and phenolics and monoterpenes (volatile oils), rather than for their triterpenoid constituents. However, their main triterpenoids, ursolic and oleanolic acids, can be obtained readily during the isolation procedures for other constituents of *Salvia* plant extracts.

## Representative *Salvia* Species

One of the most well-known medicinal *Salvia* plants, *S. officinalis* L. (sage) is native to southern Europe and is also grown in Central Asia and the United States. It is a decorative, evergreen, perennial half shrub. In the British Pharmacopeia, "Herba Salviae" is an official drug. The drug contains an ethereal oil (1−2%), diterpenoids, triterpenoids, and tannins. "Herba Salviae" and the extracts prepared from it are used as antiseptic and antiphlogistic agents in inflammation of the oral cavity and gingivitis, as well as a stomachic and antihydrotic agent.[5] Its utilization in the cosmetic and food industries is also of importance.[5] The plant extract, or essential oil, and/or its constituents show various biological activities,[5,7−13] including antioxidative, anti-inflammatory, immunomodulatory,[8] HIV-1 reverse transcriptase-inhibitory,[9] cholinesterase inhibitory,[10] anti-Alzheimer's disease,[11] and insulin-like activities, as well as inhibition of pancreatic lipase activity.[7] It has been used as a treatment to help women who have excessive perspiration and other symptoms of menopause.[3,4] It was also included among 24 herbs tested that were found to boost insulin activity 2- to 5-fold or more in patients with type II diabetes.[12] Another valuable remedy is *S. sclarea* L. (clary sage), for symptoms associated with menopause, particularly hot flashes, because of its estrogen-stimulating actions.[13] Its tea is also known to alleviate night sweats of those suffering from tuberculosis,[13] and its essential oil has been used in aromatherapy and in the cosmetic industry for many purposes[14] and also is utilized in the production of wines with a muscatel flavor. Another well-known *Salvia* is *S. fruticosa* Miller (syn: *S. triloba* L.) found in Mediterranean countries, for which the common name is "Greek sage" and/or "Turkish sage". Decoctions and infusions of the leaves are used to lower blood pressure and blood sugar levels, and a study was shown that *S. fruticosa* treatment produces hypoglycemia by reducing intestinal absorption of glucose.[15] Due to its antiseptic, antibacterial, antifungal, antioxidant, and anti-inflammatory properties,[16] it is often used for sore throats and mouth ulcers as well as for cardiac complaints, colds, coughs, nervousness, and digestive problems.

Turkish *Salvia species* are well-studied and are represented by 90 species, half of which are endemic to Turkey.[2] The teas prepared from some *Salvia* species, especially from *S. officinalis, S. triloba* L., and *S. dichroantha* Stapf., have been used against colds, sore throats, bronchitis, stomachache, and menstrual disorders[17] in traditional medicine. Almost 50 Turkish *Salvia* species have been investigated for their terpenoid constituents and, where possible, for their biological activities[18] by our group. Some species have been investigated for antibacterial,[19] cardiovascular,[19] and cytotoxic properties.[20] A series of *Salvia* species have been evaluated for their cytotoxic activity, and an endemic species to Turkey, *S. hypargeia* Fisch. et Mey., was found to be the most active one; the cytotoxic activity of its diterpenoid constituents against several human cancer cell lines has been documented.[21] From another *Salvia* species endemic to Turkey, *S. kronenburgii* Rech. f., highly cytotoxic active compounds[22] were isolated.

The other well-known and highly studied *Salvia* species is the traditional Chinese ingredient *S. miltiorrhiza* Bunge (red sage), and its root extract is called "Danshen" (in the People's Republic of China) and "Tanshen" (in Japan). It has a wide range of biological

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activities, including demonstrating effects on heart disease, such as angina pectoris and myocardial infarction,[23,24] and on liver disease.[24,25] The part used is the root, which afforded diterpenoids by extraction with nonpolar solvents and diterpenoids and phenolics when a polar solvent (alcohol or water) is used for extraction, rather than triterpenoids. As a result, tanshinones and some phenolics have been shown to be the active constituents of this drug, which is used for the treatment of heart disease, improving cardio-cerebral circulation, and for its antioxidant activity against peroxidative damage to liver microsomes, hepatocytes, and erythrocytes and antifibrotic effects in the liver.[24]

A Mexican *Salvia species*, Mexican mint *S. divinorum* Epling et Jativa, is renowned because of its hallucinogenic properties, which are attributed to neoclerodane diterpenoids, such as salvinorin A,[26] while extracts of another Mexican *Salvia, S. mexicana* L. var. *minor* Benth., showed antioxidant and anti-inflammatory activities.[27]

In Africa, sages are used against fever and digestive disorders. Three closely related South African *Salvia* species (*S. stenophylla* Burchell ex Benth., *S. repens* Burchell ex Benth., and *S. runcinata* L. f.) were investigated for their antioxidant (DPPH assay), anti-inflammatory (5-lipoxygenase and cyclo-oxygenase assays), anti-malarial (tritiated hypo-xanthine incorporation assay), and antimicrobial (disk diffusion and microdilution assays) properties and toxicity profile (tetrazolium-based assay), which has substantiated the use of these species in traditional medicine in South Africa.[28]

Many compounds isolated from *Salvia* extracts are associated with antiseptic, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, hypoglycemic, cytotoxic, and antitumor activities. Antiviral, hepatotoxic, antihyperlipidemic, cytotoxic, and antitumor activities are particularly attributed to their triterpenoids, rather than other constituents.

## New Triterpenoids from *Salvia* Species

Ursolic and oleanolic acids are very common constituents in the plant kingdom, and both these pentacyclic triterpenes have been found in almost all *Salvia* species studied. Among *Salvia* species, they were found first in *S. officinalis* L.[29] Along with both these parent triterpene acids, many triterpenoids with ursane and/or oleanane skeletons have been isolated from *Salvia* species, as seen in Table S1 (Supporting Information). Lupane-type pentacyclic triterpenes[30−36] are also common, and two *Salvia* species, *S. nubicola* Wall. ex Sweet[37] and *S. roborowski* Maxim.,[38] afforded the nor-lupanes 3α-hydroxy-20-oxo-30-norlupane and 3*β*,11α-dihydroxy-30-norlupan-20-one, respectively. Besides known triterpenoids, new dammarane triterpenoids 20*S*,24*R*-epoxydammar-12,25-diol-3-one from *S. bicolor*,[39] salvilymitone [7*β*,25-dihydroxy-(20*S*,24*R*)-epoxydammaran-3-one], and salvilymitol (20*S*,24*R*-epoxydammarane-3*β*,7α,25-triol) were obtained from *S. hierosolymitana* Boiss. and were determined structurally by X-ray diffraction analysis.[40] A new tri-nordammarane derivative, amblyol, was isolated from a Mexican *Salvia, S. aspera* Mart. & Gall.,[41] a hopane (hopanone) from *S. multicaulis* Vahl,[42] a friedelane (friedelin) from the gummy secretion of *S. glutinosa* L.,[43] a cycloartane 24-methylenecycloartanol from *S. blepharochlaena* Hedge et Hub.-Mor,[44] and two taraxeranes from *S. przewalski* Maxim.[45] The compounds isolated from *S. przewalski* have cyclotaraxerane structures and were named przewanoic acids A (2α,3α-dihydroxy-12,13-cyclotaraxerane-14-en-28-oic acid) and B (2α,3α-dihydroxy-12,13-cyclotaraxerane-14,4(23)-dien-28-oic acid).[45] A few lactonized oleanane triterpenes have been isolated, such as 3*β*-acetoxyoleanan-13*β*,28-lactone from *S. lanigera*[46] and 3*β*-acetoxyoleanan-12*β*,28-lactone from *S. mexicana* L.[47] One of the most interesting secondary metabolites, named reglin, is an oleanolic acid esterified with a lactonized abietane diterpene quinone and was obtained from *S. regla* Cav.[48]

Most of the *Salvia* pentacyclic triterpenoids bear a hydroxyl group at C-3, and other common locations for hydroxyl groups are C-1, C-2, or C-11, as shown in Figure S1 (Supporting Information) and Table S1 (Supporting Information). However, the hydroxyl groups, particularly at C-3, can be converted to ketone groups easily and have been found in *S. lavanduloides*,[49] *S. hierosolymitana* Boiss.,[40] *S. mellifera* Greene,[50] *S. pomifera* L.,[51] *S. pratensis* L.,[34] *S. tricupis*,[52] *S. wagneriana* Polak.,[36] *S. deserta* Schang,[30] *S. haenkei* Benth.,[53] and *S. multicaulis* Vahl.[42] C-1 keto containing compounds have been found in *S. caespitosa* Mont. et Auch. ex Benth.,[54] *S. carducea* Benth.,[55] and *S. coccinea* Linn.[56] From *Salvia* species, many di- or trihydroxylated triterpenes were also isolated. However, highly hydroxylated triterpenes are known so far only from a limited number of *Salvia* species, among them, *S. argentea* L.[57] and *S. kronenburgii* Rech. f.,[22,58] which afforded highly hydroxylated ursane and oleanane triterpenoids.

A series of novel triterpenoids having a different skeleton have been isolated from *S. bucharica* M. Pop., named isoperadione,[59] peradione, perovskone, salvadiones A and B,[60] salvadiol,[61] and salvatrione.[62] In the structure elucidation of salvadiol, single-crystal X-ray analysis was also carried out.[61] These were first proposed as icetexane-based triterpenes, but salvatrione, with a similar skeleton, is considered biogenetically to be a pseudo-triterpenoid.[62]

So far, only two *Salvia* species have afforded glycosylated triterpenes, namely, *S. tricupis*[52] and *S. trijuga* Diels.[63] Eighteen pentacyclic triterpenes and triterpene glycosides and three steroids were isolated from *S. tricupis*, one being the new 11α-hydroxyurs-12-en-3-one,[52] and a new oleanane-type glycoside, trijugaoside, from the whole of plant *S. trijuga*[63] [Figure S1 (Supporting Information) and Table S1 (Supporting Information)].

Triterpenes such as ursolic acid or/and oleanolic acid are mostly isolated in high yield from *Salvia* species, as high as 0.5−1%, such as in *S. divaricata* Mont. et Auch. ex Benth.[64]

Among the ursane and oleanane triterpenes, double bonds are generally found between C-12 and C-13 and sometimes between C-18 and C-19, as in *S. pomifera*,[51] *S. deserta*,[30] and *S. broussonetii* Benth.,[65] or between C-5 and C-6, as observed in epialnusenol, isolated from *S. glutinosa* L.[66] Double bonds between C-13 and C-18 occur in *S. horminum* L. (syn.: *S. viridis* L.)[67] and *S. pinnata* L.[68] The formation of an epoxy group between C-13 and C-18 was observed in 3*β*-hydroxy-13(28)-epoxyurs-11-ene and 3-keto-13(28)-epoxyurs-11-ene, isolated from *S. mellifera*.[50,69]

## Biological Activities of Triterpenoids Found in *Salvia* Species

Among the isolated triterpenoids from *Salvia* species, each representative pentacyclic triterpene acid, oleanolic acid (OA), ursolic acid (UA), and betulinic acid (BA), corresponding to the oleanane, ursane, and lupane skeletons, respectively, exhibits a variety of biological activities.[70−76] OA and UA exhibit antimicrobial, anti-inflammatory, antihyperlipidemic,[72] antiulcer, hepatoprotective,[73] hypoglycemic, antifertility, anticarciogenic, antiangiogenic,[76] and protection against cyclophosphamide-induced toxicity activities, while BA exhibits antitumor activity against human melanoma[77] and against mouse skin two-stage carcinogenesis,[78] anti-inflammatory activity in mouse paw and ear edema assays,[79] HIV inhibitory activity,[80] leishmanicidal activity against amastigotes of *Leishmania amazonensis*,[81] spasmogenic activity on the isolated rat fundus,[82] and antimalarial activity against *Plasmodium falciparum*.[83]

The anti-inflammatory properties of OA and UA have been studied by different pathways through the inhibition of different enzymes. Their inhibition on human leucocyte elastase[74] and 12-*O*-tetradecanoylphorbol 13-acetate was also shown.[75] OA and UA were found to be aromatase inhibitors. Aromatase is a key enzyme in steroid metabolism that mediates the conversion of androgens to estrogens, causing prostatic disorders. Inhibition of the aromatase system leads to decreased estrogen levels, so these triterpenoids, or their derivatives, may play a role in the treatment of benign

prostatic hyperplasia. In fact, compared to the synthetic aromatase inhibitor 4-hydroxyandrost-4-ene-3,17-dione, OA and UA were found to be less active, but they showed still moderate activity.[84] OA and UA and some ursane derivatives were also found to play a role as DNA polymerase-$\beta$ inhibitor, as well as BA.[85] Both OA and UA exhibited inhibitory activity toward rat DNA polymerase $\beta$, with $IC_{50}$ values of 7.5 and 8.5 $\mu$M, respectively, in the presence of bovine serum albumin (BSA). The corresponding values were 3.7 and 4.8 $\mu$M in the absence of BSA ($ID_{50} = 0.4$ $\mu$mol).

OA and UA have protective effects against lipid peroxidation, and it was proposed that[72] their antioxidant potency is influenced by the methyl substituents at positions 4, 19, and 20.

The antiangiogenic activity of UA and OA was also examined in a dose-dependent manner by using a chick embryo chorioallantoic membrane (CAM) assay, and UA was found to be a more potent angiogenic inhibitor than OA.[76]

**Antibacterial and Antifungal Activities.** Antimicrobial activity studies were carried out on some di- and triterpenoid constituents of Turkish *Salvia* species[6,19] against standard bacteria and a yeast, *Candida albicans*. However, almost no activity was observed for the triterpenoids evaluated. Among the triterpenoids tested,[6,19] 3-acetylvergatic acid, isolated from *S. caespitosa*,[54] showed weak activity, while α-amyrin, 24-methylenecycloartanol, and erythrodiol 3-acetate isolated from *S. bleapharochelana* were inactive.[44] Betulin and an essential oil (Vicks VapoRub) compositon is patented as a formulation to treat fungal infections.[86]

**Antiviral Activity.** UA and its potassium salt had similar anti-HIV activities, while the potassium salt of OA was more potent. The 3-oxo derivatives of UA, OA, and BA were toxic.[87] Among the 3-*O*-acylursolic acid derivatives studied, 3-*O*-diglycorylursolic acid[87] demonstrated relatively potent anti-HIV activity. However, it was found to be less potent than the corresponding betulinic acid derivative. Another ester derivative at C-3 of betulinic acid, 3-*O*-(3′,3′-dimethylsuccinyl)betulinic acid (DSB, PA-457), has been licensed by Panacos Pharmaceuticals for preclinical development, which showed a novel mechanism of action from the current AIDS drugs.[88]

**Antioxidant Activity.** UA was developed as an antiaging agent in cosmeceuticals.[89a] Maslinic acid is used in creams for skin beautifying and even showed excellent skin-lightening effects.[89b] In a recent study, the antioxidant potential of a water infusion of common sage, *S. officinalis*, was evaluated in vivo in mice and rats by quantification of plasma transaminase activities and liver glutathione-*S*-transferase and glutathione reductase enzyme activities. The results demonstrated that the *S. officinalis* infusions improve liver antioxidant status.[90] In China, *Salvia plebeia* R. Br. was identified to be an antioxidant plant among 700 species screened.[91] Antioxidant activity has been shown in several *Salvia* extracts, including *S. officinalis*, *S. sclarea*, and *S. fruticosa* and some other species.[3,4,92,93]

**Anti-inflammatory Activity.** A survey on the anti-inflammatory potential of a selected number of triterpenoids for which the observed anti-inflammatory actions have been reflected by data from in vitro mechanistic studies included effects on mediator signaling (histamine release, hydrolytic enzymes, cytokines, reactive oxygen species, lipid peroxidation, and lipid-derived mediators).[94] Anti-inflammatory effects in animal models were reported for a number of pentacyclic triterpenes, and betulin, BA, UA, glycyrrhetinic acid, and derivatives from various sources were found to inhibit experimental edema in animals by different studies.[94] A series of pentacyclic triterpenes inhibited immunohemolysis promoted by the classical complement pathway. Activities with $IC_{50}$ values in the range of 10 to 50 $\mu$M were reported for UA, BA, and crataegolic acid, whereas OA and glycyrrhetinic acid were less potent, and $\beta$-amyrin and friedelin were inactive.[95] Common pentacyclic triterpenoids in *Salvia* species, as well as in some other plants, were found to have low acute toxicity, suggesting that defined substituents on the lipophilic pentacyclic ring system can increase selectivity. In a comparison of the anti-inflammatory activity of several triterpenoids (α-amyrin, $\beta$-amyrin, UA, OA, BA, glycyrrhetinic acid, erythrodiol, hederagenin, uvaol, lupeol, and betulin) in three models utilized, namely, TPA-, carrageenan-, and EPP-induced edemas, all of the compounds tested have anti-inflammatory activity, depending on the assay method. In the TPA method, the fact that all of the triterpenoids were active is noteworthy. In contrast, in the EPP assay, most of these compounds (OA, $\beta$-amyrin, hederagenin, glycyrrhetinic acid, and lupeol) showed reduced or no activity.[96]

In a recent study, *S. officinalis* leaves, obtained from four plant populations of different origin from Slovenia, were investigated for their topical anti-inflammatory properties by Baricevic et al.[97] UA as the main component of the chloroform extract appeared to be involved in this anti-inflammatory activity. The anti-inflammatory effect of UA ($ID_{50} = 0.14$ $\mu$mol) was 2-fold more potent than that of indomethacin ($ID_{50} = 0.26$ $\mu$mol), which was used as of reference nonsteroidal anti-inflammatory drug (NSAID). Therefore, the content of UA in sage and sage-based remedies for the topical treatment of inflammatory diseases was proposed as a parameter for quality control purposes.

The acetone and methanol extracts of the aerial parts of *S. mexicana* L. var. *minor* Benth. showed anti-inflammatory and antioxidant properties in the TPA and DPPH models, respectively. However, none of the isolated compounds ($\beta$-sitosterol, betulinol, BA, UA, and arbutin) showed antioxidant properties in the DPPH model.[27]

When the triterpenes BA, UA, 2α-hydroxyursolic acid, and 2α,3α-dihydroxyurs-12-en-28-oic acid were tested for their effects on the production of nitric oxide from cultured murine macrophages, except for 2α,3α-dihydroxyurs-12-en-28-oic acid, all of the test compounds, especially UA and 2α-hydroxyursolic acid, exhibited strong in vitro anti-inflammatory activity by inhibiting nitric oxide production from LPS-stimulated murine macrophage RAW264.7 cells.[98]

**Antiallergic Activity.** BA, UA, 2α-hydroxyursolic acid, and 2α,3α-dihydroxyurs-12-en-28-oic acid were investigated for inhibition of the release of $\beta$-hexosaminidase from cultured RBL-2H3 cells in a dose-dependent manner. Among them, 2α,3α-dihydroxyurs-12-en-28-oic acid showed the highest antiallergic activity by exhibiting significant inhibitory effects.[98]

**Antiplasmodial Activity.** Lupeol showed antiplasmodial activity, while $\beta$-amyrin and germanicol did not show any activity. BA was found to be moderately active against asexual erythrocytic stages of the human malaria parasite, *Plasmodium falciparum*.[83] A moderate antiplasmodial effect of the extract of *S. hydrangea* Benth. flowers was found to be associated with the presence of large amounts of pentacyclic triterpenes, mainly OA. The authors reported that antiplasmodial activity of OA is apparently due to its incorporation into the erythrocyte membrane, which affects adversely the growth of *Plasmodium falciparum* parasites.[99] Bioactivity-guided fractionation of the acetone extract of the roots of *S. clicica* Boiss. et Kotschy led to the isolation of two new diterpenes, besides several known di- and triterpenes. The triterpenes UA and OA were found to be strongly active against amastigotes and moderately active against the promastigote stages of two *Leishmania* species.[100]

**Cytotoxic Activity.** Due to its antineoplastic activity and a lack of toxicity, betulinic acid is considered as a promising compound against human melanoma.[77,101]

Turkish *Salvia* extracts have been screened for their cytotoxic activity in A2780 human ovarian cancer cells,[20,22] and some were found to be weakly active. Among these triterpenoids, salvinemorol, from *S. nemorosa*,[65] was the most active one ($IC_{50} = 8.6$ $\mu$g/mL) and salvistamineol,[20] the ursane isomer of salvinemorol, was found to be less potent. A series of highly hydroxylated triterpenes were

isolated from a *Salvia* species endemic to Turkey, *S. kronenburgii*,[22,58] and the most abundant compound of the extract, 1$\beta$,2$\alpha$,3$\beta$,11$\alpha$-tetrahydroxyurs-12-ene, was found to be highly cytotoxic to renal, non small cell lung and breast cancer cell lines, besides showing moderate activities against a series of cancer cell lines in the NCI 60 cell lines.[22] The dichloromethane and methanol extracts of *S. staminea* Montbret et Aucher ex Bentham were also investigated for their DNA-damaging properties,[20] but except for the diterpene constituent taxodione, no meaningful results were obtained.

**Cardiovascular Activities.** The root extract of *S. miltiorrhiza* has long been used as a therapeutic agent for heart diseases, such as angina pectoris and myocardial infarction.[24,26] The extract is considered to improve systemic circulation, in particular, coronary circulation, and this effect has been attributed to quinoid abietanes or some phenolics, rather than the triterpenoid constituents. However, some studies are still ongoing concerning the mechanism responsible for the effectiveness of "Tanshen" ("Danshen") on the ischemic heart.[103]

A few Turkish *Salvia* extracts, *S. syriaca* L.,[104] *S. amplexicaulis* Lam.,[105] *S. eriophora* Boiss. and Kotschy,[106] and some isolated constituents, including several triterpenoids, steroids, and diterpenoids, were investigated to establish their cardiovascular activities.[19] The crude extracts of *S. syriaca* L. and *S. amplexicaulis* Lam. and the common diterpenoid ferruginol showed vasodepressor effects rather than the triterpenoids tested and reduced arterial blood pressure of Wistar albino rats.

**Hypoglycemic Activities.** Several *Salvia* extracts have been used as hypoglycemic agents in traditional medicine, and some of them, including *S. officinalis*,[12] *S. aegyptiaca* L.,[107] *S. lavandulifolia* Vahl.,[108] *S. hispanica* L., and *S. fruticosa*,[15] were investigated for this effect, but no pure compounds responsible for the activity have been isolated.

**Other Activities.** *Salvia africana-lutea* L. was investigated for analgesic and antipyretic activity and significantly reduced fever induced by lipopolysaccharide.[109] On the basis of a recent study, from the testing of the antimutagenic properties of the terpenoid fractions of *S. officinalis* in mammalian systems in vivo, it was shown that the percent of aberrations decreased with increasing concentrations of sage. Therefore, only nontoxic concentrations of sage without mutagenic effects were recommended for use as inhibitors of mutagenesis or carcinogenesis.[110] The crude acetone extract of the aerial parts of *S. moorcraftiana* Wall.[111] was screened for various biological activities, including a *Lemna* bioassay and antifungal, antibacterial, leishmanicidial, and insecticidal activities and brine shrimp cytotoxicity. It was found to show strong phytotoxic activity against *Lemna aequinoctials* and moderate antifungal activity against several animal and plant pathogens.[111]

## Triterpenoids from Tissue Culture Studies

Some tissue and cell culture studies were carried out to isolate *Salvia* terpenoids. Most of these studies were done with *S. miltiorrhiza*[112] and *S. officinalis*[113] to afford abietane diterpenes, in general. During these studies, triterpenoids were also isolated. Oleanolic and ursolic acids were obtained from *S. amplexicaulis*,[114] as well as in vitro cultured shoots of *Salvia nemorosa*,[115] while maslinic acid, 3-*epi*-maslinic acid, tormentic acid, and 2$\alpha$,3$\alpha$,23-trihydroxyolean-12-en-28-oic acid were isolated from tissue cultures of *S. broussonetii* Benth.[67]

## Conclusions

Altogether 103 *Salvia* species, growing in different countries throughout the world, afforded about 450 triterpenoids, consisting of 200 distinct structures (Table S1, Supporting Information), 78 of which were characterized as new compounds (Figure S1, Supporting Information). Their structures were elucidated through spectroscopic data interpretation. Besides a large number of ursane and oleanane triterpenes, particularly the presence of oleanolic/ursolic acids in high concentrations, the diversity of the chemical structures and interesting biological activities of these triterpenoids are evident.

The mechanims should be explored to determine the biological importance of selected triterpenoids from *Salvia* species. Therefore, considering their relative yields in the extracts, more extensive structure−activity relationship (SAR) studies should be focused on the investigation of these compounds in the future.

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**Supporting Information Available:** The isolated triterpenoids from *Salvia* species (Table S1, Supporting Information) and the formulas of new triterpenoids from *Salvia* species (Figure S1, Supporting Information) are available free of charge via the Internet at http://pubs.acs.org.

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