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CONSTITUENTS AND BIOLOGICAL ACTIVITIES SOME OF THE SELECTED *SALVIA* SPECIES: A REVIEW

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ABSTRACT

Salvia is a fascinating plant genus and one of the wide spread members of the Labiate family, which comprises about 900 herbs and shrubs, growing in the temperate and warmer zones of the world. Some of these species feature prominently in the pharmacopoeias of many countries throughout the world. The range of traditional applications of the herbs in domestic medicine seems to be endless: they have been used as a medication against perspiration and fever, as a carminative; a spasmolytic; an antiseptic/ bactericide; an astringent; a gargle or mouthwash against inflammation of the mouth, tongue and throat; a wound-healing agent; skin and hair cure; against rheumatism and sexual debility; in treating mental and nervous conditions; and as an insecticide. We will discuss about the following *Salvia* species: *Salvia sharifi* Rech. f. and Esfan.; *Salvia hypoleuca* Benth.; *Salvia leriefolia* Benth.; *Salvia mirzayani* Rech f. and Esfan.; *Salvia reuterana* Boiss. and *Salvia limbata* C.A. Mey.

KEYWORDS: Salvia, Secondary metabolites, Essential Oils, Diterpenes, Sesterterpenes, biological activities.

INTRODUCTION

Salvia is the largest genus of plants in the mint family, Lamiaceae, with nearly 1000 species of shrubs, herbaceous perennials, and annuals.[1][16][17] Within the Lamiaceae, *Salvia* is part of the tribe Mentheae within the subfamily Nepetoideae. One of several genera commonly referred to as sage, it includes the widely produced herb used in cooking, *Salvia officinalis* (common sage, or just "sage"). The genus is distributed throughout the Old World and the Americas, with three distinct regions of diversity: Central and South America (approx. 500 species); Central Asia and Mediterranean (250 species); Eastern Asia (90 species).[17] The name *Salvia* ("salviya") derives from the Latin salvere ("to feel well and healthy, health, heal"), the verb related to salus (health, well-being, prosperity or salvation), referring to the herb's healing properties.

Apart from their common constituents (terpenoids and flavonoids) and their interesting biological activities, the genus *Salvia* is unusual as it is the only genus in the Labiatae that contains sesterterpenes (C25). Since these rare and interesting compounds were, for the first time, isolated and identified from Persian *Salvia* species by the senior author, their NMR spectroscopic data are briefly reviewed.[13]

Persian traditional medicine have derived benefits of infusion and decoction of aerial parts of such genus as tonic, carminative, digestive, antispasmodic,and anti-inflammatory agents for treatment of diseases stemming from reactive oxygen species (ROS).[8]

Salvia sharifi Rech. f. and Esfan.

Two flavones, ladanein and 6-hydroxy-5,7,4′-trimethoxyflavone and one labdane-type diterpene (fig.1), ent-13-epi-manoyloxide (1) were isolated from an ethyl acetate-methanol extract of the aerial parts of *Salvia sharifii*. The compounds were purified using several chromatographic methods. Structural elucidation of the compounds was performed using their ^{1}H and ^{13}C-NMR data, EI mass and UV spectral data. The compounds have been subjected to antimicrobial, antioxidant and cytotoxic activity. The diterpene showed higher cytotoxic activity than the flavones while the later compounds were better antioxidants compared with the isolated diterpene.[4]

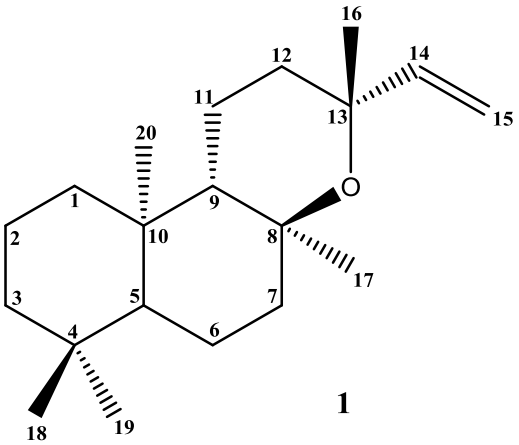
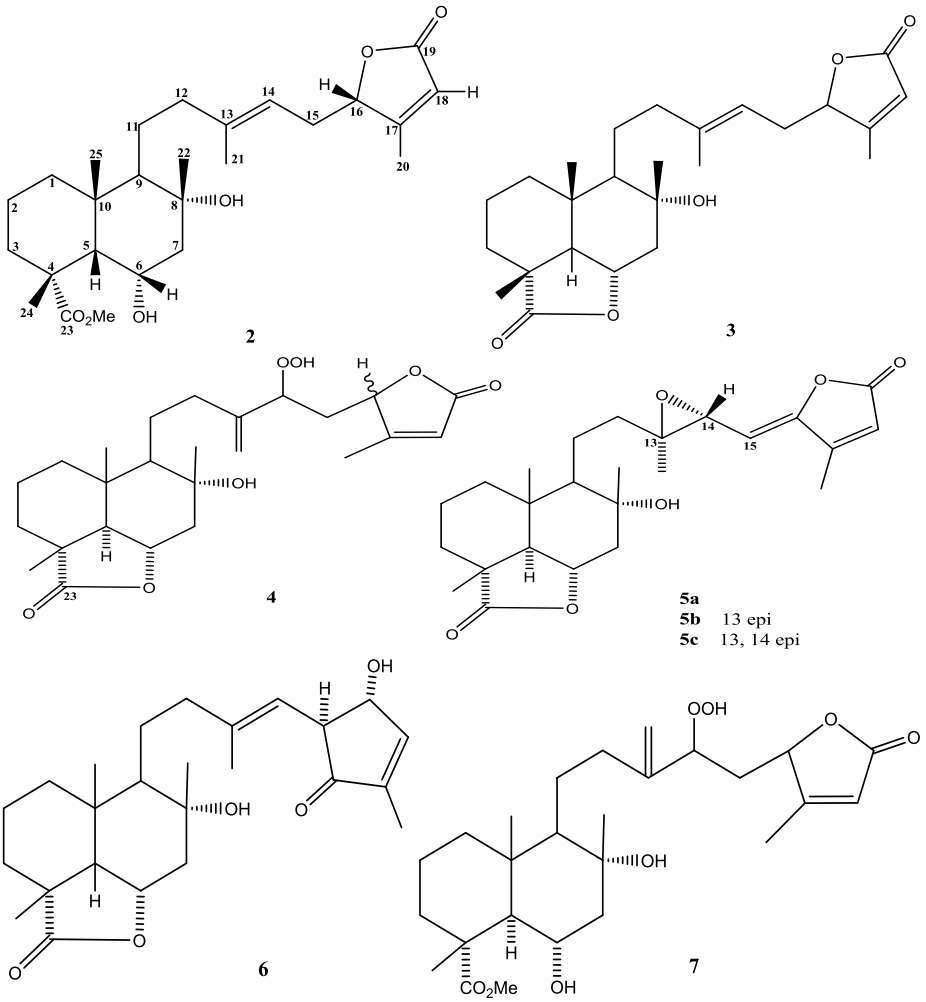


Figure 1: Chemical structures of *Salvia Sharifii* Rech. f. and Esfan (1).

***Salvia hypoleuca* Benth.**

Rustaiyan et all, in 1982 and 1988 studied the polar fractions of Salvia hypoleuca afforded two crystalline compounds with molecular formula (fig.2) $C_{26}H_{40}O_6$ namely salvileucolide methyl ester (2) and $C_{25}H_{36}O_5$ namely salvileucolide-6,23-lactone (3) and several sesterterpenes, the salvileucolide methyl ester derivatives 7, 8a, 8b and 9 as well as the isomeric epoxides 5a-5c and the hydroperoxide 4 derived from salvileucolide-6,23-lactone and sesterterpene with a further new carbon skeleton, the keton 6 that named salvileucolidone.[12] [13]



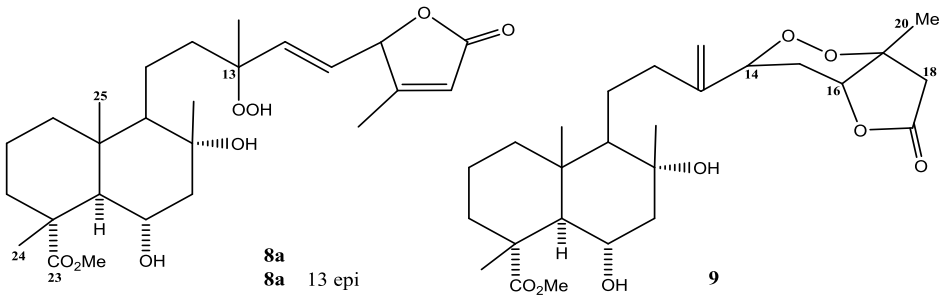


Figure 2: Chemical structures of *Salvia hypoleuca* Benth. (2-9).

The ^{1}H-NMR spectroscopic data of the two lactones were in part very similar. The ddd at δ3.61 was shifted to δ4.29 in the dilactone, indicating that the second compound was most likely to be the lactone of a hydroxy acid, which corresponded to the ester. The nature of the second lactone ring, present in both compounds, was evident from the downfield signals at δ4.90 (dd) and 5.89 (dq). The remining signals in the spectra of both compounds were similar to those of labdanes with a carboxyl group at C-4.[13]

Results of Estakhr's study indicated that *S. hypoleuca* affected sperm parameters and spermatogenesis in rat. treatment of rats with the extract of *S. hypoleuca* caused a significant increase in sperm count and motility, and decrease in sperm abnormalities compared with control group and increased testis weight of rats. CREM gene expression and protein level in rat testis treated with *S. hypoleuca* were higher compared with the control group. CREM is essential for spermatogenesis, and males lacking functional CREM gene are sterile due to their round spermatid maturation arrest 4, 5, 19. The CREM gene encodes the transcription activator CREM, which is highly expressed in male germ cells and regulates the expression of many important post-meiotic genes. In addition, infertile men have substantial reduction or complete lack of both CREM protein and CREM mRNA. *Salvia hypoleuca* caused little change in body weight and no animal died during the study; no animal exhibited noticeable adverse effect from the administration of the extract. Results showed *S. hypoleuca* may increase male fertility by elevating sperm quality due to CREM expression at mRNA and protein levels.[3]

***Salvia leriiefolia* Benth.**

Salvia leriifolia Benth. (Nuruozak and Jobleh) is a perennial herbaceous plant. The stem oil of the plant consisted mainly both monoterpenes and sesquiterpenes, while in leaf and flower oils monoterpenes predominated over sesquiterpenes. The different properties of this plant such as the attenuation of morphine dependence, hypoglycemic, antinociceptive and antiinflammatory, antioxidant, anti-ischemia, anticonvulsant, antiulcer effects, antibacterial activities and antimutagenic effects were evaluated. These effects introduce this plant for more toxicological and clinical trials evaluations as a herbal medicine.[7] Proximate compositions and chemical properties of the seeds and the oil extracted from seed of *Salvia leriifolia* Benth were investigated. Proximate analysis showed that the seeds of *S. leriifolia* contained 28.5% oil (seed dry weight), 24.7% protein, 17.1% crude fiber, 7.8 ash and 13.6% carbohydrate. The levels of minerals Ca, P, K, Mg, Na, Fe, Zn, Mn and Cu were 4000, 3009, 2700, 2300, 90, 60, 43, 19.4 and 10 mg per kg seed, respectively. The iodine value of extracted oil evaluated here (122 gIz per 100 g of oil) reflects high level of unsaturation of the extracted oil. Also saponification value, acid value, peroxide value, and refractive index were found to be 178, 1.05, 0.84 and 1.45, respectively. The Oil extracted from *S. leriifolia* had almost equal amounts of oleic and linoleic acids (41% for oleic acid and 42.3% for linoleic acid). Fatty acid profile indicated that the level of α-linolenic acid (1.7%) is lower than those of many other studied species of Salvia. The results showed that *S. leriifolia* seed was rich in minerals, oil, protein, fibers and essential fatty acids (omega-6 group) which make it a valuable oil seed.[19]

In the Hosseinpoor Mohsen Abadi's study, She has reported the total phenolic content, total flavonoid content, antioxidant and antimicrobial activity of aerial parts of *S. leriifolia* extracts and fractions. Methanolic, n-hexane, chloroform, and ethyl acetate extracts were screened to analysis their antioxidant activities by four complementary test systems, namely DPPH free radical scavenging activity (RSA), total phenolic content (TPC), total flavonoid content (TFC), and ferrous ion cheating (FIC). In most cases the leaf extracts and ethyl acetate fraction had more activity. The methanolic extracts of leaf and flower showed considerable antimicrobial activity using disc diffusion method against *Escherichia coli*, *Streptococcus pneumonia*, *Acinetobacter*, *Serratia*, *Pseudomonas aeruginosa*. Moreover, the ethyl acetate extract was shown to possess a remarkable radical scavenging activity even more than vitamin E as a positive control. So the presence of the highest phenolic and flavonoid compounds in leaves and flowers cause the maximum antioxidant activity. The data indicate that *S. leriifolia* methanolic extracts shows a wide range of antimicrobial activity against referenced strains, especially in Gram-negative bacteria.[6]

***Salvia mirzayani* Rech f. and Esfan.**

Essential oil of *Salvia mirzayanii* was obtained by hydrodistillation and supercritical (carbon dioxide)

extraction methods. The oil was analysed by capillary gas chromatography using flame ionization and mass spectrometric detections. The compounds were identified according to their retention indices and mass spectra (EI, 70 eV). The effects of different parameters such as pressure, temperature, modifier volume and extraction times (dynamic and static) on the supercritical fluid extraction (SFE) of *S. mirzayanii* oil were investigated. The results showed that, under a pressure of 35.5 MPa, temperature of 35 °C, 6% methanol, dynamic extraction time of 50 min and static extraction time of 30 min, extraction was more selective for the linalyl acetate. Thirty four compounds were identified in the hydrodistilled oil. The major components of *S. mirzayanii* were linalyl acetate (7.6%), 1,8-cineole (8.0%), linalool (9.0%) and 8-acetoxy linalool (11.0%). However, by using supercritical carbon dioxide in optimum conditions, only three components contain more than 63% of the oil. The yield of the obtained oil based on hydrodistillation was 2.2% (v/w). Extraction yield based on the SFE varied in the range of 1.5–9.6% (w/w) under different conditions. The results revealed that, in Iranian *S. mirzayanii* oil, linalyl acetate is a major component.[18]

***Salvia reuterana* Boiss.**

The phytochemical investigation of n-hexane extract from *S. reuterana* afforded five new labdane diterpenoids.

The new labdane diterpene, 4α-hydroxy-15-chlorosclareol ($C_{20}H_{37}O_3Cl$) (10), 14α-hydroxy-15-acetoxysclareol ($C_{22}H_{40}O_5$) (11), 6β-hydroxy-14α-epoxysclareol ($C_{20}H_{36}O_4$) (12), 6β, 14α-dihydroxy-15-acetoxysclareol ($C_{22}H_{40}O_6$) (13), and 14α, 15- dihydroxy sclareol ($C_{20}H_{33}O_{40}$) (14), were isolated from the aerial part of the *Salvia reuterana* Boiss. Their structures (fig.3) were established mainly by 1D and 2D NMR spectroscopic techniques, including ^1H-^1H COSY, HSQC and HMBC methods and HR-ESI-TOFMS spectral data. All compounds were tested for their inhibitory activity toward HeLa and MCF-7 cell lines. The results showed that *S. reuterana* is a rich source of labdane diterpenoids. These compounds are rather rare in *Salvia* species, although they are frequently found in other genera of the Lamiaceae. *S. reuterana* is a new source of these diterpenoids.[9] [10]

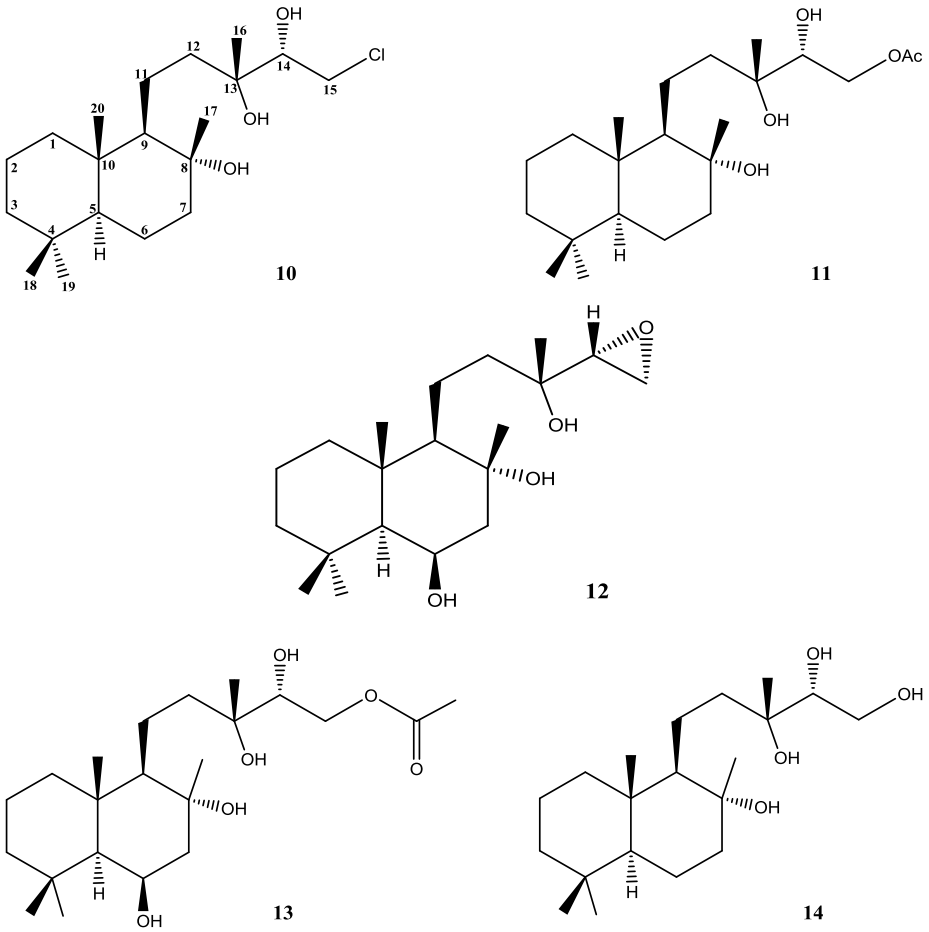


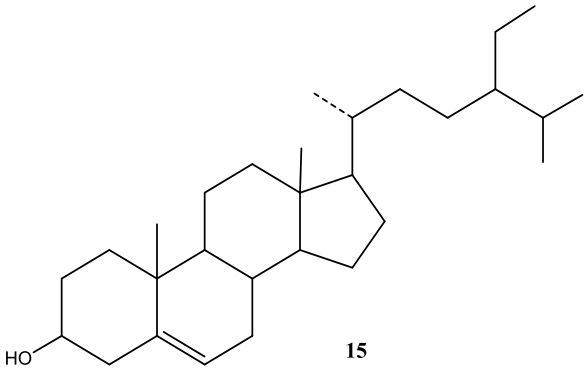
Figure 3 Chemical structures of *Salvia reuterana* Boiss. (10-14).

The essential oils obtained by hydrodistillation of the leaves, stems and flowers of *Salvia reuterana* were analysed by GC and GC/MS. Germacrene D and β-caryophyllene were the major constituents in all the three oils: (28.5, 27.7 and 32.5%) and (15.5, 11.4 and 16.6%), respectively. Bicyclogermacrene (10.2 and 13.2%) was

also prodominated in the stem and flower oils. The composition of the oils was mostly quantitativel rather than qualitatively different. All the oils consisted mainly of sesquiterpenes and a small percentage of non-terpenoid compounds. In all the three oils, monoterpenes were in a concentration less than 0.5%.[2]

***Salvia limbata* C.A. Mey.**

The isolated compounds (fig.4) from the ethyl acetate and MeOH extracts of *S. limbata* were identified as β-sitosterol (15), stigmasterol (16), daucosterol (17), stigmasterol 3-O-glucoside (18) and tryptophan (19) by comparison of their NMR spectral data with those reported in the literature Conclusions: *S. limbata* can accumulate the tryptophan as a major free amino acid together with sterols and their glucosides. Therefore, consumption of *S. limbata* (as an herbal tea or other preparations), which contains the essential amino acid tryptophan, might be useful for dietary deficiency of tryptophan.[15]



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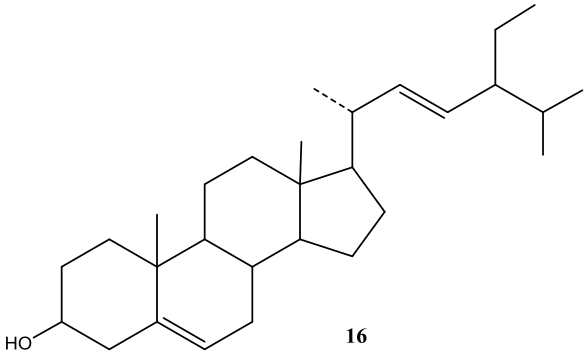

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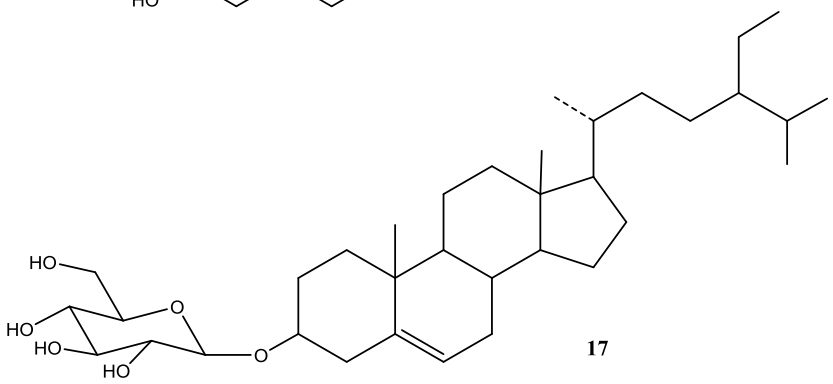

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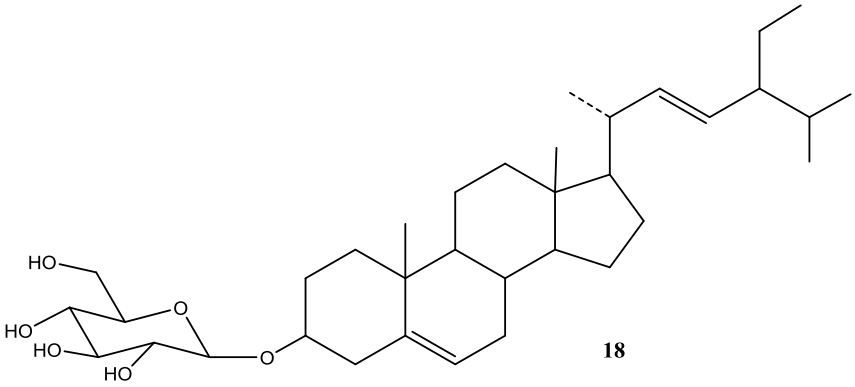

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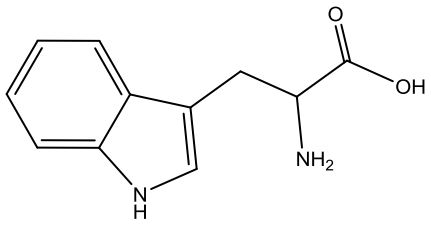

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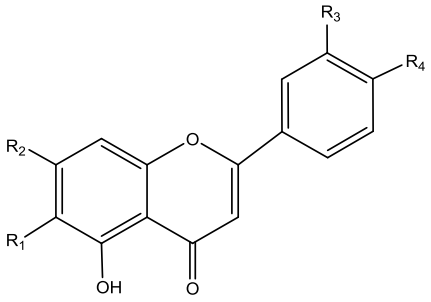
Figure 4: Chemical structures of *Salvia limbata* C.A. Mey. (15-19).

Six flavones and rosmarinic acid were isolated from the ethyl acetate and methanol extracts of the flowered aerial parts of *S. limbata* contained six flavones and rosmarinic acid (fig.5) that separated by using several chromatographic methods. The isolated compounds were identified as ladanein (20), salvigenin (21), luteolin 7-methyl ether (22), cirsiliol (23), eupatorin (24), luteolin 7-O-glucoside (25) and rosmarinic acid (26) which some of these flavonoids have been reported to show antibacterial and cytotoxic activities.[5]



	R_1	R_2	R_3	R_4
20	OH	OMe	H	OMe
21	OMe	OMe	H	OMe
22	H	OMe	OH	OH
23	OMe	OMe	OH	OH
24	OMe	OMe	OH	OMe
25	H	Glu	OH	OH

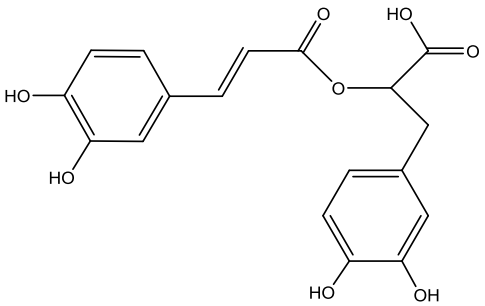


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Figure 5: Structures of the Isolated Flavones from *Salvia limbata* C.A. Mey. (20-26).

In additon, the composition of the essential oils from aerial parts of *Salvia limbata* have been analyzed by a combination of GC and GC/MS. In the oil of *S. limbata*, α-pinene (23.7%), β-pinene (18.7%) and sabinene (14.5%) were found to be the major constituents; its oil consisted mainly of monoterpenes.[11]

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