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Constituents and Biological Activities of some Iranian Artemisia species.

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Review Article

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ABSTRACT

Plants play a vital role in maintaining human health and contribute towards improvement of human life. They are important components of medicines, cosmetics, dyes, beverages etc. Plants have been one of the important sources of medicines even since the dawn of human civilization. In spite of tremendous development in the field of allopathy during the 20th century, plants still remain one of the major sources of drug in the modern as well as traditional system of medicine throughout the world. Over 60% of all pharmaceuticals are plant-based. Plants are considered as state-of-art chemical laboratories capable of biosynthesizing number of biomolecules of different chemical classes. The present review describes the chemical and biological activities of some Iranian *Artemisia* species: *A. aucheri* Boiss., *A. austriaca* Jacq., *A. chamaemelifolia* Vill, *A. ciniformis* Krasch, *A. deserti* Krasch and *A. diffusa.* Krasch.

INTRODUCTION

Artemisia is a large, diverse genus of plants with between 400 to 500 species belonging to the daisy family compositae (Asteraceae), one of the most bulky vegetal groupings, which comprises about 1000 genera and over 20,000 species. It comprises hardy herbs and shrubs known for their volatile oils. Most species have strong aromas and bitter tastes from terpenoids and sesquiterpene lactones, which exist as an adaptation to discourage herbivory the small flowers, are wind-pollinated. Within this family, *Artemisia* is included into the tribe Anthemideae and comprises itself over 500 species. The 500 species of *Artemisia* are mainly found in Asia, Europe and North America. They are mostly perennial herbs and dominating the vast steppe communities of Asia. Asia seems to show the greatest concentration of species with 150 accessions for China [1], 174 in the ex U.S.S.R. [2], about 50 reported to occur in Japan [3] and 35 species of the genus are found in Iran, of which two are endemic: A. *melanolepis* and *A. kermanensis* [4]. *Artemisia* is a highly evolved genus with a wide range of life forms, from tall shrubs to dwarf herbaceous alpine plants, occurring in a variety of habitats between Arctic alpine or montane environments to the dry deserts [5]. The Iranian species has been investigated chemically and presence of monoterpenes, sesquiterpenes, especially sesquiterpene lactones and essential oils reported. In fact the Iranian Artemisia species has yielded a considerate amount of new interesting terpenoides.

Artemisia aucheri Boissier.

Artemisia aucheri was described in 1875 by Pierre Edmond Boissier.

Characteristics

The leaves are arranged opposite one another. The flowers are many- petaled and yellow. The fruits are achenes. *Artemisia aucheri* prefers a sunny site. It grows best in soils that are dry to moderately moist.

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Chemical Constituents and Biological activities

Essential oils

A new, simple hydrodistillation-solvent micro extraction technique has been used for analysis of the volatile components of the aerial parts of *Artemisia aucheri*. The components were collected in a single microdrop, and this was injected directly for gas chromatographic-mass spectrometric (GC-MS) analysis. The effects on extraction efficiency of extraction solvent, sample mass, microdrop volume, and extraction time were optimized by use of a simplex method. The identities of the components of hydrodistillation-solvent micro extraction extracts were confirmed according to their retention indexes and mass spectra with those of standards. Forty components were extracted and identified by use of the method; 1, 8- cineol (22.8%), chrysanthenone (18.16%), α- pinene (8.33%) and mesitylene (7.41%) were the major constituents. The results obtained from the microextraction method were compared with those obtained by conventional hydrodistillation [6].

Artemisia aucheri has been widespread in Iran. In traditional medicine, *A. aucheri* is used for its astringent, disinfectant, antimicrobial and antiparasitic properties. The chemical composition and antimicrobial activity of essential oil from aerial parts of *A. aucheri* against different microorganisms including Gram positive, Gram negative bacteria, filamentous fungi and yeast by disc diffusion and micro broth dilution assays. The antioxidant activity of *A. aucheri* essential oil was evaluated by 2,2-Diphenyl-1-picrylhydrazyl free radical scavenging system. Fifty five components were identified by GC and GC/MS analysis and quantified from the essential oil of *A.aucheri,* representing 98% of total oil. The major components were geranyl acetate (17.2%), E-citral (17.1%), linalool (12.7%), geraniol (10.7%), Z- citral (10.5%). The antimicrobial results showed that *Pseudomonas aeruginosa* was resistant to the oil and *Staphylococcus aureus* and *Candida albicans* showed the best sensitivity to the oil. The *A. aucheri* has powerful antioxidant activity than that of Trolox. Some investigations were being done for evaluating the efficacy of essential oil [7].

The essential oil of *Artemisia aucheri* seed showed activity against *Escherichia coli*, *Staphylococcus aureus*, and *Listeria monocytogenes*. The essential oil constituents identified by GC-MS were as follows: linalool (27.1%), borneol (7.8%), Decane (5.4%), caryophyllene oxide (4.7), ρ-cymene (1.7%), 1, 8- cineole (3.3%), lavandulol (4.1%), bornyl acetate, and. Most of these compounds are also found in the aerial parts of *Artemisia aucheri* [8].

Effect of Methanolic Extracts of *Artemisia aucheri* on Leishmania major (In Vitro)

Methanolic extract of *A. aucheri* inhibited the parasite multiplication at doses of 150, 300 and 450 µg/ml at 48 and 72 hours of culture. Doses of 600 and 750 µg/ml showed the same effect at 24, 48 and 72 hours of culture ($P< 0.05$).

These results provide a new perspective on drug development against Leishmania. The extract of *A. aucheri* at 750 µg/ ml is strikingly potent against Leishmania, inhibiting the growth of promastigotes of L.major after 72 hours [9].

Considering the high prevalence of Trichomonas vaginalis (TV) in women and the known side effects of metronidazol and giving importance to herbal drug therapy in order to reduce side effects in the recent decades, with the effect of essential oils of *Artemisia aucheri* Boiss., in TV infection was done invitro condition

This study has been carried out as double blind in test and control groups. The essential oils prepared by hydrodistilation. The parasite was isolated from vagina and determined directly. Samples were collected from vaginal discharge identification was done through direct smear parasite was added to the 5 test tubes containing dorsse medium, metronidazole dimethyl sulfoxaide and the essential oils with concentration of (0.1, 0.01, 0.001- 0.004, 0.0002, 0.0001) in order to determine the effect of these concentration within 72 hour.

Finding in this study showed that, Trichomonas could be alived in dorsse medium for 72 hours. In presence of metronidazol for one hour and in dorsse medium for 6 hours. The results revealed that, essential oil of *Artemisia aucheri* at concentration of 0.1, 0.01, and 0.001 are effective at the beginning of the inoculation and at concentrations of 0.0004 and 0.0001 after 1 and 2 hours respectively [10].

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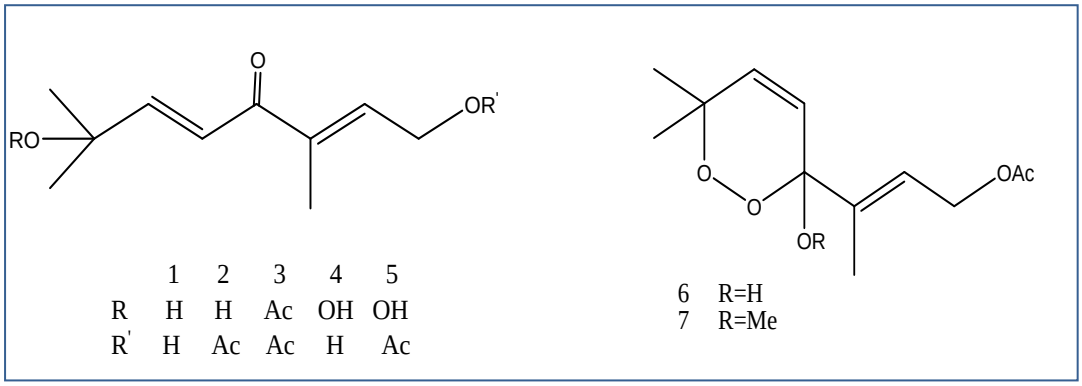
Atherosclerosis which results from gradual deposition of lipids in arteries is a leading cause of mortality worldwide. Diet is one of the most important factors underlying atherosclerosis. High-cholesterol diets enhance atherosclerosis and vegetarian diets are known to slow down the process. The effects of *Artemisia aucheri* on lipoproteins and atherosclerosis in hypercholesterolemic rabbits. Fifteen male rabbits were randomly divided into three groups. Normal diet group, high-cholesterol diet group (1% cholesterol) and *Artemisia aucheri* group (1% cholesterol diet supplemented with 100 mg/kg body weight the *Artemisi aucheri* every other day). Biochemical factors were measured at the start, end of the first and second months of the study. At the end of the study, the aorta was removed for assessment of atherosclerotic plaques. The results indicate that *Artemisia aucheri* significantly reduced the level of total cholesterol, Low Density Lipoprotein cholesterol and triglycerids and increased High Density Lipoprotein cholesterol. The degree of atherosclerotic thickness was significantly reduced in the treated group. Therefore, *Artemisia aucheri* is one of the useful herbal medicine for preventation of atherosclerosis and more studies in this regard is recommended [11].

The effects of *A. aucheri* on regression of atherosclerosis in hypercholesterolemic rabbits. Twenty five rabbits were randomly divided into five groups of five each and treated 3-months as follows: 1: normal diet, 2: hyper cholesterolemic diet, 3 and 4: hyper cholesterolemic diet for 60 days and then normal diet and normal diet + *A. aucheri* (100 mg x kg (-1) x day (-1)) respectively for an additional 30 days (regression period). In the regression period dietary use of *A. aucheri* in group 4 significantly decreased total cholesterol, triglyceride and LDL- cholesterol, while HDL-cholesterol was significantly increased. The atherosclerotic area was significantly decreased in this group. Animals, which received only normal diet in the regression period showed no regression but rather progression of atherosclerosis. These findings suggest that *A. aucheri* may cause regression of atherosclerotic lesions [12].

Monoterpenes

Acyclic monoterpenes and monoterpene hydroperoxides have been found in aerial parts of *A.aucheri* Boiss [13].



	1	2	3	4	5
R	H	H	Ac	OH	OH
R'	H	Ac	Ac	H	Ac

6 R=H
7 R=Me

Figure 1: Acyclic monoterpenes and monoterpene hydroperoxides.

The ^{1}H-NMR spectral data of 6 and 7 differed considerably from those of 1-5. A pair of olefinic doublets with a 10 Hz coupling indicated a *cis*- double bound. However, the chemical shifts of these signals were not in agreement with a *cis*- isomer of 4. The methoxy singnal in the spectrum of 7 required an acetal structure. Obviously 6 was the *cis*- isomer of 4, but due to the changed stereochemistry a hemiacetal was formed, which was transformed to an acetal in the case of 7 (Figure1).

Artemisia austriaca Jacq.

Aromatic perennial. Flowering stems branched above, 20- 25cm, ± herobaceous, densely whitish pilose, sometimes glabrescent. Leaves 1- 2- pinnatisect with very narrowly elliptic to linear-oblong, acute segments, grayish, whitish or silvery seri-ceous-pilose on both surfaces. Bracts similar to leaves but smaller. Inflorescence a widely spreading branched panicle. Capitula ± globose, or oblongglobose, 2.5- 3 mm broad. Phyllaries densely pilose, outer narrowly oblong, inner longer, oblong-ovate. Outer flowers filiform, female, inner hermaphrodite, fertile, corolla reddish or yellowish, lobes densely pilose [14].

A. austriaca is another species that typically grows wild in turkey and central part of Iran a few reports focus on its composition and biological activity. In 1995, Cubukcu and Melikoglu elucidated the

structure of flavonoids present in the aerial parts of *A. austriaca,* while some years later Guvenalp *et al.* identified in the hydrodistilled oil around 30 peaks, mainly represented by 1,8-cineole and camphor [15].

Artemisia chamaemelifolia Vill.

Artemisia chamaemelifolia was described in 1779 by Dominique Villars. The name is considered as validly published.

The perennials grow to a height of approximately 0.6 meters. The leaves are arranged opposite one another. The flowers are many-plated and yellow. The plants bloom from July to August. The fruits are achenes.

Artemisia chamaemelifolia is native to the southwest Alps and the Pyrenees in France, Italy and Bulgaria respectively, and to the Caucasus and North Iran.

It has a wide distribution in the northern hemisphere, whereas few species are representative of South America and Africa [16]. *Artemisia chamaemelifolia* Vill. is a perennial herb, which is currently forming disjunct ranges distributed in Eurasian mountain: Spanish Sierra Nevada, Cantabrian chain, Pyrenees, the Alps (Italy and France), the Balkan range (Bulgaria), Caucasus (Russia and Georgia), northeast and east Anatolia (Turkey), Armenia, Azerbaijan and the mountain of northern Iran [17, 18]. European populations are much smaller as compared to these in Georgia, Armenia and Iran and in most cases they occur in very small areas. In Spain *A. chamaemelifolia* is represented by two subspecies: subsp. Cantabrica M. Lainz and subsp. *chamaemelifolia* Vill., whereas in all other ranges of the species it is represented by subsp. *Chamaemelifolia* only [17].

Chemical Constituents

Essential Oil

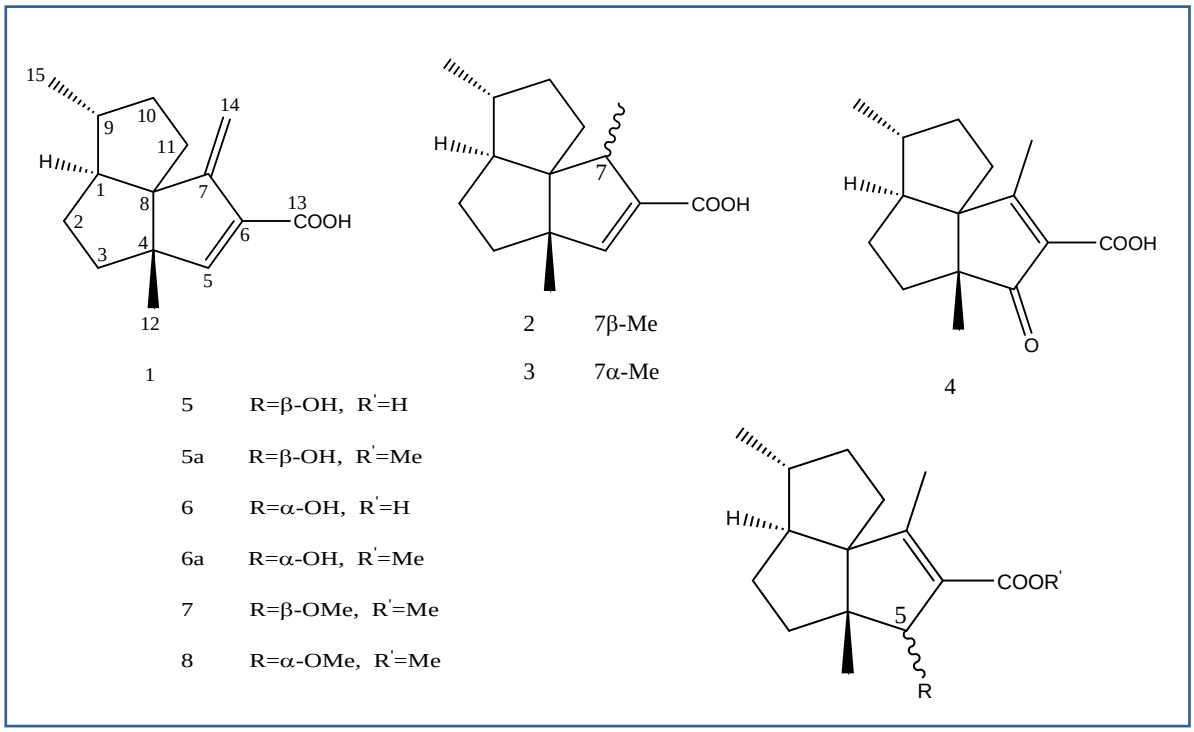


Figure 2: Cantabradienic acid; 2: Silphiperfol-5-en-13-oic acid

The essential oils obtained by hydrodistillation from the aerial parts, stem, leaf and flower of *Artemisia chamaemelifolia* Vill. and the aerial parts of *Artemisia* turcomanica Gand. were analyzed by GC and GC/MS. Thirty-one compounds representing 96.6%, 94.6%, 93.2% and 91.0% of the oil were identified in the aerial parts, stem, leaf and flower oils of *Artemisia chamaemelifolia* were identified. Menthyl acetate

(26.5%, 22.0%, 20.5% and 20.5%) and (Z)-nerolidol (20.8%, 26.3%, 14.7% and 18.1%) were the main constituents in the aerial parts, stem, leaf and flower oils, respectively.

The other main component in the aerial parts, leaf and flower oils of the plant was 1, 8-cineole (13.9%, 11.7% and 12.8%), respectively. Also yomogi alcohol (10.4%) and artemisyl acetate (10.4%) were the main components of the leaf and flower oil of the plant respectively. No significant difference was observed between compositions of aerial parts, stem, leaf and flower oils [19].

Aerial parts of *A. Chamaemelifolia* were collected from West Stara Planina Mountain (location Goliama mogila peak, altitude of ca. 1560 m).

3: 7-epi-silphiperfol-5-en-13-oic acid; 4: Cantabrenonic acid; 5: Cantabrenolic acid; 5a: Methyl Cantabre- nolate; 6: 5-epi-cantabrenolic acid; 6a: Methyl 5-epi-cantabrenolate; 7: Methyl O-methyl cantabrenolate; 8: Methyl O-methyl-5-epi-cantabrenolate.

The air-dried plant material (156 g) was extracted with petroleum ether (2 × 200 ml). The crude extract (10 g) was defatted by precipitation with MeOH (2 × 20 ml). After filtration and evaporation of MeOH the resulting residue (6.5 g) was separated into 5 fractions by column chromatography (CC) on silica gel (200 g) using hexane/EtOAc mixtures as eluents. Fraction 2 (1.1 g) was further subjected to CC (silica gel, hexane/EtOAc 4:1 v/v) to give Cantabradienic acid (1) (25 mg) and an unseparable mixture of Silphiperfol-5-en-13-oic acid (2) and 7-epi-sil- phiperfol-5-en-13-oic acid (3) (300 mg). Compound Cantabrenolate (4) (300 mg) crystallized spontaneously from fraction 3 (1.2 g) and then was purified by recrystallization (hexane) [20].

Artemisia ciniformis Krasch.

Chemical Constituents

Essential Oil

The essential oil obtained by hydrodistillation from the leaves, stems and aerial parts of *Artemisia ciniformis* Krasch. et M. Pop. ex Poljak was analyzed by GC and GC/MS. Davanone (40.1%, 32.3% and 12.6%) was the main constituent in the stem,leaf and aerial parts oils of *A. ciniformis*.

The other main components in the aerial parts oil of the plant were myrcene (19.3%), linalool (13.5%) and camphor (13.1%) [21].

Plant material

The stems, leaves and aerial parts of *A. ciniformis* were collected in July 2005 from Bojnourd, Province of Khorasan during the flowering phase.

Isolation of the oils

The stems (74 g), leaves (69 g) and aerial parts (103 g) of *A. ciniformis* were subjected to hydrodistillation using a Clevenger-type apparatus for 3h. After decanting and drying over anhydrous sodium sulfate, the corresponding yellowish colored oil was recovered.

Artemisia deserti Krasch.

Chemical Constituents

Essential Oil

Sample of essential oil from aerial parts of *Artemisia deserti* Krasch. was analyzed by GC/MS. Twenty components have been identified representing 93.8-98.8% of the oil content. The oil of *A. deserti* was characterized by piperitone (52%), camphor (15.7%) and 1, 8-cineole (11.8%) as main components [22].

The composition of the volatile oils obtained from the aerial parts of *Artemisia deserti* Krasch. was analyzed by GC and GC/MS. The oil of *A.deserti* contained camphor (45.5 %), 1, 8-cineole (16.7 %),

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piperitone (8.6 %), β-pinene (5.7 %) and isoborneol (3.2 %). The structures of camphor and 1, 8-cineole were confirmed by the interpretation of the 400 MHz ^{1}H-NMR spectrum of each of the two total oils [23].

Sesquiterpene lactones

From *Artemisia deserti* ergosterol, the flavones hispidulin, jaceosidin and eupalitin; the guaianolides matricarin, deacetylmatricarin, 8α-hydroxyachillin 3,4,5 and 6 the 1,10-secoguaianolides iso-seco-tanapartholide (7) ,its 3-O-methyl derivative 8, seco-tanapartholide A (9) and seco-tanapartholide B (10); the cyclic peroxide 11; and the monoterpenes camphor, borneol, piperitone and filifolide A were

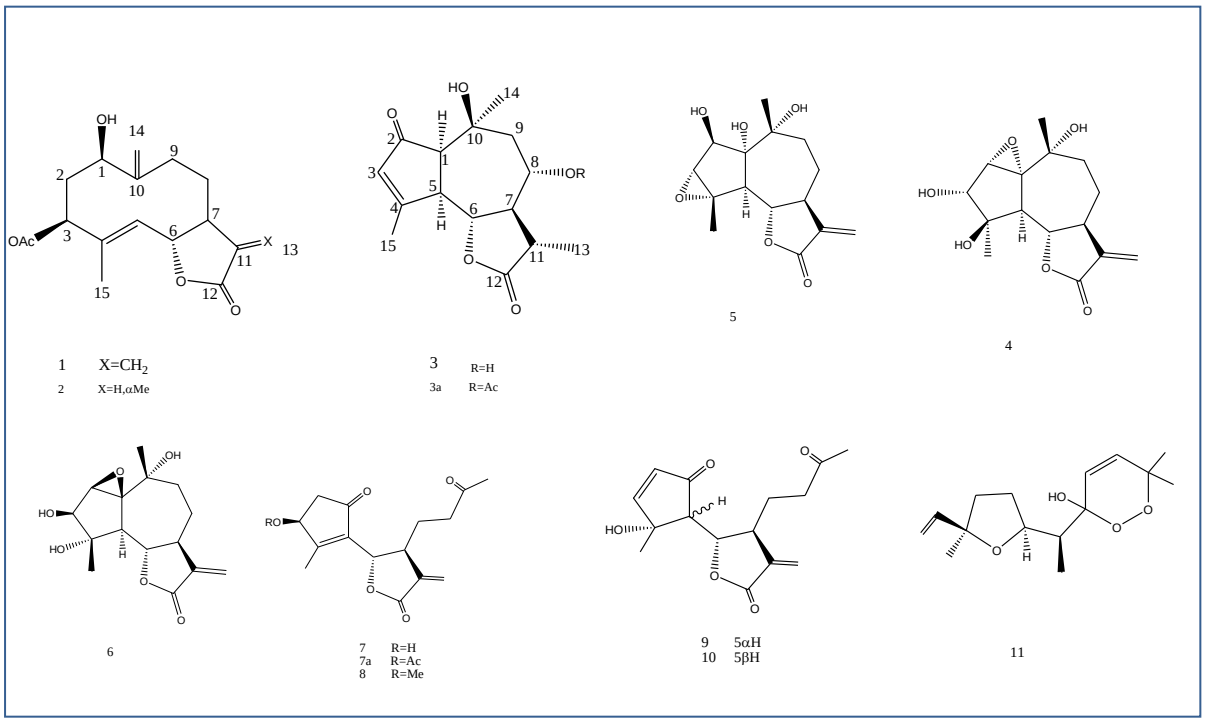

Figure 3. Sesquiterpene from Artemisia deserti

Artemisia diffusa Krasch.

Chemical Constituents

Essential Oil

Sample of essential oil from aerial parts of *Artemisia diffusa* Krasch. was analyzed by GC/MS. Twenty components have been identified representing 93.8-98.8% of the oil content. The major components of the oil *A. diffusa* were camphor (57.5%) and verbenone (13%). Air-dried aerial parts of *A.diffusa* at the flowering stage were subjected to steam distillation in all glass apparatus for 1h with an oil yield of 1.2% [32].

Chemical constituents and biological activities

The extract of the aerial parts of *Artemisia diffusa* afforded several eudesmanolides (1a, 1b, 2a, 2b, 3a, 3b, 4) and a new type of sesquiterpene lactone with unusual carbon skeleton, an eight-member ring (Tehranolide) [33] (Fig. 4).

Most likely this unusual carbon skeleton was formed by oxidative cleavage of the Δ4 bond of 2b followed by an internal aldol condensation of the intermediate 5 affording the dihydroxy ketone 6. The latter then could be rearranged to the lactone 7 by attack of HO^{+} followed by acetal formation to give the lactone 8 (Tehranolide).

The extract of the aerial parts of *A. diffusa* collected in the Province of Khorassan (Iran) afforded, in addition to several eudesmanolides a new type of sesquiterpene lactone (Tehranolide) with an

endoperoxide group that probably has the same effect as the antimalarial agent artemisinin. We have already reported the antimalarial properties of the extract and the fraction which contains sesquiterpene lactones including Tehranolide of the same species (*Artemisia diffusa*) [34]

Recently Artediffusin (Tehranolide) has been confirmed and considered as a new antimalarial Agent [35] (Fig. 5).

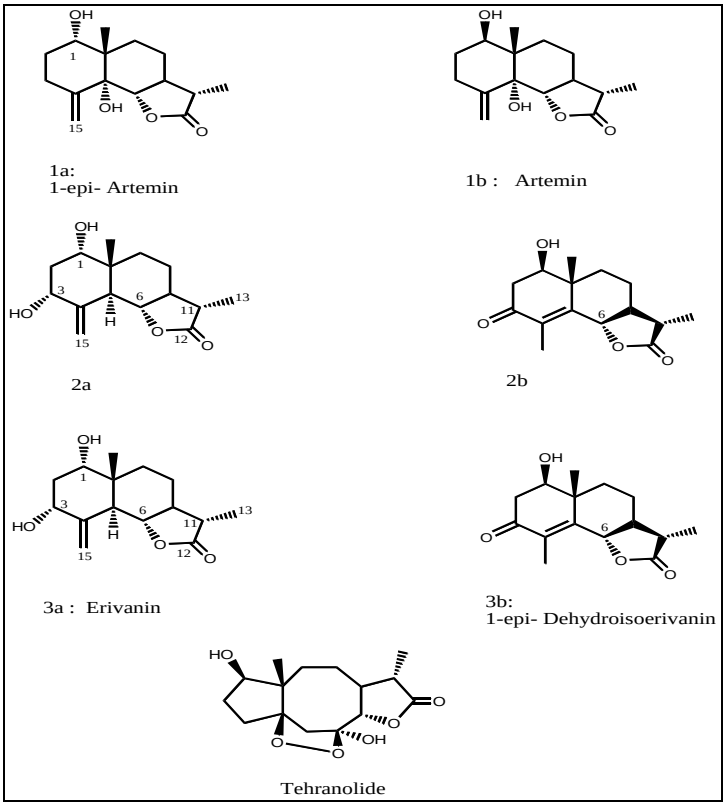

Figure 4: Sesquiterpene lactones from Artemisia diffusa

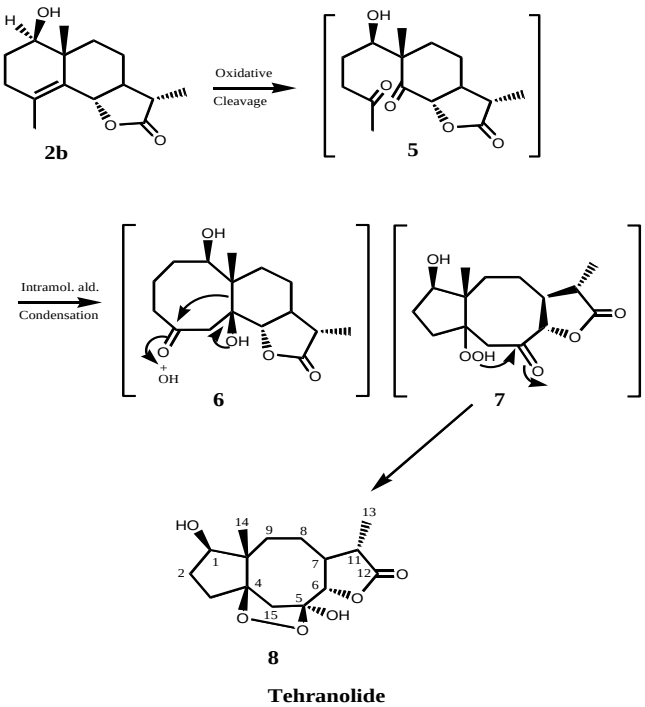

Figure 5: Biosynthesis of Tehranolide

CONCLUSION

As mentioned in this review Constituents and Biological Activities of some Iranian species including *A. aucheri* Boiss, *A. austriaca* Jacq. *A. biennis* Wild, *A. chamaemelifolia* Vill, *A. ciniformis* Krasch, *A. deserti* Krasch and *A. diffusa* Krasch. have been described.

Artemisia species produce at least three classes of compounds: Terpenoids especially Sesquiterpene lactones, Flavonoids and Polyacetylenes.

Most attention has been focused on sesquiterpene lactones for example artemisinin or qinghaosu which was found to be responsible for the antimalarial activity of *A. annua.*

Also a new type of Sesquiterpene lactone (Tehranolide) with the endoperoxide group that probably has the same effect of artemisinin which has been isolated from *A. diffusa.*

In morphology, the Artemisia genus is endowed with head-like inflorescences and is considered to be one of the most evolutionary taxa in the Dicotyledonae. This advancement in taxonomy may increase the chemical diversity as the advance species may synthesize more complex (cyclized, rearranged and/or oxygenated) secondary metabolites [36].

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