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ScienceDirect
Phytochemistry 67 (2006) 1977–1984
PHYTOCHEMISTRY
www.elsevier.com/locate/phytochem

Review

Chemistry and biological activity of secondary metabolites in *Euphorbia* from Iran

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Received 17 June 2006; accepted 22 June 2006
Available online 4 August 2006

Abstract

The chemical constituents of some species of *Euphorbia*, which grow mostly in semi-desert areas in Iran and on the Alborz Mountains in the north of Tehran, have been found to include chemotaxonomically important myrsinane diterpenoids and cycloartane triterpenoids. The *Euphorbia* plants collected in province of Azarbaijan in the northwestern part of Iran contained mostly derivatives of skin-irritating ingenol esters. Some of the diterpenoids with myrsinane carbon skeleton inhibited enzymes such as α-glycosidase, urease, HIV-1 reverse transcriptase, and prolyl endopeptidase. They also showed analgesic and DNA-damaging activities. The present review describes the chemistry and biological activity of several compounds isolated from different species of Iranian *Euphorbia:* diterpenoids with myrsinane skeletons, flavonoids, tannins, alkanes, sterols, mono-, sesqui- and triterpenoids, skin-irritating and tumor-promoting latexes and their active ingenol diterpenoids.

Keywords: Iranian *Euphorbia*; Myrsinane diterpenoids; Triterpenoids; Flavonoids; Skin irritant; Tumor promoter; Enzyme inhibitor

Contents

1. Introduction

The genus *Euphorbia* is the largest in the plant family Euphorbiaceae, comprising about 2000 known species and ranging from annuals to trees. All contain latex and have unique flower structures. A significant percentage, mostly those originating in Africa and Madagascar, are succulent (Zargari, 1993). The *Euphorbias* are named after the Greek surgeon *Euphorbus*. He was a physician of Juba II, a Romanized king of a North African kingdom, and is supposed to have used the species' milky

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0031-9422/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.phytochem.2006.06.030

latex as an ingredient in his medicine. In Iran about 70 species have been reported, 17 of which are endemic (Mozaffarian, 1996).

The plants of the family Euphorbiaceae contain the well-known skin irritating and tumor-promoting diterpenoids, which have tigliane, ingenane, and daphnane skeletons (Evans and Taylor, 1983). Some of the species are used in folk medicines to cure skin diseases, gonorrhea, migraines, intestinal parasites, and warts (Singla and Pathak, 1990), and in Iran as a purgative (Upadhyay et al., 1976c,d; Upadhyay and Mohaddes, 1987). In addition, several macrocyclic diterpenoids with antibacterial, anticancer, PGE_2-inhibitory, anti-multidrug-resistant, prolyl endopeptidase inhibitory, antifeedant, anti-HIV, and analgesic activity have recently been isolated from different *Euphorbia* species. They include jatrophane, ingol, and myrsinane diterpenoids (Abdelgaleil et al., 2001; Hohmann et al., 2000, 2002, 2003; Ravikanth et al., 2002; Wang et al., 2002; Öksüz et al., 1995).

Phorbol activates protein kinase C, which in turn leads to uncontrolled cell division (Dewick, 1999). Diterpenoids isolated and identified from Iranian *Euphorbia* species showed skin-irritating, tumor-promoting, and co-carcinogenic properties in tests on the skin and ears of mice (Upadhyay, 1996, 2000). They inhibited HIV-1 reverse transcriptase, α-glucosidase, prolyl endopeptidase, and urease, and showed analgesic and DNA-damaging activity (see Section 2.2).

2. Diterpenoids isolated from Iranian Euphorbia species

2.1. Myrsinane-type diterpenoids

From the aerial parts of the following *Euphorbia* species, diterpenoids with myrsinane or related skeletons have been isolated: *E. decipiens* Boiss. & Buhse, *E. teheranica* Boiss., *E. cheiradenia* Boiss. et Hohen. ex Boiss., *E. marschalliana* Boiss., and *E. heteradena* Jaub. & Sp. (Rechinger, 1964). The diterpenoids (Fig. 1) isolated from the plants had cyclized lathyrane skeletons, which are related to myrsinol esters (e.g., compounds **1** and **2**).

From an acetone extract of the aerial parts of *E. marschalliana* Boiss., collected from the Taleghan area near Karaj two diterpenoids with myrsinol skeletons were isolated and identified as 15-*O*-acetyl-3-*O*-propionyl-5-*O*-butanoyl-7-*O*-nicotinoylmyrsinol (**1**) and 15-*O*-acetyl-3,5-*O*-dibutanoyl-7-*O*-nicotinoylmyrsinol (**2**) (Fig. 1) (Jassbi et al., 2004). Their relative configuration have been studied using ROESY spectroscopy and modified at C-6, C-12, and C-13, which contrasts with the previous report on these compounds isolated from *E. myrsinites* (Fig. 2) (Öksüz et al., 1995). The anti-HIV properties of the compounds have been evaluated with an enzyme inhibitory test in an HIV1-reverse transcriptase assay (Öksüz et al., 1995).

Different chromatographic techniques were used to purify compound **2** from the acetone extract of the aerial parts of *Euphorbia heteradena* Jaub. & Sp. collected in Qazvin (Ahmad et al., 2002c). $NaBH_4$ reduction of **2** resulted in production of compound **3** as the major compound (Fig. 1) (Ahmad et al., 2002c). The resulting hydroxyl group at C-14 was trans-esterified in the reaction mixture spontaneously. The relative configuration of **3** was confirmed by NOESY spectroscopy. The reduction of C-14 carbonyl from the less hindered alpha face of the molecule (**2**) resulted in the formation of a β-oriented hydroxyl group in **3** (Ahmad et al., 2002c).

Decipinone (**4**) and decipidone (**5**) are the two major diterpenoids of *E. decipiens* (Ahmad et al., 1998). They have a structure similar to myrsinane diterpenoids, but the ether linkage between C-13 and C-17 is open in compounds**4** and **5**. The relative configuration of **4** was confirmed by single crystal X-ray diffraction analyses (Fig. 2) (Ahmad et al., 1998). The absolute configuration of **4** has been determined using NMR analysis of its axially chiral derivatives with (a*R*)- and (a*S*)-*N*-hydroxy-2′-methoxy-1,1′-binaphthalene-2-carboximidoyl chloride to be 2*S*, 3*S*, 4*R*, 5*R*, 6*R*, 7*R*, 11*S*, 12*R*, 13*S*, 15*R* (Fig. 2) (Jassbi et al., 2002).

The other compounds (**6**–**15**) included different esters of acetyl (Ac), benzoyl (Bz), butanoyl (Bu), and nicotinoyl (Nic) of decipinone (Ahmad et al., 1998, 2002a,b, 2005a; Ahmad and Jassbi, 1998a; Parvez et al., 2004; Zahid et al., 2001). The X-ray crystal structure of 3,7,17-tri-*O*-acetyl-5-*O*-butanoyl-13,15-dihydroxymyrsinol (**15**) has been analyzed (Parvez et al., 2004).

Isodecipidone (**10**) and isodecipinone (**11**) inhibited (IC_{50} 21.8 μM) prolyl endopeptidase (PEP). Alterations in the enzyme's levels cause different diseases such as Alzheimer's, depression, mania, thrombosis, HIV, and cancer (Ahmad et al., 2002a,b). Compound **10** (Ahmad et al., 2002a) and **14** (Ahmad et al., 2002b) also had a significant peripheral analgesic effect on an acetic acid-induced abdominal constriction test in mice. Different doses (5–20 mg/kg i.p.) of compound **14** showed significant antinociceptive activity comparable to standard analgesic drugs, aspirin and ibuprofen (100 mg/kg i.p.) (Ahmad et al., 2005a). Compounds **12** and **13** inhibited the jack bean urease enzyme (Ahmad et al., 2005b). This is the first time that a natural product has been reported to inhibit urease (Ahmad et al., 2003a, 2005b). Compounds with the urease inhibitory activity have attracted attention because of their potential as anti-ulcer drugs.

A hemiacetal bond formation of the ketone C-14 and hydroxyl at C-17 produced another novel structure for compounds **16**–**20** (Zahid et al., 2001; Ahmad et al., 2003a). The novel structure of decipinone B (**16**) and C (**17**) was confirmed by single crystal X-ray diffraction analyses (Jassbi, 2000; Zahid et al., 2001). The tetra-cyclic diterpenoid **19** and **20** derived from decipinone inhibited the PEP and jack bean urease enzymes, respectively (Ahmad et al., 2003a).

The novel skeleton of kandovanol ester A (**21**) and B (**22**) is the result of a cyclopropane formation between C-9 and C-10 (Zahid et al., 2001). An acetal formation

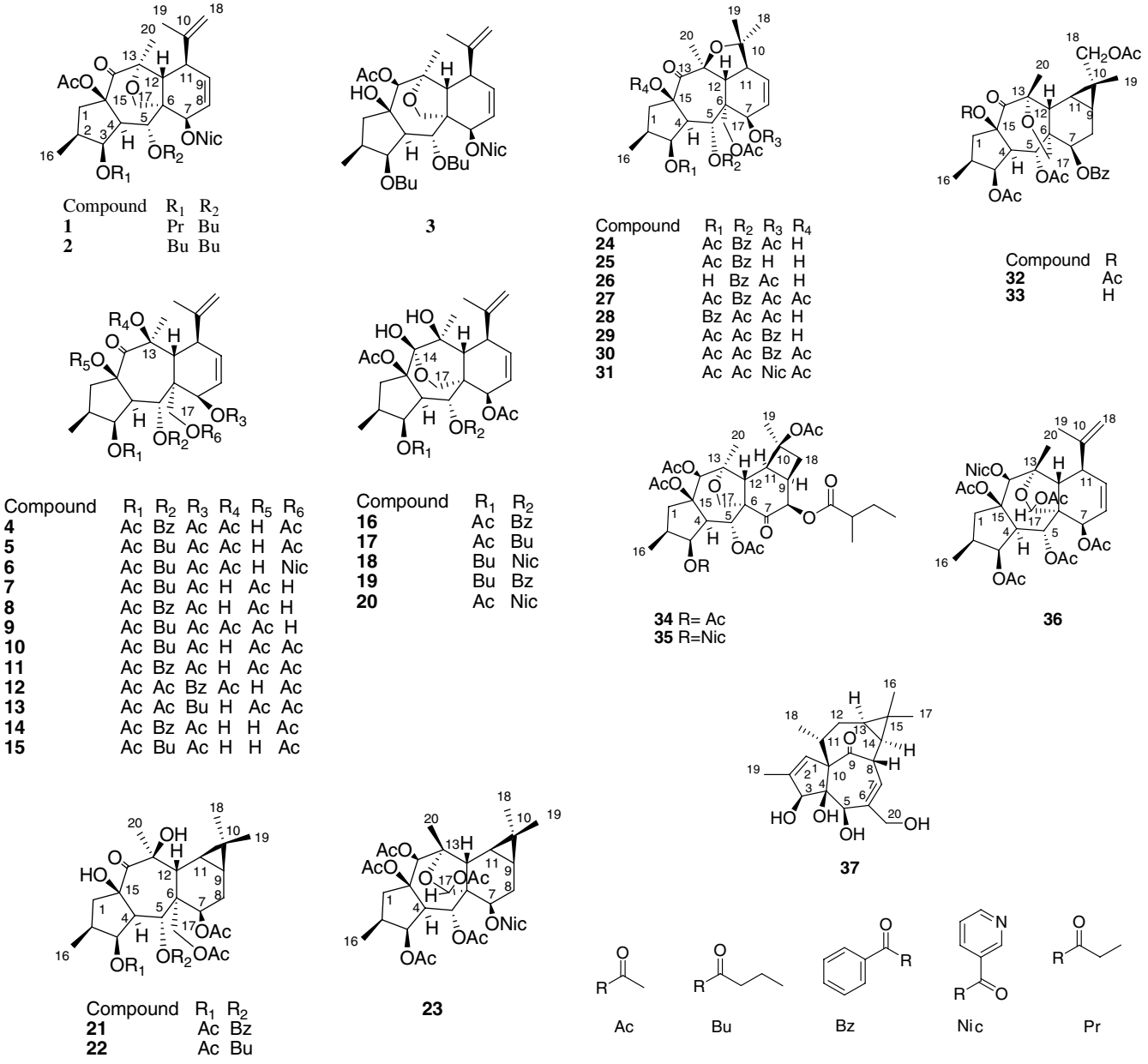

Fig. 1. Novel diterpenoids from Iranian *Euphorbia*.

between the C-17 aldehyde and a hydroxyl at C-13 resulted in a new alcohol structure for compound **23** (Zahid et al., 2001).

E. cheiradenia Boiss. et Hohen. ex Boiss. grows wild north of Tehran as well as in other parts of Iran and Iraq (Rechinger, 1964). An investigation into an acetone extract of the plant resulted in purification of three novel diterpenoids with new skeletons, cheiradone (**24**), and cheiradone A (**25**) and B (**26**) (Fig. 1) (Abbas et al., 2000). The structure is different from decipinone because a saturated furan ring forms between C-10 and C-13. The X-ray crystal structure of **24** was determined using single crystal X-ray diffraction analysis. Cheiradone inhibited α-glucosidase enzyme type V1 with $IC_{50} = 0.32$ mM (Abbas et al., 2000).

Five novel cheiradone-type skeleton diterpenoids (**27**–**31**) were isolated from *E. decipiens* as part of a search for bioactive natural products from this plant (Zahid et al., 2001; Ahmad et al., 2003a,b). Among them, compounds **28** (Ahmad et al., 2003a) and **29** (Ahmad et al., 2003b) inhibited the PEP enzyme. Compound **30** exhibited DNA-damaging activity in a mutant yeast bioassay (Ahmad et al., 2003b).

Two pentacyclic diterpenoids, karajinone A (**32**) and B (**33**), with cyclopropane rings at C-9, C-10, and C-11, were separated from *E. decipiens* (Ahmad and Jassbi, 1998b).

E. teheranica Boiss. is widespread around Tehran and in semi-desert areas in central Iran (Rechinger, 1964). Three new diterpenoids with penta- (**34**,**35**) and tetra-cyclic (**36**) skeletons (related to myrsinane and cyclomyrsinol proba-

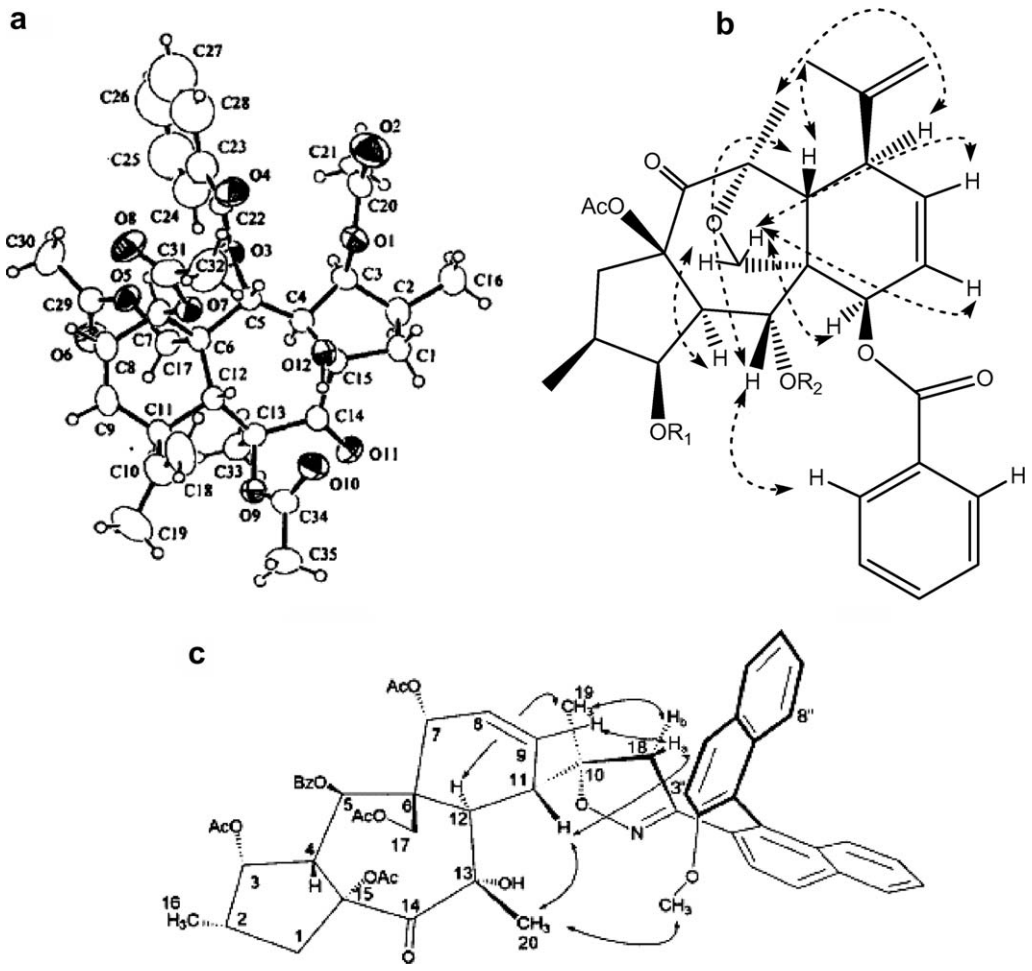

Fig. 2. Application of X-ray crystallography, and 2D NMR spectroscopy to determine relative and absolute configuration of myrsinane diterpenoids: (a) X-ray crystal-structure of **4** (Ahmad et al., 1998); (b) ROESY correlations of **2** (Jassbi et al., 2004); (c) NOESY correlations to determine absolute configuration of **11** (Jassbi et al., 2002).

bly from the cyclization of a lathyrane precursor) were isolated from the ethyl acetate-soluble parts of a methanol extract of the aerial parts of the plant (Fig. 1) (Ahmad and Jassbi, 1999).

2.2. Ingenol-type diterpenoids and tumor-promoting properties of Iranian Euphorbia

Fifteen species of *Euphorbia* growing in the province of Azarbaijan in Iran were investigated for their skin-irritating properties and the presence of ingenol diterpenoids (**37**) (Upadhyay et al., 1980a). Twelve of them showed skin-irritating properties because of the presence of the skin-irritant ingenol fatty acid esters (Upadhyay et al., 1980a). Isolation of a methanolic extract of the latex of *E. megalantha* yielded in addition to the ingenol ester, a new 4-deoxy ingenol after derivatization to its 3,5,20-triacetate (Upadhyay and Mohaddes, 1987). The latex of *E. teheranica* has been reported to be a mild skin irritant (Upadhyay et al., 1983).

The latex of *E. serrata* acts as an irritant on the ears of mice (Upadhyay et al., 1976a). The irritancy and co-carcinogenic properties of the latex are lost after chromatography on silica gel. It was suggested that the active constituent, 3-ingenol palmitate is transformed to its non-active C-20 ester derivative on contact with silica gel (Upadhyay et al., 1976a). After hydrolysis and acetylating to ingenol-3,5,20-triacetate, the parent alcohol of 3-ingenol palmitate was purified from a methanolic extract of the latex of the plant (Upadhyay et al., 1976b).

The latex of *E. seguieriana* collected from the Shahgoli area near Tabriz was found to be a co-carcinogen and an irritant on the ears and skin of mice. After being transformed to its triacetate derivative, ingenol was separated from its active fraction by chromatography (Upadhyay et al., 1976c; Upadhyay et al., 1976d).

A highly irritating ingenol ester, ingenol-3-$\Delta^{2,4,6,8,10}$ pentene tetradecanoate and a co-carcinogenic agent, ingenol-3-dodecanoate, were purified from the latex of *E. esula* (Upadhyay et al., 1978). The long-chain fatty acid substitu-

tion at C-3 hydroxyl of ingenol was suggested to be essential for the biological activity (Upadhyay et al., 1978).

The authors could not detect skin tumors after applying ingenol triacetate, but this compound did produce a high incidence of lung adenoma to female NMRI mice when applied topically (Tilabi and Upadhyay, 1983). Seven *Euphorbia* species were investigated for tumor-promoting and skin-irritating properties (Upadhyay et al., 1984). Among them *E. striatella* latex was found to be highly irritating and to produce papilloma in experiments on the skin of mice. The tumor-promoting and skin-irritating properties of the latex of the plant are reportedly due to the presence of ingenol-3-*O*-decanoate and $\Delta^{2,4,6}$ decatrienoate. The mild skin irritancy of other *Euphorbia* species was tested and suggested to be due to the presence of the ingenol with short-chain esters at the C-3 position (Upadhyay et al., 1984).

Honey samples collected from the Saidabad area of the Azarbaijan Province in Iran were moderate irritants. This was associated with the diterpene esters of ingenol, transferred from the nectar of *E. seguieriana* by honeybees (Upadhyay et al., 1980b). In addition to the bitter honey, milk can be contaminated by the co-carcinogenic products of the plants. The poisonous milk of goats fed the herb *E. peplus* showed weakly irritant activities in the mouse ear assay (Zayed et al., 1998). Three poisonous diterpenoids, ingenol-20-acetate-3-angelate, 20-deoxyingenol-3-angelate and 20-deoxyingenol-6α,7α-epoxide-3-angelate were detected in the milk extract by HPLC. The first two diterpenoids were reported to promote tumors on mouse skin. The authors suggested a possible mechanism for the development of esophageal cancer in the littoral area of the Caspian Sea in Iran (Zayed et al., 1998).

3. Triterpenoids and steroids

The lower polar fractions collected from silica gel chromatography of a chloroform extract from the aerial parts of *E. decipiens* resulted in the isolation of several known triterpenoids. They include β-amyrin, β-amyrin acetate (Ahmad et al., 2002a), cycloeucalenol, obtusifoliol, 24-methylenecycloartan-3β-ol, and β-sitosterol (Jassbi, 2000).

From a methanol extract of the aerial parts of *E. teheranica*, three triterpenoids, betulin, erythrodiol, and oleanolic acid, were purified using column chromatography over silica gel (Jassbi, 2000). β-Sitosterol glucoside was isolated from polar fractions of the above chromatography system (Jassbi, 2000).

β-Sitosterol, 29-norcycloart-5-ene, 5,8-lanostadiene-3β-ol, 3β,24(*S*),25-trihydroxycycloartane, 3β,24(*R*),25-trihydroxycycloartane, and 24-methylenecycloartan-3β-ol were identified for the first time in *E. marschalliana* (Jassbi et al., 2004).

Three triterpenoids – cycloart-23-ene-3,5-diol, betulin, and secotaraxerene – were identified in the aerial parts of *E. heteradena* (Ahmad et al., 2002c). The triterpenoids and steroids isolated from *E. larica* (Ulubelen et al., 1986), *E. petiolata* (Rustaiyan et al., 1982), *E. falcata* (Aynehchi and Hakimzadeh, 1978), *E. Lanata* (Aynehchi et al., 1978), *E. tinctoria* (Aynehchi and Kiumehr, 1972, 1974, 1977) and *E. myrsinites* (Aynehchi et al., 1972) are presented in Table 1.

Table 1
Chemical constituents of different Iranian *Euphorbia*

Euphorbia species	Flavonoids and coumarins	Triterpenoids and steroids	Other constituents
E. larica	Kaempferol-3-*O*-glucoside (**43**), quercetin-3-*O*-glucoside (**44**), kaempferol-3-rutinoside (**45**), rutin (**46**), 6-methoxyapigenin (Ulubelen et al., 1983)	β-Amyrin acetate, lupeol, lupeol acetate, ginnone, ambrein, lupeone (Ulubelen et al., 1986)	Nonacosane (**47**), octacosyl behenate (**48**) (Ulubelen et al., 1986)
E. virgata	**43**, **44**, **45**, **46**, kaempferol (**49**) (Ulubelen et al., 1983)		
E. chamaesyce	**43**, **44** (Ulubelen et al., 1983)		
E. magalanta	**43**, **44**, **45**, **46**, **49** (Ulubelen et al., 1983)		
E. petiolata		Cycloartenol, 24-methylenecycloartanol (Rustaiyan et al., 1982)	
E. falcata L.		Obtusifoldienol, γ-euphorbol (**50**), β-amyrin (**51**) (Aynehchi and Hakimzadeh, 1978)	**47**, octadecan-2-one, eicosan-2-one (Aynehchi and Hakimzadeh, 1978)
E. lanata	Kaempferol-7-*O*-rhamnoside, kaempferol-3-*O*-galactoside, quercetin-7-*O*-digalactoside, esculetin (Aynehchi et al., 1978)	Sitosteryl-3-β-D-glucoside (**52**) (Aynehchi et al., 1978)	Octacosanol (**53**), **48** (Aynehchi et al., 1978)
E. tinctoria	**46**, quercetin, quercetin-7-glucoside, kaempferol rhamnoside (Aynehchi and Ulubelen, 1974)	**50**, **52**, euphorbol (Aynehchi and Kiumehr, 1972, 1974, 1977)	**47**, **48**, **53** (Aynehchi and Kiumehr, 1972, 1974, 1977)
E. myrsinites		**51**, taraxerol (Aynehchi et al., 1972)	**47**, **53** (Aynehchi et al., 1972)

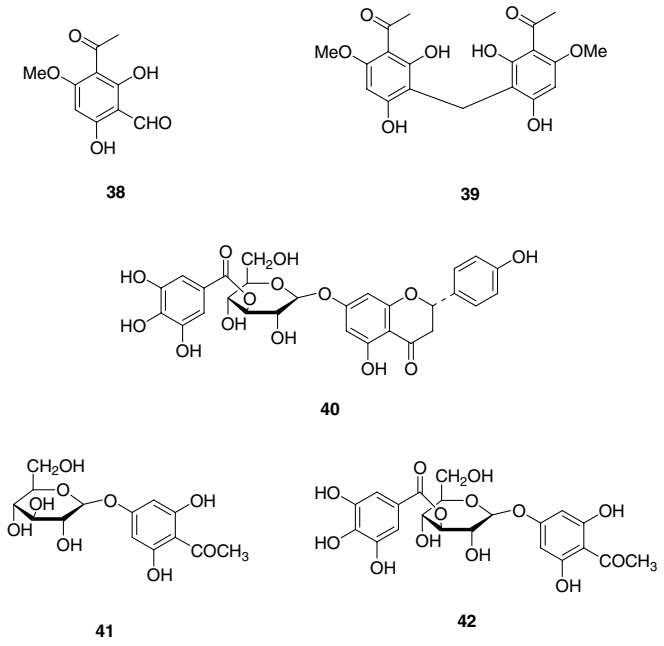

Fig. 3. Phenolics from *E. decipiens* and *E. aucherii*.

4. Flavonoids and phenolics

In addition to the novel bioactive diterpenoids from *E. decipiens,* two phenolic compounds have also been separated from this plant. They are methyl (2,4-dihydroxy-3-formyl-6-methoxy) phenyl ketone (**38**) and 1,1-bis (2,6-dihydroxy-3-acetyl-4-methoxyphenyl) methane (**39**) (Ahmad et al., 2002a). The effect of **38** on blood pressure was studied on normotensive anaesthetized Wister rats (Ahmad et al., 2002a). Methyl gallate was isolated from *E. teheranica* as the only phenolic compound (Jassbi, 2000; Ahmad and Jassbi, 1999).

Two flavonoid glycosides, myricetin-3-rhamnoside, and **40**, and two hydrolysable tannins, **41**, and **42** were identified in *E. aucherii*, which was collected in Iran (Fig. 3) (Murillo and Jakupovic, 1998). The above phenolic compounds were purified from polar fractions of the plant extract after acetylating of their hydroxyl groups (Murillo and Jakupovic, 1998).

The flavonoids and other phenolics which were isolated from *E. larica*, *E. virgata*, *E. chamaesyce*, *E. magalanta* (Ulubelen et al., 1983), *E. Lanata* (Aynehchi et al., 1978) and *E. tinctoria* (Aynehchi and Ulubelen, 1974) are listed in Table 1.

5. Essential oil, hydrocarbons and esters

The chemical constituents of the essential oil of *E. teheranica* have been analyzed by GC and GC/MS (Feizbakhsh et al., 2004), revealing 22 compounds. The major constituents were elemol (57.5%), β-caryophyllene (8.1%), and caryophyllene (7.8%), γ-eudesmol, β-eudesmol, α-eudesmol, α-humulene, humulene epoxide II, 10-epi-γ-eudesmol, and hinesol as the sesquiterpenes. The minor compounds include both monoterpenes (*cis*-sabinene hydrate, *trans*-sabinene hydrate, citronellol, terpinen-4-ol and α-terpineol) as well as *n*-alkanes (dodecane, tridecane, tetradecane, nonadecane, and henicosane). Benzyl benzoate and methyl hexadecanoate were identified in trace amounts (Feizbakhsh et al., 2004). The saturated and oxygenated hydrocarbons and esters which were isolated from *E. larica* (Ulubelen et al., 1986), *E. falcata* L. (Aynehchi and Hakimzadeh, 1978), *E. Lanata* (Aynehchi et al., 1978), *E. tinctoria* (Aynehchi and Kiumehr, 1972, 1974, 1977), and *E. myrsinites* (Aynehchi et al., 1972) are listed in Table 1.

6. Conclusion

The polycyclic diterpenoids with tigliane (phorbol esters), ingenane (ingenol esters), jatrophane, and lathyrane skeletons are among the most studied diterpenoids isolated from *Euphorbia* plants (Singla and Pathak, 1990; Valente et al., 2004; Corea et al., 2005; Hohmann et al., 2003). These diterpenoids are biologically active in diverse ways; they have been found to be skin-irritants, tumor-promoters, anti-cancer agents, and recently, agents for overcoming multidrug-resistance (anti-MDR) (Upadhyay, 1996; Valente et al., 2004; Corea et al., 2005; Hohmann et al., 2003).

Recently several novel polycyclic diterpenoids have been isolated from the genus *Euphorbia* (Vasas et al., 2004). The diterpenoids with myrsinane skeletons were first isolated from *E. myrsinites* more than two decades ago (Rentzea et al., 1982). However several of the related myrsinane diterpenoids were isolated from *Euphorbia* species in China, Turkey, and Iran (Wu et al., 1995; Öksüz et al., 1995). The present review shows that almost all of the new diterpenoids isolated from Iranian *Euphorbia* have myrsinane skeletons. However, the Iranian *Euphorbia* plants with skin-irritating and tumor-promoting diterpenoids have not been sufficiently explored using modern separation and identification methods.

Triterpenoids are often found in higher amounts among the secondary metabolites in the non-polar fractions of the extracts of the plants (Mukherjee et al., 1990; Singla and Pathak, 1990). Cycloartenol-type triterpenoids together with amyrin, betulin, oleane, and lupeol are found in different *Euphorbia* species including the Iranian *Euphorbia* (Mukherjee et al., 1990; Singla and Pathak, 1990).

Kaempferol, quercetin, apigenin, and luteolin, in addition to their glycosides and other derivatives, are among the most abundant flavonoids found in the genus as well as in some Iranian *Euphorbia* (Kawashty et al., 1990). Despite the diverse presence of tannins in the genus *Euphorbia*, those plants of Iranian origin (except *E. aucherii*) have not been investigated for these important natural products (Murillo and Jakupovic, 1998).

Since the *Euphorbia* plants are a rich source of latex and hydrocarbons, research on the Iranian *Euphorbia* may lead to new sources of hydrocarbons (Özcan and Özcan, 2004). One of the best samples for investigation is *E. larica*, an

endemic species with high latex content which grows in the southern Iran.

Acknowledgements

I am thankful to the Alexander von Humboldt foundation for granting a postdoctoral fellowship and the Research Council of Shahid Beheshti University for financial support. I also thank Emily Wheeler for editing the language of this article.

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