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Revisión | Review

Phytochemistry and Biological Activities of *Werneria* and *Xenophyllum* species

[Fitoquímica y actividades biológicas de especies de *Werneria* y *Xenophyllum*]

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Abstract: Plants of the genera *Werneria* (Asteraceae) and *Xenophyllum* (genus extracted from *Werneria*) are used in traditional medicine of Latin America for the treatment of mountain sickness, hypertension and gastrointestinal disorders. Only a small number of species of these genera have been studied, leading to the isolation of compounds belonging to the classes of benzofurans, chromenes, acetophenones, coumarates, diterpenes and pyrrolizidine alkaloids. Some of the plant extracts and/or compounds have shown antimicrobial, anti-HIV, hypotensive and photoprotective activities.

Keywords: *Werneria*; *Xenophyllum*; Medicicinal plants; Mountain sickness; Hypertension.

Resumen: Las plantas de los géneros *Werneria* (Asteraceae) y *Xenophyllum* (género extraido de *Werneria*) son usadas en la medicina tradicional de América Latina para el tratamiento del mal de montaña, hipertensión y desórdenes gastrointestinales. Solo un pequeño número de especies de estos géneros ha sido investigado, lográndose aislar compuestos que pertenecen a las clases de benzofuranos, cromenos, acetofenonas, cumaratos, diterpenos y alcaloides pirrolizidínicos. Algunos de los extractos y/o compuestos de dichas plantas han mostrado actividades antimicrobianas, anti-HIV, hipotensoras y fotoprotectoras.

Palabras clave: *Werneria*; *Xenophyllum*; Plantas medicinales; Mal de montaña; Hipertensión.

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INTRODUCTION

The genus *Werneria* was established by Carl S. Kunth and dedicated to the German geologist Abraham G. Werner. The morphological characteristics of this genus show the variability of the species and support that it is not a monophyletic genus, for this reason, almost half of the species were transferred to the new genera *Xenophyllum*, *Misbrookea* and *Anticona* (Funk 1997a; Funk, 1997b; Linares-Perea *et al*., 2014; Beltrán, 2017). Currently, the *Werneria* genus could be composed of 25-30 species, distributed in the South American Andes (2.800 m.a.s.l) from Venezuela, Colombia, Ecuador, Perú, Bolivia to northern Argentina and Chile, with an isolated population of *W. nubigena* in Mexico and northern Guatemala. The Peruvian territory hosts the greatest wealth of *Werneria* genus with 22 species, of which 5 are endemic (Beltrán, 2017). Recently, *Werneria microphylla* was described as new species from the high Andes of Peru (Beltrán & Leiva, 2018), it is likely that there are more *Werneria* species to be discovered.

The genus *Xenophyllum* consists of 22 species extracted from *Werneria*, 14 of them have been reported in Peru (Beltrán, 2016). “Xeno” means “strange” or “foreign”, while “phyllum" means “leaves”. Members of this genus grow at high elevations (3,000-5,200 m) in the Andes from Colombia to northern Argentina and Chile (Funk, 1997a).

Misbrookea is a new genus extracted from *Werneria*, named after its collector Winifred M.A. Brooke. For this genus, only one species (*Misbrookea strigosissima* (A. Gray) V.A. Funk) has been reported; it grows at the grasslands of the highlands of southern Peru and Bolivia (Funk 1997b; Linares-Perea *et al*., 2014). More recently, Linares-Perea et al. collected *Werneria glareophila* described by Cuatrecasas and found that its characters deviate from the genera *Werneria*, *Misbrookea*, and *Xenophyllum*. They described the new genus *Anticona* comprised by only one species, named as *Anticona glareophila* (Cuatrec.) E. Linares, J. Campos & A. Galán (Linares-Perea *et al*., 2014).

So far, the phytochemical study and/or biological activities of 9 *Werneria* species have been reported: *W. ciliolate* A. Gray (5 publications), *W. poposa* Philippi (4), *W. nubigena* H.B.K. (3), *W. dactylophylla* Schultz-Bip (3), *W. stuebelli* Hieron (1), *W. decora* cf. Blake (1), *W. staffordiae* Sandwith (1), *W. digitata* Wedell (1) and *W. pigmeae* Gillies ex Hooker & Arnott (1). In the case of the genus *Xenophyllum*, only two species have been investigated: *X. poposum* (Phillipi) V.A. Funk (7 publications) and *X. incisum* (Phillipi) V.A. Funk (1). It has to be noted that *W. poposa* is now known as *X. poposum*. Of the 28 publications found in the scientific literature for *Werneria* and *Xenophyllum* species, 16 refer to samples collected in Peru, 7 in Argentina, 3 in Chile, 1 in Bolivia and 1 in Ecuador.

Phytochemical studies on the genus *Werneria* have reported a variety of chemical constituents that include pyrrolizidine-type alkaloids, phenolics (such as benzofurans, benzopyrans, *p*-coumarates, coumarins, flavonoids, *p*-hydroxyacetyphenones, caffeoylquinic acids), as well as volatile terpenes, diterpenes (mainly kauran and manoyl derivatives), triterpenes and steroids; all these compounds will be presented in the following sections. Some of them have been reported in a previous review (Lock Sing, 2006).

CHEMICAL CONSTITUENTS

Alkaloids

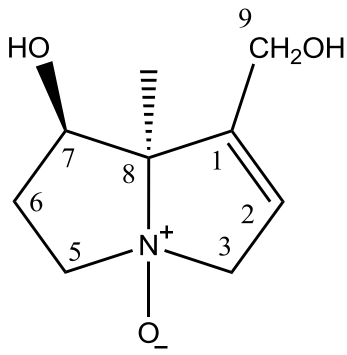
A total of 6 pyrrozilidine alkaloids (PAs) have been isolated from 2 *Werneria* species. Alkaloids N-oxoretronecine (**1**) and N-oxoretrorsine (**4**) have been isolated from *W. decora* (Lock de Ugaz *et al*., 1990), while alkaloids retrorsine (**2**), senecionine (**3**), **4**, integerrimine (**5**) and N-oxorosmarinine (**6**) were reported for *W. nubigena* (Roeder *et al.*, 1992; Piacente *et al*., 1997).

The presence of PAs is important from the chemotaxonomic point of view of *Werneria*, as it is generally regarded as a member of the tribe Senecioneae which is known to contain PAs. Pyrrolizidine alkaloids contain an azabicyclo [3,3,0] octane as a basic structure; they generally are found as esters with rare mono- or di-basic acids, the necic acids, producing a 12-membered macrocycle (**2-6**). It is also worth noting that, in general, the PAs accumulate in the plant as polar *N*-oxides (**1,4,6**).

Benzofurans

Benzofurans are commonly found in Asteraceae family. Benzofurans dihydroeuparin or 6-hydroxytremetone (**7**) (Lock de Ugaz *et al*., 1984; Palacios *et al*., 2018), 2,5-diacetyl-6-hydroxy-benzofurane (**8**) (Lock de Ugaz & Peralta, 1988), toxol (**9**) (Piacente *et al*., 1992), toxolacetate (**10**) (Córdova *et al*., 1998; de Marchese *et al*., 2007), toxolangelate

(**11**) (de Marchese *et al*., 2007) and lactone 2,3-dihydro-2-oxo-5-formyl-6-methoxy-7-(3'-methyl-3'-butenyl)-benzo-furane (**12**) (Castro *et al*., 2000) have a methylcetone group in *para* position to the oxygen of the heterocycle ring, while 2-acetyl-5-(2'-hydroxyethyl)-6-hydroxybenzofurane (**13**) (Castro *et al*., 2000) has another substituent. These benzofurans were found in *W. ciliolata, W. poposa, W. nubigena and X. poposum.*



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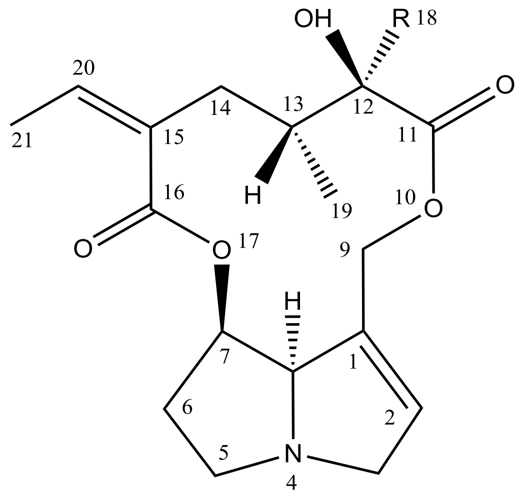
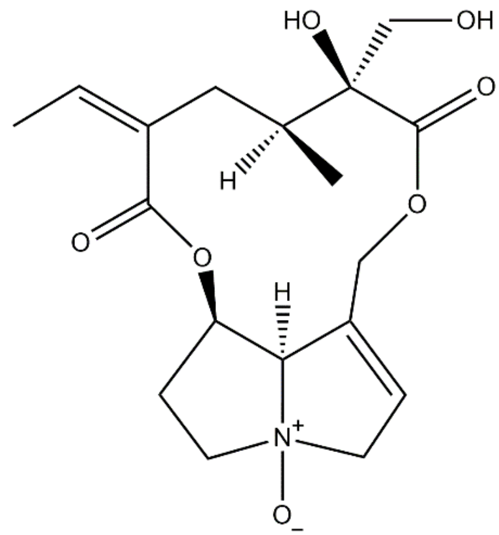


(2) R = CH$_2$OH
(3) R = CH$_3$



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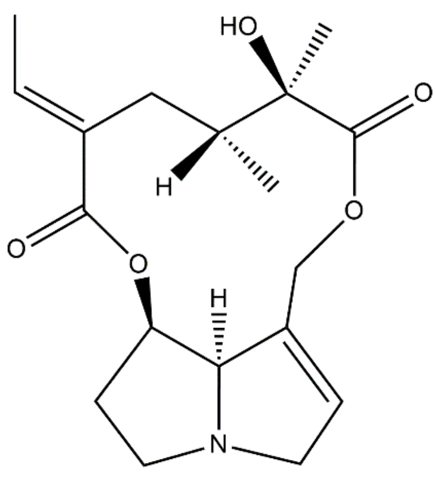

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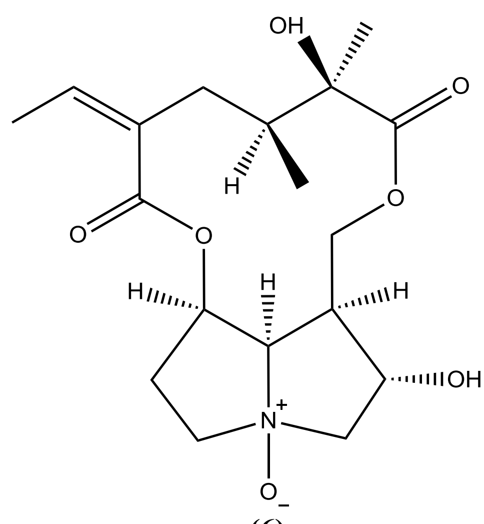

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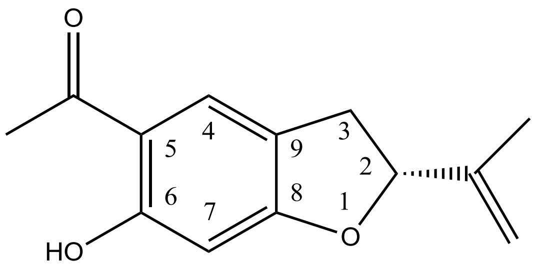

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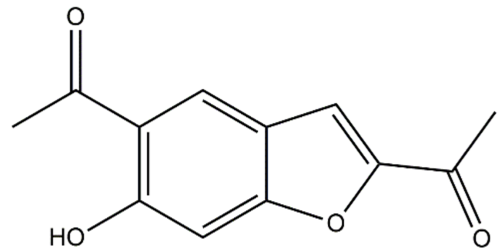
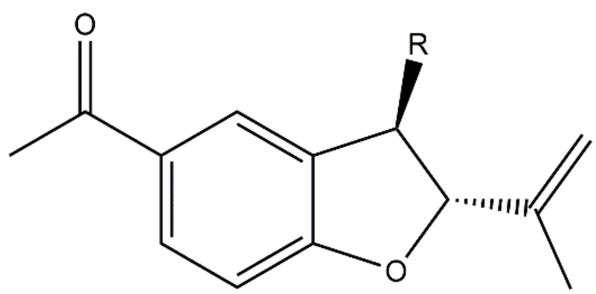
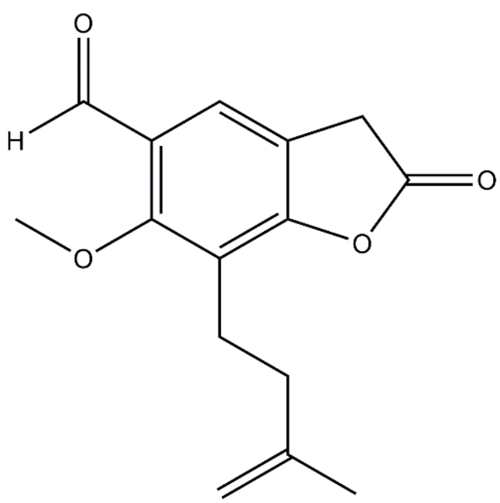


(**8**)



(**9**) R = OH
(**10**) R = acetyl
(**11**) R = angelicyl



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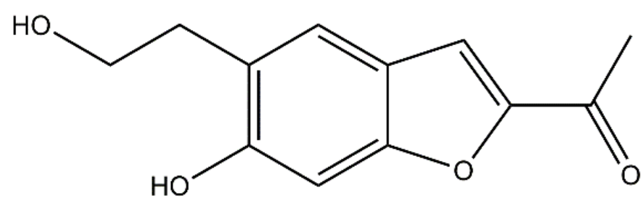
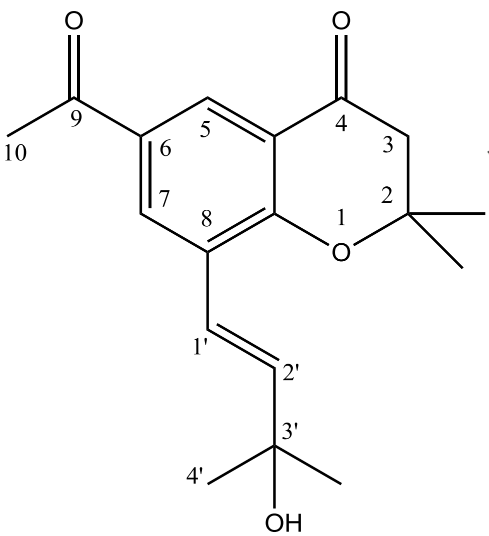


(**13**)

Benzopyran derivatives (Chromenes)

The basic structure of chromenes, which are benzopyrans derivatives, is a joined benzene and pyrane rings with two dimethyl group in position 2 and the methyl cetone group in *para* position to the oxygen of the heterocycle ring, as observed in 2,2-dimethyl-6 acetyl-8-(3’-hydroxy-3’-methyl-*trans*-but-1’-enyl)-chroman-4-one (**14**), 2,2-dimethyl-6-acetyl-8-(3’-hydroxy-3’-methyl-trans-but-1’-enyl)-chrom-3-ene (**15**) and 2,2-dimethyl-6-acetyl-3-chromene (**16**). Sometimes this substituent is different like in 9-E-werneria chromene (**17**), 9-Z-werneria chromene (**18**), 8-[3’,3’-dimethylallyl]-werneria chromene (**19**) and 8-[3’,3’-dimethyl-3’-hydroxyallyl]-werneria chromene (**20**).

Compounds **14** and **15** were found in *W. nubigena* (Piacente *et al*., 1997); **16** in *X. incisum* (de Marchese et al., 2007) and **17-20** in *W. stuebelli* (Bohlmann *et al*., 1984). Benzopyran **14** was reported as a new structure by Piacente *et al*. (1997).



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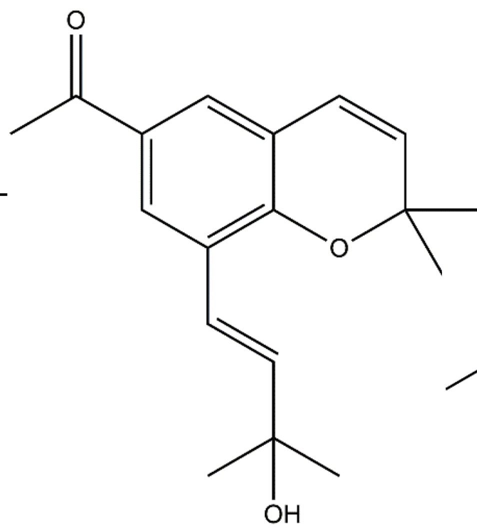

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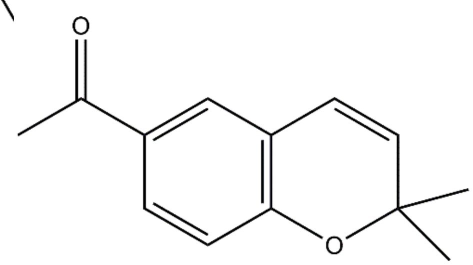

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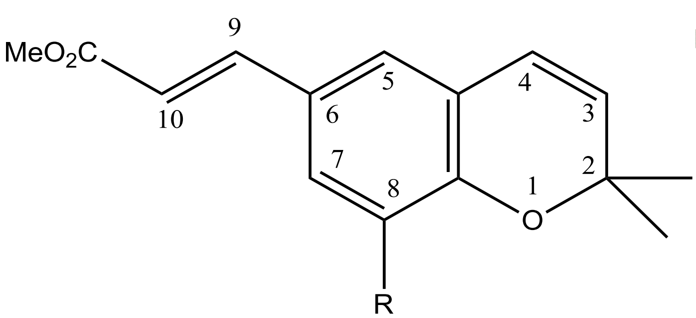
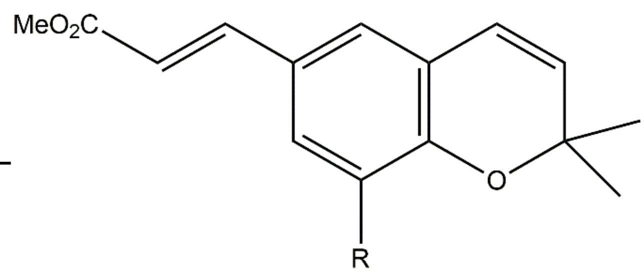


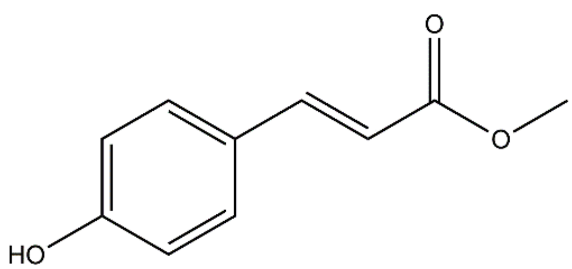
(17) 9,10-E
(18) 9,10-Z



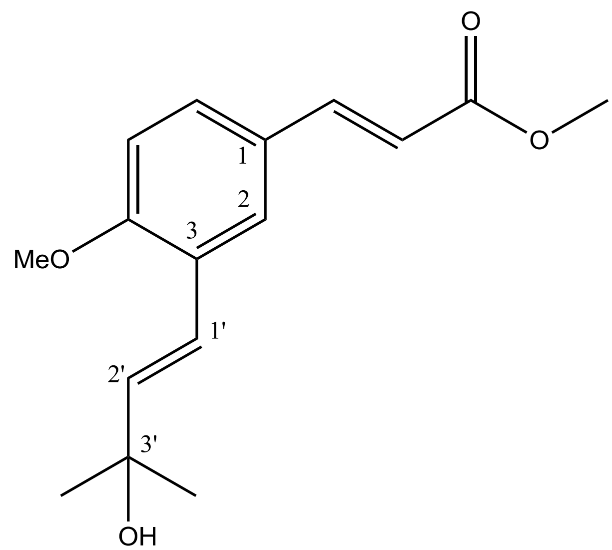
(**19**) R = 3', 3' -dimethylallyl
(**20**) R = 3', 3'-dimethyl-3-hidroxyallyl

***p*-Coumarates and derivatives**

p-coumaric acid is formed through the deamination of L-tyrosine, one simple derivative is the compound methyl *p*-coumarate (**21**). Other *p*-coumarates like methyl 3-[3’, 3’-dimethyl-3’-hydroxyallyl]-*p*-coumarate-*O*-methyl ether (**22**), ethyl-3-senecioyl-*p*-coumarate (**23**), methyl-3-[3’-methyl-1’-hydroxy-but-3’-en-1’-yl]-*p*-coumarate (**24**), Plicatin A (**25**) and Plicatin B (**26**) contain substituents in C-3 of the aromatic ring. Compounds **22-24** were reported for *W. stuebelli* (Bohlmann *et al*., 1984), while Plicatin A and B were isolated from *W. dactylopylla* (Bravo *et al*., 2009).



(**21**)



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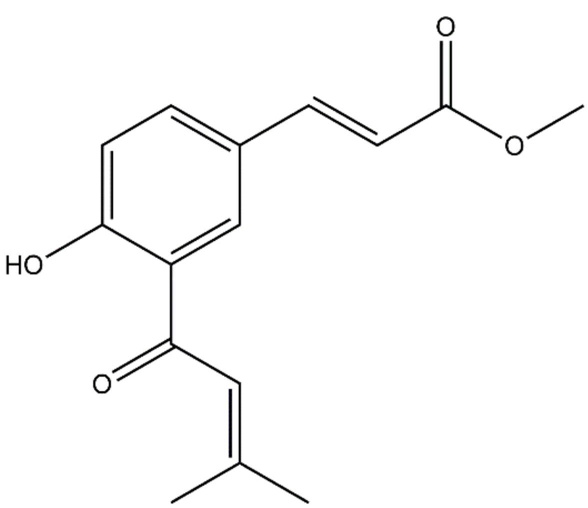
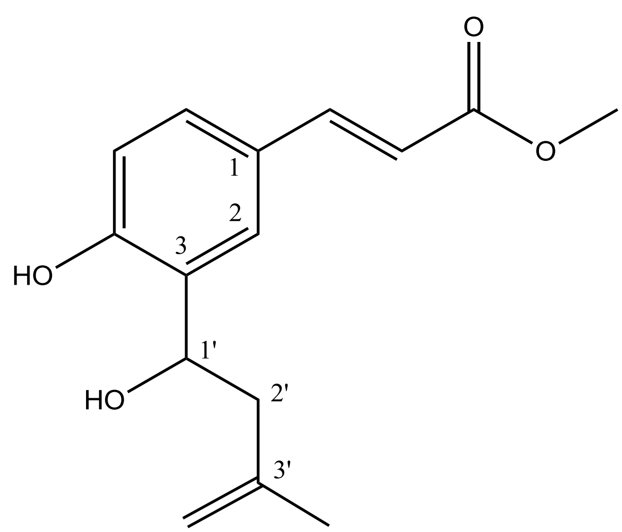


(**23**)



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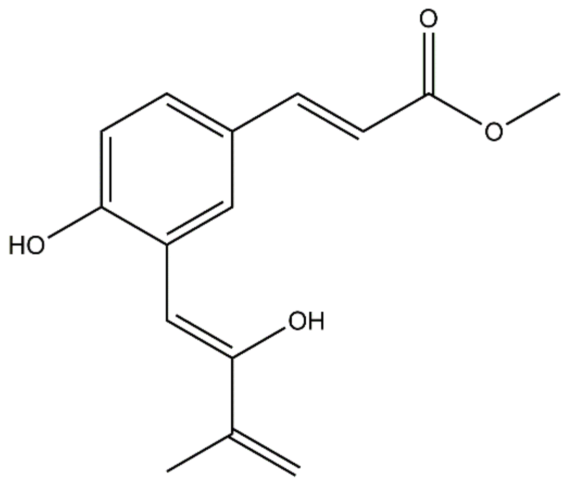

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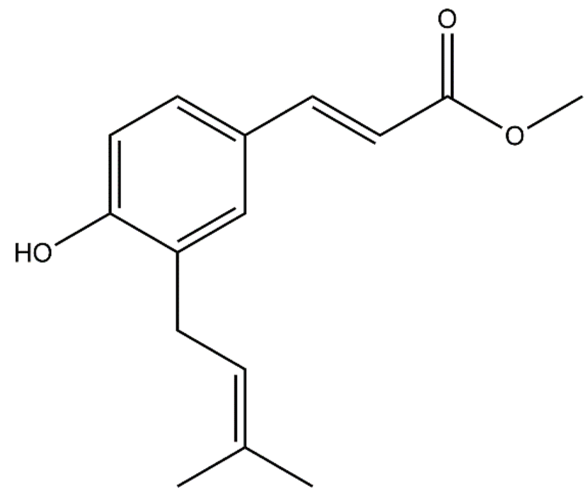
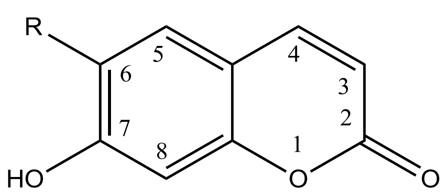


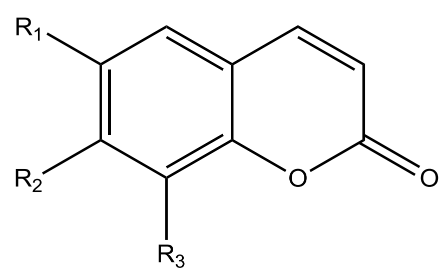
(**26**)

Coumarins

Coumarins are phenolic compounds that are much extended in the plant kingdom; however, only five coumarins were reported so far for *Werneria* species: aesculetin (**27**), aesculetin-7-*O*-β-D-glucopyranoside (**28**), scopoletin (**29**), 6-hydroxy-7-methoxycoumarin (**30**) and 7-hydroxy-8-methoxycoumarin (**31**). These coumarins were found in *W. ciliolata*, *W. dactylophylla*, *W. poposa* and *W. staffordiae* (Bonilla *et al*., 1991; Ponce & Gros, 1991; Piacente *et al*., 1994; Chavez & Lock de Ugaz, 1997; Córdova *et al*., 1998).



(27) R = OH
(28) R = Glc

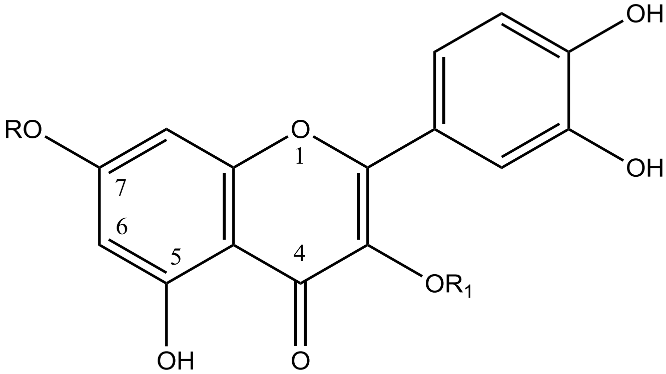


(29) $R_1 = CH_3O$, $R_2 = OH$, $R_3 = H$
(30) $R_1 = OH$, $R_2 = CH_3O$, $R_3 = H$
(31) $R_1 = H$, $R_2 = OH$, $R_3 = CH_3O$

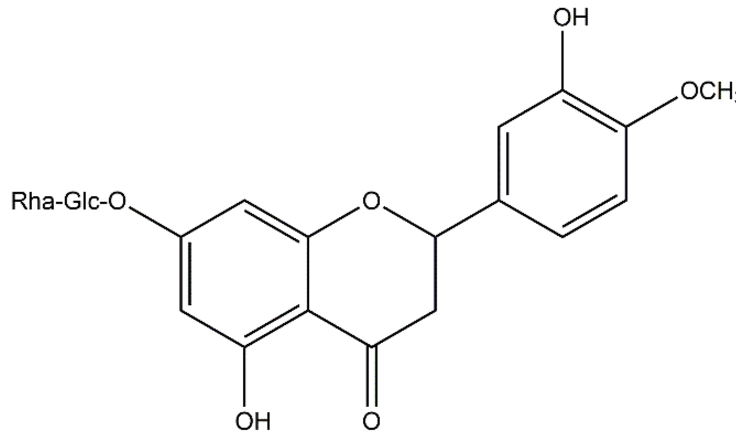
Flavonoids

Flavonoids are one of the most numerous and widely distributed compounds in plants which exhibit diverse biological activities. They appear usually as mixtures of aglycones and glycosides containing different classes and number of sugar units. The flavonoids reported for *Werneria* species were quercetin (**32**), rutin (**33**), Quercetin-3-*O*-glucorhamnoside (**34**), Quercetin-7-*O*-rhamnoside (**35**), Quercetin 3-*O*-(β-D glucopiranosyl-1''→2'')-β-D-galactopyranoside (**36**) and hesperidin (**37**).

Compounds **32** and **33** were isolated from *W. poposa* and *W. dactylophylla* (Bonilla *et al*., 1991; Córdova *et al.*, 1998), **34** and **36** from *W. staffordiae* (Chavez & Lock de Ugaz, 1997), while compounds **35** and **37** were reported in *W. dactylophylla* (Bonilla *et al*., 1991).



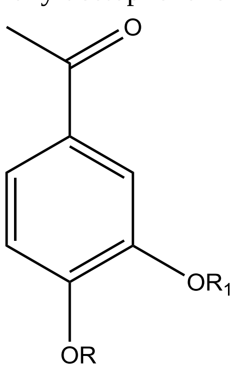
(32) R = R_1 = H
(33) R = H, R_1 = Rha-Glc
(34) R = H, R_1 = Glc-Rha
(35) R = Rha, R_1 = H
(36) R = OH, R_1 = Glc-Gal

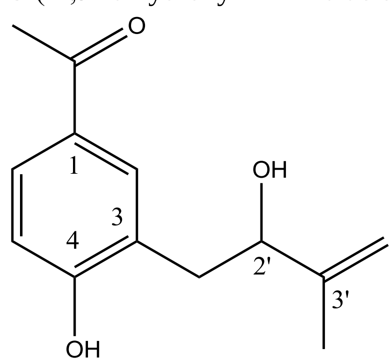


(37)

p-hydroxyacetophenones

p-hydroxyacetophenone (**38**) and its glucopyranoside (**39**) were isolated from *W. nubigena* and *W. poposa* (Piacente *et al*., 1997; Córdova *et al.*, 1998). Compounds 3-(2'-hydroxy-isopent-3'-enyl)-4-hydroxy-acetophenone (**40**) and 3-(2',3'-dihydroxy-isopentyl)-4-hydroxy-acetophenone (**41**) were reported in *W. ciliolata* (Piacente *et al*., 1992); while 4-hydroxy-3-(isopenten-2'-yl)-acetophenone (**42**) and 4-hydroxy-3-metoxy-acetophenone (**43**) were found in *X. incisum* and *X. poposum* (de Marchese *et al*., 2007; Palacios *et al*., 2018).





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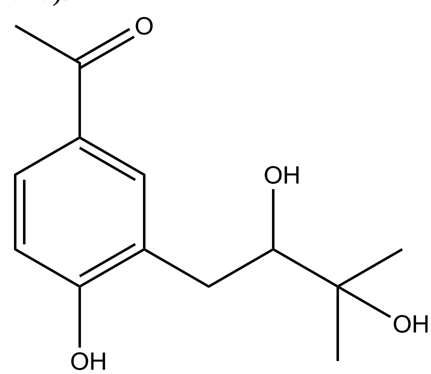
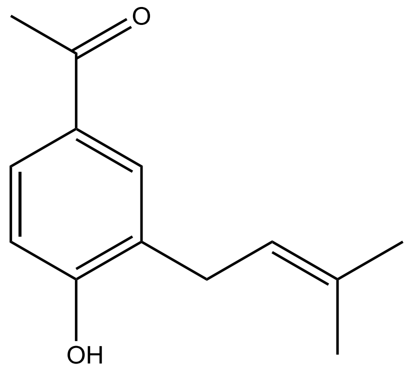


(41)

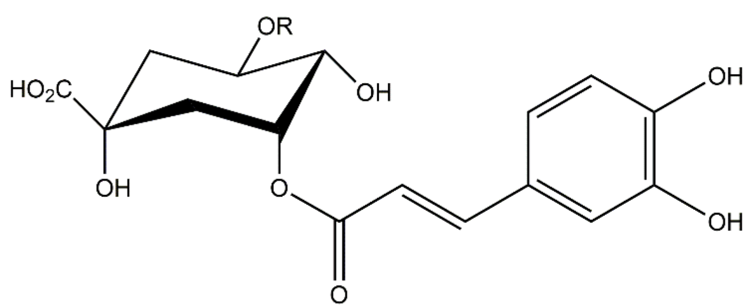
(38) R = R_1 = H
(39) R = Glc, R_1 = H
(43) R = H, R_1 = OCH_3



(42)

Caffeoylquinic acids

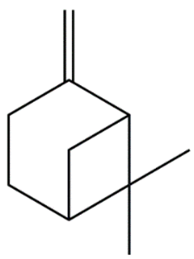
Caffeic acid is formed after a *p*-coumaric acid oxidation which introduces an OH group in *orto*-position to the existent OH. They usually are alone as caffeic acids or combined with quinic acid to form *O*-caffeoylquinic acids (**44**) or di-*O*-caffeoylquinic acids (**45**); in general they are called phenolcarboxylic acids and are very common in plants, in *Werneria* genus they have been reported in *W. nubigena* (Piacente *et al*., 1997).



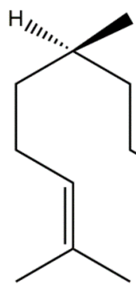
(**44**) R = H
(**45**) R = 3-O-caffeoylquinic acid

Volatile terpenoids

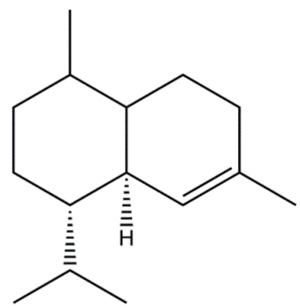
The essential oils of *X. poposum* (=*W. poposa*) from Argentina and Chile have been studied by GC-MS by Gonzáles et al. (2003, 2012), Mercado *et al*. (2015), Benites *et al.* (2011) and Abella *et al*. (2000). A sample of *X. incisum* from Argentina was studied by de Marchese *et al.* (2007). It is clear that we cannot compare these results because there are many factors that can influence the composition of the essential oils; i.e. vegetative cycle, environmental factors, extraction Methods, among others. In general, the essential oils contain 20-60 compounds; we are reporting here only those with a yield greater than 5%. These volatile compounds include terpenoids that are found frequently in other essential oils like β-pinene (**46**), β-citronellol (**47**), δ-cadinene (**48**), γ-cadineno (**49**), T-cadinol (**50**), α-cadinol (**51**); as well as terpenoids that are less common like the tricyclic kessane (**52**), the alcohol incisol (**53**) and the macrocyclic (11C ring) compound zerumbone (**54**). Dihydroeuparin (**7**) is sometimes obtained as part of the essential oil.



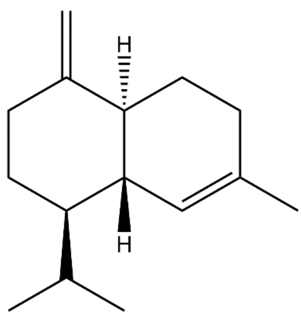
(**46**)



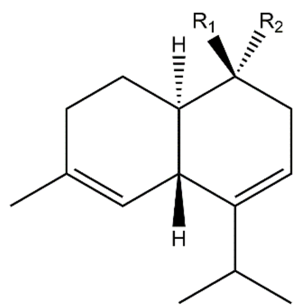
(**47**)



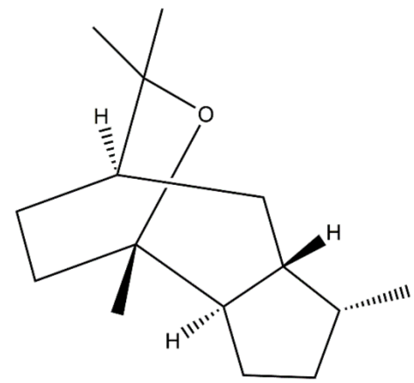
(**48**)



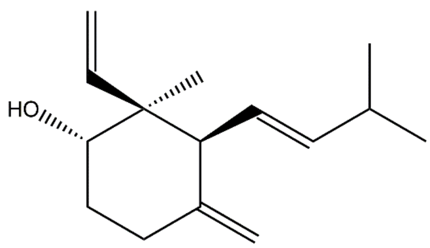
(**49**)



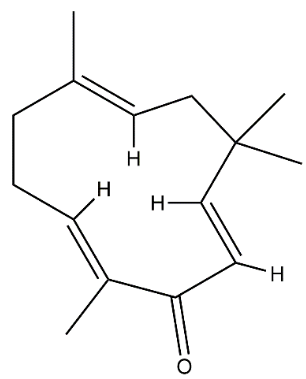
(**50**) R_1 = OH, R_2 = H
(**51**) R_1 = H, R_2 = OH



(**52**)



(**53**)



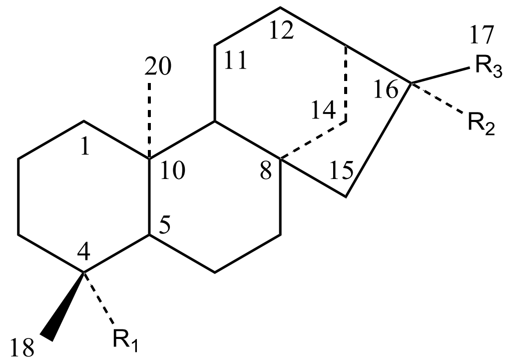
(**54**)

Diterpenes

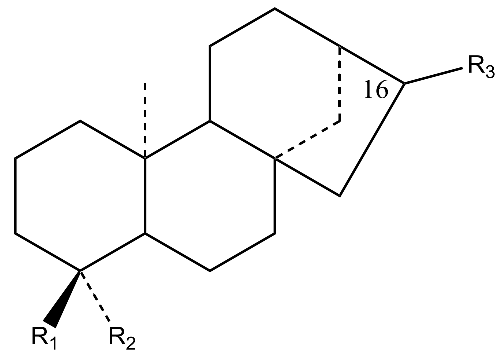
Diterpenes **55-70** found in *Werneria* genus correspond mainly to *ent*-kauran and *ent*- manoyl oxide patterns. The prefix *ent* is used to indicate enantiomeric. Some new structures were found in *W. ciliolata* (Piacente *et al*., 1994): 16α,17-dihydroxy-*ent*-kauran-19-al (**56**) and 16α-methoxy-17-hydroxy-*ent*-kauran-19-al (**57**), 17-nor-16-oxo-kauran-19-oic acid (**59**), *ent*—3β,16-dihydroxy-13-*epi*-manoyl oxide (**67**), 14,15-dihydroxy-*ent*-manoyloxide and acid 17-al-*ent*-kauran-19-oic acid (**70**), this last compound is a dimeric structure between a kaurenoic acid and manoyl oxide units linked by an oxygen atom.

Other known kauran derivative structures found were: kauran-16α-ol (**55**) from *W. poposa* (Córdova *et al*., 1998), **55** and (-)-kaur-16-en-19-oic acid (**58**) from *W. decora* (Lock de Ugaz *et al*., 1990), 17-hydroxy-16α-*ent*-kauran-19-oic acid (**61**) from *W. staffordiae* (Chavez & Lock de Ugaz, 1997), *ent*-kaur-16(17)-en-19-oic acid (**60**), 17-hydroxy-*ent*-kaur-15(16)-en-19-oic acid (**62**), 17-hydroxy-15α, 16α-epoxy-*ent*-kauran-19-oic-acid (**63**) and 17-al-*ent*-kaur-

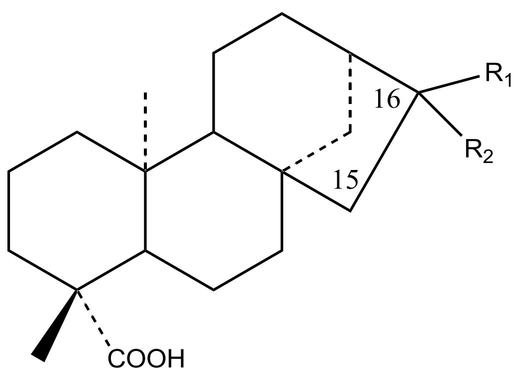
15(16)-*ent*-19-oic-acid (**64**) from *W. ciliolata* (Piacente *et al*., 1994). Manoyloxide compounds like *ent*-13-*epi*-manoyl oxide (**65**), *ent*-16-hydroxy-13-*epi*-manoyl oxide (**66**), *ent*- 14ξ,15ξ -epoxy-13-*epi*-manoyl oxide (**68**) and *ent*-16-hydroxy-14ξ,15 ξ -epoxy-13-*epi*-manoyl oxide (**69**) were found in *Werneria dactylophylla* (De Tommasi *et al*., 1992). Compound **68** was isolated for the first time from a natural source.



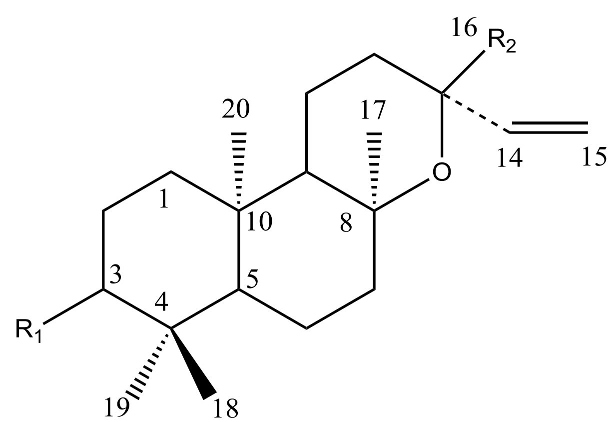
(**55**) $R_1 = R_3 = CH_3$, $R_2 = OH$
(**56**) $R_1 = CHO$, $R_2 = OH$, $R_3 = CH_2OH$
(**57**) $R_1 = CHO$, $R_2 = OCH_3$, $R_3 = CH_2OH$

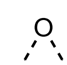
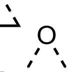


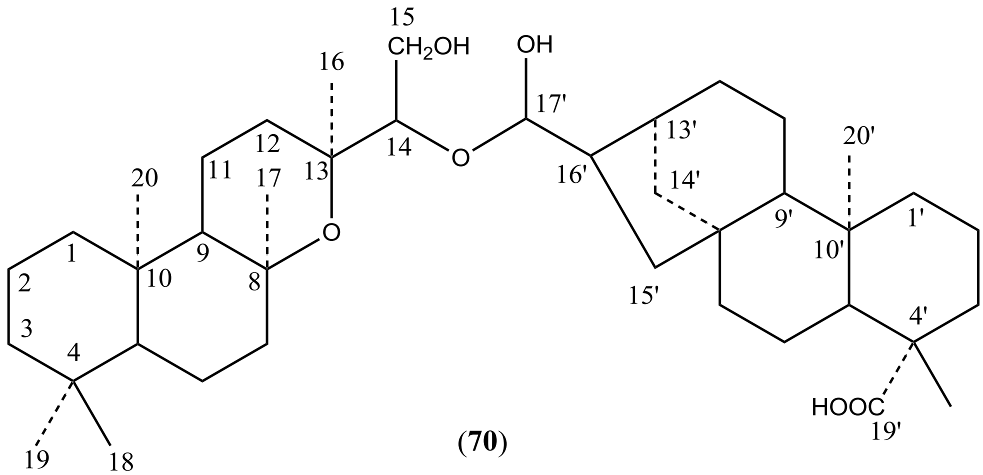
(**58**) $R_1 = COOH$, $R_2 = CH_3$, C_{16}-R_3 = ═
(**59**) $R_1 = CH_3$, $R_2 = COOH$, C_{16}-R_3 = C═O
(**60**) $R_1 = CH_3$, $R_2 = COOH$, C_{16}-R_3 = ═



(**61**) $R_1 = CH_2OH$, $R_2 = H$
(**62**) $R_1 = CH_2OH$, C_{15}-C_{16}= ═
(**63**) $R_1 = CH_2OH$, C_{15}-C_{16} = 
(**64**) $R_1 = CHO$, C_{15}-C_{16} = ═



(**65**) $R_1 = H$, $R_2 = CH_3$
(**66**) $R_1 = H$, $R_2 = CH_2OH$
(**67**) $R_1 = OH$, $R_2 = CH_2OH$
(**68**) $R_1 = H$, $R_2 = CH_3$, C_{14}-C_{15}= 
(**69**) $R_1 = H$, $R_2 = CH_2OH$, C_{14}-C_{15} = 

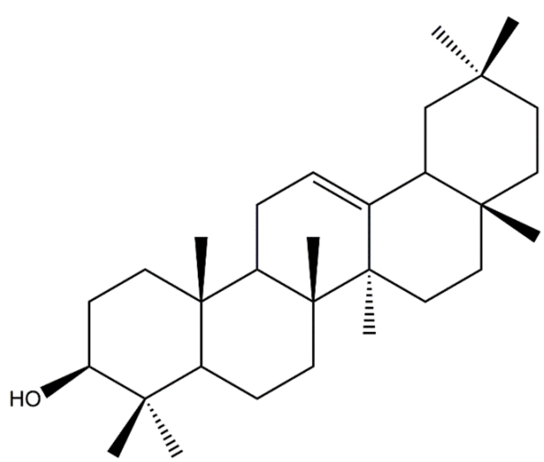


(**70**)

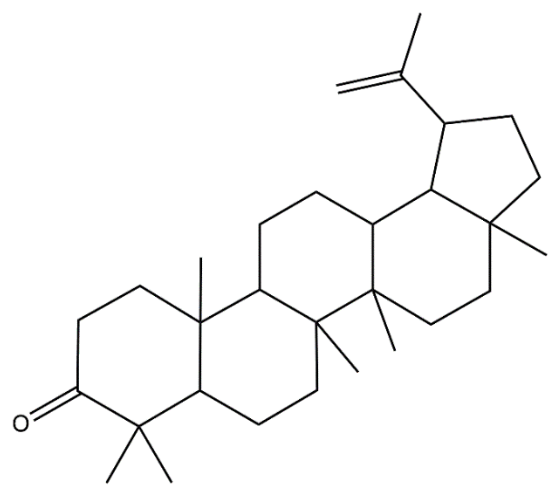
Triterpenes and Steroids

Few triterpenes (**71**- **74**) and steroids have been detected or isolated from *Werneria* species. Triterpenes are found in many different skeletons mainly as tetracyclic and pentacyclic rings. Very common pentacyclic triterpenes like β-amirin (**71**), lup-20(29)-en-3-one (**72**), friedours-7-en-3-one (**73**), friedolean-6-en-3-one (**74**) were reported for *W. nubigena* (Castro *et al*., 2000). β-amirin was also isolated from *W. pigmea* (Aguilar *et al.*, 2000).

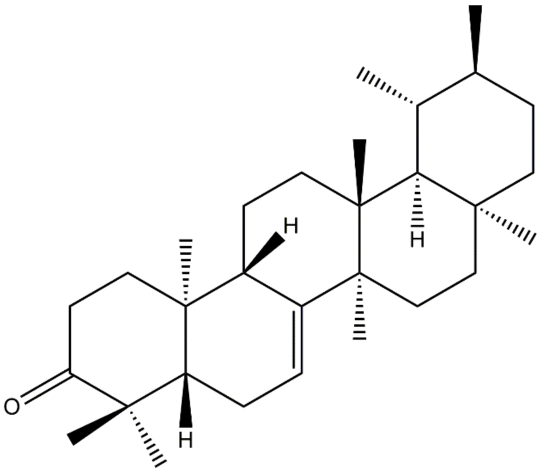
In these same species, only β-sitosterol and stigmasterol derivatives like stigmast-5,23-dien-3β-ol, stigmast-5,28-dien-3β-ol, stigmasta-5,22-dien-3-ol and stigmast-5-en-3-one were reported (Castro *et al*., 2000; Aguilar *et al*., 2000).



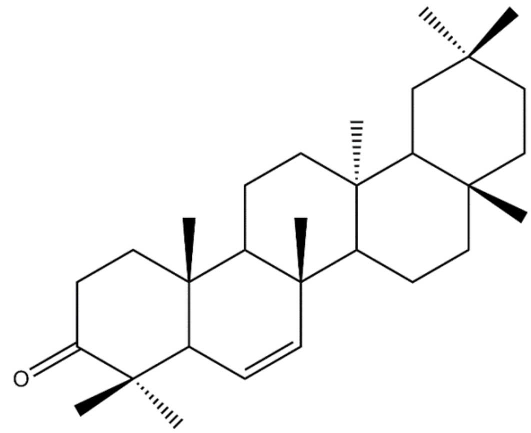
(**71**)



(**72**)



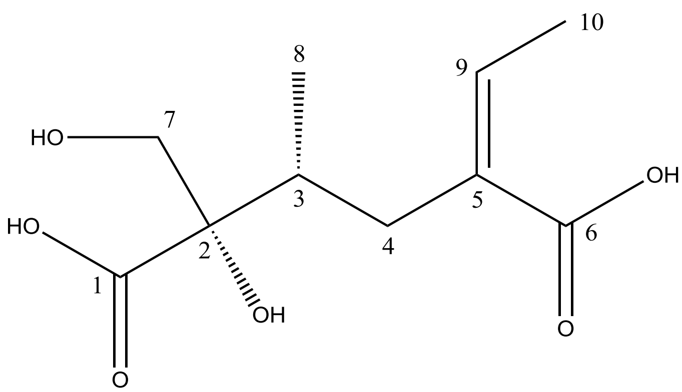
(73)



(74)

Hydrocarbons and acids

We considered not as important to describe the hydrocarbons and carboxylic acid open chains that have been detected or isolated in *Werneria* or *Xenophyllum* species, except for isatinecic acid (**75**) (Lock de Ugaz *et al*., 1990), a dicarboxylic acid which can form a macrocyclic diester (12C) with the alkaloid retronecine and other derivatives.



(**75**)

Biological activities

A whole plant decoction of *Werneria villosa* is traditionally used for improving blood circulation, to treat general body pain and uterus swelling (Macía *et al*., 2005).

Werneria dactylophylla is a plant used in Peruvian traditional medicine as a home remedy for inflammatory and gastrointestinal diseases (Valdizan & Maldonado, 1922).

Werneria poposa is used mainly as an infusion of leaves and stems for the treatment of "soroche" (mountain sickness). Other uses include as a digestive or to treat coughs and bronchitis (Abella *et al*., 2000). Martinez *et al*. (2006) reported that *W. incisa* and *W. poposa* are used in traditional Chilean medicine for the treatment of hypertension and mountain sickness.

Werneria nubigena is used as a tea because of its digestive and antihelmintic properties (Fournet *et al*., 1994). The ethanol extract of the whole plant of *Werneria nubigena* showed activity *in vitro* against *Leishmania braziliensis*, *L. amazonensis* and *L. donovani* at a concentration of 100 µg/mL (Fournet *et al*., 1994; Rocha *et al*., 2005).

Erazo *et al*. (2006) found that, at a concentration of 100 µg/mL, the essential oil, hexane, dichloromethane and methanol extracts of *Xenophyllum poposum* showed antimicrobial activity *in vitro* against *Staphylococcus aureus*, *Bacillus subtilis* and *Saccharomyces cerevisiae*. The topical application of dichloromethane and hexane extracts of *X. poposum* decreased 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-induced mouse ear edema by 80.9% and 60.6%, respectively. These results were compared to indomethacin, which reduced edema by 92.9%. These extracts showed also good analgesic activity in the acetic acid-induced writhing test. They caused an inhibition in the writhing response by 62.2% and 57.1%, respectively, which were similar to the inhibition showed by ibuprofen (76.5%).

The hydroalcoholic extract of *X. poposum* administered orally at 40 mg/kg significantly reduced blood pressure and heart rate in normotensive rats. The hypotensive activity is due in part to the decrease in heart rate and increased vasodilation. The compounds that caused the greatest vasodilation were 4-hydroxy-3-(3-methyl-2-butenyl) acetophenone (**42**) and dihydroeuparin (**7**). These results could support the use *X. poposum* in traditional medicine in the treatment of altitude sickness and hypertension (Palacios *et al*., 2018).

The essential oil of *X. poposum* collected in Argentina showed good antimicrobial activity *in vitro* against the bacterium methicillin-resistant *Staphylococcus aureus* and the fungi *Trichophyton rubrum* and *Aspergillus fumigatus*, the MIC values were 0.25, 0.05 and 0.025 mg/mL, respectively. The antimicrobial activity of the methanol extract was very similar to the one reported for the essential oil. The most active compound isolated from *X. poposum* methanol extract was dihydroeuparin (**7**), this compound was very active against *A. fumigatus*, although its MIC value was equal to that of the essential oil (0.025 mg/mL) (González *et al*., 2012).

Piacente *et al*. (2004) tested the anti-HIV activity *in vitro* of the compounds isolated from *Werneria ciliolata* and *W. dactylophylla*. The *p*-hydroxyacetophenones and benzofurans were inactive, however, interesting results were obtained with the compound dihydroeuparin (7) that was isolated from *W. dactylophylla* (Piacente *et al*., 1994). At a concentration of 16 µg/mL, dihydroeuparin was able to reduce by 50% the P24 antigen in infected cell cultures, while at a concentration of 40 µg/mL it inhibited by 50% the growth of the uninfected C8166 cells (TC_{50}). The drug AZT was used as a positive control; this compound was very active *in vitro* (EC_{50}= 0.016 µg/mL) and showed very low toxicity (TC_{50}>1000 µg/mL) (Piacente *et al*., 1994).

Artemia salina, the brine shrimp larva, was used to determine the toxicities of Plicatin A and Plicatin B. The medium lethal concentrations (LC_{50}) of both compounds were 0.96 ± 0.17 ppm (Bravo *et al*., 2009).

Ávila Illanes *et al*. (2011) found a LD_{50} greater than 5000 mg/kg for the aqueous extract of *Werneria dactylophylla* (pupusa) when administered orally to albino Swiss mice.

Although *Werneria* and *Xenophyllum* extracts are used in traditional medicine and show no toxicity in animals, it has to be taken into account that they contain Pyrrolizidine alkaloids (PAs) that can cause veno-occlusive disease and liver damage. The acute toxic effects of PAs are characterized by hemorrhagic necrosis, hepatomegaly and ascites; while chronic intoxication causes necrosis, cirrhosis, liver failure and death. PAs with 1,2 double bond, like for example retronecine and **1,** are associated with hepatic toxic effects. PAs with cyclic diesters, like in structures **2-6**, are considered the ones with the highest toxicity (Moreira *et al*., 2018).

The compound 4-hydroxy-3-(isopenten-2'-yl)-acetophenone (**42**) is the main secondary metabolite of the aerial parts of *Senecio nutans* and *X. poposum*. At a concentration of 5 mg/L this compound showed a synergistic effect in combination with Fluconazole or with Caspofungin against *Candida albicans* ATCC 10231. Such synergistic activity could be explained by the fact that these compounds have different mechanisms of action. Fluconazole inhibits the synthesis of ergosterol, Caspofungin inhibits cell wall β-glucan synthesis and 4HMBA inhibits *C. albicans* filamentation (Soberón *et al.*, 2015).

The benzofuran derivative dihydroeuparin can be found in *Werneria ciliolata* and in the shrub *Senecio graveolens* with isolation yields of near 3%. Photochemical and photophysical results indicate that this benzofuran can be considered as a sunscreen for the 270-340 nm zone, with high photostability, low water solubility and high solubility in miscellar system (Ortega *et al*., 2000).

CONCLUSIONS

Werneria and *Xenophyllum* species are plants that are widely used in traditional medicine for the treatment of hypertension, mountain sickness and inflammatory disorders. Some interesting anti-HIV, antifungal and photoprotective activities have been reported. However, it has to be noted that these plants contain pyrrozilidine alkaloids that could be hepatotoxic. Only 9 species of *Werneria* and 2 of *Xenophyllum* have been studied for their chemical and biological activities; thus, there are more than 50 species that deserve to be further investigated.

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