REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Genus *Chiliadenus* is a Unique Supplier of Several Chemical Flocks

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Received on: 27. 11. 2020

Revised on: 17. 12. 2020

Accepted on: 25. 12. 2020

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Abstract

Nature stands as an infinite resource for drug development, novel chemotypes and pharmacophores. Natural products have high structural diversity and unique pharmacological activities that can be used in treating various kinds of diseases. They have been the backbone for almost half of U.S. Food and Drug Administration (FDA) approved drugs .Medicinal plants have been utilized by humans for millennia as they serve as safe and effective therapeutic agents. *Asteraceae* is the largest family of plant kingdom with more than 25,000 species around the globe. *Chiliadenus* Cass., a small genus of ten species of the Inuleae-Inulineae of the daisy family (*Asteraceae*) consisting of ten species with allopatric distributions along the southern edge of the Mediterranean Sea. Phytochemical investigation of chiliadenus genus afforded the isolation of numerous natural compounds of several classes. The current review revealed that genus *Chiliadenus* is a precious source of monoterpenes, sesquiterpenes, diterpenes and methoxy flavonoids and it possesses several medicinal uses.

Key words: Natural products, *Asteraceae*, *Chiliadenus*.

1. Introduction

Natural products have played an essential role throughout the world in the treatment and prevention of human diseases. The majority of new drugs have been discovered from natural products and from compounds derived from natural products. According to the National Cancer Institute, natural products inspired 61% of the 877 small molecule new chemical entities introduced as drugs worldwide during 1981 – 2002 **(Newman *et al.*, 2003)**. Natural products are a precious source for new drugs and also are lead compounds that can undergo further modification during drug development. They show more " drug likeness and biological friendliness " than totally synthetic making them good candidates for further drug development **(Chin *et al.*, 2016)**. The rich chemical diversity of the plant kingdom is largely made up of an inspirational startling array of natural products. Medicinal plants constitute a

tremendous resource of potential medicines for all of humanity. It is well known that many of these plants contain potent biologically active compounds and at least 25% of the drugs presently used in modern medicine are derived from plants **(Lahlou, 2007)**.

Family Asteraceae is the largest family of the flowering plants and the widest spread. It includes about 1600 genera and 25000 species forming about 10% of the world flora **(Boulos, 2002)**. *Chiliadenus* Cass., a small genus of ten species of the Inuleae-Inulineae of the daisy family **(Englund *et al.*, 2009)**, consisting of woody perennial herbs or shrublets with (mostly) discoid heads and yellow flowers **(Englund *et al.*, 2009) ;(Nylinder and Anderberg, 2015)**. The species of the genus have often been treated as members of *Jasonia* Cass. and/ or *Varthemia* DC. in foras, but were moved into the genus *Chiliadenus* by **(Brullo, 1979)** based on morphology. *Chiliadenus montanus* (Vahl.) Brullo [= *Jasonia montana*, *Varthemia montana* (Vahl.) Boiss] known as Heneida **(Taeckholm, 1974)**, a medicinally used herb indigenous to Sinai Peninsula **(Boulos, 2002)** belongs to the Asteraceae (Compositae) family. *C. montanus* occurs in the Mediterranean and adjacent areas, desert east of the Nile, El-Tih Desert east of the Suez Canal and rocky wadis and hillsides of Sinai Peninsula in Egypt, Palestine, and Arabia **(Taeckholm, 1974) (Boulos, 2002)**.

In addition, Danin recorded *C. montanus* in crevices and fissures of smooth-faced hard limestone and dolomite rock outcrops of southern Sinai **(Danin, 1978)**.

C. montanus is considered by Abd El-Wahab *et al.* **(El-Wahab *et al.*, 2008)** as one of the vulnerable medicinal plant species growing in Sinai. *C. montanus* is yellowish-green, appressed-pubescent glandular low shrub, 20-60 cm; stems much branched; leaves 1-2 x 0.3-0.7 cm, oblong-elliptic or oblanceolate, sessile, glandular-hairy on both surfaces, the margins undulate, the apex acute or obtuse; capitula numerous, solitary, in broad lax paniculate inflorescence to 40 cm; peduncle 1-2.5 cm, bracteates; involucre 1-1.2 cm, campanulate; phyllaries 3-4 seriate, loosely imbricate, glandular-hairy, yellow, the outer and middle greenish at the obtuse apex; inner scarious and longer; achenes 3-3.5 x 0.5-0.6 mm, ellipsoid, densely hairy and pappus 4-5 mm of reddish brown bristles **(Boulos, 2002)**. *C. montanus* is reported to be used in folk medicine by Bedouins **(Zaghloul and Moustafa, 2004)** to treat diarrhea, flu, stomachache, chest and kidney diseases **(Hussein, 2011)**. That's why it is subjected to cutting by Bedouins for their primary healthcare needs. It is also used as a herbal tea for the treatment of renal troubles **(soliman *et al.*, 2009)**. Thus, it is extensively sold in local herbal markets, which affects the occurrence and distribution of the species. Phytochemical investigation of genus *Chiliadenus* has led to the isolation and identification of numerous bioactive phytoconstituents of diverse chemical classes. Based on the aforementioned reports, the aim of this review is to provide a comprehensive update on the chemistry of genus *Chiliadenus* belonging to family *Asteraceae*.

2. Chemical constituents reported from some species of *Chiliadenus*:

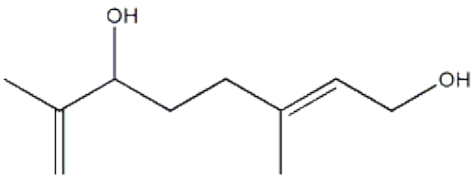
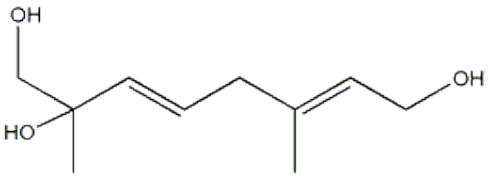
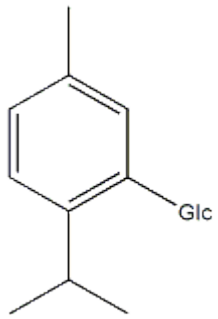
2.1. Chemical constituents of genus *Chiliadenus*:

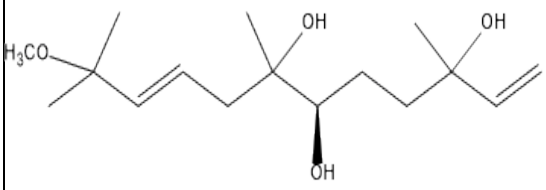
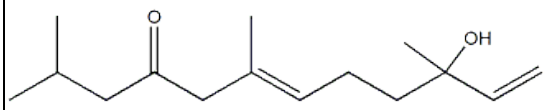
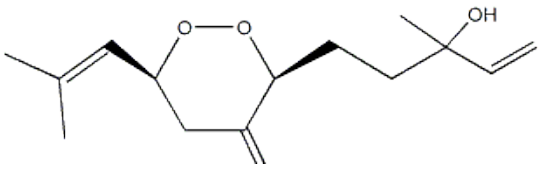
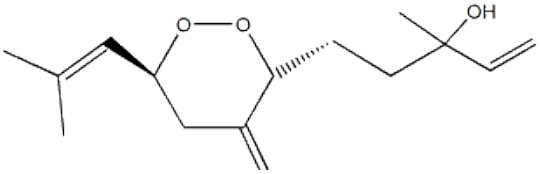
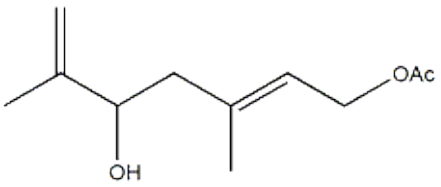
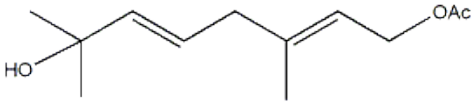
Phytochemical investigation of genus *Chiliadenus* has led to the isolation and identification of numerous bioactive phytoconstituents of diverse chemical classes.

2.1.1. Monoterpenes:

Several monoterpenes have been isolated from genus *Chiliadenus*. The aerial parts of *C. montanus* afforded two geraniol derivatives which are 1,6-Dihydroxy-3,7-dimethyl-octa-2*E*,7-diene and 1,7,8-trihydroxy-octa-2*E*,6*E*- diene along with Thymol-*β*-glucopyranoside **(Ahmed and Jakupovic, 1990)**, Chiliadenol A, B, C, D **(Hegazy *et al.*, 2014)** and two derivatives of geranyl acetate named 6 – Hydroxy-7 (9) dehydro-6,7 dihydrogeranyl acetate **(Zdero *et al.*, 1986)** and 7-Hydroxy -5, 6*E* dehydro-6,7 dihydrogeraneryl acetate **(Fraser and Lewis, 1973)** were also reported in genus *Chiliadenus*. The structures of the isolated compounds were listed in (**Table 2)**.

Table (2): Monoterpenes reported in genus *Chiliadenus*.

Species	Compound Name	Compound structure	Reference
C. montanus	1, 6-Dihydroxy-3, 7-dimethyl-octa-2*E*, 7-diene		(Ahmed and Jakupovic, 1990)
C. montanus	1, 7, 8-Trihydroxy-octa-2*E*, 6*E*- diene		(Ahmed and Jakupovic, 1990)
C. montanus	Thymol-*β*-glucopyranoside		(Ahmed and Jakupovic, 1990)

C. montanus	3, 6, 7-trihydroxy-11-methoxy-3, 7, 11-trimethyldodeca-1, 9-diene (Chiliadenol A)		(Hegazy *et al.*, 2014).
C. montanus	3-hydroxy-3, 7, 11-trimethyl-1, 6-dodecadien-9-one (Chiliadenol B)		(Hegazy *et al.*, 2014).
C. montanus	3-hydroxy-3, 11-dimethyl-6*β*, 9*α*-epidioxy-dodeca-1, 7(14), 10, triene (Chiliadenol C)		(Hegazy *et al.*, 2014).
C. montanus	3-hydroxy-3, 11-dimethyl-6*α*, 9*α*-epidioxy-dodeca-1, 7(14), 10-triene (Chiliadenol D)		(Hegazy *et al.*, 2014).
C. montanus	6 – Hydroxy-7(9) dehydro-6, 7 dihydrogeranyl acetate		(Zdero *et al.*, 1986)
C. montanus	7-Hydroxy -5,6*E* dehydro-6, 7 dihydrogeraneryl acetate		(Fraser and Lewis, 1973)

2.1.2. Sesquiterpenes:

Numerous sesquiterpenes heve been isolated from genus *Chiliadenus*. The structures of the isolated compounds were listed in (**Table 3)**.

2.1.2.1. Costic acid derivatives:

Phytochemical investigation of *C. montanus* afforded costic acid derivatives; 3-oxo-γ-costic acid *β*-D-glucopyranoside ester, 3*β*-methoxy isocostic acid, 3*α*-methoxy isocostic acid **(Hegazy *et al.,* 2014)**, 5*α*-Hydroxycostic Acid, 5 *β* - Hydroxycostic acid and 3*α*, 5*α*-Dihydroxycostic acid **(Ahmed and Jakupovic, 1990)**.

2.1.2.2. Eudesmanes:

Several sesquiterpenes of eudesmane type were reported in genus *Chiliadenus* which were the seco- eudesmane derivatives named 11-Hydroxy-4, 5-seco-eudesmune-4,5dione **(Zdero *et al.,* 1987)**, the epimeric 5-hydroxy-*β*-eudesmols, 5*α*-Hydroxy-*β* eudesmol and 5*β*-Hydroxy-*β*-eudesmol, the δ-lactone eudesm-4(15), 11(13)-diene-12,5*β*-oIide **(Ahmed and Jakupovic, 1990)** and the other eudesmane derivatives called eudesm-11,13 ene-1*β*,4*β*,7*α*-triol **(Hegazy *et al.,* 2014)** and eudesmane-1β, 4β, 7α-triol **(Sung *et al.,* 1992)**. Sánchez-Martínez and co-workers reported two eudesmane alcohols; called (11 R)-eudesm -4-en-11, 12-diol and (11 R)-eudesmane-5*α*, 11, 12-triol **(Sánchez-Martínez *et al.,* 2000)**. Besides, in 2000 Villaescusa-Castillo and co-workers reported [11R]-eudesm-4(14)-en- 5*β*, 11, 12 triol and [11R]-eudesm-4(14)-en-5*α*, 11–12-triol from *C. glutinosus* **(Villaescusa-Castillo *et al.,* 2000)**. Ahmed and his research team have investigated the *n*-hexane-Ethyl acetate –Methanol (1:1:1) extract of air dried leaves of *C. candicans* and isolated a rare eudesmane containing a 6/6/4 membered ring system (Jasonol) and two 7-epi-eudesmanes named 12-hydroxyisointermedeol and 7-epi-ilicic acid **(Ahmed and Mahmoud, 1998)**. Moreover, phytochemical study of *C. montanus* led to the isolation of the rearranged eudesmane 3*β*-11-Dihydroxyisoiphion-4-one, 3-*β* - Hydroxyisoiphion-11(13)-en-12-oic acid **(Ahmed and Jakupovic, 1990)**, isoiphionane sesquiterpene montanone **(El-Bassuony and Kabbash, 2006)** and nor eudesmane Jasomontanone **(Ahmed and Jakupovic, 1990)**. Chemical investigation of *C. candicans* afforded the iphionane derivative named 4-Oxo-lphionan-3(5), 11(13)-dien-12-oic acid) and the cadinane-triol named 3*β*, 4*β*, 10*α*-Trihydroxy-1*β*, 6*α*, 7*β* (H)-cadinane **(Ahmed and Mahmoud, 1998)**.

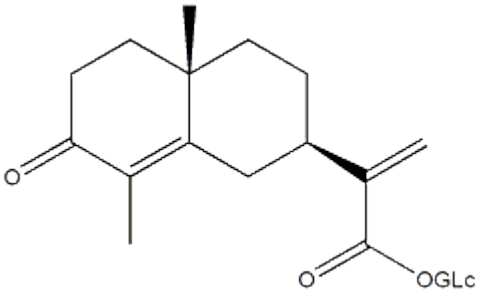
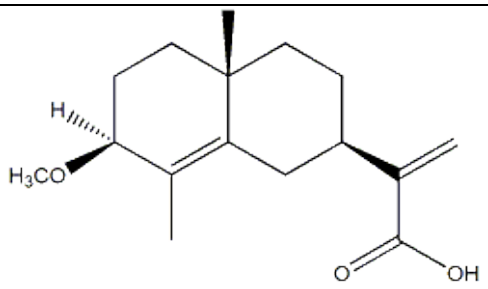
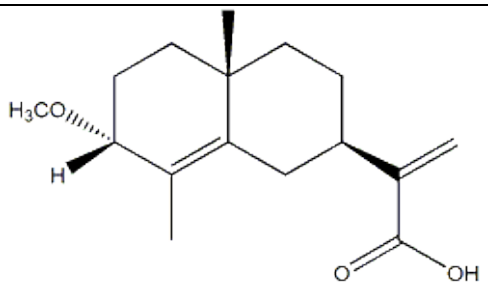
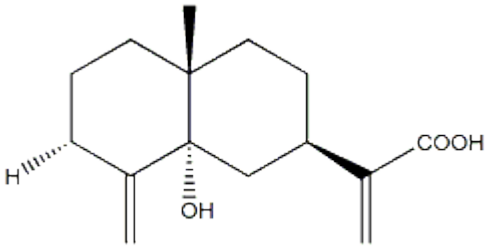
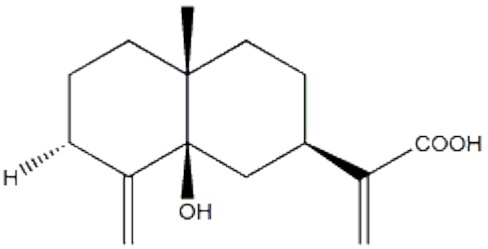
2.1.2.3. Germacranolides and guaianolides:

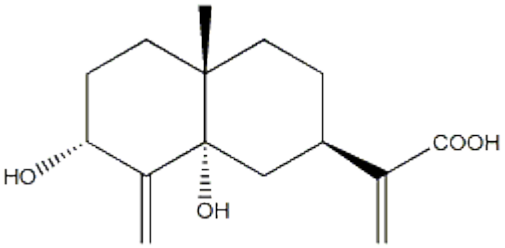
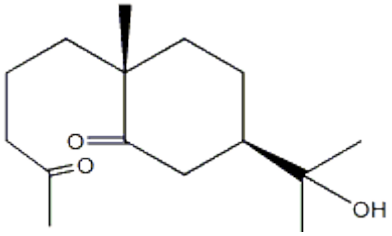
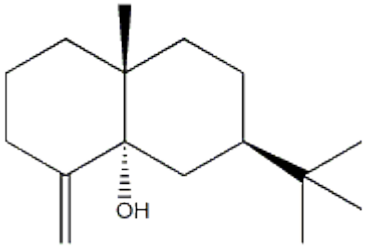
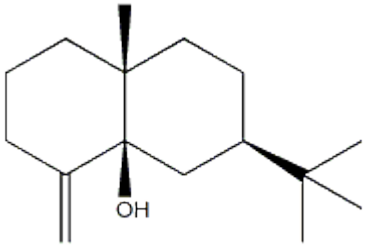
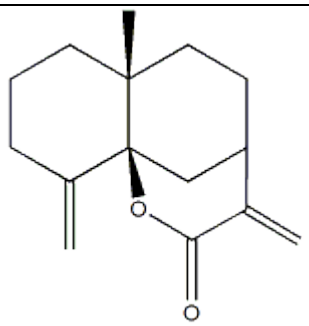
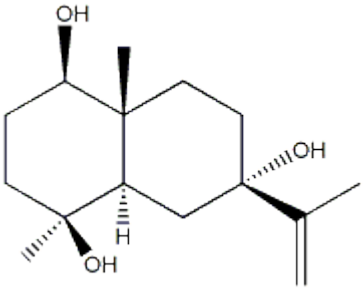
Phytochemical investigation of *C. montanus* afforded two sesquiterpenes characterized as germacradiene 6*β*, 9*α* diol designated as *α*-pulignene and its *β*-isomer germacradiene-6*β*, 9*β* diol named as *β*-pulignene **(Ahmed *et al.,* 2004)**.In addition, two guaianolides named l*β*-hydroxy-8-epi-inuviscolide and 5*β*-hydroxy-10*α*, 14H-4- epi-inuviscnlide (**Ahmed and Mahmoud, 1998)**.

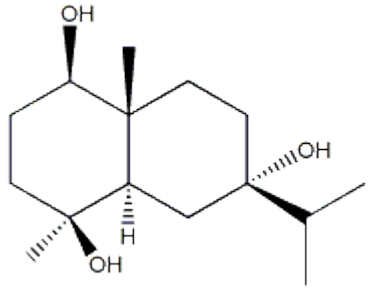
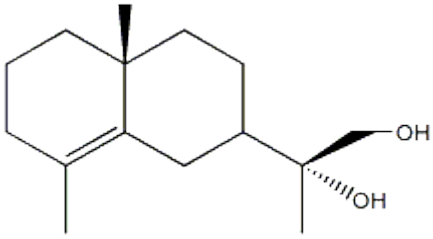
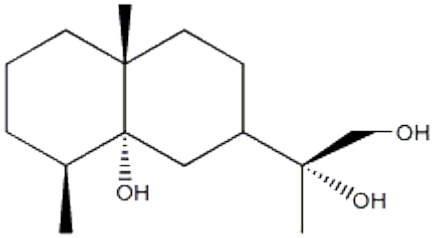
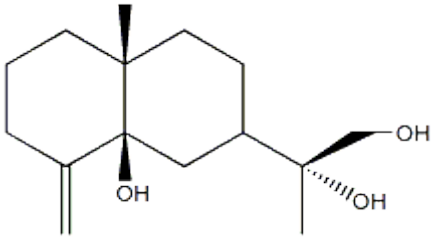
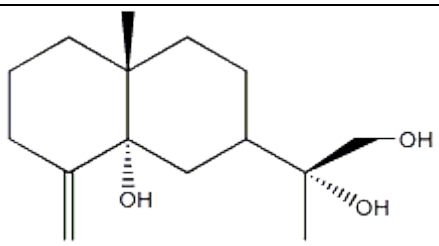
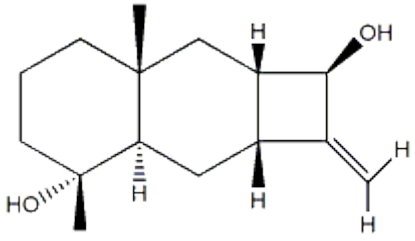
2.1.2.4. Other Sesquiterpenes types:

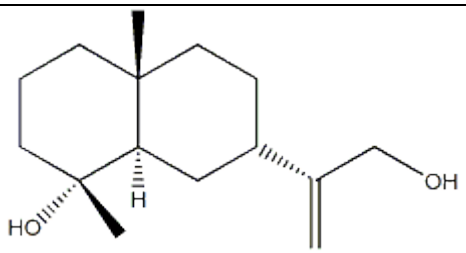
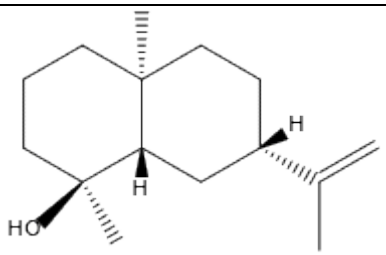
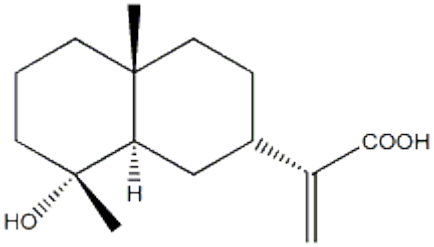
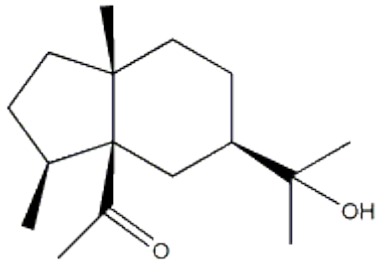
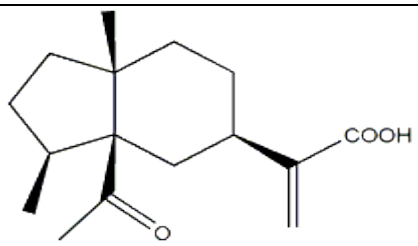
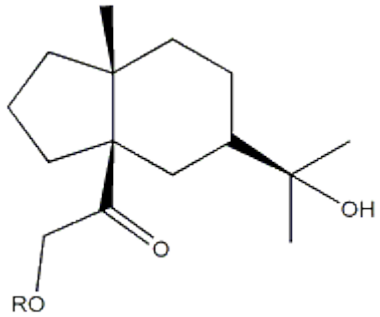
The unusual eight-membered ring ketone named 11-hydroxyjasionone **(Ahmed *et al.,* 1988)** and two natural nor-sesquiterpene; jasonone and teuhetenone A **(Mohamed, 2007)** were isolated from *C. montanus* .Moreover, four sesquiterpenes named lucinone , glutinone , 5-*epi*-kutdtriol and kutdtriol **(Benito *et al.,* 2002)** were isolated from *C. glutinosus*.

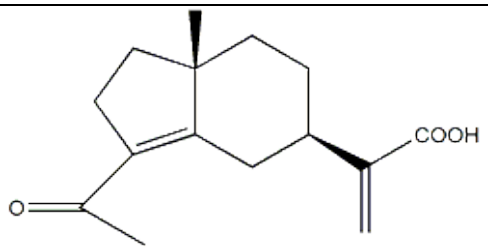
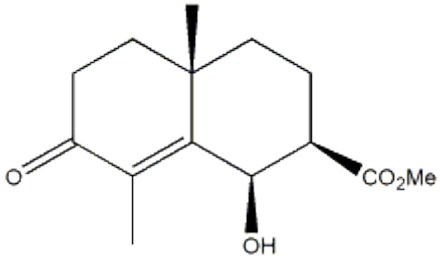
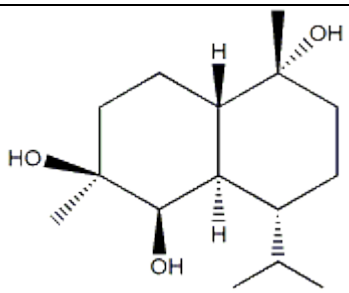
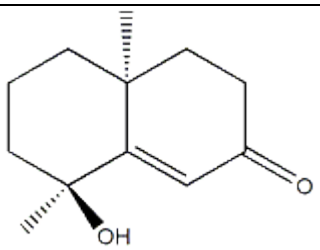
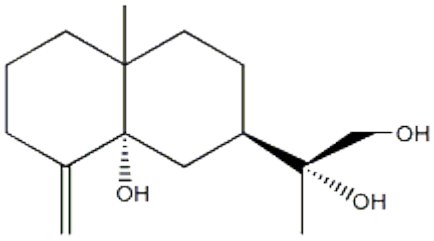
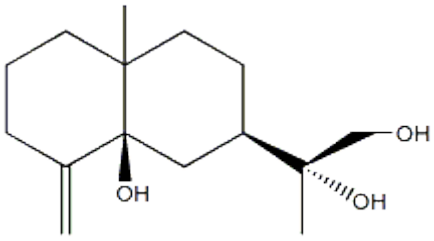
Table (3): Sesquiterpenes reported in genus *Chiliadenus*:

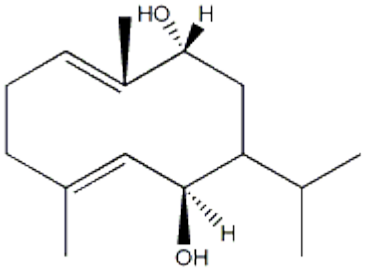
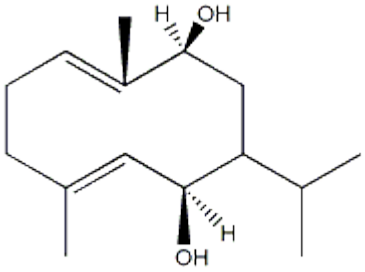
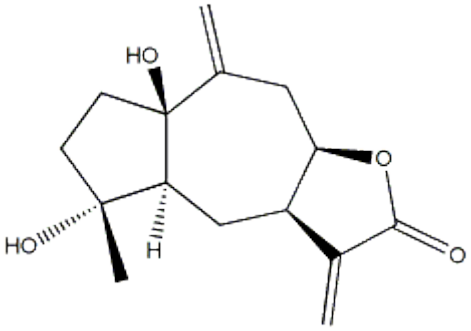
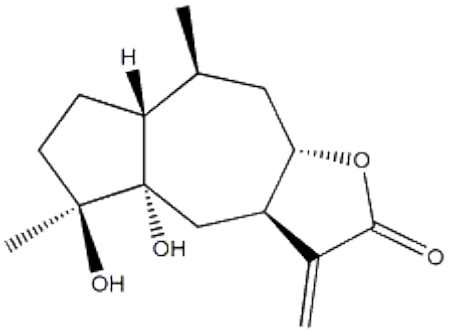
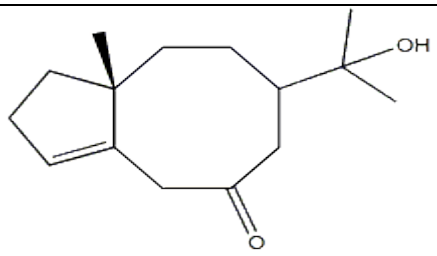
Species	Compound Name	Compound structure	Reference
C. montanus	3-oxo- γ -costic acid *β*-D-glucopyranoside ester		(Hegazy *et al.*, 2014)
C. montanus	3*β*-methoxy isocostic acid		(Hegazy *et al.*, 2014)
C. montanus	3*α*-methoxy isocostic acid		(Hegazy *et al.*, 2014)
C. montanus	5 *α*-Hydroxycostic acid		(Ahmed and Jakupovic, 1990)
C. montanus	5 *β* -Hydroxycostic acid		(Ahmed and Jakupovic, 1990)

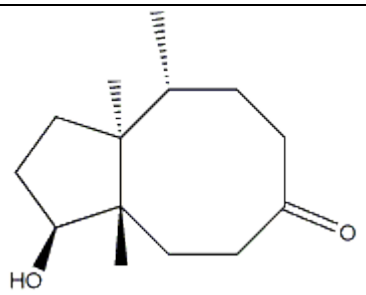
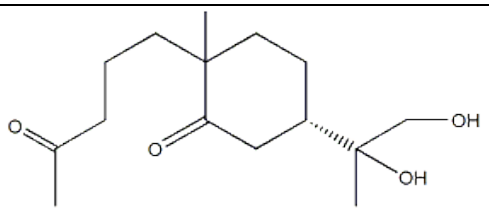
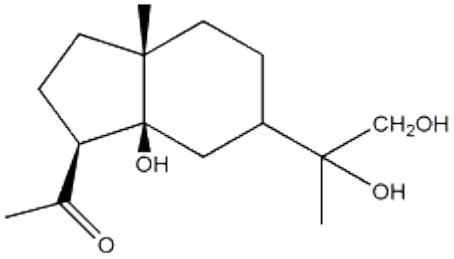
C. montanus	3*α*, 5*α*-Dihydroxycostic acid		(Ahmed and Jakupovic, 1990)
C. montanus	11-Hydroxy-4, 5-seco eudesmune 4,5 dione		(Zdero *et al.*, 1987)
C. montanus	5*α*-Hydroxy-*β* eudesmol		(Ahmed and Jakupovic, 1990)
C. montanus	5*β*-Hydroxy-*β*-eudesmo1		(Ahmed and Jakupovic, 1990)
C. montanus	Eudesm-4(15), 11(13)-diene-12, 5*β*-oIide		(Ahmed and Jakupovic, 1990)
C. montanus	Eudesm-11,13-ene-1*β*, 4*β*, 7*α*-triol		(Hegazy *et al.*, 2014)

C. montanus	Eudesmane-1*β*, 4*β*, 7*α*-triol		(Sung *et al.*, 1992)
C. glutinosus	(11 R)-eudesm -4-en-11, 12-diol		(Sánchez-Martínez *et al.*, 2000)
C. glutinosus	(11 R) - eudesm ane-5*α*, 11, 12-triol		(Sánchez-Martínez *et al.*, 2000)
C. glutinosus	[11R]-eudesm-4(14)-en- 5*β*, 11, 12 triol		(Villaescusa-Castillo *et al., 2000*)
C. glutinosus	[11R]-eudesm-4(14)-en- 5*α*, 11, 12-triol		(Villaescusa-Castillo *et al.*, 2000)
C. candicans	Jasonol		(Ahmed and Mahmoud, 1998)

C. candicans	12-hydroxy isointermedeol		(Ahmed and Mahmoud, 1998)
C. montanus	Isointermedeol		(Thappa *et al.*, 1979)
C. candicans	7-epi-ilicic acid		(Ahmed and Mahmoud, 1998)
C. montanus	3*β*-11-Dihydroxyisoiphion-4-one		(Ahmed and Jakupovic, 1990)
C. montanus	3*β*-Hydroxyisoiphion-11(13)-en-12-oic acid		(Ahmed and Jakupovic, 1990)
C. montanus	11, 15-dihydroxy-iphionane-4-one (Montanone)		(El-Bassuony and Kabbash, 2006)

C. candicans	4-Oxo-lphionan-3(5), 11(13)-dien-12-oic acid		(Ahmed and Mahmoud, 1998)
C. montanus	Jasomontanone		(Ahmed and Jakupovic, 1990)
C. candicans	3*β*, 4*β*, 10*α*-Trihydroxy-1*β*, 6*α*, 7*β* (H)-cadinane		(Ahmed and Mahmoud, 1998)
C. montanus	Teuhetenone A		(Mohamed, 2007)
C. glutinosus	Kutdtriol		(Benito *et al.*, 2002)
C. glutinosus	5-epi-kutdtriol		(Benito *et al.*, 2002)

C. montanus	Germacradiene 6*β*, 9*α* diol (*α* –pulignene)		(Ahmed *et al.*, 2004)
C. montanus	germacradiene-6*β* , 9*β* diol (*β*-pulignene)		(Ahmed *et al.*, 2004)
C. candicans	l*β*-hydroxy-8-epi-inuviscolide		(Ahmed and Mahmoud, 1998)
C. candicans	5*β*-hydroxy-10*α*, 14H-4- epi-inuviscnlide		(Ahmed and Mahmoud, 1998)
C. montanus	11-hydroxyjasionone		(Ahmed *et al.*, 1988)

C. montanus	4-hydroxy-5,10-dimethyl-octahydro-azulen-8-one(1) (Jasonone)		(Mohamed, 2007)
C. glutinosus	Lucinone		(Benito *et al.*, 2002)
C. glutinosus	Glutinone		(Benito *et al.*, 2002)

2.1.3. Diterpenes:

Diterpene compounds are not common in *Chiliadenus* species, they were only isolated from *C. montanus* **(Al-Howiriny *et al.*, 2005)**. Three diterpenes namely jasonin-a , jasonin-b and jasonin-c were isolated from *C.montanus*. Their structures were listed in **(Table 4)**.

2.1.4. Flavonoids:

Phytochemical investigations of the genus *Chiliadenus* revealed the presence of several methoxy flavonoids as shown in **(Table 5).**

2.2. Biological activities reported from genus *Chiliadenus*:

2.2.1. Antibacterial Activity:

Zeedan and coworkers reported that *C. montanus* acetone extract exhibited highest antibacterial activity against S. agalactiae, E. coli, S. aureus, Klebsiella spp and coagulase-negative Staphylococci when compared to the antibacterial activity of Artemisia herb alba plant acetone extract. Other extracts of *C. montanus* and A. herb alba with petroleum ether, methanol and chloroform solvent exhibited less antibacterial activities than acetone solvent extract **(Zeedan *et al.*, 2014)**.

Table (4): Diterpenes reported in genus *chiliadenus:*

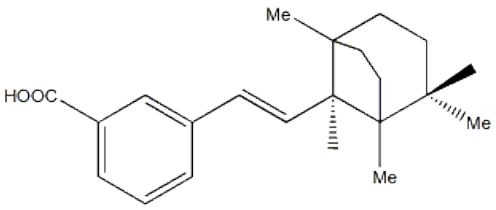
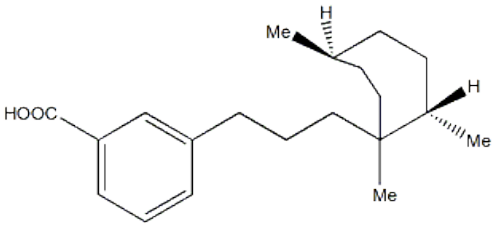
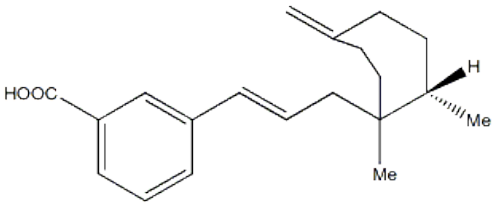
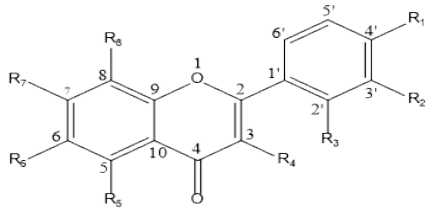
species	Compound Name	Compound structure	Reference
C. montanus	[(1*E*)-2-((2*S*)-1,2,5-trimethylbicyclo[3.2.1]octan-8-yl)vinyl]benzene-3carboxylicacid (Jasonin-a)		(Al-Howiriny *et al.*, 2005)
C. montanus	,[3-((2*S*,5*S*)-1,2,5-trimethylcycloheptanyl)propyl]benzene-3-carboxylicacid (Jasonin-b)		(Al-Howiriny *et al.*, 2005)
C. montanus	[(1*E*)-3-((7*R*)-1,7-dimethy-4-methylenecycloheptanyl)prop-1-enyl]benzene-3-carboxylicacid (Jasonin-c)		(Al-Howiriny *et al.*, 2005)

Table (6): Flavonoid aglycones reported in genus *chiliadenus*



Species	Compound Name	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Ref
C. montanus	5,7- dihydroxy-3,3',4'-trimethoxyflavone	OCH_3	OCH_3	H	OCH_3	OH	H	OH	H	(Hamed *et al.*, 2016)
C. montanus	5,4`-dihydroxy-3,6,7,3`-tetramethoxyflavone	OH	OCH_3	H	OCH_3	OH	OCH_3	OCH_3	H	(Hamed *et al.*, 2016)
C. montanus	5,4`-dihydroxy-3,7-dimethoxyflavone	OH	H	H	OCH_3	OH	H	OCH_3	H	(Hamed *et al.*, 2016)
C. montanus	Centaureidin	OCH_3	OH	H	OCH_3	OH	OCH_3	OH	H	(Hamed *et al.*, 2016)
C. montanus	5,7-dihydroxy-3,6,3',4'-tetramethoxyflavone	OCH_3	OCH_3	H	OCH_3	OH	OCH_3	OH	H	(Hamed *et al.*, 2016)

C. montanus	5,3`,4`-trihydroxy-3,6,7-trimethoxyflavone	OH	OH	H	OCH_3	OH	OCH_3	OCH_3	H	(Hamed *et al.*, 2016)
C. montanus	5-Hydroxy-3,6,7,3`,4`,-pentamethoxy flavone	OCH_3	OCH_3	H	OCH_3	OH	OCH_3	OCH_3	H	(Hamed *et al.*, 2016)
C. candicans	6, 4'dihydroxy-3, 5, 7, 3'-tetramethoxyflavone	OCH_3	OH	H	OCH_3	OCH_3	OH	OCH_3	H	(Ahmed *et al.*, 1993)
C. candicans	Quercetagetin 3, 5, 7, 4'-tetramethyl ether	OH	OCH_3	H	OCH_3	OCH_3	OH	OCH_3	H	(Ahmed *et al.*, 1993)
C. montanus	Quercetagetin 3,5,6,7,3'-pentamethyl ether	OH	OCH_3	H	OCH_3	OCH_3	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Quercetagetin hexamethyl ether	OCH_3	OCH_3	H	OCH_3	OCH_3	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Artemetin	OCH_3	OCH_3	H	OCH_3	OH	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)

C. montanus	Casticin	OCH_3	OH	H	OCH_3	OH	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Chrysosplenetin	OH	OCH_3	H	OCH_3	OH	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Penduletin	OH	H	H	OCH_3	OH	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Centaureidin	OCH_3	OH	H	OCH_3	OH	OCH_3	OH	H	(Ahmed *et al.*, 1989)
C. montanus	Jaceidin	OH	OCH_3	OCH_3	H	OH	OCH_3	OH	H	(Ahmed *et al.*, 1989)
C. montanus	5,3',4'-trihydroxy-3,6,7,-trimethoxyflavone	OH	OH	H	OCH_3	OH	OCH_3	OCH_3	H	(Ahmed *et al.*, 1989)
C. montanus	Patuletin	OH	OH	H	OH	OH	OCH_3	OH	H	(Ahmed *et al.*, 1989)
C. montanus	Pachypodol	OH	OCH_3	H	OCH_3	OH	H	OCH_3	H	(Ahmed et al., 1989)
C. montanus	5,7,3'-trihydroxy-3,4'-dimethoxyflavone	OCH_3	OH	H	OCH_3	OH	H	OH	H	(Ahmed *et al.*, 1989)
C. montanus	5,7,4’-trihydroxy-3,3’-dimethoxyflavone	OH	OCH_3	H	OCH_3	OH	H	OH	H	(Ahmed *et al.*, 1989)

2.2.2. Antioxidant Activity:

Shoman and coworkers reported that the ethanolic extracts of *Jasonia candicans* or *chiliadenus montanus* ameliorate the oxidative stress resulted from $AlCl_3$ intoxication. Thus, these extracts may have therapeutic applications in the management of oxidative stress related diseases **(Shoman *et al.*, 2014).**

2.2.3. Antioxidant and cytoprotective activity:

C. montanus hydro alcoholic extracts exerted a protective action by decreasing cell death and by inhibiting intracellular ROS production, suggesting these polyphenol enriched extracts may be useful for those oxidative stress-related neurodegenerative diseases **(Eissa *et al.*, 2013)**.

2.2.4. Protective effect against ethinylestradiol-induced cholestasis in rats:

The ethanolic extract of aerial parts of *Chiliadenus montanus* effectively normalize the impaired antioxidant status in ethinylestradiol (EE)-cholestatic model. Thus, the extract may have a therapeutic value in drug-induced biliary cholestasis as well as in hormonal therapy due to High content of flavonoids and phenolic compounds found in ethanolic extract **(Hussein and Abdel-Gawad, 2010)**.

2.2.5. Anti- Alzheimer disease:

Oral administration of the ethanolic extract of the aerial parts of *C.candicans* and *C. montanus* effectively ameliorate the inflammation and neurodegeneration characterizing AD. High content of terpenes, sesquiterpenes and flavonoids in the ethanolic extract may responsible for the anticholinesterase activity, anti-inflammatory action, antioxidant capacity and neurotropic effect. These extracts may have therapeutic application in the treatment of Alzheimer's disease **(Ahmed *et al.*, 2013)**.

2.2.6. Protective Effects Against Lipid Peroxidation in Liver and Kidney of Iron-overloaded Rats:

Massive iron deposition in parenchymal organs, particularly in the liver, causes organ dysfunction, fibrosis, cirrhosis, and hepatocellular carcinoma. *C. montanus* extract prevented the increase in liver, kidney and serum iron, serum ferritin, serum transferrin levels, γ-GT, α-GST and γ-GT activities as well as serum NO and TNF-α level and hepatic MDA level as compare to iron-overloaded treated rats. The treatment also resulted in a significant increase in hepatic and kidney SOD, GPx, GR and CAT activities compare to iron-overloaded treated rats. High content of flavonoids and phenolic compounds was found in ethanolic extract may be responsible for free radical activity. *C. montanus* extract normalize the impaired antioxidant status in iron-overloaded rats model experiment. Thus, the extract may have a therapeutic value in iron-overloaded-induced haemostasis **(Hussein and Farghaly, 2010).**

2.2.7. Antidiabetic Activity

In 2015 Helal and coworkers demonstrated that administration of aqueous extract of *C. montanus* had ameliorated the biochemical parameters in diabetic rats. It reduced fasting blood glucose, serum creatinine, urea concentrations and liver enzymes while increased serum insulin level, body weight, total proteins, albumin, globulin and high-density lipoproteins (HDL). In contrast, the untreated diabetic rats exhibited marked decrease

in serum insulin level and body weight and total proteins while increased fasting blood glucose level, creatinine, uric acid, serum total lipids (TL), total cholesterol, triglycerides TG, low density lipoproteins (LDL), and very low-density lipoproteins (VLDL), risk ratios of TC/HDL and LDL/HDL were recorded. Therefore, *C.montanus* aqueous extract can be used as antidiabetic drug that can lower blood glucose concentration and guard against the negative effects of diabetes **(Helal *et al.*, 2015)**. In addition, Oral administration of the ethanolic extract of the aerial parts of *C.montanus* in Streptozotocin-Induced Diabetic rats effectively normalize the impaired antioxidant status in Streptozotocin-Induced Diabetes than glibenclamide treated groups. The extract exerted rapid protective effects against lipid peroxidation by scavenging of free radicals by reducing the risk of diabetic complications **(Hussein, 2008)**.

2.2.9. Anti-obesity, antiatherogenic, anti-diabetic and antioxidant activities in obese diabetic rats fed high-fat diet:

The ethanolic extract of *C.montanus* prevented the decrease in the levels of hepatic oxidative stress biomarkers reduced Glutathione (GSH), Glutathione peroxidase (GPx), Glutathione reductase (GR), Superoxide dismutase (SOD) and Catalase (CAT). *C.montanus* has anti-obesity actions and potential as a preventive agent for type 2 diabetes mellitus **(Hussein, 2011)**.

2.2.10. Antitumor activity

Eudesmane sesquiterpene named as 3-oxo-γ-costic acid isolated from *C. montanus* exhibited anti-proliferative activity against human colon (Caco-2) **(Hegazy *et al.*, 2017)**. The ethanolic extract induce NAD (P) H: quinone oxidoreductase 1 (NQO1) using a quantitative bioassay in a murine hepatoma cell line.it revealed dose-dependent NQO1 inducing properties with a concentration that doubled the specific enzyme activity by 2-fold (CD value) of *7.0 μM*, and a magnitude of induction of 3.3-fold at the highest concentration tested *(100 μM)* (**Hamed *et al.*, 2016)**. Furthermore, Soliman, F. and co-workers had investigated the cytotoxic activity of *C. montanus* ethanolic, aqueous extracts as well as the isolated flavonoids against several cancer cell lines. The results showed that only chrysosplenetin, centaureidin, quercetin-3-O-*β*-D-4C1-glucopyranoside and aqueous extract possessed moderate cytotoxic activity against human cervix carcinoma HeLa cell line **(Soliman *et al.*, 2009)**.

2.2.11. Anti-platelet aggregation, anti-inflammatory and hypotensive effects

C.montanus aqueous extract had anticoagulant, antiplatelet aggregation and anti-inflammatory effects in carrageenan-induced rat paw edema. More ever, the mean blood pressure lowered by administration of aqueous extract of *C.montanus* compared with nifedipine treatment in a dose dependent manner **(Nada *et al.*, 2006)**. **3.**

Conclusion:

In this review, we discussed comprehensively the isolated phytochemicals and the biological activities of *Chiliadenus* species. Our review showed that this species is an abundant source of several natural products especially sesquiterpenes, flavonoids, monoterpenes and diterpenes and it possesses several medicinal uses.

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