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Review

Phytochemical investigation, anti-inflammatory and antinociceptive activities from some Species of *Cleomaceae* family: A systematic review

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ABSTRACT

The scientific advances on phytochemistry, antinociceptive and anti-inflammatory activities from *Cleomacea* family are described. A systematic review was performed according to PRISMA statement. A search of scientific literature was performed in specialized database (Scopus, Science Direct, PubMed, Google Scholar) to obtain information and Iltis & Cochrane taxonomic classification was employed. Some genus (C*leome*, *Corynandra*, *Gynandropsis*, *Cleoserrata*, *Tarenaya)* are widely used in traditional medicine for treatment of inflammatory diseases (rheumatic and skin diseases), fever, malaria and diabetes, and its polar extracts have been described as anti-inflammatory and antinociceptive agents. *C. rutidosperma, C. arabica, C. viscosa* and *C. droserifolia* showed *in vitro* inmunomodulador activity in macrophages and PMN. Also, *T. spinosa*, *C. chelidonii*, *C. arabica*, *C. viscosa, C. rutidosperma* and *G. gynandra* have shown anti-inflammatory activity an *in vivo* carrageenan and chronic inflammation AFC models. Only, from *C. droserifolia* and *C. viscosa* anti-inflammatory compounds have been isolated and were identified as flavonoids and cumarinolignoids. Others compounds isolated from these plants are steroids, phenolic acids, anthocyanins, terpenes, and alkaloids, but some of these compounds still have not been investigated; in addition, the essential oils from *C. amblyocarpa, C rutidosperma, C. viscosa, T. spinosa* and *C. chelidonii* have significative antinociceptive activity; this effect was comparable to morphine, aspirine, diclofenac, dipyrone or pentazocine. *Cleomaceae* family is a potential source of active principles that will allow the development of new therapeutic alternatives for the treatment of diseases in which an inflammatory process and/or pain occurs.

Keywords: Anti-inflammatory, anti-nociceptive, immunomodulator, phytochemistry, *Cleomaceae*, *Cleome*, flavonoids.

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INTRODUCTION

Family *Cleomaceae* are described in the taxonomy catalogs by Iltis & Cochrane (Iltis and Cochrane, 2014a), and includes some genus such as: *Andinocleome* Iltis & Cochrane*, Podandrogyne* Ducke, *Mitostylis* Raf., *Physostemon* Mart. & Zucc., *Tarenaya* Raf. (Iltis and Cochrane 2014b), *Cleoserrata* Iltis*, Hemiscola* Raf., *Peritoma* DC. (Iltis and Cochrane 2007; Neto et al., 2017), *Corynandra* Schrad. Ex Spreng. (Cochrane and Iltis, 2014) *Polanisia* Raf, *Gynandropsis* DC., Cleome L., with 270 species, which are small trees, herbs or shrubs and have cosmopolitan distribution, although are more abundant in tropical and subtropical regions (Iltis and Cochrane, 2014a). This family was previously grouped as a subfamily *Capparaceae* (Pax and Hoffmann, 1936). However, phylogenetic and molecular studies, allowed it to demonstrate its monophyly and phylogenetic

relationship with the family *Brassicaceae* (Hall et al., 2002; Hall, 2008; Iltis et al., 2011).This family has problems in taxonomic classification because of the generic boundaries and geographical distribution among species from the New World (America) and Old World (mostly in Africa, India and the Middle East), leading to the generic segregation of some genus (Cochrane and Iltis, 2014). However, molecular data and morphological analysis were needed to support changes in the taxonomy of this family (Patchell et al., 2014). In recent years, several studies have focused on the precise identification of the species and attempts have been made to reconstruct the phylogenetic origin of this family by analyzing the genetic regions of chloroplasts and mitochondria using DNA sequence analysis and internal transcribed spacer of the DNA (ITS) region of the nuclear ribosomal DNA (rDNA) (Hall, 2008; Patchell et al., 2014; Feodorova et al., 2010; Tamboli et al., 2016). The *Cleomaceae* family is important for research on floral morphogenesis evolution (Bhide et al., 2014), *Cleomaceae* is a model to study C3-C4 photosynthetic pathway, phylogenetic origins (Feodorova et al., 2010) pollination ecology importance (for the study of self- and cross-pollination through polymorphism) (Machado et al., 2006), climate resilient species suitable for the ecological restoration (Raju and Rani, 2016). One of the genera with the highest number of species and widely used in traditional medicine is *Cleome*, which has been divided recently into two segregated genus: *Corynandra* Schrad. ex Spreng and *Cleoserrata* (Jacq.) Iltis (Iltis and Cochrane, 2007; Neto et al., 2017). The name *Corynandra* was first used by Schrader (1825) and subsequently Rafinesque (1838) proposed the name *Arivela* Raf. The latter name has been used in some floristic catalogs (Zhang and Tucker, 2008; Tucker and Vanderpool, 2010; Acevedo-Rodríguez and Strong, 2012); however, *Corynandra* is the first legitimate name (Cochrane and Iltis, 2014).

In countries from Africa and Asia, some wild or semi-domesticated species of the *Cleomaceae* family are used as medicinal plants in health systems and as a nutritional supplement (Schönfeldt and Pretorius, 2011). An ethnobotanical study performed by Ahouansinkpo et al. (2016) describes that the leaves of *Gynandropsis gynandra* (L.) *Briq* (Syn. *Cleome gynandra* L.) and *Corynandra viscosa* (L.) Cochrane & Iltis (Syn. *Cleome viscosa* L.) are consumed as vegetables in the locality of Benin, located in West Africa; in addition, *G. gynandra* is used as food by 70% of those interviewed and 38% described that this specie is used as medicinal plant; while *C. viscosa* is more widely used in traditional medicine by 45% of those interviewed (Ahouansinkpo et al., 2016). Some species (Table 1) are used in traditional medicine to treat diseases in which there is an inflammatory process, such as rheumatic diseases, earaches, stomach pain, fever and skin wounds. It is well known that natural products have been a main source of therapeutic alternatives and it has been reported in the scientific literature that some species of the family *Cleomacea* have important pharmacological activities such as: antioxidant, analgesic (antinociceptive), anti-inflammatory, antipyretic, antimicrobial, anticancer, and others (Djeridane et al., 2010; Bose et al., 2007; Bose et al., 2011; Ranjitha et al., 2014; Tigrine et al., 2013).

Inflammation is defined as a process of defense of vascularized tissues, in which the immune system is activated to eliminate, destroy or isolate the noxious stimulus (injuries due to trauma, irritants, infection by microorganisms or parasites (Ashley et al., 2012). This process involves early vascular changes due to the release of molecules by inflammatory cells and those found at the site of the injury, allowing an increase in vascular permeability and the blood flow that facilitates the infiltration of cells such as polymorphonuclear lymphocytes (PMN) and macrophages (innate immune response); they generate the characteristic signs of local inflammation: heat, redness, pain, swelling and loss of function. If the stimulus is persistent and the defensive capacity of the innate immune system is exceeded, they lead to the activation of a more specialized response (adaptive immune response) as performed by T lymphocytes, plasma cells that produce antibodies. During the inflammatory process proinflammatory cytokines such as Tumor Necrosis Factor (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6) are released, involved in the initiation and maintenance of inflammatory responses. In this process, other molecules also are generated that allow the elimination of antigens that have been phagocytosed, such as nitric oxide (NO), catalyzed by inducible nitric oxide synthase (iNOS) in macrophages (Mittal et al., 2014). If the inflammatory process is prolonged, inefficient or there is deregulation of the mechanisms, this progresses to a chronic inflammation which can generate damage to the tissues of the host. Chronic inflammation is associated with cardiovascular diseases, cancer and rheumatic conditions such as rheumatoid arthritis (RA), lupus and osteoarthritis (OA) (McInnes and Schett, 2011).

In a tissue with injury or damage, the inflammation can generate peripheral sensitization in the environment close to sensory nerve fibers (nociceptors); this condition can cause pain, due to chemical changes generated by the accumulation of inflammatory molecules released by cells such as mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells and fibroblasts. The nociceptors express one or more cell surface receptors that can respond to each of these pro-inflammatory molecules (Basbaum et al., 2009). For example, bradykinin is a vasodilator that acts by binding to receptor B2 (RB2), which activates phospholipase C and the production of second messengers to elevate intracellular Ca^{2+} to sensitize nociceptors (Brown and Passmore, 2010).The arachidonic acid generated by the cyclooxygenase (COX) enzymes, as well as

Table 1. Chemical constituents of some species of the *Cleomaceae* family*.

Species	Medicinal use	Used part	Isolated compounds	Reference
Cleome amblyocarpa Barratte & Murb. (Syn. *Cleome Africana* Botsch)	Rheumatic fever, inflammation, rubefaciente, scabies, colic and diabetes (Edziri et al., 2013)	Aerial parts	cleomblynol A **(1)** cleomblynol B cleocarpanol **(2)** cabraleahydroxy lactone **(3)** amblyone **(4)** isocleomblynol A luteolin 3'-methyl ether luteolin 3'- methyl ether 7-glucoside	(Harraz et al., 1995)
		Whole plant	17*α*- hydroxycabraleahydroxylactone **(5)** 3-*O*-acetyl- 12*β*-acetoxy-17α-hydroxycabraleahydroxylactone **(6)** 17α-hydroxycabralealactone **(7)** 12*β*-acetoxycleocarpone **(8)** 12*β*-acetoxycleocarpanol **(9)** 3-O-acetyl-12*β*-hydroxycleocarpanol **(10)** 3-O-acetyl-12*β*-acetoxy-25-*O*-ethylcleocarpanol (29) **(11)** $\Delta^{1,2}$-dehydro-cabralealactone **(12)** 12*β*-acetoxy- $\Delta^{1,2}$-dehydrocabralealactone **(13)**	(Nagaya et al., 1997)
		Aerial parts	cleomblynol A 11α,15α-diacetoxybrachycarpon-22(23)-ene (15α-acetoxycleomblynol A **(14)**	(Ahmed et al.,2001)
Cleome chrysantha Decne.		Aerial parts	1-epibrachyacarpone *β*-sitosterol daucosterol	(Qin et al., 2000)
Cleome arabica L.	Scabies, inflammation, rheumatic and abdominal pain (Boulos, 1983)	Leaves and branches	3-*O*-glucosyl-7-*O*-rhamnopyranosides **(15-17)** 3,7-di-*O*-rharnnopyranosides **(18-20)** 3-*O*-glucopyranosides of quercetin, kaempferol, and isorhamnetin, **(21-23)** cleomin **(24)**	(Ismail et al., 2005)
		Aerial parts	(17-(4-hydroxy-1,5-dimethylhexyl)-2,3,7-(acetyloxy) gona-1,3,5(10)-trien-15-ol) **(25)**	(Djeridane et al., 2010**)**
		Sheath or pod	11-α-acetylbrachy-carpone-22(23)-ene **(26)** *β*-sitosterol **(27)** 17-α-hydroxycabraleactone **(28)** amblyone **(29)** calycopterin **(30)**	(Ladhari et al., 2013)
		Seeds	cleomblynol A 1-deacetylbrachycarpon-22(23)-ene **(31)**	(Ladhari et al., 2014)
Cleome droserifolia (Forssk.) Delile	Diabetes (El Naggar et al., 2005)	Aerial parts	5,4'-dihydroxy-6,7,8,3',5'-pentamethoxyflavone **(32)** 5,4'-dihydroxy-6,7,8,3'-tetramethoxyflavone [8-methoxycirsilineol] **(33)**	(Fushiya et al., 1999)

Table 1. Continues.

	drosericarpone **(34)** buchariol (4,10-epoxy-6α–hydroxyguaiane) **(35)** stigmasterol glucoside teucladiol **(36)** daucosterol (*β*-sitosterol glucoside) **(37)** 5,3'-dihydroxy-3,6,7,4',5'-pentamethoxyflavone **(38)** 5'-hydroxy-3,6,7,3',4',5'-hexamethoxyflavone **(39)** luteolin **(40)** 3'-methoxy-3,5,4'-trihydroxy flavone-7 neohesperidoside **(41)** (1*R*,2*R*,3*E*,7*E*,11*R*,12*S*)-2-*O*-acetyl-16-*O*-(3-hydroxy-3-methylglutaryl)-dolabella-3,7-dien-2,16,18-triol **(42)** 6*S*,9*R*)-roseoside **(43)**	(El-Askary, 2005) (Abdel-Kader et al., 2009)
	6-di-(7-hydroxy,1, 5-epoxy germacrane) **(44)** 4(15)-guaiane-6-ol **(45)** 7α-germacra-1(10),4(15)-diene-5β, 6α-diol **(46)** 4,7,8-eudesma-triol **(47)** 2,18-*O*-diacetyl-16-*O*-(3-hydroxy-3-methylglutaryl)-7-hydroperoxydolabella-3,8(17) diene-2,16,18 triol **(48)** pinocembrin **(49)** quercetin-3-glucoside-7-rhamnoside **(50)**	(Aboushoer et al., 2010)
	guai-7(11),8-diene 1-hydroxy-guai-3,10 (14)-diene 18-hydroxy-dollabela-8 (17)-ene (24*E*) stigmasta-5,8-dien-3*β*-ol Isorhamnetin-3-O-β-D-glucoside quercetin-3'-methoxy-3-O-(4''-acetylrhamnoside)-7-O-α-rhamnoside kaempferol-4'-methoxy-3,7-dirhamnoside	(Motaal et al., 2011)
	guai-7(11),8-diene **(51)** 1-hydroxy-guai-3,10(14)-diene **(52)** 18-hydroxydollabela-8(17)-ene **(53)** (24*E*)-stigmasta-5,8-dien-3*β*-ol **(54)** isorhamnetin-3-*O*-*β*-D-glucoside **(55)** quercetin-3'-methoxy-3-*O*-(4''-acetylrhamnoside)-7-*O*-*α*-rhamnoside **(56)** kaempferol-4'-methoxy-3,7-*O*-dirhamnoside **(57)**	(Ezzat and Motaal, 2012)
	5-hydroxy-2-methoxy-1-methyl-1*H*-indole-3-carbaldehyde **(58)** veratrol **(59)** 2-methoxy-4-methylacetophenone **(60)**	(Hussain et al., 2015)

Table 1. Continues.

Cleome khorassanica Bunge & Bien. ex Boiss.		Aerial parts	3-oxo-4-oxa-A-homo-25,26,27-trinordammarano-24,20-lactone **(61)** 20,25-dihydroxy-3-oxodammarane **(62)** 5-hydroxy-3,6,7,8,3',4',5'-heptamethoxyflavone	(Sajjadi et al., 2018)
Cleome rupicola Vicary	Drops for the eyes, Cataracts (Al-Rehaily et al., 2017)	Aerial parts	cleomdiolic acid **(63)** shoreic acid **(64)** foveolins B isorhamnetin-3,7-*O*-α-*L*-dirhamnoside-3''-*O*-acetyl **(65)** isorhamnetin-3-β-*D*-glucoside-7-α-*L*-rhamnoside	(Al-Rehaily et al., 2017)
Cleome rutidosperma DC.	paralysis, epilepsy, seizures, pain and skin diseases	Aerial parts	2-ethyl-cyclohex-2-ene-6-hydroxy-methylene-1-carboxylic acid 3β-hydroxy-lup-20(29)-en-28-oic acid	(Rahman et al., 2008)
Corynandra chelidonii (L. f.) Cochrane & Iltis ex Spreng. (Syn. *Cleome chelidonii* L.f.)	Dysentery, headache, otitis, rheumatism and skin diseases (Parimalakrishnan et al., 2007)	Aerial parts	quercetin 3-O-*β*-*D*-glucopyranosyl-(1 →2)-α-*L*-rhamnopyranosyl-7-O-α-L-rhamnopyranoside **(66)** quercetin 3-O-(6-O-*E*-*p*-coumaroyl)-β-*D*-glucopyranosyl-(1 → 2)-α-L rhamnopyranosyl-7-O-α-L-rhamnopyranoside **(67)** quercetin 3-O-(6-O-*E*-caffeoyl)-*β*-D-glucopyranosyl-(1 →2)-α-L-rhamnopyranosyl-7- O-α-*L*-rhamnopyranoside **(68)** cleomeside A and cleomeside B **(69** and **70)** cleomeside C [quercetin 3-O-*β*-D-glucopyranosyl-(1→2)-α-*L*-rhamnopyranosyl-7-O-(3-acetyl)-α-*L*-rhamnopyranoside] **(71)** cleomeside D [quercetin 3-O-*β*-D-glucopyranosyl-(1→2)-α-*L*-rhamnopyranosyl-7-O-(2-acetyl)-α-*L*-rhamnopyranoside] **(72)** cleomeside E [quercetin 3-O-*β*-D-glucopyranosyl-(1→2)-a-L-rhamnopyranosyl-7-O-(2,4-diacetyl)-α-L-rhamnopyranoside] **(73)** cleomeside F [quercetin 3-O-*β*-D-glucopyranosyl-(1 →2)-α-*L*-rhamnopyranosyl-7-O-(3,4-diacetyl)-α-L-rhamnopyranoside] **(74)** cleomeside G [quercetin 3-O-*β*-D-glucopyranosyl-(1 / 2)-α-*L*-rhamnopyranosyl-7-O-(2,3,4-triacetyl)-α-*L*-rhamnopyranoside] **(75)** cleomeside I [quercetin3-O-(6-O-E-*p*-coumaroyl)-*β*-*D*-glucopyranosyl-(1 →2)- α-*L*-rhamnopyranosyl-7-O-(3,4-O-diacetyl)-α-L-rhamnopyranoside] **(77)**	(Nguyen et al., 2017)

Table 1. Continues.

			cleomeside J [quercetin 3-O-(6-O-*E*-caffeoyl)-*β*-*D*-glucopyranosyl-(1 → 2)-α-*L*-rhamnopyranosyl-7-O-(4-O-acetyl)-α-*L*-rhamnopyranoside] **(78)**	
			cleomeside K [kaempferol 3-O-*β*-glucopyranosyl-(1 →2)-α-rhamnopyranosyl-7-O-(4-acetyl)-α-rhamnopyranoside] **(79)**	
			cleomeside L [kaempferol 3-O-*β*-*D*-glucopyranosyl-(1 →2)-α-*L*-rhamnopyranosyl-7-O-(2,4-diacetyl)-α-*L*-rhamnopyranoside] **(80)**	
			cleomeside M [kaempferol-3-O-*β* glucopyranosyl (1 →2)-α-rhamnopyranosyl-7-O-(2,3-diacetyl)-α-*L*-rhamnopyranoside] **(81)**	
Corynandra viscosa (L.) Cochrane & Iltis (Syn. *Cleome viscosa* L.)	Diarrhea, fever, malaria fever, chronic malaria, hypotension, eye disorders, earache, neuralgia, inflammation, liver and skin diseases, bronchitis, convulsions and magic-religious protection (Ahouansinkpo et al., 2016; Mali, 2010)	Seeds	cleomiscosins A **(82)**, B **(83)**, C and D	(Ray et al., 1985; Kumar et al., 1988)
		Root exudates	[2-amino-9-(4-oxoazetidin-2-yl)-nonanoic acid **(84)**	(Jana and Biswas, 2011)
		Flowers	quercetin 3-*O*-(2''-acetyl)-glycoside **(85)**	(Senthamilselvi et al., 2012)
		Seeds	Nevirapine **(86)** salicylic acid	(Chatterjee et al., 2013)
		Seeds	Lupeol **(87)**	(Singh et al., 2017)
Gynandropsis gynandra (L.) Briq (Syn. *Cleome gynandra* L.)	malaria, jaundice, anemia, fever, chronic malaria, eye disorders, chronic constipation, hypotension and hypertension, earaches and neuralgia (Ahouansinkpo et al., 2016)	Whole plant	cleogynol ((20*S*,24*S*)-epoxy-19,25-dihydroxydammarane-3one hemiketal) **(88)**	(Das et al., 1999)
		Leaves	α-amyrin acetate **(89)** α-amyrin **(90)** sitosterol stigmasterol **(91)**	(Ranjitha et al., 2009)
		Whole plant	protocatechuic acid *p*-hydroxybenzoic acid salicylic acid caffeic acid *p*-coumaric acid ferulic acid sinapic acid ascorbic acid *β*-carotene	(Moyo et al., 2018)
		Stem	*β*-amyrin *β*- amyrin-3-O-*β*-glucopyranoside stigmasterol sitosterol	(Ranjitha et al., 2014)

Table 1. Continues.

Tarenaya hassleriana (Chodat) Iltis. (Syn. *Cleome hassleriana* Chodat.)	Flower	3-(2''-(6'''-caffeoyl-*β*-glucopyranosyl)-6''-(*E*-*p*-coumaroyl)-*β*-glucopyranoside)-5-*β* glucopyranoside cyaniding 3-(2''-(6'''-*E*-sinapoyl-*β*-glucopyranosyl)-6''-(*E*-p-coumaroyl)-β-glucopyranoside)-5-*β*-glucopyranoside **(92)** cyanidin 3-(2''-(6'''-feroyl-*β*-glucopyranosyl)-6''-(*E*-*p*-coumaroyl)-*β*-glucopyranoside)-5-*β*-glucopyranoside pelargonidin 3-(2''-(6'''-*E*-sinapoyl-*β* glucopyranosyl)-6''-(*E*-*p*-coumaroyl)-*β*-glucopyranoside)-5-β-glucopyranoside pelargonidin 3-(2''-(6'''-*E*-*p*-coumaroyl-*β*-glucopyranosyl)-6''-(*E*-*p*-coumaroyl)-*β*-glucopyranoside)-5-*β*-glucopyranoside **(93)**	(Jordheim et al., 2009)
Tarenaya spinosa (Jacq.) Raf. (Syn. *Cleome spinosa* Jacq.)	Aerial parts	cleospinol A **(94)** B, C y D 3'-hydroxy-*iso*-pentan-10-oate ester of cleospinol A **(95)** Flindulatin **(96)**	(Collins et al., 2004)

*The chemical structure of each compounds are shown in Figure 1.

prostaglandins E_2 (PGE_2), induces an increase in cyclic adenosine monophosphate (cAMP) and directly stimulates the nociceptor (Pitchford and Levine, 1991). Some proinflammatory cytokines such as IL-1β, IL-6 y TNF-α are involved in the process of pathological pain. IL-1β increases the production of substance P and PGE_2 in neuronal and glial cells. IL-6 is involved in the regulation of the expression of neuronal neuropeptides and contribute to the development neuropathic pain by nerve injury. The cytokine TNF-α, through TNF-receptors cell surfaces, can participate in inflammatory hyperalgesia, as in neuropathic (Zhang and An, 2007).

In this paper, we describe the pharmacological potential (specifically anti-inflammatory and antinociceptive properties), as well as the phytochemical research through the analysis of information published in sources such as PubMed, Scopus, Science Direct, Google Scholar for some species of the *Cleomaceae* family.

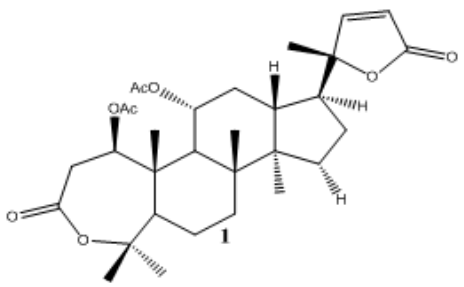
METHODS

The systematic review was performed according to the PRISMA statement (Moher et al., 2015). The information from articles and books was obtained from 1980 until February 2018 and was obtained from different scientific database (Scopus, Science Direct, PubMed, Google Scholar), we found 93 articles and 7 books. The following English and Spanish keywords were used to search for the academic information: anti-inflammatory activity, anti-nociceptive activity, genus *Cleomaceae* family, chemical composition, immune system, pain. The articles were stored in a digital folder according to the year and the subject, were reviewed by two independent investigators. The criteria for the selection of reports in this review were as follows: i) information the genus belonging to the family *Cleomaceae*, using the accepted scientific name in specialized database and its synonyms; ii) Information describes the scientific evidence on anti-inflammatory and antinociceptive activities from *Cleomaceae* family, iii) Information describes chemical composition of some genus from the *Cleomaceae* family. The thesis book was excluded. The taxonomic classification was done in according to the Iltis & Cochrane. The scientific names of the species were consulting Missouri Botanical Garden (http://www.tropicos.org) and The Plant List (2013). Version 1.1. (http://www.theplantlist.org/).

RESULTS

In vitro anti-inflammatory activity from some species of the *Cleomaceae* family

The scientific literature has described that some species



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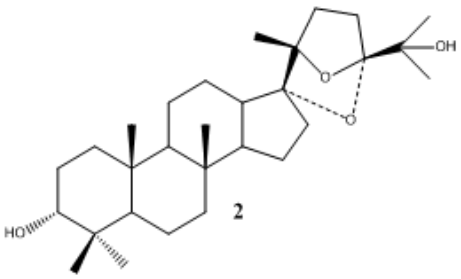

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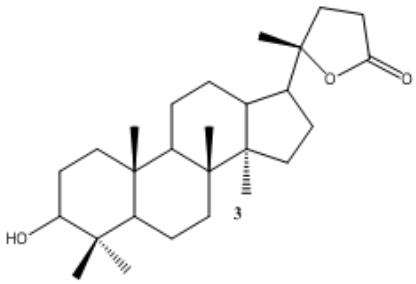

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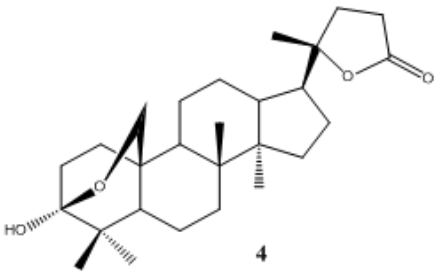

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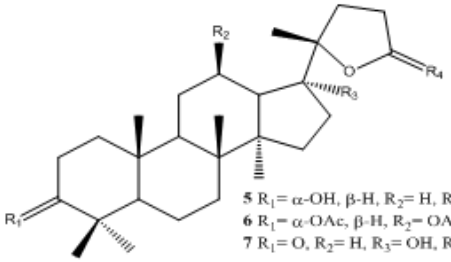
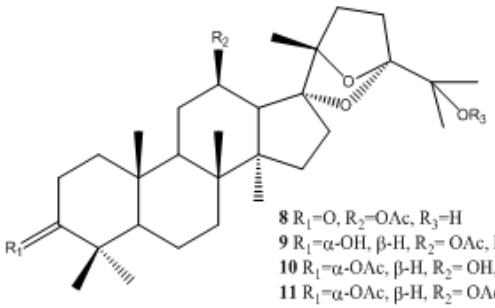
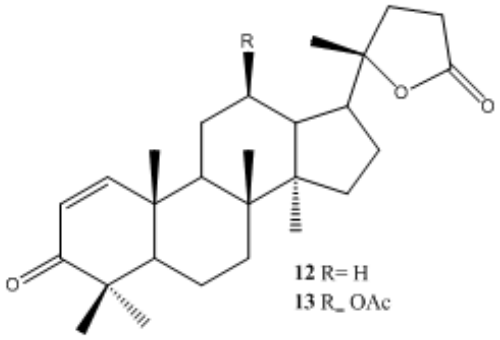


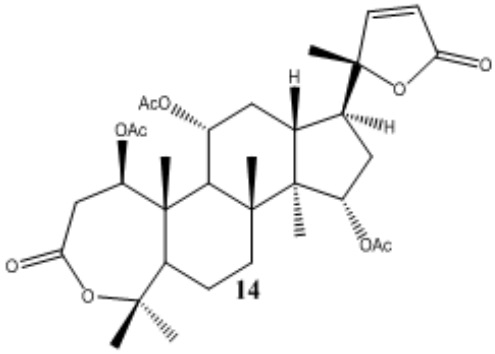
5 R_1= α-OH, β-H, R_2= H, R_3= OH, R_4= O
6 R_1= α-OAc, β-H, R_2= OAc, R_3= OH R_4= O
7 R_1= O, R_2= H, R_3= OH, R_4 = O



8 R_1=O, R_2=OAc, R_3=H
9 R_1=α-OH, β-H, R_2= OAc, R_3= H
10 R_1=α-OAc, β-H, R_2= OH, R_3= H
11 R_1=α-OAc, β-H, R_2= OAc, R_3= CH_2CH_3



12 R= H
13 R_ OAc



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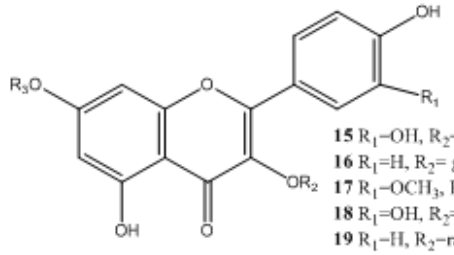
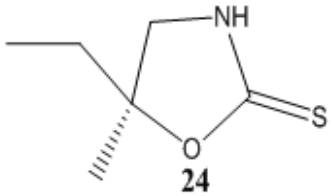


15 R_1=OH, R_2= glucosil, R_3= ramnosil
16 R_1=H, R_2= glucosil, R_3= ramnosil
17 R_1=OCH_3, R_2= glucosil, R_3= ramnosil
18 R_1=OH, R_2=ramnosil, R_3= ramnosil
19 R_1=H, R_2=ramnosil, R_3= ramnosil
20 R_1= OCH_3, R_2=ramnosil, R_3= ramnosil
21 R_1=OH, R_2= glucosil, R_3= H
22 R_1=H, R_2= glucosil, R_3= H
23 R_1= OCH_3, R_2= glucosil, R_3= H



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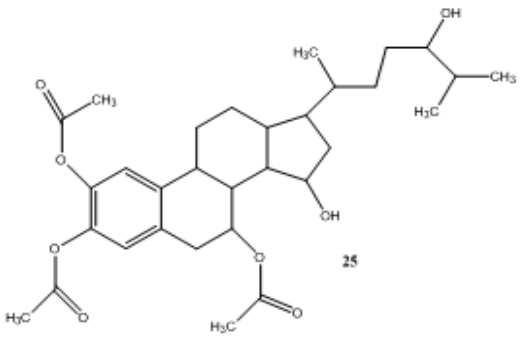

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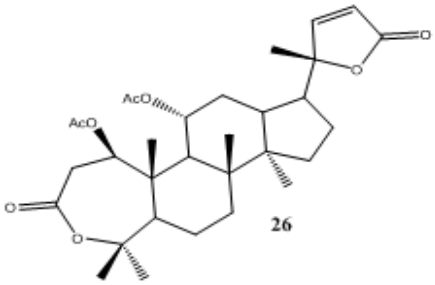

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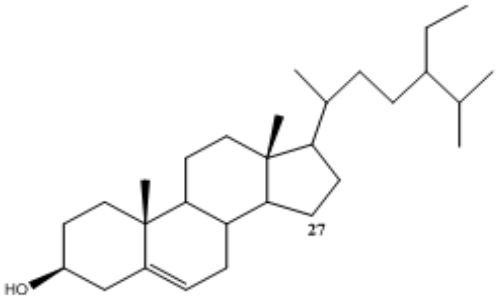

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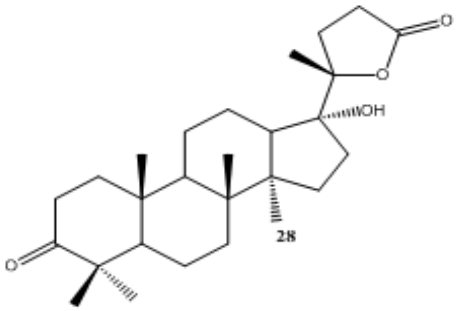

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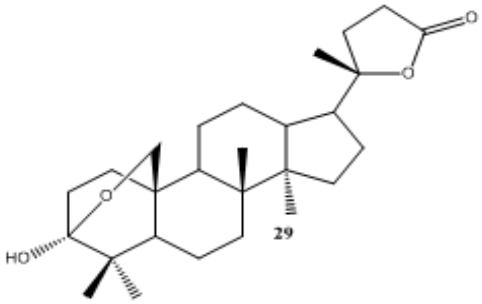

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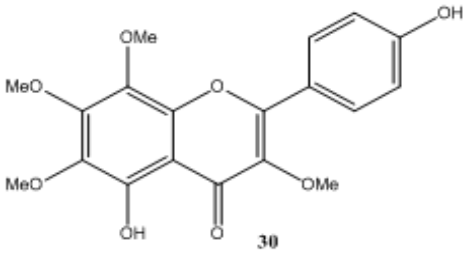

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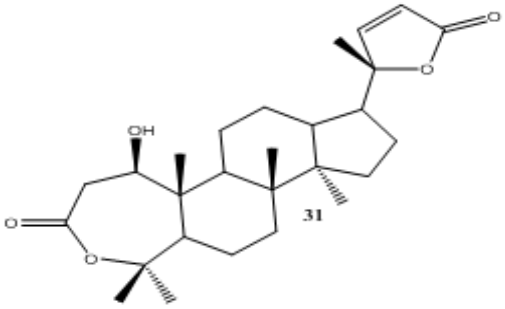

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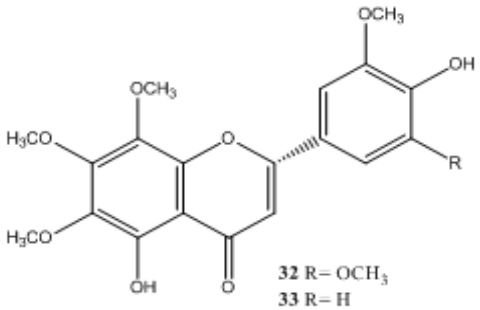
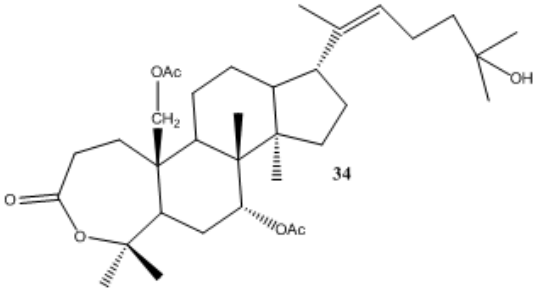


32 R= OCH_3
33 R= H



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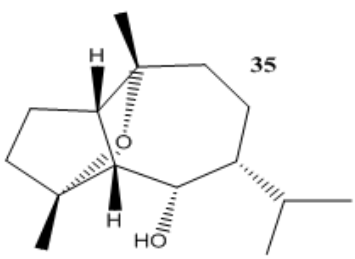

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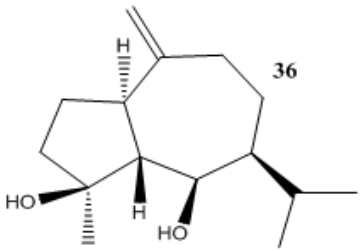
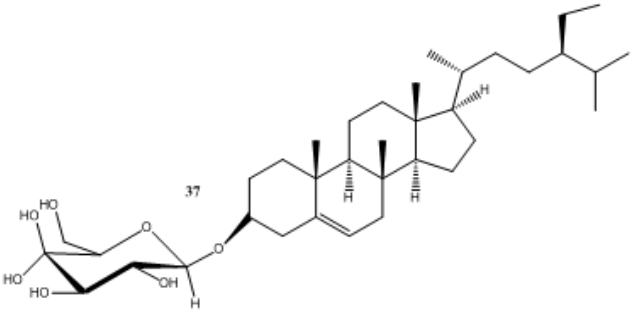
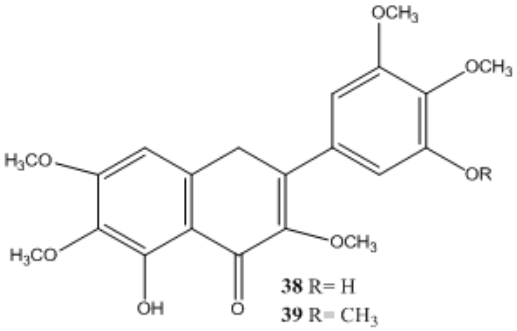
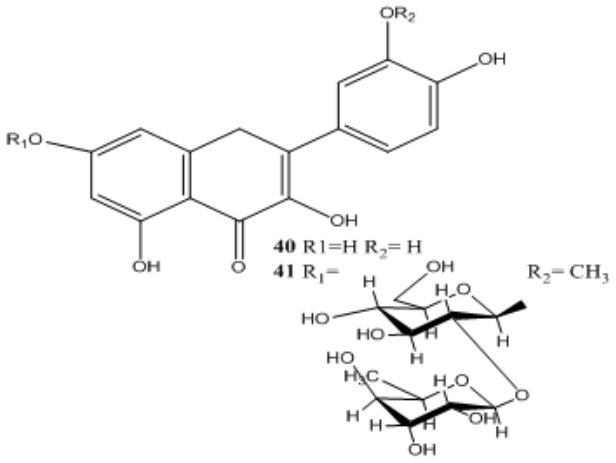
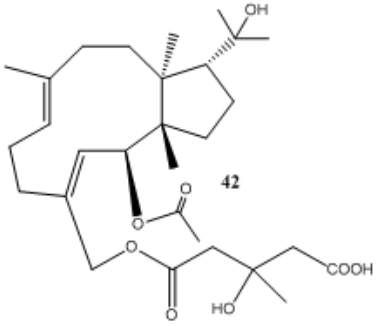
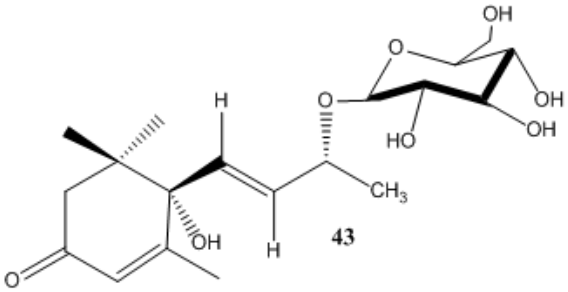

36
H
HO
H
HO

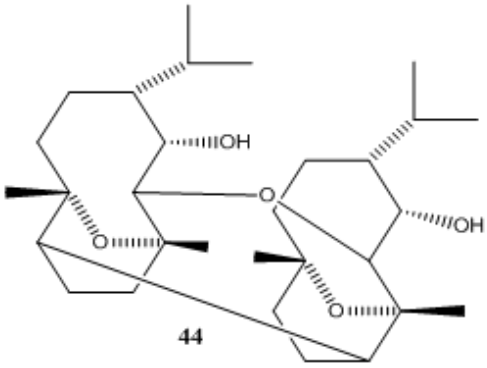

37
HO
HO
HO
HO
O
O
OH
H
H
H
H

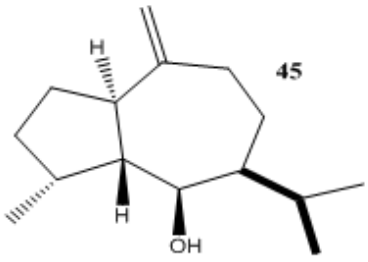

OCH3
OCH3
H3CO
H3CO
OR
OCH3
OH
O
38 R= H
39 R= CH3

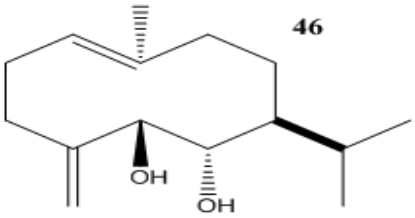

OR2
OH
R1O
OH
OH
O
40 R1=H R2= H
41 R1=
R2= CH3
OH
H
HO
HO
H
H
HO
H3C
H
H
H
OH
H
OH
O
H


OH
42
O
O
O
COOH
HO


OH
O
H
O
OH
HO
OH
CH3
OH
H
43
O


OH
O
O
OH
44


H
45
H
OH



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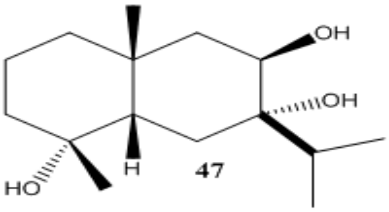

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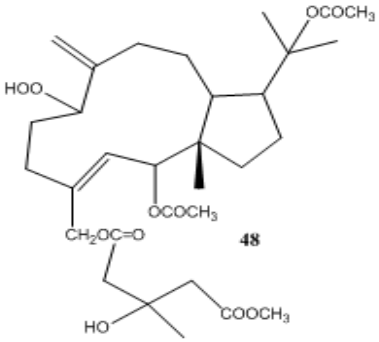

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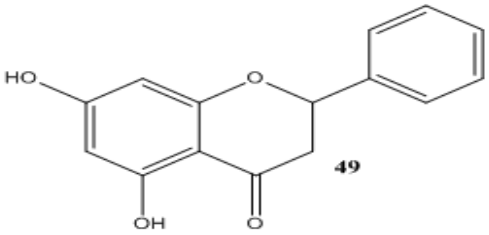

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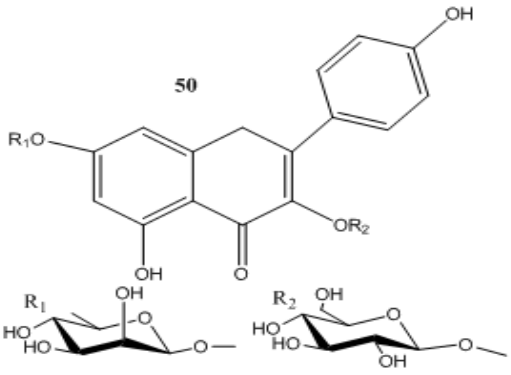

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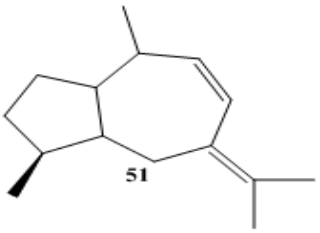

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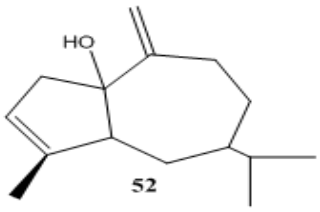

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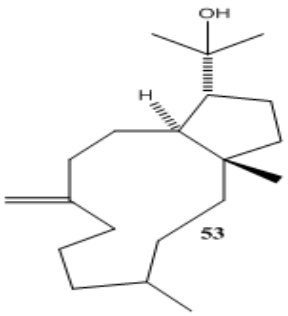

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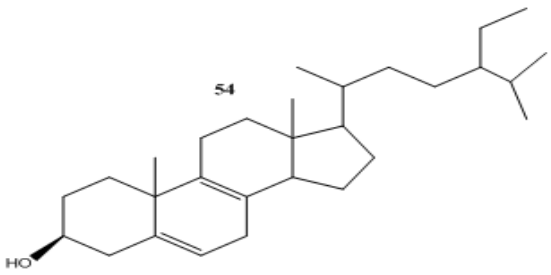

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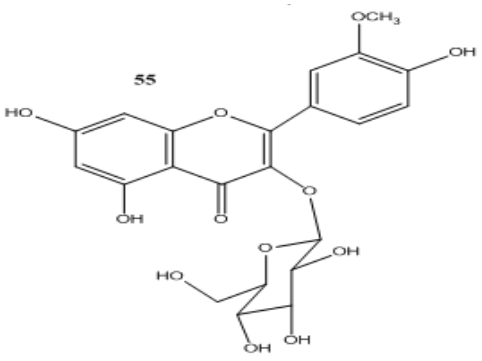

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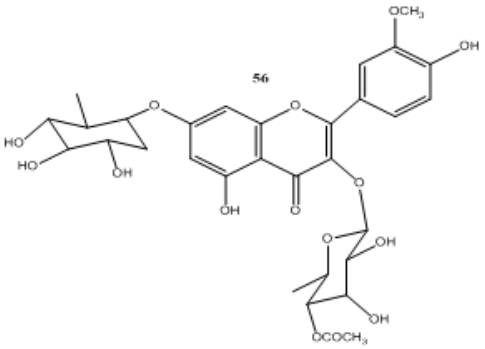

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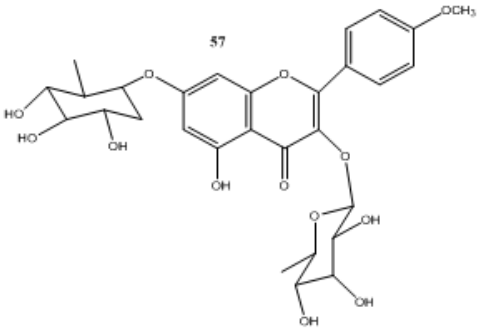

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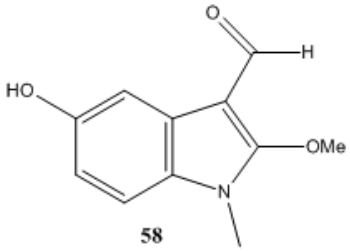

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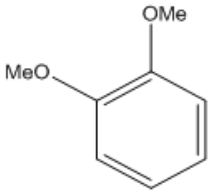

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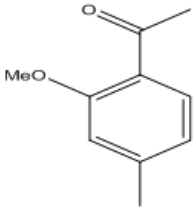

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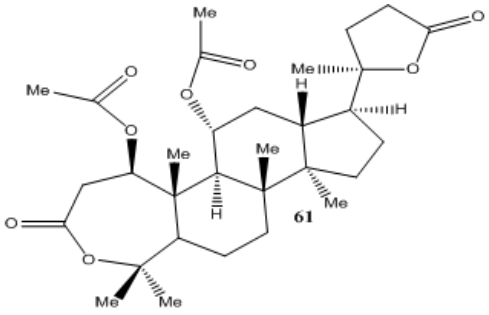

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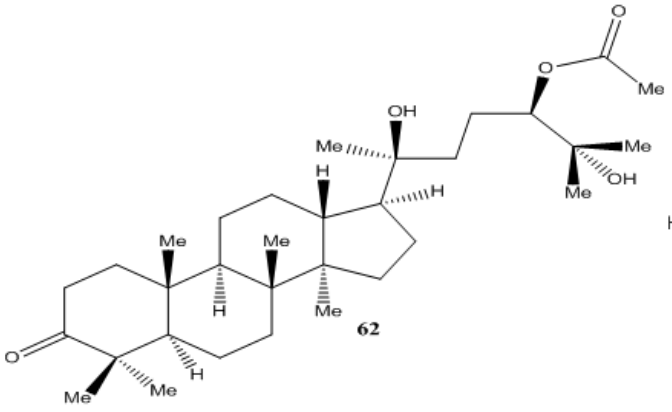

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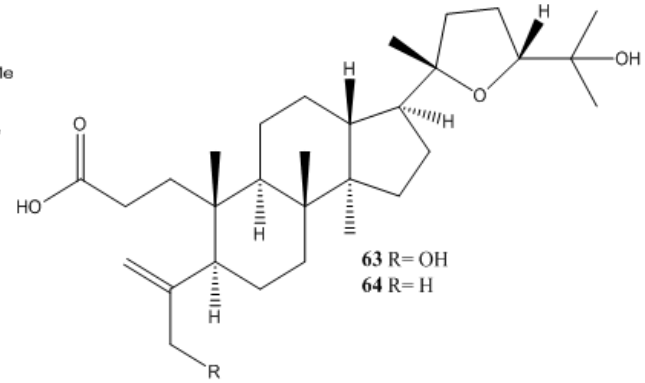
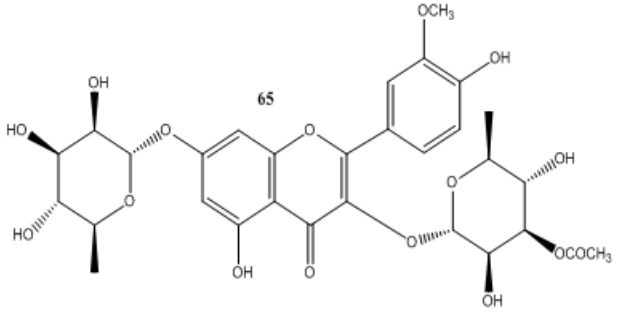


63 R= OH
64 R= H



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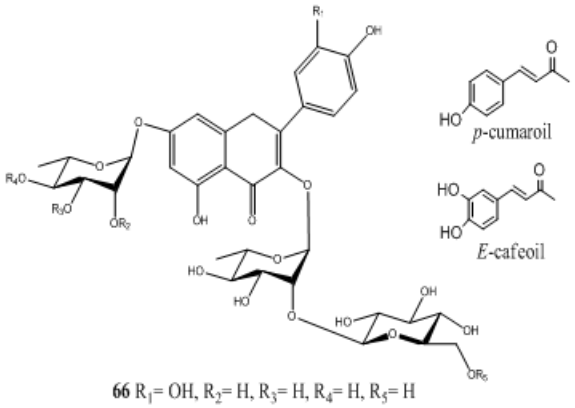
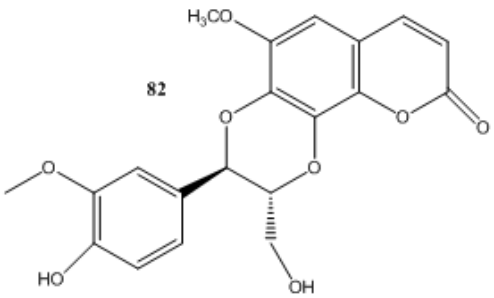


p-cumaroil

E-cafeoil

66 R_1= OH, R_2= H, R_3= H, R_4= H, R_5= H
67 R_1= OH, R_2= H, R_3= H, R_4= H, R_5= *p*-cumaroil
68 R1= OH, R_2= H, R_3= H, R_4= H, R_5= *E*-cafeoil
69 R_1= OH, R_2= H, R_3= H, R_4= CH_3CO, R_5= H
70 R_1= OH, R_2= H, R_3= H, R_4= CH_3CO, R_5= *p*-cumaroil
71 R_1= OH, R_2= H, R_3= CH_3CO, R_4= H, R_5= H
72 R_1= OH, R_2= CH_3CO, R_3= H, R_4= H, R_5= H
73 R_1= OH, R_2= CH_3CO, R_3= H, R_4= CH_3CO, R_5= H
74 R_1= OH, R_2= H, R_3= CH_3CO, R_4= CH_3CO, R_5= H
75 R_1= OH, R_2= CH_3CO, R_3= CH_3CO, R_4= CH_3CO, R_5= H
76 R_1= OH, R_2= H, R_3= CH_3CO, R_4= H, R_5 = *p*-cumaroil
77 R_1= OH, R_2= H, R_3= CH_3CO, R_4= CH_3CO, R_5= *p*-cumaroil
78 R_1= OH, R_2= H, R_3= H, R_4=CH_3CO, R_5 = *E*-cafeoil
79 R_1= H, R_2= H, R_3= H, R_4= CH_3CO, R_5= H
80 R_1= H, R_2= CH_3CO, R_3= H, R_4= CH_3CO, R_5= H
81 R_1= H, R_2= CH_3CO, R_3= CH_3CO, R_4= H, R_5 = H



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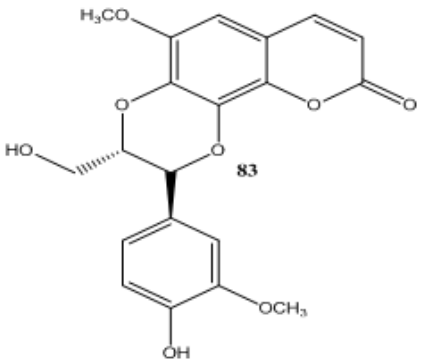

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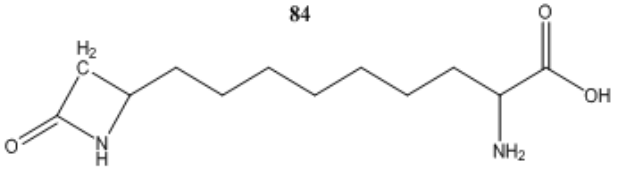

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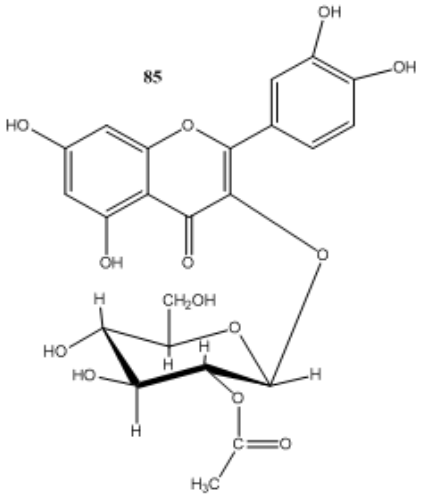

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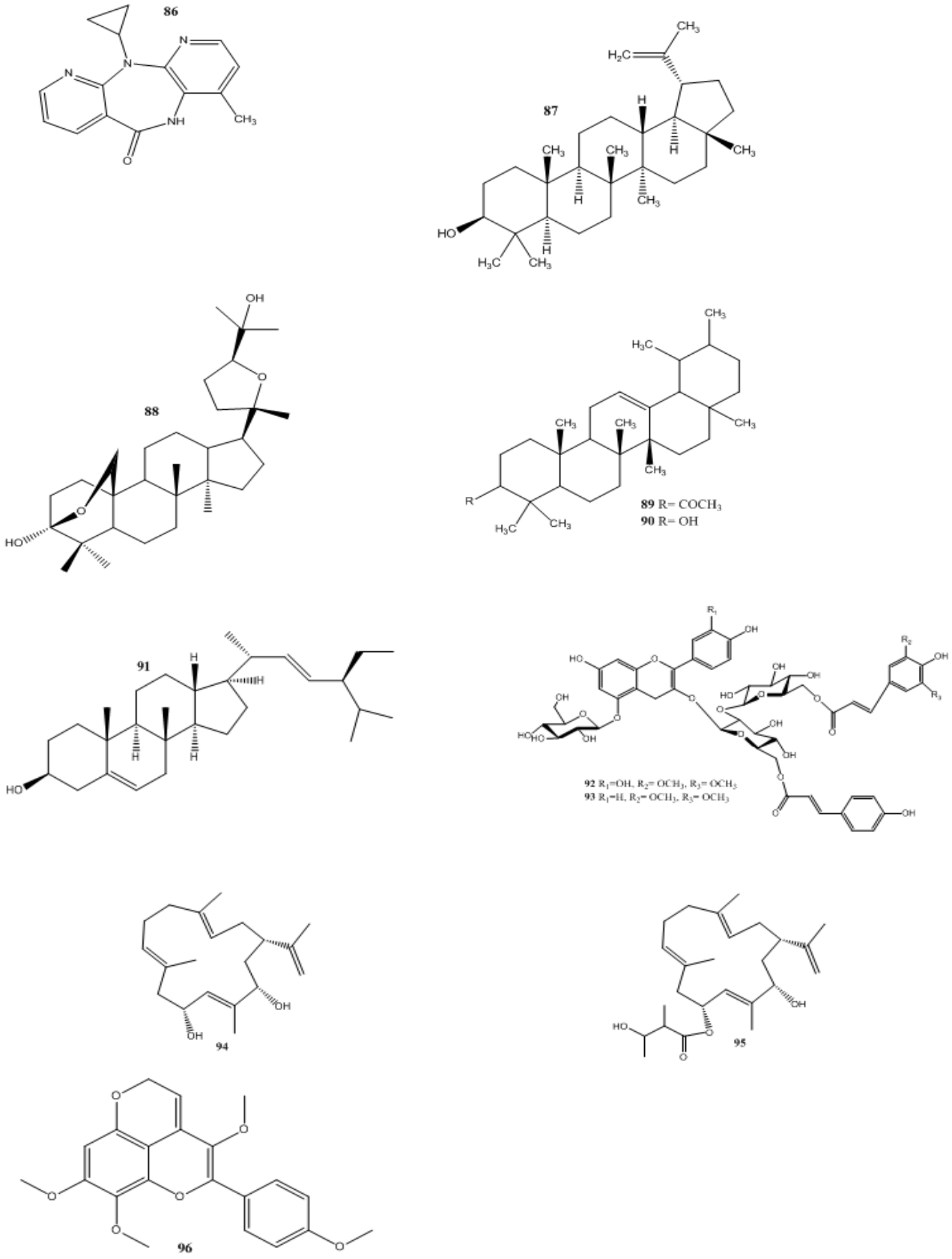

Figure 1. Chemical compounds isolated from some species of the *Cleomaceae* family.

of this family have activity on cells of the immune system (immunomodulator activity), such as macrophages and PMN and generate inhibition of molecules involved in the inflammatory process. Ding et al. (2016) reported that the EtOH extract (95%) of *Cleome rutidosperma* DC. inhibited the expression and production of pro-inflammatory mediators in macrophages from central nervous system (murine microglial cell line, BV-2), stimulated with lipopolysaccharides (LPS). At concentrations of 0.05 and 0.1 mg/ml, it inhibits NO production in LPS-activated BV-2 cell by attenuated expression of the iNOS enzyme. It attenuates mRNA production and expression of COX-2. In addition, it inhibits levels of IL-6, TNF-α and suppresses the transcriptional activity of IL-1β and the chemokine CCL2/MCP-1 or monocyte chemoattractant protein and increases the expression of antioxidant enzymes such as hemo-oxygenase, glutamate cysteine ligase and quinone oxidoreductase. The authors propose that the anti-inflammatory activity of this extract is due to the inhibition of the nuclear transcriptional factor kappa B (NF-κB), through sub-regulation of the phosphorylation of p65 and by modulation of the activation of the amino terminal kinase of c-Jun (JNK).

On the other hand, in neutrophils (isolated from healthy individuals) was stimulated with different concentrations (0.1, 1, 10 or 100 µM) of the calcium ionophore (A23187), the release of leukotriene B4 (LTB4) and the production of PGE_2 can be induced. In this model, the MeOH (70%) extract from *Cleome arabica* L. leaves at 25 µg/ml inhibits the release of LTB_4 over all tested concentrations of ionophore A23187; but at the concentration 100 µM of the A23187 ionophore (maximum production of LTB4); the *C. arabica* extract (25 µg/ml) reduced the production of LTB4 by 25% compared to rutin and quercetin (25 µM); these two flavones showed 35 and 95% inhibition, respectively. In addition, the extract at 25 µg/ml and rutin at 25 µM increased the production of PGE_2 in the presence of the calcium ionophore at 1 and 10 µM. Also, this extract inhibited 26.1% of the PGE_2 production when the calcium ionophore (A23187) was tested at 100 µM and quercetin inhibited the PGE_2 production at concentrations of 1-100 µM of A23187 (Bouriche et al., 2005). These same authors describe that the MeOH (70%) extract inhibited the soybean lipoxygenase; in this case, the extract showed an inhibitory concentration medium (IC_{50}) = 10 µg/ml, while rutin and quercetin (the positive control) showed an IC_{50} = 11 and 14 µM, respectively.

In the inflammatory process, among the first cells to migrate and accumulate in tissue with injury or damage are PMN lymphocytes, which release proteolytic enzymes capable of eliminating pathogens; but their prolonged activity can damage tissues. A yellow precipitate obtained from the MeOH (70%) extract of the leaves of *C. arabica* was evaluated on the migration of PMN isolated from the blood of healthy donors using as chemotactic factor N-formyl-L-methionyl-L-phenylalanine in a chemotaxis chamber. The percentage of neutrophil inhibition was 83.9% at extract concentration of 50 µg/ml and the reference drug (aspirin) at 50 µM showed 66.23% inhibition (Bouriche et al., 2003).

Pillai and Nair (2014) reported that the MeOH and $CHCl_3$ extracts from *C. viscosa* (L.) Cochrane & Iltis and *C. burmanni* Wight & Arn. inhibited protein denaturation in the albumin assay, as well as proteinase inhibitory activity and the inhibition of hyaluronidase *in vitro*. In chronic inflammation, these processes are involved in the contribution to tissue damage. In the albumin denaturation test, the MeOH extract of *C. viscosa* at 0.8 mg/ml inhibited the protein denaturation with 88.92% and the $CHCl_3$ extract had an inhibition of 59.75%, while aspirin at the same dose inhibited 95.82%. In addition, the MeOH and $CHCl_3$ extract from *C. burmanni*, had a lower activity, with 78.92 and 50.42% inhibition, respectively, in the same model. The MeOH extract of *C. viscosa* at a concentration of 0.6 and 0.8 mg/ml showed the best activity in the proteinase inhibition assay with values of 59.70 and 78.26 %, respectively, while aspirin at 0.6 and 0.8 mg/ml showed 64.44 and 88.20% of the inhibition. The MeOH extract of *C. viscosa* and *C. burmanni* (0.8 mg/ml) inhibited the hialorunidase activity with 82.11 and 70.89%, respectively; these values were similar to indomethacin (0.8 mg/ml) with 91.33%.

In vivo anti-inflammatory activity of some genus of the *Cleomaceae* family

One of the main models used for the discovery of non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin is the murine model of plantar edema induced with carrageenan, which increases the volume of the animal's paw (Winter et al., 1963). In this model, the edema is generated in two phases; in the first phase (1-2 h), vasoactive amines (histamine, serotonin, bradykinin) are released and in the last phase (3-5 hours), the COX-activity is observed. In addition, there is a local infiltration of neutrophils that contributes to the production of reactive species; also, the release of NO is generated (Salvemini et al., 1996). In this last phase, NSAIDs, COX-2 inhibitors and monoclonal antibodies directed to PGE_2 are effective (Cong et al., 2015; Portanova et al., 1996). Some species belonging of *Cleome, Corynandra, Gynandropsis* and *Tarenaya* genus have shown a significative anti-inflammatory effect. For example, the MeOH extract from leaves collected in the wild and produced by biotechnological process from the *Tarenaya spinosa* (Jacq.) Raf. (Syn. *Cleome spinosa* Jacq.), was tested on carrageenan model at doses between 1 to 50 mg/kg, administered intraperitoneally (i.p.). Both extracts (from biotechnological material and wild) have anti-inflammatory activity, showed edema inhibition between 40 and 50% on the 3rd hour with respect to the reference

drug (indomethacin, 10 mg/kg, i.p., 55 to 60%) (Albarello et al., 2013).

On the other hand, the MeOH extract from *Corynandra chelidonii* (L. f.) Cochrane & Iltis ex Spreng. (Syn. *Cleome chelidonii* L.f.) whole plant was tested on the carrageenan model at dose of 200 mg/kg administrated by intragastric route (i.g), showed an inhibition of 54.6% of the edema, with respect to the reference drug aspirin (10 mg/kg, i.g), which inhibited 60.6% at 3 h (Parimalakrishnan et al., 2007).

The MeOH extract, $CHCl_3$ fraction and ethyl acetate fraction of *C. viscosa* were tested at a dose of 50 mg/kg/i.g in the carrageenan model, obtaining at 4 h, a significant anti-inflammatory activity being of 66.67, 89.33 and 100% of inhibition, respectively; this effect was similar to indomethacin 100% (at 10 mg/kg) (Khanam et al., 2015). On the other hand, the MeOH extract was evaluated against carrageenan-histamine and dextran-induced rat paw edema. The results were similar compared to the reference diclofenac sodium (20 mg/kg) (Parimala et al., 2003).

The MeOH extract (70%) of *C. arabica* leaves possesses anti-inflammatory activity in carrageenan-induced rat paw edema; at 100, 200 and 300 mg/kg, it reduced the edema formation with 34.46, 42.14 and 58.46%, respectively, when was administered by i.g at 5 h. This extract showed ED_{50} = 231 mg/kg and aspirin at 100 mg/kg with 73.63 % inhibition of edema (Bouriche et al., 2003). The EtOH extract (200 and 400 mg/kg/i.g. via) and the diethyl ether, ethyl acetate and *n*-butanol fractions from the aerial parts of *C. rutidosperma* at 200 mg/kg showed anti-inflammatory activity in the carrageenan model at the 3rd hour. The EtOH extract at a dose of 200 mg/kg reduced the volume (0.44 ml) and the three fractions showed values between 0.39 and 0.44 ml, with respect to diclofenac control (12.5 mg/kg), it which showed a reduction of 0.31 ml (Bose et al., 2007). However, the same extract at doses of 200 and 400 mg/kg by i.g and the same fractions at 200 mg/kg by i.g also showed inhibitory activity in the chronic inflammation model (arthritis induced by Freund's complete adjuvant-ACF) in rats; the samples were administered during 30 days. In this assay, the extract at 400 mg/kg reduced the size of the edema with 0.48 ml, the fractions at 200 mg/kg reduced the size of the edema with values between 0.44 and 0.60 ml, the effect of the extract and fractions was lower with respect to the reference drug diclofenac (12.5 mg/kg) with 0.41 ml (Bose et al., 2007).

In AFC model, the histopathological analysis of the hind limbs from arthritic rats generated an increase in paw volume, with alteration in tissue architecture, also showing synovial hyperplasia, monomorphonuclear and polymorphonuclear cell accumulation in the joint space. Narendhirakannan et al. (2005) described that the EtOH 95% extract from *G. gynandra* leaves at 150 mg/kg/i.g. during 30 days in rat showed an anti-inflammatory activity; in this assay the edema volume decreased from the third week of treatment with the highest activity in the fourth week with significative reduction of inflammatory exudates. Subsequently, in 2007 the same author reported that in the plasma of the arthritic rat, showed an increase of TNF-α levels and in the liver tissue an increase of alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, captesin-D, β-glucuronidase, N-acetyl-β-glucosaminidase, lactate dehydrogenase and glycoproteins. This specie showed a significant anti-inflammatory activity in acute and chronic models; therefore, it is necessary to carry out additional studies that confirm its pharmacological activity and allow the isolation and chemical identification of the active principles.

Phytochemistry and anti-inflammatory activity of the pure compounds isolated from genus of the *Cleomaceae* family

From organic extracts of the whole plant, stems, flowers, roots, seeds and leaves of some species of the *Cleomaceae* family several secondary metabolites have been reported by qualitative analysis tests, such as: polyphenols, flavonoids, coumarins, quinones, carbohydrates/glucosides, alkaloids, steroids, saponins, terpenes among others, without chemical identification for each component (El-Wahab et al., 2016; Singh et al., 2017; Alamilla-Fonseca et al., 2018). On the other hand, Table 1 describes the main metabolites isolated from *Cleome, Corynandra, Gynandropsis* and *Tarenaya* genus. In Table 2, we describe the main components from essential oils by *Cleome, Corynandra*, *Tarenaya* and *Cleoserrata*.

The main metabolites that biosynthesize the species of *Cleomaceae* family are phenolic compounds. Sharaf et al. (1992), and Wollenweber et al. (2007) reported polymethoxyflavonols, glucoflavonoids, flavanones and their glycosides for genus *Cleome* and bioactive cumarinolignoids have been described for *Corynandra* genus.

From MeOH extract of *Cleome droserifolia* (Forssk.) Delile aerial parts, two active flavonoids identified as 5,4'-dihydroxy-6,7,8,3',5'-pentamethoxyflavone (**32**) and 5,4'-dihydroxy-6,7,8,3'-tetramethoxyflavone (8-methoxycirsilineol, **33**) were isolated and reduced the NO production in peritoneal macrophages induced with the Bacillus Calmette-Guerin and stimulated with LPS. Compound **32** inhibited the production of NO by 60% at 10 µg/ml; it was more active than genistein (positive control), and suppresses NO production by 41% at 20 µg/ml, and compound **33** was less active. A correlation was observed between NO production and cell viability RAW 236.7 murine macrophages stimulated with LPS. Compounds **32** and **33** in a range of 0 to 20 µg/ml inhibited NO production, with IC_{50} = 50.5 and 85.5 µM, respectively, while genistein showed an IC_{50} = 9.6 µM

Table 2. Main chemical constituents of the essential oil from some species of the *Cleomaceae* family.

Species	Part used	Main constituent essential oils	References
Cleome burmanni Wight & Arn.	Whole plant	24(s)- ethyl-3-α,5-α-cyclocholest-22(*E*)-en-6-one (19.29%); Δ-4-sitosterol-3-one (14.75%); cholest-4-en-3-one (12.35%); stigmasta-5, 23-dien-3-ol,(3-β) (12.17%); neophytadiene (6.83%); hexatriacontane (6.22%); 1-alanine, N-(3-fluorobenzoyl)-undec-10-enyl ester (5.96%); phytol (5.67%); tetracontane (4.30%); 1,2-benzenedicarboxylic acid (3.25%)	Pillai and Nair (2013)
Cleome droserifolia (Forssk.) Delile	Aerial parts	E)-3,7,11-trimethyl-1,6,10-decatrien (11.8%); carotol (10.1%); δ-cadinene (8.9%); *β*-eudesmol (7.0%); benzyl isothiocyanate (5.9%)	Muhaidat et al. (2015)
Cleome heratensis Bunge & Bien. ex Boiss.	Aerial parts	Hexanal (7.57%-33.96%), α-phellandrene (6.08% -13.17%), α-farnesen (7.54%- 10.9%), methyl eugenol (6.74%-8.31%), eugenol (3.94%-7.4%), verbenone (3.98%- 6.24%), myrcene (1.54%-5.75%), hexadecane (2.34%-4.82%), linalool (1.59% - 3.53%), α-humulene (1.01%-1.93%)	Nasseri et al. (2017)
Cleome iberica DC.	Aerial parts	Carotol (21.8%), germacrene D (15.8%), *β*-cubebene (15.5%), *trans*-nerolidol (5.6%), δ-cadinene (4.5%) hexyl acetate (4.0%).	Mirza et al. (2005)
Cleome monophylla L.	Aerial parts	Terpenolene (14%),1-α-terpeneol (10%), pentacosane (9%), (α + β)-humulene (8%), phytol (5%), 2-dodecanone (4%)	Ndungu et al. (1995)
Cleoserrata serrata (Jacq.) Iltis (Syn. *Cleome serrata* Jacq.)	Aerial parts	(*Z*)-phytol (53%), di (2-ethylhexyl)-phthalate (14.7%), piperonal (11.5%), 3-α-acetoxymanool (3.1%), (Z,Z)-6,9-*cis*-3,4-epoxy nonadecadiene (2.4 %), 2,6,10,14,18-pentamethyleicosane (1.8%)	McNeil et al. (2012)
Corynandra viscosa (L.) Cochrane & Iltis (Syn. *Cleome viscosa* L.)	Seeds	Palmitic (10.6%), stearic (4.9%), oleic (14.4%), linoleic (68.6%) acids	Rao et al. (1980)
	Aerial parts	(Z)-phytol (31.3%), integerrimine (5.5%), incensole (4.0%)	
Tarenaya spinosa (Jacq.) Raf. (Syn. *Cleome spinosa* Jacq.)	Aerial parts without	Caryophyllene oxide (10.5%), (-)-spathulenol (7.5%), Z-phytol (6.9%)	McNeil et al. (2010)
	Flowers	7-alpha-hydroxy manool (23.8%), incensole (9.2%) sclareol (8.7%)	
	Fruits	Tetradecanoic acid (40.6%), (Z)-phytol (6.58%), sclareol (4.5%)	
	Leaves	(Z)-phytol (19.5%), 7-α-hydroxy manool (6.8%), caryophyllene oxide (4.36%)	

(Fushiya et al., 1999).

The mixture of cleomiscosins A-C (**85-87**) obtained from the MeOH extract of *C. viscosa* seeds inhibited the production NO, modulated pro-inflammatory and anti-inflammatory cytokines *in vivo* and *in vitro* model. For example, in mice healthy were administered the cleomiscosins mixture at 10, 30 and 100 mg/kg/day (solubilized in carboxymethylcellulose at 0.5%, and administerd by i.g. via) for 14 consecutive days; after that, peritoneal macrophages and spleenocytes were isolated. In supernatant culture from the mouse peritoneal macrophages stimulated with LPS (1 µg/ml) increased IL-6, TNF-α and NO expression; the mixture of cleomiscosins at 10 and 30 mg/kg decreased the ON levels with values of 122.51 and 129.23 nM/ml, respectively, compared with LPS control-macrophages 312.31 nM/ml. Also, the pro-inflammatory mediator IL-6 in LPS-macrophages control increased (2033.67 pg/ml);

however, the cleomiscosin mixture at 10 mg/kg decreased the IL-6 values (1067.58 pg/ml). Likewise, the cleomiscosin mixture at 10 and 30 mg/kg inhibited the production TNF-α in culture with values of 286.87 and 299.06 pg/ml, respectively, with respect to LPS-macrophage control (430.97 pg/ml) (Bawankule et al., 2008). In murine spleenocytes stimulated with Concavalin A (Con-A,5 µg/ml), the expression level of IL-4 in supernatant culture was 235.47 pg/ml, and the cleomiscosin mixture at 10 mg/kg increased the production of IL-4 with values of 327.50 pg/ml. These authors carried out an additional study to confirm the expression of pro-inflammatory mediators (TNF-α and IL-6) in serum and acute toxicity using an *in vivo* model treated with LPS (250 µg/kg), which induced lethal toxicity. The cumarinolignoids A-C was administered by i.g via at 10 and 30 mg/kg during 14 days; after the last administration the mice were injected LPS. The mixture of compounds inhibited the production of pro-inflammatory mediators, also reduced the animal mortality in dose dependent manner (Bawankule et al., 2008).

The quercetin-3-O-(2''-acetyl)-glycoside (**85**) isolated from the 85% MeOH extract of *C. viscosa* fresh flowers at a dose of 100 and 200 mg/kg administered by i.p. via showed anti-inflammatory activity with 51.7 and 45% inhibition in the second phase (3 h) on the carrageenan model; the effect was compared to phenylbutazone at 100 mg/kg/i.p. via with 70% inhibition (Senthamilselvi et al., 2012).

The anti-inflammatory potential of some species from *Cleomacea* family has been demonstrated; however, but some species have only phytochemical studies; for example, from *Tarenaya hassleriana* Chodat) Iltis (Syn. *Cleome hassleriana* Chodat) only anthocyanins have been isolated (Jordheim et al., 2009); other species with phytochemical potential are *C. chrysantha, C. haratensis, C. iberica* (Tables 1 and 2). In addition, from *Cleome rupicola* Vicary triterpenes (**64**) and flavonol glycosides **(65**) have been isolated with cytotoxic activity on the HeLa cell line (Al-Rehaily et al., 2017) and from *C. khorassanica* Bunge & Bien. ex Boiss. (aerial parts) dammarane triterpenes (**61** and **62**) with cytotoxic activity against prostate cell lines (DU-145 and LNCaP) have been described (Sajjadi et al., 2018).

On the other hand, the essential oils of the *C. droserifolia*, *C. serrata* and *C. spinosa* showed antimicrobial activity against Gram-positive and Gram-negative microoorganisms (Muhaidat et al., 2015; McNeil et al., 2010; 2012); however, these species have not yet the anti-inflammatory evaluation. Phytol is main component from essential oils of *C. burmanni, C. monophylla, Cleoserrata serrata* and *Tarenaya spinosa,* and this diterpene showed a good anti-inflammatory activity by inhibition of the migration of neutrophils, reducing the IL-1β and TNF-α levels and reducing the oxidative stress (Silva et al., 2014) (Table 2).

Antinociceptive activity of some genus of *Cleomaceae*

Pain is a symptom of many chronic degenerative diseases, and their transmission involves the activation of peripheral nociceptors by harmful stimulus that can be sensitized by inflammatory mediators (neuropathic pain mechanisms). Some species of the family *Cleomacea* have shown analgesic activity.

The main model used for the evaluation of antinociceptive activity is the acetic-acid (a.a.)-induced abdominal constriction test in mice (its model induce visceral inflammation) and this provoke release of endogenous mediators such as bradykinin, serotonin, histamine, substance P and PGE_2, triggering the activation of peripheral nociceptive neurons (Koster and Anderson, 1959). Another assay is formalin-induced paw licking test, in which two phases are distinguished, in the first phase (0 to 5 min) the sensitization of the nociceptors (neurogenic pain) is involved and in the second phase (15 to 30 min) an inflammatory process is involved which is triggered by the production of histamine, serotonin, PGE_2 and bradykinin (Hunskaar and Hole, 1987). Another model is the tail immersion assay, which is a thermal test for evaluating the analgesic potential in warm water (55°C), or tail-flick and hot plate test, which measures the latency time to the thermal stimuli reflecting the central antinociceptive activity (acute pain) (Srinivasan et al., 2003).

The *n*-butanol fraction from 80% EtOH extract of *Cleome amblyocarpa* Barratte & Murb. (Syn. *Cleome africana* Botsch, medicinal plant is use as analgesic in Rafha city, Northern Border of Saudi Arabia), at 50 mg/kg/i.g via after 60 min showed 80.6% nociceptive activity in the hot plate model and after 90 min its activity was 65.67% and the control diclofenac sodium showed 40% (at 60 min) and 42.8 % (at 90 min) inhibition (El-Wahab et al., 2016). *C. rutidosperma* polar extracts has shown central and peripheral analgesia with anti-inflammatory activity. The MeOH extract was tested on the mouse models of tail removal and hot plate at doses of 100 and 200 mg/kg/i.g; it showed an increase on the response to thermal stimuli. The extract raised the latency time in the tail-flick test, with 3.11 and 3.22 min, respectively; effect similar to the reference drug morphine (5 mg/kg i.p.) with 4.41 min. In hot plate test at 120 min, the extract (200 mg/kg) showed a response time of 13.22 min (53.52%), this data is very close to morphine with a response time of 15.35 min (67.27%). These results suggest that the antinociceptive effect of the extract is related to opioid receptors. In the abdominal contortion test induced with a.a., extract at 100 and 200 mg/kg/i.g. via inhibited in 39.38 and 47.32%, respectively, the effect was compared to morphine (60.12%). In the paw lick test induced with formalin, in both phases the number of licks was reduced in the early phase 106.0 (19.57%) and 100.6 (23.67%) and in the late phase the number of licks

was reduced from 13.40 (85%) and 8.00 (91.30 %) for doses of 100 and 200 mg/kg (Ansari et al., 2016).

The EtOH extract from *C. rutidosperma* (aerial parts) showed antinociceptive activity at 200 and 400 mg/kg (administered by i.g.); this extract reduced the number of contortions, being 28.5 and 14.5, respectively, and their diethyl ether fraction at 200 mg/kg also inhibited the contortion number with 14.0 contortions with respect to reference drug (acetylsalicylic acid at 200 mg/kg) with 21.8 contortions. In the tail immersion test, the butanolic fraction (200 mg/kg) induced protection with a reaction time of 7.47 sec, this response time was comparable to refence drug (pentazocine at 30 mg/kg/i.g. via) that showed 8.48 s; therefore, it has been proposed that this activity is due to the fact that this fraction inhibited the prostaglandin production (Bose et al., 2007).

The analgesic activity in mice was evaluated using the a.a.-induced writhing and the tail flick, tail clip, tail immersion methods; MeOH extract from *C. viscosa* at 100, 200 and 400 mg/kg/i.g. via showed important activity in all assays (Parimaladevi et al., 2003). Likewise, the 80% MeOH extract from *C. viscosa* (leaves) at 250 and 500 mg/kg, administered by i.g, inhibited the number of contortions, with 35.80 and 47.94%, respectively; this effect was comparable to diclofenac sodium, which showed 64.17% inhibition at 25 mg/kg (Bose et al., 2011). On the other hand, Khanam et al. (2015) described the antinociceptive activity from the MeOH extract, and from chloroform and ethyl acetate fractions, these samples showed 79.16, 81.25 and 70.83% writhing inhibition, respectively. The effect was similar to diclofenac sodium with 83.33% writhing inhibition.

The MeOH extract of leaves and stems from *Cleome spinosa* (plants obtained in the wild and by biotechnological process) at 50 mg/kg administered by i.p. via showed antinociceptive activity, which was similar to dipyrone (100 mg/kg/s.c., reference drug); in this assay, the stem extract from wild plant was more active with a 68% reduction in the number of contortions (Albarello et al., 2013).

MeOH extract of the whole plant *C. chelidonii* at 200 mg/kg showed antinociceptive activity; it decreased the number of contractions to 45.8% compared to the drug aspirin (100 mg/kg/i.g.) with 64.0%, and increased the response to the stimulus in the hot plate test in mouse in a time of 30 min with 13.74 s, in comparison with morphine (5 mg/kg/i.p.) with 17.17 sec (Parimalakrishnan et al., 2007).

CONCLUSION AND PERSPECTIVES

Four genera of the *Cleomaceae* family (*Cleome*, *Corynandra*, *Gynandropsis* and *Tarenaya)* have been described with anti-inflammatory and antinociceptive activities. These genera are widely used in traditional medicine for the treatment of diseases in which there are inflammatory process and pain among other diseases. The polar extracts (MeOH or EtOH) prepared from leaves or aerial parts were the most used for the biological tests. *Cleome arabica, Corynandra viscosa* and *Cleome rutidosperma* showed a good *in vitro* and *in vivo* anti-inflammatory activity; in addition, *Cleome rutidosperma* and *Gynandropsis gynandra* presented anti-inflammatory effect using *in vivo* CFA chronic model. *Cleome burmanni* has only been evaluated *in vitro* assay and *Corynandra chelidonii* and *Tarenaya spinosa* have been evaluated *in vivo* (carrageenan model). The bioactive compounds from only two species with anti-inflammatory activity have been isolated, from *Cleome droserifolia* two flavonoids (32 and 33) with anti-inflammatory activity was isolated using peritoneal macrophages (*in vitro* model). From *Corynandra viscosa* has been isolated cumarinolignoids [cleomiscosins A, B, C) and quercetin-3-O-(2''-acetyl)-glucoside] and these compounds showed a significant anti-inflammatory activity.

Respect to antinociceptive activity, acetic-acid-induced abdominal constriction test, hot plate test, tail immersion assays are the most used. To date, only five species: *Cleome amblyocarpa*, *Cleome rutidosperma*, *Corynandra viscosa*, *Tarenaya spinosa* and *Corynandra chelidonnii* have been reported with antinociceptive activity. However, to date there are few or no, manuscripts that describe of the bioactive compounds biologically tested of these active species.

It is important to redouble efforts to explore the phytochemistry and pharmacological potential by the *Cleomaceae* family because some species has an important pharmacological activity but has not yet been isolated the active compounds. On the other hand, it was found that 12 species of the *Clemaceae* family have phytochemical studies and report the presence of steroids, phenolic acids, anthocyanins, terpenes and alkaloids; however, many of these compounds have not yet been investigated from the pharmacological point of view. Finally, only for 8 species (*Cleome burmanni*, *C. droserifolia*, *C. heratensis*, *C. iberica*, *C. monophylla*, *Cleoserrata serrata*, *Corynandra viscosa* and *Tarenaya spinosa*) the chemical composition of essential oils has been described.

Therefore, this family can be a potential source of active compounds that will allow the development of new therapeutic alternatives for the treatment of diseases in which an inflammatory and/or pain process occurs. Based on this review (including chemical and biological research), the species of the *Cleomaceae* family are a potential source of anti-inflammatory and antinociceptive compounds.

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