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The species of genus *fagonia* in Libya: A comprehensive review

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Abstract
The Plants of the genus *Fagonia* have been broadly utilized as adjunctive therapy, to treat several conditions involving high fever, diabetes, asthma, stoma chache, dental pain, and renal problems using their aqueous extracts as medicines. This genus is a valuable source that comprises a variety of Triterpenes, flavonoids, and Saponins. The herbal chemistry as well as the biological action of *Fagonia* species have been a candidate for many researchers. The *in vivo* pharmacological screening of their extracts has manifested some other significant properties such as cytotoxic and anti-cancer activity. This review study has gathered the important research that has been carried out on the species that grow in Libya. It includes an exhaustive survey of literature about the medicinal value and the bioactivities of various extracts obtained from these *Fagonia* species using references from major databases.

Keywords: *Fagonia*, zygophyllaceae, cytotoxic, triterpenes, flavonoids and saponins

Introduction
According to several reports documented by the WHO, eighty percent of the populations around the globe prefer and rely on nonconventional therapies, mostly of herbal origin, in their primary healthcare [1]. Medicinal plants have global importance and are considered a local heritage. Due to the worldwide trend toward better "quality of life", there is considerable evidence of increasing demand for herbs with therapeutic value [2]. Natural products have been utilized to treat a variety of ailments for as long as humans have existed. All the sections of society widely use herbal medicine whether directly employing them as traditional remedies or indirectly as pharmaceutical products [3]. Currently, the focus on the research for bioactive phytochemicals has dramatically spread all over the world and significant number of evidences was set to prove the enormous medical activities of plants utilized in several common folk systems. Various biodynamic compounds with considerable therapeutic value are contained in medicinal herbs. Furthermore, the diverse variety of plants offers different numerous properties with immense therapeutic potential [4]. The present review highlights the Ethnopharmacologically, botanical, phytochemical, and pharmacological reports as well as clinical studies on *Fagonia* species that grow in Libya. The systemic investigation of this genus is highly required, so that the potent species can be employed as therapeutic agents.

The genus *Fagonia*
The family that comprises the genus *Fagonia* is Zygophyllaceae, which is considered as a one of the dicot groups of flowering plants (angiosperms) [5, 6]. This genus consists of fifty different species propagated throughout the aired regions and deserts of the south and southwest America, Asia, and North Africa with 12 species in Libya alone [7]. All *Fagonia* species are ranged from shrubs to herbs, rarely reaching from 60 to 100cm in height, and about 100cm in width. It has pointed stipules or very little spines, purple or pink petals, and an obconical, loculicidal capsule that is to some extent pubescent. *Fagonia* has notoriously difficult circumscription [8]. The shrublets of this species are annual to perennial. The Stems are slightly woody, surrounded by whitish granules or sessile glands, or somewhat are glabrous. the branches are procumbent, cylindrical, and striate, internodes 2.5-5cm in length. The leaves are typically unifoliolate or upper unifoliolate and the basal ones are trifoliate, the leaflets are lanceolate or linear-oblong, 3-4mm wide, 6-35mm long, mucronate, short to long sessile or petioled; patent to ascending, stipular spines shaped, equal to shorter than leaves, in some cases minute or deficient [9].

In the Unani alternative medicine, this plant is well known to be bitter, astringent, antiseptic, analgesic, febrifuge, antipyretic, stimulant, tonic, diuretic antiemetic, and DE obstruent; as well as it used in the management of different illness, *viz* asthma, fever, urinary discharge, dysentery, vomiting, leucoderma, typhoid, bilious and for snakebite [9]. Occasionally, the whole plants and their ashes have been utilized as homemade. Remedies, while the most commonly used preparation of this herb which prescribed by the physicians are their aqueous and alcoholic tinctures. Preliminary pharmacological screening confirmed the medicinal significance of these plants and their effectiveness in the treatment of various health conditions [10].

Research has demonstrated the pharmacological values as well as the ethnomedicinal uses of these herbs, however, there are no review articles available in the literature to collect all the required data together and offer clear insights for the future investigations on *Fagonia*. The aim of this work is to present the phytochemical composition and therapeutic significance of *Fagonia* species growing in the Libyan Desert based on comprehensive literature research. Eleven species were employed in this research, *F. bruguieri* DC. *Fagonia arabica* L., *F. cretica* L., *F.* indica Burm., *F. glutinosa* Delile, F. *microphylla* Pomel, *F. sinaica* Boiss., *F. tenuifolia* Steud., *F. schweinfurthii* Hadidi, *F.* the baica Boiss, and *F. taeckholmiana*. Table 1 displays selected *Fagonia* species and their geographical distribution in Libya [11].

Table 1: The studied *Fagonia* species and their locations in Libya

No	*Fagonia* Species	Distribution in Libya
1	*F. arabica* L.	Bark - Tijarbi - Wadi Bughrara (Tumb) - sabha - Gebel Uweinat- Hun.
2	*F. cretica* L.	WadiMalah (Nalut)- shik Shook (Jadoo) - Gharian (Gebel Nafousa) - El Homs, - El-Naggaza (Khoms) - Sharshara, near Tarhuna - WadiDerna - Derna - Wadi al-Ramlah - Tobruk.
3	*F. bruguieri* DC.	El-Washka - Gara Al -Tifarni, (Weshka) - Fezzan, - Wadi Soda- Sebha, along Hun highway.
4	*F.* indica Burm.	Al-Abiad - Sebha on Sebha-hun- Brak, - wadiBughrara, - Tuarbi- WadiAtiq.
5	*F. sinaica* Boiss.	Gharian Hills, Roadside,- Wadi Malah, (Nalut)- Shak Shook
6	*F. microphylla* omel.	Nalut
7	*F. tenuifolia* Steud.	Besalt hillock, nearby Hun, Wadi-Malah (Nalut) - Wadi Sada - Wehka.
8	*F. schweinfurthii* Hadidi.	Hun- Gare al Tifarmi (Weshka) -El - Fezzan Soda Mountains.
9	*F. the*baica Boiss.	Karkur Ibrahim heights of Jebel Uweinat
10	*F. glutinosa* Delile.	Gebel Nefousa, - Wazen, Libyan Tunisian Boundary - Hun - Gara El-Tifarni, - wadi Soda. - Weshka
11	*F. taeckholmiana*	The desert between Libya and Egypt

Plant Taxonomy

The taxonomical classification of genus *Fagonia* is very challenging due to its ability to adapt to different climatic conditions, which makes it have a high degree of morphological flexibility. Some articles [12, 14] classified the *Fagonia* species of North Africa into four natural groups, which according to vegetative morphological features, can be reviewed as sections: (1) *F. kahirinacretica*- flamandii (2) *F. glutinosa-latifolia* (3) *F. Arabica bruguieri* and (4) *F. microphylla*- group. Additionally, other articles grouped it into three categories, *arabica-bruguieri*, sinica, and *glutinosa* group [11, 15, 16]. The pubescence and structure of the leaves were prioritized in the species identification process.

Fig 1: The aerial parts of *Fagonia glutinosa* (Benghazi, Libya)

Fig 2: The aerial parts of *Fagonia cretica* L. (Benghazi, Libya)

Phytochemistry

A comprehensive literature investigation of several reports regarding the phytochemicals of the *Fagonia* genus shows that those species are abundant in secondary metabolites, chiefly Saponins, terpenoids, alkaloids, anthraquinones, iridoids, sterols, coumarin, flavonoids, etc. [17, 23]. Various studies linked to qualitative phytochemical assays by using different solvent, methanolic, aqueous and n-hexane extracts of finally grounded dried plant material. The identification of these classes was conducted by applying a well-established technique. Table 2 represents the phytoconstituents of *Fagonia*, and Figure 1 demonstrates the structures of the most predominant compounds that isolated and identified from this genus. The screening of *F. arabica* revealed the presence of flavonoids, terpenoids, Saponins, glycosides, alkaloids and tannins phytochemicals [24]. On the contrary, there is no data was published concerning the active constituents of *F. schweinfurthii.*

Table 2: Phytoconstituents of various species of *Fagonia*

Species	Phytoconstituents
F. Arabica	Sulfated Triterpenes [22], Triterpenoid Saponins [25, 27], phenol and tannins [21] and flavonoids [28].
F. Cretica L	Flavonoid glycosides [29], Saponins [25, 30, 33].
F. Bruguieri DC	Phenol and flavonoids [34], Flavonol glycosides [35], and diterpenes of erythroxan-type [36].
F. indica	Flavonoids [37], Triterpenoid Saponins[37, 39], steroidal saponin glycoside [40], (indicasaponin A) and (indicasaponin B) [41], and Taraxast-20-en-28-oic acid Saponins [42].
F. Sinaica Boiss	flavonol glycosides [43, 44].
F. Microphylla	Flavonol glycosides [39, 45] and Triterpene Saponins [39].
F. Tenuifolia Steud	Flavonol glycosides [43].
F. Thebaica Boiss	Flavonol glycosides [43, 46].
F. Glutinosa Delile	Triterpene Saponins [47], diterpenes [48], and flavonol glycosides [45].
F. Taeckholmiana	Flavonoid glycosides [19].

Saponins

Fagonia species have been employed to isolate and characterize several types of Saponins such as ursolic acid, Hederagenin [32, 41, 42], and nahagenin [49]. 2D experiments were utilized to recognize the structures of the Saponins by analyzing their NMR spectra. These compounds were oleanane Triterpenoid linked with mono or disaccharides, including Hederagenin, oleanolic acid, and 27 ydroxyoleanolic acid, as well as ursane Triterpenoid, including 27-hydroxyursolic acid, ursolic acid, and quinovic acid. The position of carbonyl C-28 was either free or esterified by a gentiobiosyl unit (b-D-glucopyranosyl-(1 /6)-b-D-glucopyranosyl) or by b-D-glucopyranosyl unit. The hydroxyl in C-3 was also glycosylated by arabinopyranosyl or glucopyranosyl that can be substituted in C-3 and/ or C-2 positions by xylopyranosyl and/or glucopyranosyl units.

The first isolated Triterpenoid saponin from the aerial part of *F. Arabica* is 3-O-β-D-glucopyranosyl-oleanolic acid (1) and it was structurally elucidated by Shoeb *et al.* [27]

seven new Triterpenoid Saponins was isolated from the aerial parts of *F. arabica* grown in Egypt by [25]. They were characterized as 3-O- β-D-xylopyranosyl (1→.2)-[β-D-glucopyranosyl (1→3)]-α-L-arabinopyranosyl oleanolic acid 28-O-β-D-glucopyranoside, 3-O-β-D-glucopyranosyl(1→2)-[β-D-glucopyranosyl(1→3)]-α-L-arabinopyranosyl oleanolic acid 28-O- β -D-glucopyranoside, 3-O-β-D-xylopyranosyl(1→2)-[β-D-glucopyranosyl(1→3)]- α L-arabinopyranosyl oleanolic acid, 3-O-β -D-glucopyranosyl (1→.2)- β-D-glucopyranosyl(1→3) -α-L-arabinosyl oleanolic acid, 3-O- β -D-xyiopyranosyl(1 →2)-[β -D-glucopyranosyl (1→3)]- α -L-arabinopyranosyl 27-hydroxyoleanolic acid, 28-O- β -D-glucopyranoside, 3-O- β -D-xylopyranosyl(1 → 2)-[β -D-glucopyranosyl(1 → 3)]- α -L-arabinopyranosyl ursolic acid 28-O- β -D-glucopyranoside **(2)** and 3-O- β -D-xylopyranosyl (1→2)-[β -D-glucopyranosyl (1→ 3)- α -L-arabinopyranosyl-27-hydroxyursolic acid 28-O-β-D-glucopyranoside (3).

The butanol layer extract of *F. arabica* aerial parts was used to isolate four Triterpenoidal Saponins. Their structures were elucidated according to their chemical and spectral data as 3-O-α-L-arabinopyranosyl quinovic acid 28-O-β-D-glucopyranoside, 3-O-β-D-glucopyranosyl-(1→3)-α -L-arabinopyranoside oleanolic acid, and 3-O-β-D-glucopyranosyl-(1→3)-α-L-arabino-pyranosyl quinovic acid 28- O- β-D-glucopyranoside (4), which were documented for the first time in this species, on the other hand, 3-O-β -D-glucopyranosyl- (1→2) - β -D-glucopyranosyl-(1→3)-α-L-arabinosyl oleanolic acid (5) was previously isolated [25, 26].

Perrone *et al.,* [22] have isolated new disulfated oleanene Triterpenes derivative and four sulfated derivatives of the rarely existing sapogenins. 3-O-sulfonyl-27-hydroxyoleanolic acid (6) and its glycoside as 3-O-sulfonyl-27-hydroxyoleanolic acid-28-O-β-D-glucopyranoside-3β, 23-disulfonyl-nahagenin (7) from the aerial parts of *F. Arabica* which was collected from the Egyptian desert. Additionally, the first recorded saturated and sulfated naturally occurring pentacyclic Triterpene of the taraxastane series with a C-20,28 lactone unit were also isolated and identified as 3β,23-disulfonyl-nahagenin and 3, 23-disulfate ester of 3β,23-dihydroxyolean-13(18)-en-28-oic acid-28-O-β-Dglucopyranoside from *F.arabiac* aerial parts (8.9) [22].

Melek *et al.*, [30] have previously studied *F.cretica* for its saponin content to isolate and identify three bisdesmosides of oleanolic acid and Hederagenin. Moreover 3-O-β-D-glucopyranosyl-Hederagenin (10) was isolated from the aerial part of *F.cretica* [39].

The isolation of a new Triterpene glycoside;3-β-O-[(6-deoxy-α-L-talopyranosyl)oxy]-22-α-hydroxyurs-12-en-28-oic acid (fagonoside A) (11) from the whole plant of *F. cretica* has been recognized by Anjum *et al.* [50].

Further study revealed that other four Triterpenoid Saponins were also isolated from *F. cretica* aerial parts and identified as a new compounds. They were characterized as 3-O-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl-Hederagenin-28-O-β-Dglucopyranoside (12), 3-O-β-D-glucopyranosyl-(1 →2)-α-L-arabinopyranosyl-oleanolicacid-28-O-[βD-glucopyranosyl-(1→6)-β-D-glucopyranosyl-] ester (13), 3-O-β-D-glucopyranosyl-(1 → 2)-α-L-arabinopyranosyl-27-hydroxyoleanolic acid-28-O-[β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-]ester (14) and 3-O-β-D-glucopyranosyl-(1 → 2)-a-L-arabinopyranosyl-olean-12-en-27-al-28- oic acid-28- O-[β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-] ester (15) [32]. Moreover, sapogenin 27-hydroxy oleanolic acid was also reported in *F. arabica* [25].

Bioactivity-guided isolation was employed to isolate and identify two Saponins for the first time from *F. cretica*; quinovic acid-3β-O-β-D-glucopyranosyl-(28-1)-β-D-glucopyranosyl ester and quinovic acid-3β-O-β-D-glycopyranoside [33].

Ursane Triterpenoid type of saponin such as ursolic acid was isolated from *F.* indica, carbonyl in C-28 position was glycosylated by a b-D-glucopyranosyl unit. The hydroxyl in C-3 position was also glycosylated by a sulfated L-arabinopyranosyl which can be substituted in C-2 position by a b-D-xylopyranosyl units, these compounds known as indicasaponin C (16) and indicasaponin D(17) [39].

A noval steroidal saponin was isolated from *F.* indica, which recognized as: 12-(4-methyl-pent 3enoyloxy)-20-(4-methyl-pent-3-enoyloxy)-3β,12β,20 β-trihydroxypregnane-3-ylO-β-D-cymapyranosyl-(1 → 4)-3-methoxy-6-deoxy-β-D-glucopyranoside (18) [40].

several Saponins have been separated from *F.* indica that involve two taraxast-20-en-28-oic acids [42]. The ursolic acid and sapogenins Hederagenin could be found after the hydrolysis of the ethanolic extract of *F.* indica aerial parts [51]. Another research by [41] studied the identification and structure elucidation of two new (Indicasaponin A (19) and indica Saponin B) and two previously known Triterpenoid Saponins with oleanolic and ursolic acid as aglycones. The structures were revealed primarily by H1 and C13 NMR spectroscopy.

Furthermore, new Triterpenoids saponin; 28-O-[β-Dglucopyranosylester-(1→3)-β-D-glucopyranosyl] oleanolic acid (20) was separated for the first time from *F.* indica [37].

Phytochemical screening of *F.*indica Burm aerial parts resulted in the detection and isolation of seven compounds comprising two characterized taraxastane Saponins represented as,3 β -Hydroxy-23-O- β -D-glucopyranosyl-28-carboxy-O- β -Dglucopyranosyl-taraxer-20- en and 3 β -O- β -D-Glucopyranosyl-20-en-23-hydroxytaraxer-28-oic acid, as well as one new Triterpenoid saponin namely, indicacin [38].

Concerning *F. glutinosa*, Melek *et al.* [47] isolated and determined twelve Triterpenoid Saponins from the aerial parts extracts of this species. Six of which are new, and were identified as 3-O-α-L-arabinopyranosyl-ursolic acid-28-O-β-D-glucopyranoside (21), 3-O-β-D-glucopyranosyl-(1→3)-α-L-arabinopyranosyl-ursolic acid (22), 3-O-β-D-glucopyranosyl-(1→3)-[β-D-xylopyranosyl-(1→ 2)-]α-Larabinopyranosyl-ursolic acid (23), 3-O-β-D-glucopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)-] -α-Larabinopyranosyl-ursolic acid -28-O-β-D -glucopyranoside (24), 3-O-β-D-glucopyranosyl-(1 →3)-[b-D-glucopyranosyl-(1 →2)-]α-Larabinopyranosyl-27-hydroxyursolic acid-28-O-β-D-glucopyranoside (25) and 3-O-β-D-glucopyranosyl-(1 →3)-[β-D-glucopyranosyl-(1→ 2)-]α-Larabinopyranosyl-27-hydroxyoleanolic acid-28-O-β-D-glucopyranoside.

Other types of Saponins, including chikusetsaponin IVa, pseudoginsenoside RT1, quinosid D, spinasaponin A 28-O-β-D-glucopyranoside, 3-O-b-D-xylopyranosyl-(1 →3)-[β-D-glucopyranosyl-(1→2)]-β-D-glucuronopyranosyl-28-O-β-D-glucopyranosyl-oleanolic acid, matesaponin B and matesaponin C were isolated and identified from *F. microphylla* [39].

Flavonoids

Based on the accessible data about the presence of flavonoid glycosides among the studied *Fagonia complex*es, there is a remarkably homogeneous profile of flavonoids in which isorhamnetin, kaempferol, quercetin, herbacetin, and herbacetin 8-methyl ether along with their glycosides are the predominant [26, 36, 43]. As evidence, this is the first isolated flavonoid with luteolin as aglycone identified from the genus of *Fagonia* and its Zygophyllaceae family [43, 45].

The aglycones of the *F. arabica complex* include herbacetin, isorhamnetin, and herbacetin-8-methyl ether; moreover, herbacetin8-methyl ether-3-rutinoside is the main flavonoid glycoside [28, 43]. The similarity in the profile flavonoids between *F. the*baica and *F. Arabica* is manifested by the buildup of major amounts of herbacetin 8-methyl ether 3-rutinoside in both of them. On the contrary, *F. the*baica *complex* was distinguished by building up considerable amounts of quercetin glycosides accumulated along with herbacetin 8-methyl ether 3-glucoside traces [43].

Two compounds of flavonoid glycosides namely, acacetin-7-Orhamnoside and kaempferol-7-O-rhamnoside) were spotted in the alcoholic extract of *F. cretica* aerial parts [29].

Another study specified that seven different flavonol glycosides were recognized from the main taxa of the *F. bruguieri complex*, involving Quercetin 3-rhamnogalactoside, kaempferol 3-rhamno-galactoside, and Quercetin 3-galactoside as new phytochemicals reported for the genus of *Fagonia* L. It may be clear that the species of *F. bruguieri complex* are marked by the occurrence of quercetin (3-rutinoside, 3-galactoside, and 3-rhamnogalactoside) [35]. Furthermore, one new 4'-methoxy-luteolin-7-phosphate and three known flavones namely apigenin, luteolin, and tricin were identified for the first time after the phytochemical screening of *F. bruguieri* [52].

Saleh *et al.* [43] stated that the *F.* indica *complex* comprises the glycosides of quercetin, isorhamnetin, and kaempferol. According to the available literature, the main compounds of the *F. bruguieri* and *F.* indica *complex*es are kaempferol glycosides; 3-O-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl]-kaempferol has been documented as one of the flavonoid glycosides isolated from n-butanol fraction extract of *F.* indica [37].

Concerning the *F. sinaica,* eight compounds of flavonol glycosides were spotted in the *F. complex*. They were confirmed as the 3-glucosides of quercetin isorhamnetin and kaempferol, as well as 37-diglucoside of isorhamnetin and quercetin in addition to 3-rutinoside of quercetin. Two more glycosides were to some extent recognized as quercetin 3-diglycoside and kaempferol 3,7-diglycoside [44].

Similarly, *F. the*baica *complex* major class of flavonoids was flavonol-O-glycoside. Implied as quercetin 3,7-diglucoside and 3-rutinoside, isorhamnetin 3-rutinoside, 3-glucoside and 3,7-diglucoside, in addition to herbacetin 8-rutinoside as well as the 3-rutinoside and 3-glucoside of herbacetin 8-methyl ether [46].

The previous literature indicated that isorhamnetin 3,7-diglycosides were abundant in *F. tenuifolia*, *F. critica*, *F. sinaica*, and partly *F.* indica *complex*es while lacking from the *F.arabica* [13, 43].

In addition to isorhamnetin 3, 7-diglycosides, *F. tenuifolia* extract is rich in 3, 7-diglucosides of quercetin and isorhamnetin 3-glucoside, together with a trace amount of quercetin 3-rutinoside and a partially identified quercetin 3-diglycoside [43, 46].

As mentioned before The *F. glutinosa complex* includes two species, namely *F. microphylla* Pomel and, *F glutinosa* Del. [11, 15, 16, 53, 55]. The pattern of flavonoids in *F. microphylla* and *F. glutinosa* revealed a homogeneous profile of flavonol that was entirely based on quercetin with a vast multiplicity in its glycosidic combination. The major two glycosides in both taxa are quercetin-3-gentiobioside-7-glycoside and 3-rhamnogalactoside. Furthermore, elevated quantities of 3-rutinoside, 3-gentiobioside, and 37-diglucoside of quercetin were confirmed in *F. glutinosa* in comparison with only negligible amounts that existed in *F. microphylla*. Kaempferol-7-glucoside and 3-gentiobioside-7-glucoside are also available in greater concentration in *F. glutinosa* than in *F. microphylla*. The remaining two compounds, quercetin-3-gentiobioside and 3-gentiobioside-7-glucoside are characteristic of *F. microphylla* and *F. glutinosa* as they have not been detected before in the *Fagonia* genus [45].

Another research indicated that luteolin-7-O-b-D-glucopyranoside is the chief flavonoid glycoside component of the hydro-methanolic *F. microphylla* extract (scabra Forssk as a synonym) [39].

Along with apigenin, apigenin 7-O-glucoside, kaempferol 3-O-glucoside, kaempferol 3,7-di-O-rhamnoside, and quercetin

3-O-glucoside, *Fagonia taeckholmiana* methanolic extract yielded a new component recognized as kaempferol 3- O-β-L-arabinopyranosyl-(1!4)-α-L-rhamnopyranoside-7-O-α-L-rhamnopyranoside [19].

Terpenes

F. bruguieri aerial parts revealed two new erythroxan-type diterpenes: 16-O-acetylfagonone and 15 16-dihydroxy-7-oxo-cisent-erythrox-3-ene (fagonene). The structures of 16-0-acetylfagonone were determined using spectroscopic methods and a single-crystal X-ray diffraction analysis. Five previously known substituted 8-methoxyflavones were also discovered. This is the first report of diterpenes in the Zygophyllaceae family, as well as the first known enterythroxane [36].

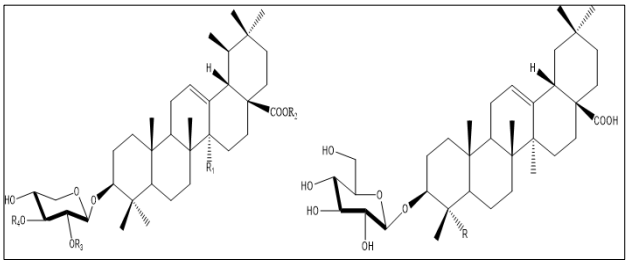
F. arabica was shown to be the richest in total phenol and tannins among the several identified *Fagonia* species growing as a wild plant in Libya [21].

Other components such as docosyl docosanoate was extracted from air-dried *F. cretica* plants in hexane [56]. Water soluble protein was isolated and purified from the water extract fraction of dried *Fagonia cretica* plant. Furthermore acid hydrolysate of the material showed the presence of phosphate, sugar and amino acids [57]. Saleem *et al*. was the first to isolate quinovic acid and stigmasterol from the same species [33].

Several Triterpenes derived from *F.* indica have been recognized, involving betulic acid, nahagenin [49], ursolic acid, and Hederagenin [51].

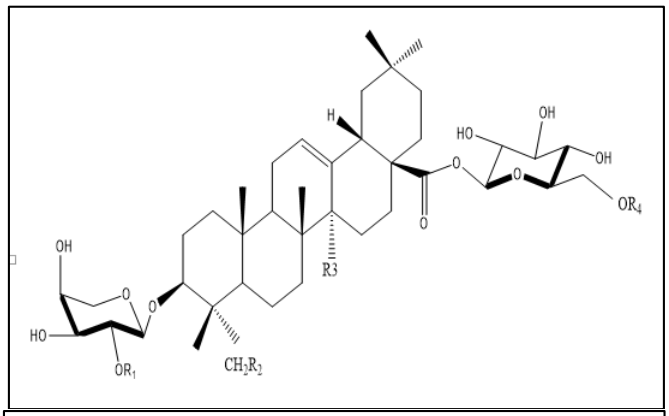
Fagonicin, a new Triterpene isolated from *F.* indica, was identified along with amyrin, -sitosterol, and lupeol by matching their NMR data with the published values [38].

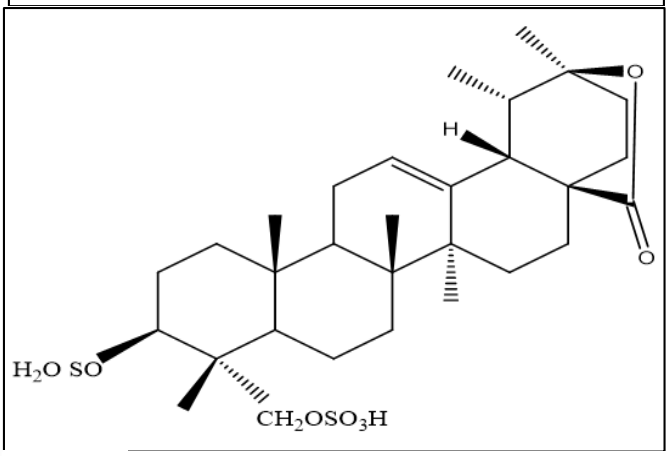
Further analysis of the ether extract of *F. glutinosa* aerial parts led to the discovery of two novel cytotoxic erythroxan diterpenes; 110-epoxy-2-oxofagonene and 1,10-epoxy-2-oxofagonene. In addition, 2-oxofagonene and its previously described isomer 2-oxo-5-epi-fagonene were isolated as inactive diterpenes [48].



	R1	R2	R3	R4
2	CH3	Glc	Xyl	Glc
3	CH2OH	Glc	Xyl	Glc
4	COOH	Glc	H	H
5	COOH	Glc	H	Glc
19	CH_3	Glc	Glc	Ara
21	CH_3	Glc	H	H
22	CH_3	H	H	Glc
23	CH_3	H	Xyl	Glc
24	CH_3	Glc	Glc	Glc
25	CH_2OH	Glc	Glc	Glc

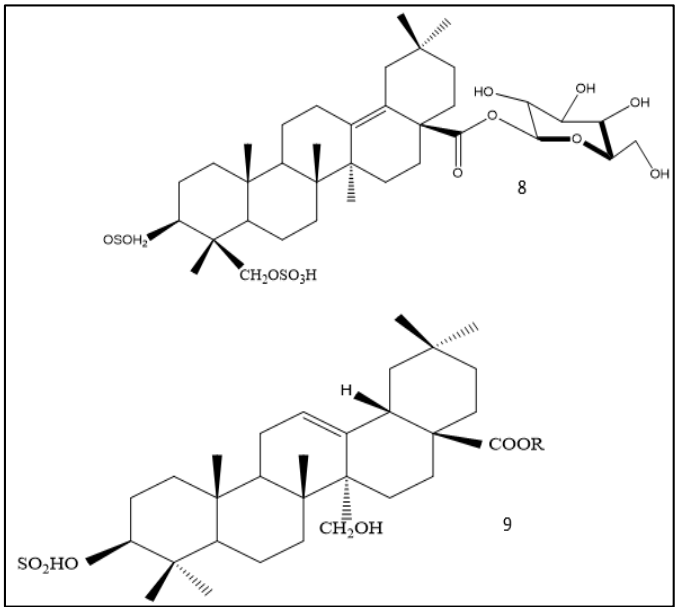
	R
1	H
10	CH_2OH





	R
6	H
7	Glc

	R1	R2	R3	R4
12	Glc	OH	CH_3	H
13	Glc	H	CH_3	Glc
14	Glc	H	CH_2OH	Glc
15	Glc	H	CHO	Glc



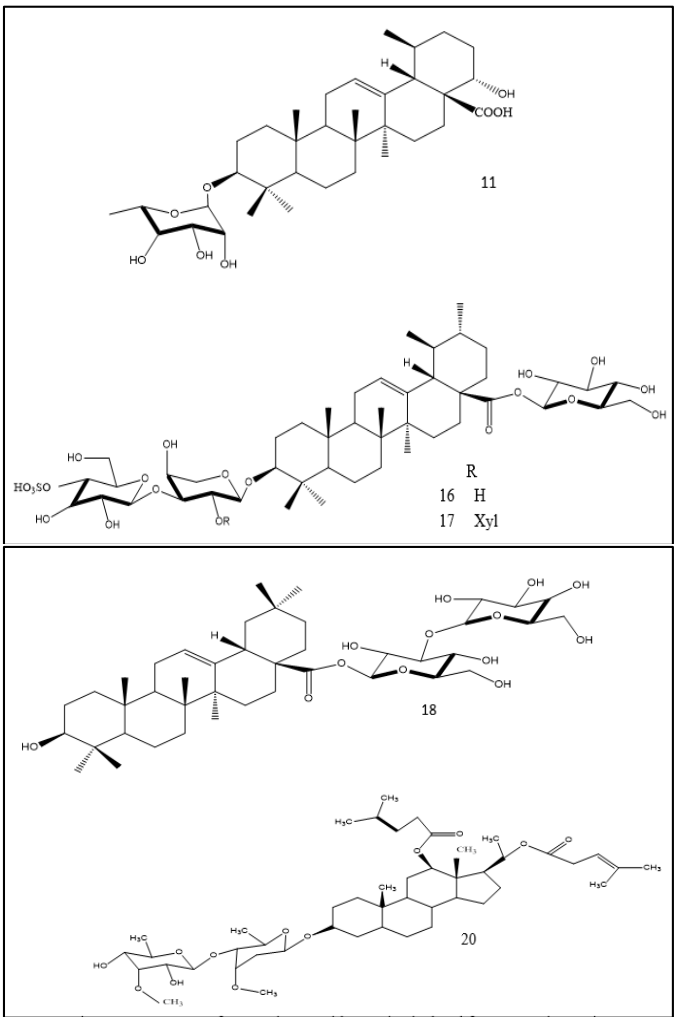
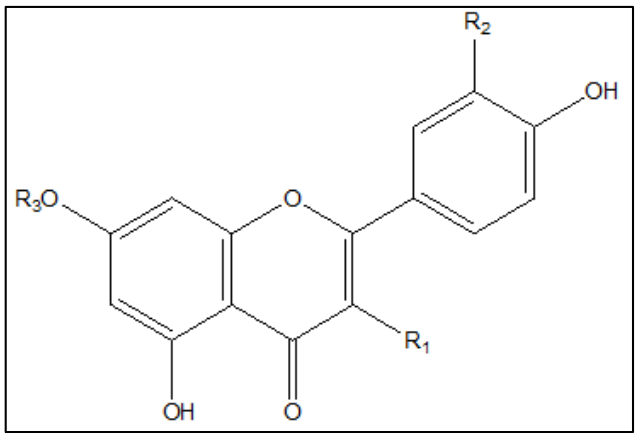


Fig 3: Structures of some triterpenoid saponins isolated from Fagonia species.



Name	R_1	R_2	R_3
Quercetin	OH	OH	H
Rutin	O-Glucose	OH	H
Luteolin	H	OH	H
Isorhamnetin	OH	OCH_3	H
Apigenin	H	H	H
Quercetin 3-galactoside	O-D-Gluct	OH	H
Isoquercetin	O-D-Glc	H	H
Luteolin-7-O-D-Glc	H	OH	D-Glc
kaempferol 3-O-α-L-rhamnoside	O-L-Rha	H	H

Fig 4: Selected flavonoids isolated from Fagonia species

Pharmacological Activity of *Fagonia* Plant

Various species of *Fagonia* have have been used for treatment of different types of disease since ancient time. The pharmacological value of these medicinal plants is highlighted in this review.

Many studies researched and evaluated the anticancer, analgesic, Antioxidant, febrifuge, astringent, and hepatoprotective therapeutic activities of *Fagonia* species. These plants were also utilized to cure asthma, fever, urine drainage, toothaches, stomach problems, and renal ailments [58].

The anti-inflammatory and analgesic activities

The formulation of *F. schweinfurthii* gel extract displayed significant reduction in the progress of paw edema in rats that induced by carragenen, and revealed a substantial anti-inflammatory effect comparing with the effect produced by diclofenac sodium ointment [59]. Also, a similar important wound healing potential to povidone-iodine has been demonstrated. The wound healing process was improved by supporting cellular defense mechanisms, proliferation, and contraction of collagen tissue using developed gel [59].

Rawal *et al*. Investigated the anti-inflammatory efficacy of *F. cretica* L. in rat hippocampus slices exposed to ischemic-reperfusion damage. *F. cretica* L. suppresses the expression rate of the genes that code for cyclooxygenase (COX2) as well as vascular cell adhesion molecules while increasing the process of vascular endothelial growth factor production and inhibiting aggregation of platelet, hence regulating inflammation [60].

The analgesic efficacy of ethanol and aqueous extracts of *F. indica* was evaluated using tail-flick method in rats. The outcome revealed that the ethanolic tincture had a considerable inhibitory impact against *Bacillus cereus* but showed less potential against *Pseudomonas aeruginosa* [20].

The writhing and hot plate tests is other technique used to determine the analgesic capacity of the alcoholic extract of the entire plant of F. indica, with employing acetylsalicylic acid and morphine as reference medicines, this method showed a promising analgesic effect, which is may due to two main mechanisms, centrally and peripherally and does not appear that the opioid receptors involved in this pathway [61].

Antimicrobial activity

One study demonstrated that the ethanolic extract of *F. cretica* has significant antibacterial activity against *Klebsiella pneumonia* and *Proteus mirabilis* when compared to an aqueous extract of the plant [62].

The antimicrobial effect of β-sitosterol-O-β-D-(6'-hexadecanoyl)-glucopyranoside, taraxerone, taraxerol, arjunolic acid, and 23- hydroxy ursolic acid isolated from EtOAc and n-hexane soluble fractions of *F. cretica* against *Shigella flexneri*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Trichophyton longifusus*, *Aspergillus flavus*, *Fusarium solani Microsporum canis*, *Candida albicans*, and *Candida glabrata* was significant [62].

The *F. cretica* extract in all solvents showed noticeable antibacterial and antifungal activity against different strains. nHexane fraction inhibited the growth of *S. marcescens* while EtOAc fraction extremely inhibited the growth of the same bacteria strain and both fractions demonstrated slight activity against *S. mutans* and *S. aureus*, respectively [63].

The antibacterial activity of different concentration of the alcohol extracts of *F.* indica leaves against Gram-negative and

Gram-positive bacterial strains (*E. coli*, *P. aeruginosa*, *S. aureus*, and *B. cereus*) was determined by examining the zone of inhibition. In comparison, ethanol extract had the greatest inhibitory impact against *Bacillus cereus* and the least against *Pseudomonas aeruginosa* [20].

Disc diffusion was used to test the antimicrobial activity of different extracts of the whole plant of *F. cretica* against *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The MIC of plant extract against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* was also determined. When compared to ethanolic extract, aqueous and methanolic extracts showed greater efficacy against all of the tested microorganisms [64].

N-hexane and methanol extracts of *F. cretica* L. inhibited *Salmonella typhi*, *P. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, and *S. aureus*, demonstrating the plant's antibacterial activity of the plant with broad-spectrum potency [65].

F. indica extracts were examined to test the antibacterial activity against four gram + ve (*S. epidermidis*, *S. aureus*, *M. luteus*, and *L. bulgarricus*,) and four gram -ve bacterial strains (*K. pneumoniae*, *E. coli*, *S. typhi* and, *P. aeruginosa*). All extracts demonstrated antibacterial activity against the tested bacterial strains. The effectiveness was in the order of Acetone > Ethyl acetate > Butanol > Ethanol > Chloroform > N-hexane and > Methanol [66].

The antibacterial effect of *F.arabica* leaves extract in dichloromethane, hexane, ethyl acetate, and ethyl alcohol against bacteria (*Escherichia coli*, *Staphylococcus epidermidis*, *Staphylococcus aureus and Bacillus subtilis*) were evaluated by applying well diffusion assay and the Agar disc diffusion technique. The data analysis revealed that the dichloromethane extract of *F. arabica* had higher efficacy against *S. epidermidis* and *E. coli*. The finding was compared to streptomycin as a reference antibacterial [24].

F. arabica and *F. criticus* methanol extracts have a broad spectrum (87.5 percent each) against Gram-negative and Gram-positive. Furthermore, in the case of *F. arabica*, the pathogens *Escherichia coli* and *Streptococcus pyogenes* were the most sensitive microorganisms [21].

Another investigation revealed that silver nanoparticles (NPs) generated using an efficient bioreducing agent from *F. cretica* extract had effective antibacterial action against *Escherichia coli*, *Proteus vulgaris*, and *Klebsiella pneumoniae*. It was discovered that Ag NPs encourage the highest level of reactive oxygen species (ROS) formation in *Proteus vulgaris* when compared to *Klebsiella pneumoniae and Escherichia coli.* In the three bacterial strains, ROS generation is 30% higher in the presence of Ag NPs than in the control and the plant extract without Ag NPs [67].

The antifungal properties of *F.* indica and *F. bruguieri* methanolic extracts were shown to be effective against all the observed fungal strains [34].

Cytotoxic and antitumor activity

The alcohol and water extracts of *F. taeckholmiana* L. were assessed for thier cytotoxic activity against MCF7 human breast carcinoma cell line in vitro. The results revealed that both extracts have significant activity, with IC50 values of 8.72 and 9.80 lg/ mL, respectively. There was no effect on the HEPG2 liver cancer and U251 brain tumor systems [19].

The aqueous extract of *F. cretica* has been noticed to have anti-tumer properties, acting either alone or in combination against the cell growth of the breast cancer via p53 inducing DNA damage. (Tumor suppressor gene) and (Forkhead box class O) expression. Furthermore, it had a significantly lower effect on primary human mammary epithelial tissues [68].

The extract of *F. tenuifolia* exhibited a significant anticancer activity (low GI50) against three human cancer cell lines. Moreover, the growth of breast tumor and CNS cell lines were strongly inhibited, but showed little effect on lung cancer cell lines [69].

Additionally, the cytotoxicity of two different isolated Saponins from the methyl alcohol extract of *F.* indica, indicacin, and fagonicin, was investigated against the human colorectal tumor cell line H-29. It was concluded that indicacin had a significant cytotoxic effect with an IC50 of 51.40% at 6 mM/mL, followed by fagonicin [38].

On experimentally induced soft tissue tumors in albino rats, the crude water extract of the entire *F.* indica plant demonstrated a significant tumorostatic activity. This influence was more noticeable in female rats than in male rats [60].

A new saponin glycoside isolated from *F.* indica has underlined the capabilities of Saponins in their cytotoxic impact on cancerous cells.

Antioxidant and hepatoprotective activity

F. cretica L. suppressed cellular oxidative stress (Nuclear gene expression profiles and cytosol enzymatic level), as well as reducing the reactive free radicals concentration directly in rat hippocampus cells exposed to oxygen-glucose deficiency [60, 70, 71].

The Antioxidant and hepatoprotective properties of *F. schweinfurthii* ethanolic extract (FSEE) on HepG2 cell line and rats received carbon tetrachloride (CCl4) to generate hepatotoxic alterations were investigated. According to the findings of this experiment, FSEE exhibits a strong *in vivo* hepatoprotective effect. This impact could be attributed to the extract's capacity to reduce lipid peroxidation and enhance anti-oxidant enzymatic activity. Furthermore, the FSEE demonstrated significant in vitro Antioxidant activity [72].

Another research was intended to test *F. arabica's* Antioxidant capability in addition to its neuroprotective activity on chemically induced ischemia in PC12 cells. *F. arabica* revealed significant Antioxidant activity. The Antioxidant capacity of a herbal extract was determined utilizing DPPH and ABTS•+ scavenging tests, as well as (FRAP) test. In the ischemic injury, on the other hand, the reduced energy status and lower ATP levels in the cells were the main characteristic evidence, which accompanied by elevated lactic acid concentration. Both effects offered by *F. arabica* provided significant neuroprotection properties from ischemia and contributed to the maintenance of vitality of the cells and mitochondrial function [73].

Serum biochemical and histological tests were conducted to determine the effect of *F.* indica extract on the level of liver damage subjected by thioacetamide in the mouse model. The findings demonstrated how the plant extract restored normal hepatic function and architecture in mice. Furthermore, proinflammatory (IL-6, IL-1, TGF- and TNF-) and hepatic (Albumin and krt-18) expression were changed. Additionally, innate immune components were modulated. The utilization of *F.* indica as a hepatoprotective agent was supported by this research [74].

F. indica and *F. bruguieri* methanolic extracts showed substantial free radical scavenging and Antioxidant properties. The DPPH scavenging, total Antioxidant, and total reducing power data show that *F.* indica has a higher Antioxidant potential than *F. bruguieri* [34].

The Antioxidant capacity of *F.* indica aerial parts was investigated. According to electron paramagnetic resonance spectroscopy, the extract displayed substantial Antioxidant and scavenging action of the free radicles against both nitrogen species and reactive oxygen, lowering the expression of iNOS gene. As a result, it decreases cell damage induced by oxidative stress during oxygen-glucose deprivation (OGD) [75].

Other actions

F. arabica tested for its thrombolytic activity by using an in vitro thrombolytic model and Streptokinase (86.2 percent) as a positive control, while the water used as a blank. The results of the lysis potency of this plant demonstrated considerable effect (75.6 percent) [76].

F. indica extract caused a partially atropine-sensitive laxation in loperamide-induced constipation in rats, comparable to ursolic acid; these results supported its traditional use in constipation [77].

The freeze-dried aqueous extract of *F. bruguieri* and its components are being suggested as a potential new therapy for allergic bronchoconstriction. The impact could be attributed to its antagonistic effect on the activities of histamine induced by capsaicin. The antagonistic reaction may include the suppression of substance P and neurokinins A and B release or the blockage of their receptors. The histamine antagonistic effect seemed to be primarily due to the reduction of pulmonary H1 receptors numbers [78].

The effects of *F. cretica*, as well as the two main Triterpenoid Saponins isolated from the ethanolic extract of the same plant (Saponin-I and saponin-II), were evaluated with different blood endocrinological parameters of healthy male rabbits, involving Prolactin, thyrotropin, thyroxine, thyrotropin, and cortisol using a radio-immunological biomarker. When compared to the control groups and crude drug treatment, both Saponins caused a significant drop in prolactin and serum thyrotropin levels. While, the levels of thyroxine were also considerably decreased by saponin-II, whereas thyroxine level not affected by saponin-I and the crude drug. On the other hand the serum cortisol was increased by the crude drug and both Saponins, particularly saponin-II [31].

F. cretica linn ethanolic extracts exhibited an increasing effect on the fasting blood sugar in doses of (ranged from100 mg, to 600 mg per kilogram of the body weight). This effect could be attributed with the raise of cortisol hormone by saponin I & II as the crude plant [79].

Conclusions

This study provides data on the chemical and biological characterization of *Fagonia*. This plant distributed in the desert of Africa, and represented by 12 species in Libya. *Fagonia* was studied by many researchers regarding to its phytochemicals and medicinal uses. According to the literature, the pharmacological activities of Libyan *Fagonia* species were attributed to the Triterpenoid saponin and flavonoid glycoside. However, there is a limited data were found concerning the toxicity, and clinical features of this plant, as well as the phytochemicals still need further investigation and analysis, to help the workers in the medical field for using this plant in treatment of various ailments.

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