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REVIEW ARTICLE

An overview on pharmacological, ethnomedicinal, and phytochemical investigations of *Zygophyllum gaetulum Emb. & Maire - an endemic species of* southeast of Morocco

Iman Janah[1], Abdelhadi Elhasnaoui[2], Mohamed Ben Bammou[3], Ayoub Amssayef[2] & Mohamed Eddouks[2*]

[1]Laboratory of Agro-Food, Biotechnology, and Valorization of Plant Bioresources (AGROBIOVAL), Department of Biology, Faculty of Science Semlalia, Cadi Ayyad University (UCA), BP 2390, Marrakesh, 40000, Morocco.

[2]Laboratory of Ethnopharmacology and Pharmacognosy, Faculty of Sciences and Techniques Errachidia, Moulay Ismaïl University of Meknes, 52000, Morocco.

[3]Center for Research in Plant and Microbial Biotechnologies, Biodiversity, and Environment, Faculty of Sciences, Mohammed V University, Rabat, 10080, Morocco.

*Email: mohamededdouks2017@gmail.com

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Abstract

Zygophyllum gaetulum Emb. Maire (Zygophyllaceae), commonly known as *"El Aggaya"* or *"El Berraya"*, is a medicinal plant Indigenous to the Moroccan Sahara. It exhibits endemic characteristics and is notably prevalent in the Drâa-Tafilalet region. Within Moroccan folk medicine, this plant holds a reputation for its efficacy in treating various ailments. It is recognized for its traditional applications in alleviating stomach pain, and addressing eczema and dermatitis, and stands out as one of the frequently employed plants for managing diabetes. The purpose of this review paper was to highlight the importance of *Zygophyllum gaetulum* (*Z. gaetulum*) by summarizing the literature investigations reported on various ethnopharmacological and phytochemical aspects as well as biological properties to stimulate interest in promoting its domestication and commercialization for global markets. The data and information on *Z. gaetulum* were collated from various resources like ethnobotanical textbooks and literature databases such as Springer, Scopus, PubMed, Science Direct, Wiley, Tailor and Francis, and Google Scholar. The phytochemical screening of the different parts of *Z. gaetulum* indicates that the leaves are rich in saponins (bisdesmosidic triterpene saponins), terpenes, and sterols. 33 compounds were identified from fruits, leaves, and stem roots. They are generally composed of terpenoids, such as caryophyllene E, decanone and bornylacetate. In addition, *Z. gaetulum* demonstrated several biological properties such as antioxidant, antidiabetic and anti-inflammatory effects. These activities allow the application of *Z. gaetulum* in the medicinal field. Hence, it is crucial to conduct thorough investigations into the phytochemical composition of the plant and to assess its pharmacological activity. This approach is essential for future drug discovery and development endeavors.

Keywords

ethnomedicine; medicinal herbs; pharmacological activity; phytotherapy; *Zygophyllum gaetulum*

Introduction

The use of medicinal plants as alternatives to conventional medicines dates back millennia and continues to be explored for a variety of therapeutic applications. Medicinal plants represent an abundant source of bioactive compounds that exert beneficial effects on human health. In the vast arid expanses of the Moroccan Sahara, a remarkable plant known as *Zygophyllum* *gaetulum* or *Tetraena gaetula* grows widely. Belonging to the Zygophyllaceae family, this species stands out for its exceptional ability to thrive in semi-desert and Mediterranean environments, where harsh climatic conditions shape its unique resilience (1). *Z. gaetulum*, deeply rooted in the ancestral traditions of Saharan populations, and over time has become an invaluable resource in the arsenal of traditional medicine. For centuries, the inhabitants of the Sahara have exploited the plant's properties to treat a variety of diseases, making *Z. gaetulum* an essential component of their local pharmacopeia. Traditional uses of *Z. gaetulum* cover a wide spectrum of medical needs. Among the most frequent applications, the plant is used to relieve stomach pains, a common ailment in the harsh environmental conditions of the desert (2, 3). *Z. gaetulum* extracts are also traditionally used to treat skin conditions such as eczema and dermatitis (2). As a potential source of active compounds, the plant is of particular interest in the field of pharmacology. Studies are focusing on understanding the anti-inflammatory properties of *Z. gaetulum*, suggesting that its compounds could modulate inflammatory responses, offering promising prospects for the development of anti-inflammatory drugs (4, 5). *Z. gaetulum*'s antioxidant properties are also attracting the attention of researchers (6). Evolving in environments exposed to high levels of oxidative stress, the plant may be equipped with biochemical mechanisms to neutralize free radicals, underlining its potential role as a cell-protecting agent against oxidative damage. Several researchers are interested in the pharmacological effects of *Z. gaetulum* and have evaluated their antioxidant, antidiabetic, and anti-cancer properties (7, 8). However, other potential pharmacological effects of this plant have not yet been evaluated. The present review provides a comprehensive summary of the ethnobotanical and ethnopharmacological uses, chemical composition, and biological activities of *Z. gaetulum.*

Research Methodology

A literature survey was conducted to gather all the essential information surrounding *Z. gaetulum* using electronic databases including Springer, Scopus, PubMed, Science Direct, Wiley, Tailor and Francis, and Google Scholar. Authors searched for the data using keywords including "*Zygophyllum gaetulum*," "*Tetraena gaetula*" "Ethnopharmacology," "Traditional uses," "Ethnobotany," "Chemical profiling," "Pharmacological properties," "Medicinal properties", which resulted in the gathering of much literature. Also, chemical structures and IUPAC names were added using PubChem. The right plant name was confirmed on The Plant List (theplantlist.org) website.

2. Botanical background

2.1. Taxonomy and classification

Z. gaetulum is classified within the order of Zygophyllales. Member species of the Zygophyllaceae family are known to inhabit arid and semi-arid biogeographic zones. This family spans several continents, including Africa, Asia, Australia, and the Americas, predominantly composed of small trees, shrubs, and herbs. According to the integrated taxonomic information system, *Z. gaetulum* is placed in the Kingdom Plantae, Class Magnoliopsida, Order Zygophyllales, Family Zygophyllaceae and Genus Zygophyllum. There are about 27 genera in the family and 80 species for the genus Zygophyllum (9). The plant is locally known as "*El Aggaya*" or "*El Berraya*". The synonym of *Z. gaetulum* is *Tetraena gaetula*.

2.2. Distributions and botanical description

Z. gaetulum is an endemic medicinal plant widespread in the Moroccan Sahara (Fig.1), particularly in the Drâa-Tafilalt region (1). It is a succulent perennial shrub (Fig. 2), growing to about 50 cm, with a woody base and dense branching. Young shoots are slender and covered with white hair. The leaves of *Z. gaetulum* are small, with two

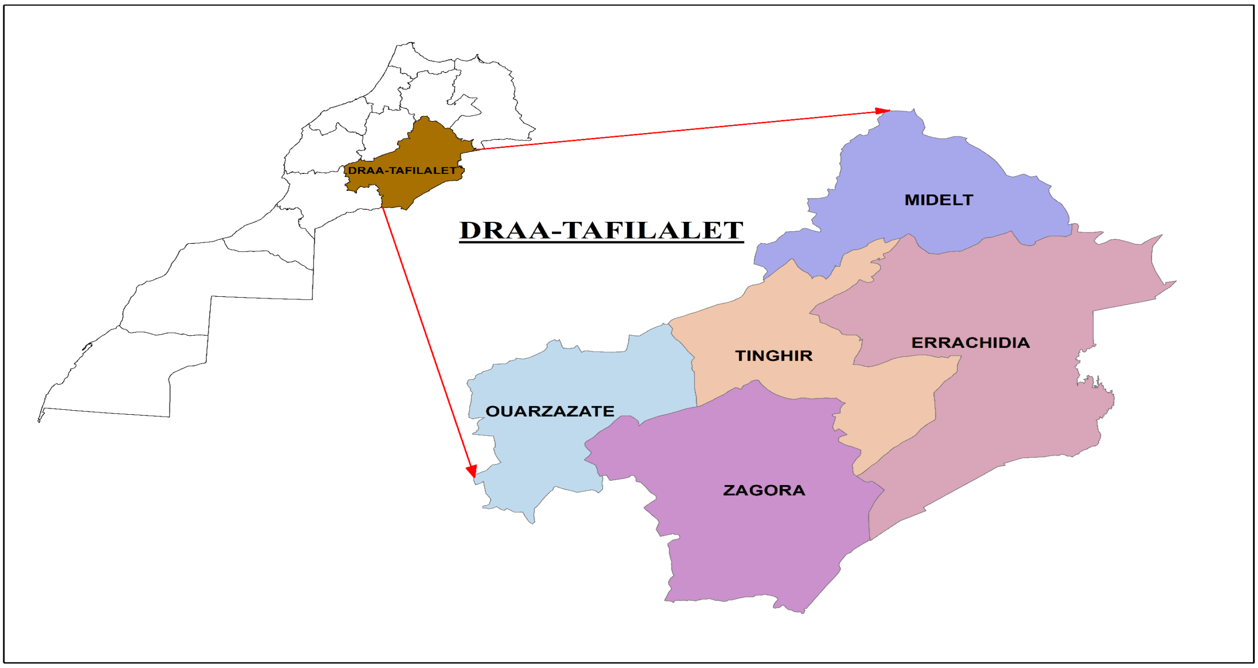

Figure 1. Geographical distribution of *Z. gaetulum.*

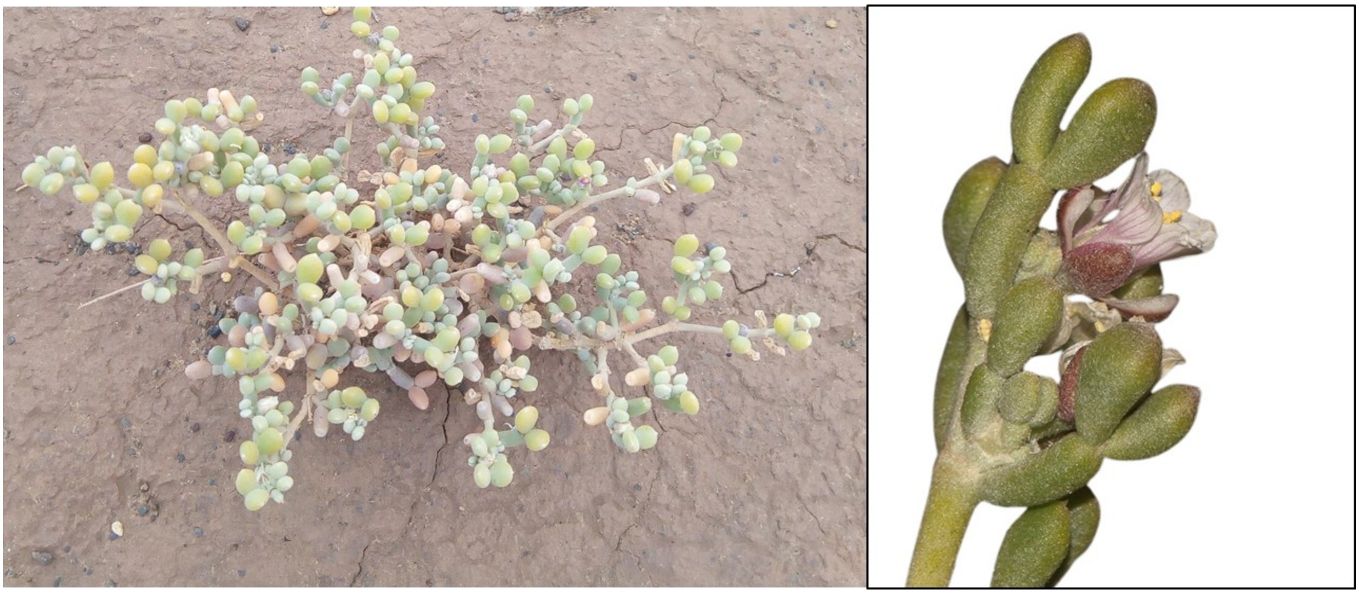

Figure 2. *Zygophyllum gaetulum*.

fleshy leaflets (stipules) at the base. The flowers, borne on small hairy stalks, are tiny (about 5 mm), ovoid, with five white petals. The fruit has a tubular base, with five lobes and reaching a length of about 2 cm. The plant usually flowers in spring, but observations have shown that it can also flower in autumn (2).

3. Ethnomedicinal use

In Morocco, *Z. gaetulum* is used in folk medicine to treat diabetes, eczema, liver, and stomach pain. The leaves and flowers of *Z. gaetulum* are harvested in spring and autumn and then prepared in various forms such as infusion, decoction, powder, and mixed with other plants. The dried flowering tops are used to make a refreshing drink or added to tea (2). *Z. gaetulum* is also integrated into traditional ethnoveterinary systems (10). It is often used by nomads to treat camel diseases and other veterinary ailments. In some practices, *Z. gaetulum* is combined with other plants such as *Ammodaucus leucotrichus* and *Artemisia herba-alba* in unique recipes to treat specific ailments such as mastitis in animals (10).

4. Phytochemistry

Phytochemicals are chemical substances synthesized by plants via primary or secondary metabolism that contribute to their color, flavor, and disease resistance. They have been implicated in a variety of health benefits and may play a role in preventing certain diseases. The Zygophyllum genus is abundant in a mix of phytochemicals like saponins, triterpenes, sterols, phenolic compounds, and flavonoids (11). Phytochemical screening of *Z. gaetulum* (Table 1) indicated a high concentration of saponins (pentacyclic triterpenoid saponins) in the leaves, followed by terpenes, sterols, and flavonoids (12). Safir and Fkih-Tetouani (13) have demonstrated the existence of three triterpenes bisdes-mosidic saponins with a skeleton ofursane or oleanane, i.e.

Table 1. Chemical compounds isolated/detected from *Z. gaetulum*

Compound name	Plant organ/ material	Molecular formula	Compound classification	Method	Ref
Zygophyllosides I	Aerial part	$C_{53}H_{86}O_{24}S$	Saponins	Column chromatography	(13)
Zygophyllosides L	Aerial part	$C_{48}H_{74}O_{19}$	Saponins	Column chromatography	(13)
Zygophylosides M	Aerial part	$C_{53}H_{86}O_{21}$	Saponins	Column chromatography	(13)
(E)-3- sulfooxymegastigm-7- en-9-one	Aerial part	$C_{15}H_{24}O_{3}S$	Saponins	Column chromatography	(14)
Zygophyloside H	Aerial part	-	Saponins	Column chromatography	(14)
Zygophyloside D	Aerial part	$C_{38}H_{58}O_{22}S$	Saponins	Column chromatography	(14)
3-O-[β -D-quinovopyranosyl]- quinovic acid	Aerial part	$C_{33}H_{50}O_{17}$	Saponins	Column chromatography	(14)
Cincholic acid 3-O-β-D-quinovopyranoside	Aerial part	$C_{36}H_{54}O_{18}$	Saponins	Column chromatography	(14)
Cincholic acid 3-O-β-D-quinovopyranoside	Aerial part	$C_{33}H_{50}O_{16}$	Saponins	Column chromatography	(14)
Cincholic acid 3-O-β-D-glucopyranoside	Aerial part	$C_{33}H_{50}O_{15}$	Saponins	Column chromatography	(14)
Quinovic acid-3-O-β-Dquinovopyranosyl-(28→1)-β-Dglucopyranosyl ester	Aerial part	$C_{53}H_{82}O_{27}$	Saponins	Column chromatography	(14)
3-O-β-Dquinovopyranosylcincholic acid 28-O-β-D-glucopyranosyl ester	Aerial part	$C_{57}H_{88}O_{28}$	Saponins	Column chromatography	(14)
Quinovic acid-3-O-β-Dglucopyranosyl-(28 → 1)-β-Dglucopyranosyl ester	Aerial part	$C_{54}H_{84}O_{28}$	Saponins	Column chromatography	(14)

3-O-β-D-glucopyranosyl cincholic acid 28-O-β-Dglucopyranosyl ester	Aerial part	$C_{54}H_{84}O_{28}$	Saponins	Column chromatography	(14)
Zygophyloside E	Aerial part	-	Saponins	Column chromatography	(14)
Zygophyloside G	Aerial part	-	Saponins	Column chromatography	(14)
Quinovic acid 28-O-β-Dglucopyranosyl ester	Aerial part	$C_{48}H_{74}O_{23}$	Saponins	Column chromatography	(14)
Cincholic acid 28-O-β-Dglucopyranosyl ester	Aerial part	$C_{48}H_{76}O_{23}$	Saponins	Column chromatography	(14)
1,8-Cineol	Leaves essential oils	$C_{10}H_{18}O$	Terpenes	GC-MS	(12)
Camphor	Leaves essential oils	$C_{10}H_{16}O$	Ketone	GC-MS	(12)
Isoborneol	Leaves essential oils	$C_{10}H_{18}O$	Terpene alcohol	GC-MS	(12)
Trans pinocamphone	Leaves essential oils	$C_{10}H_{16}O_2$	Ketone	GC-MS	(12)
Verbenone	Leaves essential oils	$C_{10}H_{14}O$	Ketone	GC-MS	(12)
Isobornyl acetate	Leaves essential oils	$C_{12}H_{20}O_2$	Ester	GC-MS	(12)
Bornyl acetate	Leaves essential oils	$C_{12}H_{20}O_2$	Ester	GC-MS	(12)
A-copaene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
Caryophyllene (E)	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
A-humulene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
A-trans-bergamotene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
(Z) farnescene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
B-amorphene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
Drima-7,9 (11)-diene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
Y-(Z) bisabolene	Leaves essential oils	$C_{15}H_{24}$	Sesquiterpenes	GC-MS	(12)
A-(Z) santalol	Leaves essential oils	$C_{15}H_{26}O$	Esquiterpenol	GC-MS	(12)
A-trans (Z) bergamotol	Leaves essential oils	$C_{15}H_{26}O$	Esquiterpenol	GC-MS	(12)
Eicosane	Leaves essential oils	$C_{20}H_{42}$	Hydrocarbon	GC-MS	(12)
N-heneicosane	Leaves essential oils	$C_{21}H_{44}$	Hydrocarbon	GC-MS	(12)
Decanone	Fruits essential oil	$C_{10}H_{20}O$	Ketone	GC-MS	(12)
Heptadecane	Fruits essential oil	$C_{17}H_{36}$	Hydrocarbon	GC-MS	(12)
N-pentadecanol	Fruits essential oil	$C_{15}H_32O$	Alcohol	GC-MS	(12)
N-nonadecane	Fruits essential oil	$C_{19}H_{40}$	Hydrocarbon	GC-MS	(12)
1-eicosene	Fruits essential oil	$C_{20}H_{40}$	Hydrocarbon	GC-MS	(12)
Ethyl hexadecanoate	Fruits essential oil	$C_{18}H_{36}O_2$	Ester	GC-MS	(12)

zygophyllosides I(3β-O-α-L-rhamnopyranosyl-(1==>2)-α-L-arabinopyranosyl-(1==>2)-β-D-glucopyranosylurs-20(21)-en-28-oic acid 28-O-[β-D-2-O-sulfonylglucopyranosyl] ester), zygophyllosides L (3β -O-[α-L-rhamnopyranosyl-(1==>2)-α-L-arabinopyranosyl-(1==>2)- β-D-glucopyranosyl]urs-20(21)-en-28-oic acid 28-O-[β-D-glucopyranosyl] ester), and zygophylosides M (3β-O-β-D-quinovopyranosyl-27-nor-olean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester) and three quinovic acid glycosides. The chemical compositions of essential oils from leaves, fruits, and stem roots were assessed using the GC-MS method, resulting in the identification of a total of 33 compounds. Essential oils isolated from *Z. gaetulum* leaves demonstrated the presence of 1,8-Cineol (1.57%), camphor (6.06%), isoborneol (11.18%), *trans* pinocamphone (2.12%), verbenone (7.49%), isobornyl acetate (8.70%), bornyl acetate (1.35%), a-copaene (1.29%), caryophyllene (E) (19.18%), a-humulene (3.32%), a-*trans*-bergamotene (2.19%), (Z) farnesene (3.33%), drima-7,9 (11)-diene (2.58%), b-morphine (4.89%), y-(Z) bisabolene (5.27%), a-(Z) santalol (6.12%), a-*trans* (Z) bergamotol (2.60%), eicosane (4.12%), and n-heneicosane (2.01%). Regarding the fruit essential oil, the following compounds were identified; decanone (31.5 %), heptadecane (2.9%), n-pentadecanol (2.2%), n-nonadecane (5.1%), 1-eicosene (4.2%), and ethyl hexadecanoate (2.7%). Seven compounds were identified in the stem roots: bornyl acetate (33.84%), linalool (25.71%), α-terpineol (13.96%), geranyl acetate (8.29%), neryl acetate (6.93%), d-nonalactone 1387 (6.24%), and terpinyl acetate (5.03%) (12). These results provide a comprehensive overview of the diversity of chemical compounds present in the stem roots, fruits, and leaves, which contribute to the overall complexity and unique properties of the essential oil extracted from *Z. gaetulum.* Phytochemical investigations by Belguidoum et al. (14) showed that the aerial Part of *Z. gaetulum* contain (E)-3- sulfooxymegastigm-7- en-9-one, 3-O-α-L-arabinopyranoside (1→2) β-Dquinovopyranoside quinovic acid 28-O- β-D-glucopyranoside ester (Zygophyloside H), Quinovic acid-3-O-β-D-2-Osulphonylquinovopyranoside (Zygophyloside D), 3-O-[β -D-quinovopyranosyl]- quinovic acid, Cincholic acid 3-O-β-D-quinovopyranoside, Cincholic acid 3-O-β-D-quinovopyranoside, Cincholic acid 3-O-β-D-glucopyranoside, Quinovic acid-3-O-β-Dquinovopyranosyl-(28→1)-β-Dglucopyranosyl ester, 3-O-β-Dquinovopyranosylcincholic acid 28-O-β-D-glucopyranosyl ester, Quinovic acid-3-O-β-Dglucopyranosyl-(28 → 1)-β-Dglucopyranosyl ester, 3-O-β-D-glucopyranosyl cincholic acid 28-O-β-Dglucopyranosyl ester, Zygophyloside E, Zygophyloside G, quinovic acid 28-O-β-Dglucopyranosyl ester, Cincholic acid 28-O-β-Dglucopyranosyl ester (Fig.3).

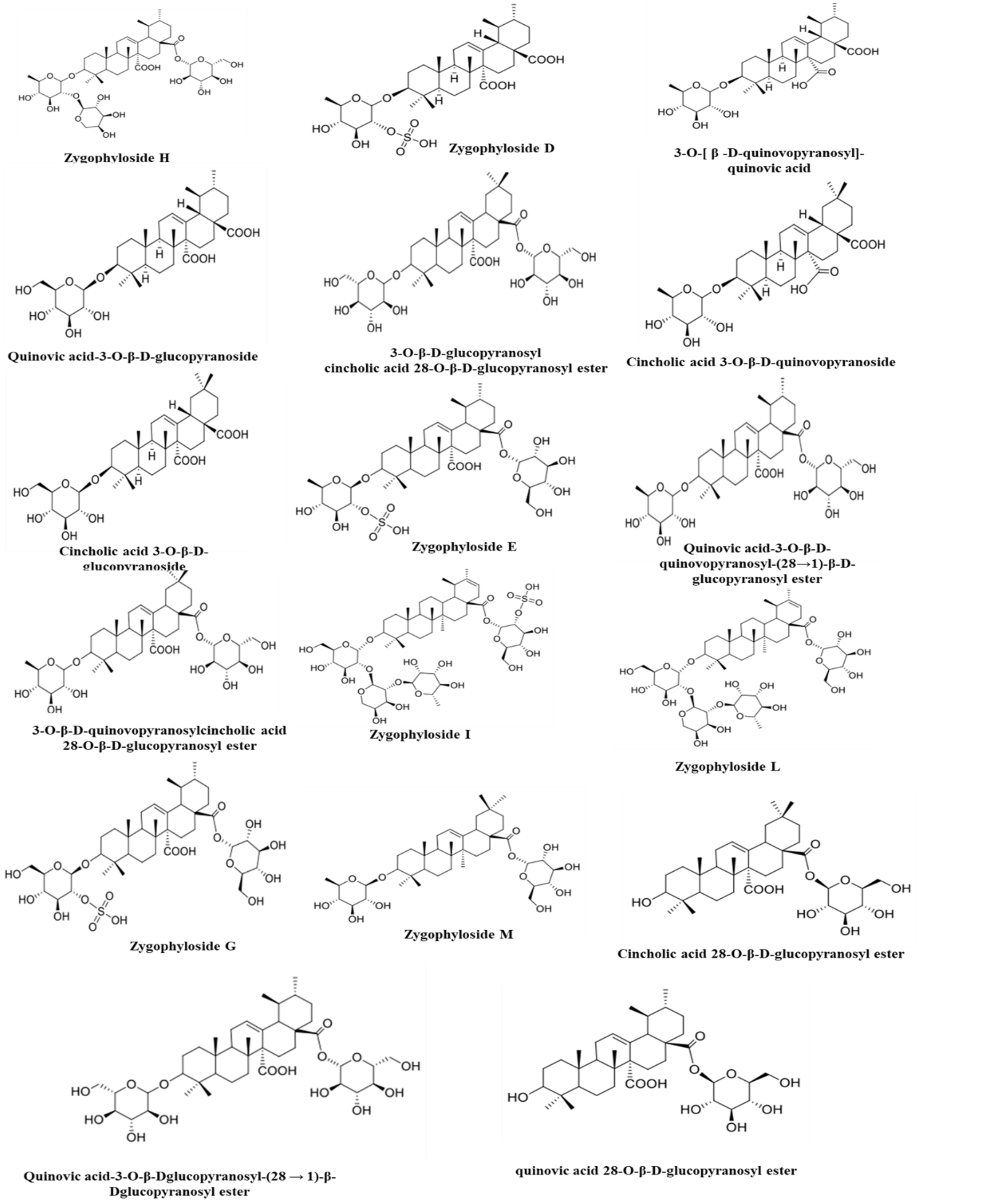

Figure 3. Chemical structure of some saponins compounds in the aerial part of *Zygophyllum gaetulum.*

These phytochemicals compounds contribute to the healing properties of *Z. gaetulum.* Hence, further phytochemical investigations on the polyphenolic phytochemicals of this plant are needed.

5. Pharmacological studies

Z. gaetulum is a plant known for its diverse pharmacological properties. Extensive research has been carried out to explore its therapeutic potential, i.e. antioxidant, antispasmodic, and antidiarrheal activities. Table 2 provides a summary of the pharmacological properties of *Z. gaetulum*.

5.1. *Antioxidant activity*

Antioxidants are substances able to neutralize free atoms in the human body, thereby preventing the damage caused by free radicals and oxidative stress. Antioxidants play a very important role in maintaining cellular health and have been associated with a variety of health benefits. They contribute to the prevention of acute and chronic diseases, including certain cancers, cardiovascular diseases and neurodegenerative diseases. Medicinal plants are excellent sources of natural antioxidants. Several studies were carried out using different tests, specifically DPPH and FRAP. The DPPH test is the most frequently used to evaluate antioxidant

Table 2. Summary of the pharmacological properties of *Z. gaetulum.*

Pharmacological activity	Type of Study	Models used	Plant part/ material	Type of extract/ compound	Doses used	Controls	Results	Ref
Activités antioxydante	*In vitro*	Radical scavenging activity using DPPH	Aerial parts	Aqueous extract	2 mg/ 50 ml	Not defined	IC_{50} of 0.855 mg/ml compared to BHT and ascorbic acid (0.070 and 0.055 mg/ml respectively)	(6)
	In vitro	FRAP and DPPH	Leaves	Aqueous extract	4 to 25 g/l	Not defined	IC_{50}(DPPH)=25.84±6.44 IC50(FRAP)=29.60±3.78	(15)
	In vivo	Antioxidant enzyme levels in male Wistar rats	Leaves	Aqueous extract	1 g/kg	0.23-0.25 ml of citrate buffer	The activities of superoxide dismutases, glutathione peroxidase, glutathione reductase, and catalase in treated rats were enhanced	(15)
Antidiabetic activity	*In vivo*	Humans	Leaves	Aqueous extract	440 mg/ kg	Water	The antihyperglycaemic effect (by reducing plasma glucose levels) was seen both after acute and subacute administration of *Z. gaetulum* in non-insulin-dependent diabetic patients	(7)
	In vivo	Male Wistar rats	Leaves	Aqueous extract	1 g/kg	0.23-0.25 ml of citrate buffer	The aqueous extract of *Z. gaetulum* possesses antihyperglycemic (by reducing blood glucose levels (-58%) and inducing a significant decrease of glycosylated hemoglobin levels) and hypolipidemic (by increasing LCAT and PON1 activities) activities in streptozotocin-induced -diabetic rats	(15)
Anti-inflammatory activity	*In vivo*	Wistar albino rats	Aerial parts	Aqueous extract	5oo mg/ kg	Isotonic saline nac1 9%	The extract has potent anti-inflammatory potential	(18)
	In vivo	Wistar albinos rats	Aerial parts	Ethanolic and aqueous extract	5oo mg/ kg	Isotonic saline	The ethanolic and aqueous extracts of *Z. gaetulum* reduced the increase of the paw volume with a percentage of inhibition of 46% and 47.48%, respectively	(23)
Antispasmodic Activity	*In vivo*	Male Charles River guinea-pigs	Roots	Petroleum ether, chloroform, and methanol extracts	3.95, 4.06, and 10.03 g of dried residue	-	The results indicate that the MeOH can reduce dose-dependently the electrically stimulated contractions of guinea pig ileum.	(20)
Antidiarrheal activity	*In vitro*	Female Wistar rats	Aerial parts	Aqueous extract	20 ml/ml	-	The results show a decrease in the resistance of the intestinal epithelium following the addition of the aqueous extract of *Z. gaetulum.*	(24)

activity. Using this test, the aqueous extract *Z. gaetulum* (1 g/ml) showed a high antioxidant activity when compared to ascorbic acid and BHT (6). Another study demonstrated that the aqueous extract of *Z. gaetulum* exhibited a ferric-reducing antioxidant power value of 29.60±3.78 gallic acid equivalent in mg/100 g dry weight, compared to ascorbic acid (15).Total phenolic, flavonoid, and tannins content were 90.94±12.73 gallic acid equivalent in mg/100 g dw, 16.98±2.46 quercetin equivalent in mg/100 g dw, and 28.38±12.41 gallic acid equivalent in mg/100 g dw, respectively (15). Moreover, the robust antioxidant capacity identified in *Z. gaetulum* is typically linked to the abundance of potent phenolic compounds (flavonoids and tannins). Lipid peroxidation is one of the processes by which free radicals can damage cells, affecting cell membranes and triggering a cascade of reactions that can impair cellular function. An *in vivo* investigation was conducted on rats with hypercholesterolemia, administering lyophilized aqueous extract at a level of 1g/100 g (16). The aqueous extract of *Z.gaetulum* reduced TBARS (an indicator of lipid peroxidation) levels in the liver, plasma, heart, aorta, and brain compared to untreated rats. This effect could be attributed to the *Z.gaetulum's* potential to neutralize free radicals. Moreover, Berzou et al.(16) studied the protective effects of *Z.gaetulum* on oxidative stress in rats fed a high-cholesterol diet. The results of this study showed that in *Z.gaetulum*-treated rats, there was an elevation in hepatic antioxidant enzyme activities, including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px),and catalase (CAT). The heightened activity of hepatic SOD, induced by plant extract, suggests a significant reduction in superoxide anions ($O2•^{-}$) and, consequently, an inhibition of hydroxyl radical ($•OH^{-}$) formation, potentially safeguarding the liver against deleterious effects of ROS. Additionally, in the aorta, *Z. gaetulum* extract stimulated the activities of SOD, CAT, GSH-Px, and glutathione reductase, collectively contributing to reducing lipid peroxidation in the aorta of hypercholesterolemia-treated rats.

5.2. *Antidiabetic activity*

The antidiabetic activity of natural compounds has attracted significant attention in recent years due to their potential therapeutic effects. Various studies have explored the ability of these compounds to modulate key factors involved in diabetes management. For instance, certain medicinal plants have demonstrated efficacy in regulating glucose metabolism and improving insulin resistance. The antidiabetic activity of *Z. gaetulum* has become a subject of interest in recent research. Several studies have explored the potential of *Z. gaetulum* in managing diabetes. In streptozotocin-induced diabetic rats, *Z. gaetulum* has been investigated for its ability to modulate glycemia, and serum lipids and stimulate lecithin -cholesterol acyltransferase and paraoxonase 1 activities (15). Moreover, another study evaluated the effects of a three-week treatment with *Z. gaetulum* on plasma glucose levels, comparing it with sulphonylurea (glipizide) in volunteers with non-insulin-dependent diabetes mellitus. Indeed, the findings clearly showed the capacity of the plant to lower plasma glucose levels (7). The antidiabetic effect of the plant is attributed to the presence of flavonoids (15). Flavonoids possess the capability to hinder the digestion of carbohydrates and the absorption of glucose. Additionally, they play a role in regulating insulin secretion through various signaling pathways. This is accomplished by the inhibition of enzymes responsible for carbohydrate digestion and glucose transporters, contributing to the maintenance of normal blood glucose levels (17).

5.3 *Anti-inflammatory activity*

The anti-inflammatory activity of *Z. gaetulum* refers to its ability to reduce inflammation in biological systems. Studies conducted by Khabbal et al. (18) indicate that rats treated with *Z. gaetulum* extract (500 mg/kg) showed significant edema inhibition throughout all phases of the experiment. These findings suggest that *Z. gaetulum* possesses properties capable of alleviating inflammatory responses. This activity is generally attributed to the presence of flavonoids. Flavonoids have garnered increasing interest as potential therapeutic agents for inhibiting or even reducing inflammatory activity. They achieve this by inhibiting various enzymes, including ATPase, prostaglandin, cyclooxygenase, lipoxygenase, NADH oxidase, protein kinase, hydrolases, peroxidases, metallopeptidases, tyrosinases, and phospholipases (19).

5.4. *Antispasmodic and antidiarrheal activity*

Functional gastrointestinal disorders often manifest with symptoms like abdominal pain, bloating, and changes in bowel habits, such as diarrhea or constipation. The antispasmodic action of *Z. gaetulum* was investigated on isolated ileum of male Charles River guinea pigs with significant results (20). The electrically induced contractions of the guinea pig ileum were inhibited by *Z. gaetulum* methanolic extracts. It has been observed also that Zygophyloside N is one of the major bioactive constituents with antispasmodic activity in the plant. The evaluation of the antidiarrheal effect of *Z. gaetulum* was studied on the rat intestine using the Ussing chamber (24). The results demonstrated a decrease in the resistance of the intestinal epithelium after the addition of the aqueous extract, which is linked to the presence of bioactive compounds responsible for the antidiarrheal effect. In-depth studies are necessary to thoroughly understand the mechanisms that regulate this activity.

5.5. *Immunomodulatory potential*

Youbi et al. (6) demonstrated significant antiproliferative activity with the aqueous extract of *Z. gaetulum* (300 mg/kg body weight), inducing a cycle arrest in G0/G1 phase (85%), accompanied by the appearance of sub-G0/G1 peak detection (14%) for *Z. gaetulum*. The effects of plant extracts on immune cells were examined by Youbi et al. (22). They demonstrated that the aqueous extract and, notably, the protein extract showed an increase in thymocyte proliferation, excluding any cytotoxicity. However, splenocytes were inhibited, suggesting a negative impact on the proliferation of both B lymphocytes and macrophages. The decrease in macrophage proliferation was associated with a reduction in their phagocytic activity, potentially affecting cellular immunity. Additionally, a decrease in hemolysis zones in B lymphocytes, especially with the aqueous extract, indicates an inhibition of humoral response.

These observations suggest that *Z. gaetulum* contains non-protein compounds, such as saponins and flavones, capable of suppressing the specific production of antibodies. In summary, while the plant stimulates thymocyte proliferation, it may have complex effects on the overall immune response, with potential implications for both cellular and humoral immunity.

6. Safety aspects

For centuries, the population of Southern Morocco has used *Z. gaetulum* without showing any side effects. Studies on the acute toxicity of the plant have shown that all rats treated (via oral administration) with varying concentrations of aqueous extract from *Z. gaetulum* survived throughout the 7-day observation period. The findings suggest that the lethal dose of 50 for *Z. gaetulum* aqueous extract was higher than 10 g/kg (21). In a separate study, the acute toxicity of *Z. gaetulum* aqueous extract was investigated intraperitoneally in mice, revealing a lethal dose 50 of 1.2 g/kg of body weight (6). This variation in acute toxicity is directly linked to the mode of administration.

Conclusion

In conclusion, the pharmacological, ethnomedicinal, and phytochemical investigations of *Zygophyllum gaetulum* have revealed promising insights into its medicinal potential. The studies discussed in this context highlight its antidiabetic, antioxidant, anti-inflammatory, antispasmodic, and antidiarrheal properties. The presence of bioactive compounds, particularly saponins and flavonoids, has been identified as contributing to these beneficial effects. While the results are encouraging, further research is warranted to deepen our understanding of the mechanisms underlying these pharmacological activities. Additionally, exploration into the safety profile, optimal dosage, and potential side effects is crucial for considering *Z. gaetulum* as a therapeutic agent. Integrating traditional knowledge with modern scientific methods will enhance our comprehension of its ethnomedicinal uses and promote its acceptance in mainstream healthcare.

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None

Authors' contributions

IJ has contributed to the conceptualization and design of the study. AE has participated in the writing of the manuscript. MBB and AA have contributed to the analysis and interpretation of the literature data. ME has supervised the writing of the correction of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: The authors do not have any conflict of interest to declare.

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