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Review Article

VARIATIONS IN VOLATILE OIL CONSTITUENTS OF ECHINOPS SPECIES GROWING IN THE MIDDLE EAST AND THE MEDITERRANEAN REGIONS: MINI REVIEW

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ABSTRACT

The genus Echinops of the family Asteraceae has commonly been a subject of interest because its members have various chemical constituents and crucial pharmacological activities of great medicinal importance over the last decade (2010-2023). Therefore, this genus has attracted serious research in pharmacognosy and herbal medicine. Detailed studies revealed that Echinops species contain numerous bioactive compounds, such as sesquiterpene lactones, essential oils, flavonoids, and polyacetylenic aliphatic acids, largely in plant parts that are important for therapeutic use. These bioactive constituents have been associated with a wide diversity of pharmacological activities such as anti-inflammatory, antimicrobial, and cytotoxic underlined while proceeding to show some antioxidant activity and even hepatoprotective action of the genus, hence encouraging the further development of novel therapeutic agents. Most of these activities have been studied both *in vitro* and *in vivo* to establish their underlying effects. This will help us evaluate pharmacological properties attributed to the genus Echinops and pave the way for future studies to validate traditional uses and optimize extraction methods and their clinical applications. This work highlighted the position of Echinops species in Mediterranean areas, especially essential oils as a source of bioactive compounds useful in the well-being of humans and its variation concerning several factors. It has reaffirmed the place of natural products in drug discovery and development.

Keywords: Echinops, Essential oils, Sesquiterpenes, Flavonoids, Mediterranean region, Biological activity

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INTRODUCTION

The genus Echinops, considered a member of the Asteraceae family, is characterized by inflorescences of distinctive, round shape and a thorny surface, which has contributed to the common name globe thistles. This genus is originally found in a diversified range of habitats, from Europe, east to Africa, and Mediterranean regions. That seems an extensive ecological amplitude and correspondingly a capacious distribution. Recent phylogenetic studies have thrown considerable light on the evolutionary pathways of Echinops, underlining much of their adaptability under varied environmental and ecological gradients [1]. Such reports suggest that the Genus Echinops originated alongside the evolutionary dynamics of the family Asteraceae and flourished in various climatic conditions over thousands of years.

The benefits of the Echinops genus extend to both ecological and medicinal domains. Recent pharmacological studies have identified potential anti-inflammatory, antimicrobial, and analgesic activities of the bioactive compounds from Echinops extracts. Such findings point toward the importance of the genus in ethnopharmacological and plant-based drug discovery [2].

It needs well-drained, alkaline soils for best growth. For most species of Echinops that can tolerate alkaline and fresh soils, the variation in soil types is high.

The genus Echinops comprises over 120 different species that are widely distributed through various regions, predominantly in the Mediterranean area, Central Asia, Africa, and Eastern Europe. In line with such rich botanical diversity, the Echinops' range varies from temperate grasslands through desert settings to alpine regions. The Mediterranean basin, characterized by its unique climate and ecological conditions, serves as a significant center of diversity for Echinops species. The Mediterranean region's mild, wet winters and hot, dry summers create a conducive environment for the proliferation of these thistles. Echinops species thrive in rocky and well-drained soils, often found in grasslands, open forests, and scrublands. Their distinctive spiky flower heads and robust adaptability to arid conditions underscore their ecological importance and potential medicinal value. The adaptive traits and wide distribution of Echinops highlight the evolutionary success of this genus in the Mediterranean and beyond [3].

Traditionally and historically, different species of the genus Echinops are used as bitter stomachic, treat pain, microbiological infections, kidney inflammation, gastrointestinal disorders, hepatoprotective, antifertility, analgesic, antipyretic, wound healing, anthelmintic, and insecticidal which are some biological activities that have been reported [4]. The other typical traditional usage included the treatment of respiratory tract disorders like cough and sore throat [5].

Molecules of the Echinops genus have proved very useful biologically in several therapies. Studies on the species of Echinops indicated that the extracts of many species have anti-inflammatory, antimicrobial, antioxidant, and cytotoxic activities, among other bioactivities. All the biological activities indicate that the genus may offer potential help to infectious diseases, inflammations, and of course, some forms of cancers. This wide variety of biological activities in various species of Echinops stipulates the importance of the biological constituents of this genus as a source of future drug discoveries [6].

MATERIALS AND METHODS

The exploration begins with data collection from 2005 to 2024 about echinops species, using different resources, including journals, databases, and other trustable sources. Genus echinops accumulates a wide array of secondary metabolites, mainly terpenoids, phenolic compounds, and essential oils. Each class of compounds contributes to the distinctive chemical profiles, structures, and potential therapeutic properties.

The second facet of this review focuses on the variation of volatile oil constituents in each species and the biological activities exhibited by juniper constituents. From antimicrobial and antioxidant properties to anti-inflammatory effects, the spectrum of pharmacological actions attributed to echinops compounds is broad and intriguing.

Table 1: Illustrations of different main species of *echinops*

Juniperus species	Illustration	Origin	Reference
Echinops ritro (Small Globe Thistle)		Syria Lebanon China Palestine	[7]
Echinops bannaticus (Blue Globe Thistle)		Turkey Lebanon Siberia	[8]
Echinops spinosus (Great Globe Thistle)		Egypt Algeria Morocco	[9]
Echinops erinaceus		Saudi Arabia	[10]
Echinops polycares		Lebanon Syria Palestine Jordan China	[11]
Echinops heterophyllus		Iraq	[12]
Echinops shakrokii		Kurdistan	[13]

Echinops ritro (Small globe thistle)

Echinops ritro belongs to the Asteraceae family, which is distributed worldwide except Antarctica. It is a perennial herbaceous plant up to 1 meter high. Stems are simple and solitary. The leaves are alternate, oblong, solitary, or doubly pinnate, dark green at the top with white felt below. The flowers are blue, tubular, and collected in spherical heads 3-5 cm in diameter. The fruits are achenes, densely pubescent, with a tuft. Most often, *Echinops ritro* grows on hillsides, steppes, wastelands, riverbanks, ravines, and thick bushes on the edges. The plant is drought-resistant and not demanding of the soil [14].

Plants belonging to the genus have been used as aphrodisiacs and for the treatment of tumors of the uterus, esophagus, and stomach. In Central Asian folk medicine, Echinops ritro L. fruits are used in decoctions to treat hypertension and atherosclerosis. In Chinese medicine, *Echinops ritro L.* is used as a hemostatic agent as well as in the treatment of skin diseases. In Mongolian folk medicine, *Echinops ritro L.* root is used in the treatment of blood diseases, stomach tumors, and neuropsychiatric disorders. The root powder of the plant is also used in the treatment of angina, diseases of the lungs and throat, liver echinococcus, cancer of the esophagus, and as a tonic [15].

Echinops spinosus (Great globe thistle)

Echinopsis spinnosus is a perennial herb that can grow to over 1 meter in height. It has upright, brownish-red stems, and a few long hairy, arachnoid leaves 10 to 15 cm long. The plant has very long spines. Its flowering period is characterized by an inflorescence that is often a single hemispherical globe up to 5 cm in diameter, surrounded by numerous long spines. The small hermaphroditic flowers within the dense head are tubular and change from green to white and yellowish when in full bloom. The fruits are small achenes topped by membranous scales to aid in dispersion. Traditional preparations of *E. spinosus* are frequently used in folk medicine as an abortifacient, as a diuretic, and for blood circulation, diabetes, gastric pain, indigestion, and spasmolytic problems. In Algeria, the roots or flower heads of *E. spinosus* have been used in the treatment of prostatism and dysmenorrhea. This botanical remedy has also been used as a peripheral vasoconstrictor in the treatment of hemorrhoids, varicose veins, and varicocele in various venous hemorrhages and in metrorrhagia. It is considered as a hypertensive drug [16].

Echinops bannaticus (Blue globe thistle)

This species yields much larger flowers than *Echinops ritro,* reaching around 6 centimetres across in a deep blue or violet color. This robust habit of *Echinops bannaticus* reaches up to 120 centimeters tall, with coarse, deeply lobed, spiny, and woolly leaves. This makes its stem stature and leaf morphology an excellent effort to adapt to an environmentally deverbal gamut of stresses uncommon in some other garden plants.

The size of its big flower heads, from deep blue to violet, singles out *Echinops bannaticus* for possible candidacy in ecological landscaping and habitat restoration programs. In this context, the increased adaptation of these plants to different soil types, accounting for soil stabilization efforts, and the increased functioning of ecosystems are singled out. It underlines and reflects the best biodiversity and ecological resilience strategies in any ecological engineering project [17].

Studies have reported its antioxidant properties, which are linked to the presence of flavonoids and phenolic compounds. Additionally, extracts from *Echinops bannaticus* have shown antimicrobial activity against various pathogens, suggesting its potential as a natural antimicrobial agent. Furthermore, research indicates that *Echinops bannaticus* extracts possess anti-inflammatory properties and show that they may include anticancer and hepatoprotective activity. Other reported biological activities include anticancer effects, hepatoprotective properties, and anti-diabetic potential [18-21].

Echinops erinaceus

Echinops erinaceus, commonly known as the "Hedgehog Globe Thistle," is a perennial herbaceous plant. It features striking, spherical, spiny flower heads that resemble small hedgehogs, typically blooming in shades of blue or purple. The plant's unique globe-shaped and spiky texture makes it a distinctive addition to gardens and floral arrangements. Traditionally, *Echinops erinaceus* has been used in various folk medicinal practices. In traditional medicine, it is often employed for its potential anti-inflammatory and analgesic properties. The plant is also believed to enhance vitality and treat ailments such as joint pain and muscular disorders. Its roots and seeds are typically the parts utilized in these traditional remedies [10].

Research indicates that extracts from *Echinops erinaceus* exhibit significant antioxidant properties, which can help neutralize harmful free radicals in the body and protect cells from oxidative damage and, thus antimicrobial activity against various pathogens. *Echinops exaltatus* has shown anti-inflammatory effects, which could be beneficial for conditions characterized by inflammation, such as arthritis and inflammatory bowel disease. Moreover, preliminary research suggests that this species extracts may have anticancer properties, with potential applications in cancer prevention and treatment [22].

Echinops polycares

This plant species can be described as a perennial, spiny, and hairy plant that grows 60-100 cm long. The leaves are long and dissected, with spiny segments. The flower heads are spherical, spiky, 4-5 cm in diameter, and have a pale blue color. In the Arab region, particularly in Jordan, this plant is known as "chouk el Jemel" and grows wild in waste places and hills. The plant is also found growing wild in the Mediterranean region, including countries like Iraq, Lebanon, Syria, Jordan, Palestine, Saudi Arabia, and along the North African Mediterranean coast.

This plant, known as E. polyceras, has been used in the traditional medicine of many cultures to treat a variety of ailments. In the Mediterranean region, a decoction made from the roots is used to treat kidney diseases and kidney stones [23]. In Saudi Arabia, the plant is used to treat gastric pain, indigestion, and spasms [24]. In Algeria, the plant has been used to treat dysmenorrhea (painful menstruation) and prostatism (prostate problems) [25, 11].

Echinops shakrokii

Echinops shakrokii is readily separated from the other Southwest Asian species of the genus by having smaller compound heads 1.5–2.5 cm in diameter with some 100 small capitulae collectively subtended by 27–33 phyllaries that are not plumose. *Echinops shakrokii* is easily distinguished from other southwest Asian species of *Echinops* by its smaller compound heads, 1.5–2.5 cm in diam., with ca. 100 flowering capitulae subtended by 27–33 phyllaries. It belongs to section *Echinops*, which is distinguished from other sections by having distinct inner phyllaries and non plumose outer and middle ones; none of the southwest Asian species of section *Echinops* have small heads as in *E. shakrokii*. it is widely distributed in the Middle East but mainly in Iraq, Kurdistan, and Kara Dagh [13].

Chemical composition

Numerous compounds have been extracted from various species of the Echinops genus using different spectroscopic and spectrometric techniques. The components of Echinops are thiophenes and terpenes, flavonoids and other phenolic compounds, alkaloids, and essential oils. The plant's roots are the main source of thiophenes, whereas the aerial parts/whole plants contain most of the terpenes and flavonoids. Essential oils are also present in all morphological parts of the plants. Around 53 of the isolated and characterized compounds are known to have various biological activities [26].

Terpenoids

Sesqui-and triterpenoids are chemical compounds found mainly in the whole plant and aerial parts of the echinops genus. The majority of the sesquiterpenoids contain lactones, the most common secondary metabolites in the Asteraceae family. Conversely, Triterpenoids exist in various forms, such as lactones, esters, sterols, and glycosides. The most reported sesquiterpenoids are costunolide, lupeol, and lupeol acetate [27].

Flavonoids and other phenolic compounds

Flavonoids (fig. 2) are natural products that have gained interest due to their different pharmacological activities. Flavones were the main flavonoids found in the whole plant and aerial parts of Echinops species. Apigenin is the most common flavonoid aglycone and was isolated from the flower and whole plant of *E. niveus Wall., E. echinatus, E. integrifolius Kar. and Kir., and E. albicaulis Kar. and Kir* [28].

Flavonoids are highly potent antioxidants that can protect the body against free radicals. Thanks to their hydrogen-donating ability, they can do this by scavenging free radicals. Additionally, flavonoids possess anti-inflammatory, anti-bacterial, and anti-fungal properties. They can also safeguard the gastrointestinal mucosa from damage caused by various ulcer models and necrotic agents. Moreover, flavonoids have anti-carcinogenic effects, as they can hinder the development and progression of cancer by modulating cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis [29, 30].

Alkaloids

According to research Plants of the family Asteraceae demonstrate significant therapeutic applications because of their unique and diverse pool of secondary metabolites, such as phenolics, sesquiterpene lactones, alkaloids, and triterpenes. Unfortunately, research concerning alkaloids was somehow preliminary [12] however, All the alkaloids isolated from different species of Echinops till now are related to the quinoline type, mainly 1-methyl-4-quinolone [7].

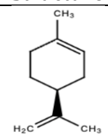
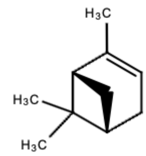
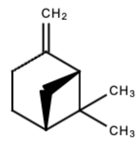
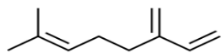
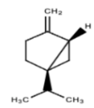
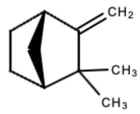
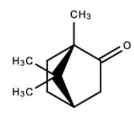
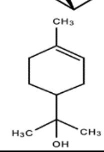
According to Chaudhuri, the first isolated alkaloids from echinops were echinopsine, echinozolinone, and echinopsidine from the aerial parts of *E. echinatus* [7].

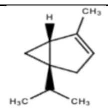
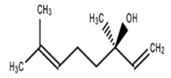
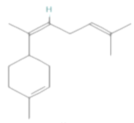
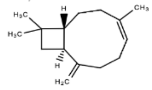
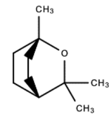
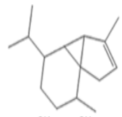
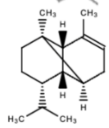
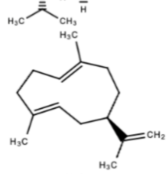
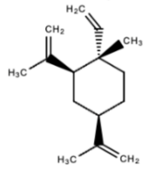
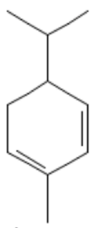
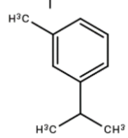
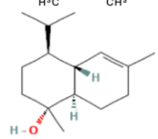
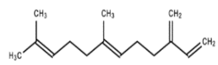
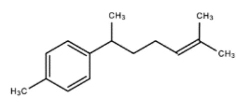
Thiophenesand polyacetylenes

Thiophenes, the main bioactive constituents of the genus Echinops, are biosynthetically derived from fatty acids and reduced sulfur. Recent studies reveal that many constituents of Echinops polyacetylenes, where possess antimicrobial and antifungal properties; however, the main recent new polyacetylene ester discovered in 2019 was ritroyne A [7].

Another research showed that the most abundant thiophenes which were reported from nine different species of echinops were 5-(but-3-en-1-ynyl)-2,2'-bithiophene and α-terthiophene. 5-(4-hydroxybut-1-ynyl)-2-(pent-1,3-diynyl)-thiophene, 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene, and 5-(4-hydroxy-1-butynyl)-2,2'-bithiophene were isolatedas well. Thiophenes were detected in essential oils obtained from the different plants of this genus, like the roots of *E. grijsii* Hance, *E. bannaticus*, and *E. sphaerocephalus* L. [31].

Table 2: Illustrative table about different essential oils, structures, organs, and methods of extraction of different *echinops species*

Essential oils	Species	Organ	Method of extraction or identification	Structure	Ref
Limonene	• E. polycares • E. latifolus • E. spinosus • E. heterophyllus • E. ritro L.	• Fresh Flowers • Aerial parts • Dried Roots • Roots • Dried Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation • steam distillation at flowering stage • hydro-distillation (GC-MS)		[11] [32] [33] [34] [35]
Alpha – pinene	• E. polycares • E. latifolus • E. kebericho • E. spinosus • E. heterophyllus • E. ritro L.	• Fresh flowers • Aerial parts • Fresh roots • Dried Roots • Fresh roots • Dried Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation • steam distillation at flowering stage • hydro-distillation then gc-ms		[11] [9] [32] [33] [34] [35]
Beta – pinene	• E. kebericho • E. latifolus • E. spinosus • E. heterophyllus • E. ritro L.	• Fresh Roots • Aerial parts • Dried Roots • Roots • Dried Aerial parts	• Hydro-distillation • Steam distillation • GC-MS		[9] [32] [33] [34] [8]
Myrcene	• E. sphaerocephalus • E. bannaticus • E. adenocaulos L • E. kebericho • E. latifolus • E. ritro L.	• Roots • Roots • Fresh aerial parts • Fresh Roots • Aerial parts • Dried Aerial parts	• Hydro-distillation • by retention index, mass spectra comparison and co-injection of authentic sample • GC-MS		[36] [8] [9] [32] [8]
Sabinene	• E. polycares • E. ritro L.	• Flowers • Dried Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation • Hydro-distillation GC-MS		[11] [8]
camphene	• E. polycares • E. kebericho • E. spinosus • E. heterophyllus • E. ritro L.	• Fresh aerial parts • Fresh Roots • Dried Roots • Roots • Dried Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation • Hydro-distillation • GC-MS		[11]]9] [33] [34] [8]
Camphor	• E. polycares • E. latifolus • E. spinosus	• Fresh aerial parts • Aerial parts at flowering stage • Dried Roots	• GC-MS pre-full-and post flowering after hydro-distillation • Hydro-distillation GC-MS		[11] [32] [34]
terpinol	• E. sphaerocephalus • E. bannaticus • E. kebericho • E. latifolus • E. heterophyllus	• Roots • Roots • Fresh Roots • Aerial parts • Roots	• Hydro-distillation,GC-MS		[36] [9] [32] [34]

Alpha-thujene	• E. spinosus • E. heterophyllus • E. ritro L.	• Dried Roots • Aerial parts	• Hydro-distillayion		[33] [34] [8]
linalool	• E. sphaerocephalus • E. bannaticus • E. adenocaulos L • E. polycares • E. latifolus • E. spinosus	• Roots • Roots • aerial parts • flowers • aerial parts • dried roots	• GC-MS pre-full-and post-flowering after hydro-distillation • Fresh and dry hydrodistillation		[8] [36] [11] [32] [33]
Bisabolene	• E. polycares • E. ritro L.	• Flowers • Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation		[11] [8]
Caryophyllene	• E. kebericho • E. polycares • E. ritro L.	• Dried Roots • Flowers • Dried Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation		[9] [11] [8]
1.8-cineole	• E. ritro L. • E. polycares • E. keberichi • E. latifolus • E. spinosus	• Aerial parts • Flowes • Dried Roots	• GC-MS pre-full-and post-flowering after hydro-distillation		[37] [11] [9] [32] [34]
Cubebene	• E. adenocaulos L • E. kebericho • E. latifolus • E. ritro L.	• Fresh and dried aerial parts • Roots • Aerial parts	• Hydro-distillation • GC-MS		[8] [9] [32]
Copaene	• E. adenocaulos L • E. polycares • E. ritro L.	• Fresh and dried aerial parts • flowers • Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation		[16] [20] [16]
Germacrene	• E. sphaerocephalus • E. bannaticus • E. adenocaulos l • E. heterophyllus • E. ritro L.	• Roots • Roots • Aerial parts	• Hydro-distillation • GC-MS		[36] [8] [34] [8]
Beta-Elemene	• E. sphaerocephalus • E. bannaticus • E. adenocaulos L • E. polycares • E. kebericho • E. heterophyllus • E. ritro L.	• Roots • Roots • Leaves • Flowers • Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation		[8] [36] [11] [9] [34]
Alpha-phelladrine	• E. sphaerocephalus • E. bannaticus • E. polycares • E. kebericho • E. latifolus • E. spinosus • E. heterophyllus • E. ritro L.	• Roots • Roots • Flowers • Roots • Aerial parts • Roots • Roots • Aerial parts	• GC-MS pre-full-and post-flowering after hydro-distillation • Hydro-distillation, GC-MS		[8] [36] [11] [9] [32] [34] [33] [8]
Cymene	• E. kebericho • E. spinosus • E. ritro L.	• Roots • Roots • Aerial parts	• Hydro-distillation, GC-MS		[9] [34] [8] [37]
Cadinol	• E. sphaerocephalus • E. bannaticus • E. kebericho • E. spinosus • E. ritro L.	• Roots • Roots • Roots • Roots • Aerial parts	• Hydro-distillation • GC-MS		[8] [36] [9] [34] [8]
Alpha-farnesene	• E. sphaerocephalus • E. bannaticus • E. adenocaulos L • E. ritro L.	• Roots • Roots • Aerial parts • Aerial parts	• Hydro-distillation • GC-MS		[36] [8] [37]
Curcumene	• E. sphaerocephalus • E. bannaticus • E. ritro L.	• Roots • Roots • Aerial parts	• Hydro-distillation • GC-MS		[37] [36] [8]

Pharmacological activity

Antioxidant activity

Many of the articles attributed the antioxidant activity of the genus echinops to the presence of many essential oils and other constituents.

Echinops species are confirmed to have antioxidant studies. A 2016 study on two species of echinops showed that *E. tournefortii and E. ritro* possess high antioxidant activity. The dried leaves and seeds of *E. ritro and E. tournefortii* were extracted separately with ethanol, methanol, chloroform, and dH2O. Antioxidant activities of the extracts were determined by two test systems namely, radical scavenging on DPPH and β-carotene bleaching methods [38].

Echinops spinosus essential oil also showed antioxidant activity in research by Amira *et al.* in 2018. Radical-scavenging activity was determined by using stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical according to the procedure reported before [33].

A study aimed to evaluate the antibacterial and antioxidant activities of the ethyl acetate extract and some isolated compounds from aerial parts of *Echinops gracilis*. The extract and isolates were evaluated for their antioxidant properties. The EtOAc extract and other two compounds showed the ability to scavenge 2,2′-zino-bis-(3-ethylbenzothiazoline-6-sulfonic acid) radical cation (ABTS) with scavenging concentration (SC50) values of 13.6±0.8 μg/ml, 108.2±4.3 μg/ml, and 28.5±2.2 μg/ml, respectively [30].

Echinops erinaceus showed to possess antioxidant activity in a study published in 2022 where the activity was studied for different fractions of constituents of this plant extract [10].

Antimicrobial activity

A remarkable finding is that various extracts from different parts of Echinops demonstrate significant antimicrobial effects against various pathogenic bacteria and fungi. This has been mainly attributed to the contents of different compounds such as saponins, tannins, alkaloids, flavonoids, and essential oils.

A previous study investigated the antimicrobial activity of different extracts and fractions from *echinops erinaceus (E. erinaceus)* against a panel of pathogenic microorganisms, including two *Gram-positive bacteria (Bacillus subtilis and methicillin-resistant Staphylococcus aureus, MRSA),* two *Gram-negative bacteria (Pseudomonas aeruginosa and Escherichia coli), and two fungus and yeast-like microorganisms (Aspergillus niger and Candida albicans).* The antimicrobial activity was assessed using the agar well diffusion assay, which measured the diameter of the inhibition zones (DIZ). The results showed that the total methanol (MeOH) extract had the highest antimicrobial activity against all the tested strains, except MRSA. Notably, the MeOH extract exhibited significant antibacterial activity against *B. subtilis* (DIZ = 27.5±0.7□□27.5±0.7 mm), which was more potent than the reference drug, *streptomycin* (DIZ = 18±1.41□□18±1.41 mm), and pronounced antifungal activity against *C. albicans* (DIZ = 26±1.41□□ 26±1.41 mm), which was almost comparable to the reference drug, clotrimazole (DIZ = 28±2.82□□ 28±2.82 mm). The n-hexane and Ethyl Acetate (EtOAc) extract also showed strong antibacterial and antifungal activities, while no antimicrobial activity against MRSA was detected in any of the investigated *E. erinaceus* samples. Additionally, the chloroform ($CHCl_3$) extract exhibited good activity against *B. subtilis, P. aeruginosa, and E. coli* [4].

Similarly, a study conducted by M. Rafay *et al.* [39] investigated the antibacterial properties of the methanolic extract derived from various parts of the plant *Echinops echinatus.* The researchers evaluated the extract's effectiveness against several strains of bacteria, including the Gram-positive *bacterium Staphylococcus aureus and the Gram-negative bacteria Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli*. The results showed that the methanolic extract of the plant's leaves exhibited the greatest inhibitory effect against *Klebsiella pneumoniae*, with an inhibition zone of 10 mm. Furthermore, the methanolic extract of the plant's flowers demonstrated a strong sensitivity against *Staphylococcus aureus*, with an inhibition zone of 19 mm. Additionally, the methanolic extract of the plant's roots displayed the largest zone of inhibition, measuring 18 mm, against *Staphylococcus aureus*.

The antibacterial properties of the ethanolic extract from the tuber of *Echinops kebericho*, its various fractions, and the essential oils extracted from the herb were investigated. The essential oils exhibited activity against Methicillin-Resistant *Staphylococcus aureus* (MRSA), with Minimum Inhibitory Concentrations (MICs) ranging from 78.125 to 625 μg/ml. The ethyl acetate fraction demonstrated the highest activity against MRSA, with a MIC of 39.075 μg/ml, followed by *Enterococcus faecalis* and *Klebsiella pneumoniae*, with MICs of 78.125 μg/ml and 1,250 μg/ml, respectively. *Enterococcus faecalis* exhibited the maximum sensitivity to the hexane fraction, with an MIC of 156.2 μg/ml, while the chloroform fraction had the greatest activity against *Staphylococcus aureus*, with an MIC of 312.5 μg/ml. The n-butanol fraction was found to be pharmacologically ineffective, with an MIC of 2,500 μg/ml for all species and no significant activity against Escherichia coli [40].

The antimicrobial activity of the methanolic extract of the aerial parts of *Echinops lanceolatus* and its various fractions was evaluated against eight bacterial strains, including Gram-positive (*Staphylococcus aureus and Enterococcus faecalis) and Gram-negative bacteria (Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii, Salmonella enterica, Enterobacter cloacae, and Pseudomonas aeruginosa*). The methanolic extract and its fractions exhibited weak to moderate antibacterial activity. The ethyl acetate fraction showed the highest activity, followed by the dichloromethane fraction, then the n-hexane and butanol fractions, and finally the methanolic extract, which was the least active. The MIC values ranged from 256 to 1024 μg/ml, with the methanolic extract being the least effective among the tested samples. However, all the extracts were effective against *Salmonella enterica, Staphylococcus aureus, and Enterobacter cloacae* [41].

Anti-inflammatory activity

The possible anti-inflammatory effect of Echinops is due to sesquiterpene lactones and flavonoids acting as synthesis and release inhibitors of mediators of inflammation. In research, *Echinops kebericho* methanolic extracts have shown considerably statistically significant antinociceptive activity in both chemicals-induced peripheral and thermal-induced central pain in a dose-dependent manner. The greater analgesic activity was observed by the maximum dose of the extract (400 mg/kg) in both the acetic acids-induced writhing test (57.84%) and the hot plate method (69.40%) [42].

Echinops gracilis in research reported anti-inflammatory activity, and Ethyl acetate extract showed potent inhibitory activity against protein denaturation (IC_{50} = 125.54 μg/ml). Erythrinasinate (1) and vogelate (2) showed significant anti-inflammatory activity with an IC_{50} value of 469.43 and 413.71 μg/ml, respectively [43].

Cytotoxic and anticancer activities

Multiple studies have demonstrated the anti-cancer activity of various species within the Echinops genus against different cancer cell lines. The most prevalent activity has been observed against colorectal carcinoma, which is one of the most dangerous and prevalent forms of cancer.

S. H. Sweilam *et al.* [4] evaluated the potential cytotoxic activity of the methanolic extract of *Echinops erinaceus* and its fractions using a cell viability assay on HCT-116 cells (human colon cancer cell line) and $CACO_2$ cells (human colorectal intestinal carcinoma). The chloroform extract exhibited the greatest activity among the tested fractions. It had a moderate cytotoxic effect against HCT-116 and $CACO_2$ cells, with IC_{50} values of 67.30±4.87 μg/ml and 81.95±4.63 μg/ml, respectively.

Similarly, the antiproliferative properties of the methanolic extract and its fractions from the aerial parts *of Echinops lanceolatus* were investigated against HepG2 (human liver cancer cell line), HeLa (cervical cancer cells), HT-29 (human colon cancer cell line), and A549 (adenocarcinomic human alveolar basal epithelial cells) human tumor cell lines. The methanolic extract showed antiproliferative activity at a fixed dose of 100 μg/ml [41].

Furthermore, several species within the Echinops genus have demonstrated potent antiproliferative activity against various cancer cell lines, including HepG2, HeLa, and HT-29. This suggests that the Echinops genus is a valuable natural source for anti-tumor secondary metabolites, such as flavonoids and terpenes, which have exhibited strong cytotoxic activity with IC_{50} values comparable to or better than the standard drug doxorubicin. [41, 44, 45].

Hepatoprotective activity

The genus Echinops has been shown to possess hepatoprotective and antioxidant properties, with the majority of studies conducted using the carbon tetrachloride (CCl_4)-induced liver damage model. The methanolic root extract, as well as the n-butanol and aqueous fractions of *E. grijsii*, demonstrated hepatoprotective activity in CCl_4-induced liver damage in rats.

The aqueous and butanol fractions, at a dose of 300 mg/kg, significantly decreased the levels of Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), indicating a prominent hepatoprotective effect. Additionally, a study conducted by Eram *et al.* (2013) [46] on CCl_4-intoxicated rabbits supported the traditional claim of *E. echinatus* to treat jaundice [47].

Furthermore, the ethanolic extract of the aerial parts of *E. echinatus*, at a dose of 500 mg/kg, showed a greater effect in reducing the levels of ALT and AST compared to the 750 mg/kg dose. These findings provide scientific evidence to support the traditional use of these Echinops species in the treatment of liver-related disorders [28].

Anti-alzheimer disease

Alzheimer's disease is one of the most prevalent forms of age-related neurodegenerative dementia affecting the elderly population worldwide. One of the mechanisms of anti-Alzheimer's drugs involves the inhibition of the enzyme Acetylcholinesterase (AChE). In a study, the anti-cholinesterase (AChE and butyrylcholinesterase, BChE) activity of extracts from *E. ritro* was investigated using different extraction methods, including Homogenizer-Assisted Extraction (HAE) and Maceration (MAC). The HAE extract exhibited a strong AChE inhibitory effect, with a galantamine equivalent value of 2.41±0.04 GALAE/g. The HAE and MAC extracts showed potent BChE inhibitory activity, with values of 0.80±0.10 and 0.87±0.11 mg GALAE/g, respectively [48].

Another study by N. Jamila *et al.* [49] examined the AChE and BChE inhibitory potential of different extracts from the leaves, stems, flowers, and achenes of *E. echinatus*, using galanthamine and physostigmine as standards. The methanol and ethyl acetate extracts were the strongest AChE and BChE inhibitors. The ethyl acetate extract of the stem and leaves exhibited potent AChE inhibition, with IC_{50} values of 15.3 and 15.8 μg/ml, respectively, compared to physostigmine and galanthamine (IC_{50} 0.05 and 2.1 μM/ml, respectively).

Furthermore, the ethyl acetate extract of the leaves and stem was the most potent BChE inhibitor, with IC50 values of 17.5 and 16.3 μg/ml, respectively, compared to physostigmine and galanthamine (IC_{50} 0.08 and 19.3 μM/ml, respectively) [9].

Anti-diabetic activity

E. spinosus total extract and its flavonoid fraction showed promising anti-diabetic activity in Streptozotocin (STZ) induced diabetic rats. Both the flavonoid fraction and total extract significantly increased the serum levels of insulin, leading to a marked reduction in blood glucose levels along with increased glycogen levels and Insulin Receptor (IR) gene expression rates compared with metformin. The flavonoid fraction was found to be more potent than the total extract [50].

K. Benrahou *et al.* [51] evaluated the anti-diabetic enzymatic activity of aqueous and ethanolic extracts of *E. Spinosus* roots using three *in vitro* assays and an ex-vivo oral starch tolerance study. The results showed that the macerated ethanolic extract effectively inhibited ?-amylase, α-glucosidase, and lipase with IC_{50} values of 371±0.62, 18.6±1.2, and 10.44±1.08 μg/ml, respectively. On the other hand, the aqueous extract was less potent against the three enzymes with IC_{50} values of 668.8±1.45, 19.68±0.46, and 24.96±1.52 μg/ml, respectively. Furthermore, both aqueous and ethanolic extracts significantly ($p<0.05$) lowered blood sugar levels to 0.96 g/l and 0.93 g/l, respectively after 90 min.

S. R. Y. Chaudhry *et al.* [52] studied the antidiabetic activity of the aqueous methanolic root extract of *E. echinatus* using two rat models (fructose-fed induced insulin resistance and alloxan-induced diabetes) with oral doses of 100, 300, and 500 mg/kg. It was observed that the extract significantly ($P<0.001$) lowered the fasting blood glucose levels in a dose-dependent pattern in both diabetic models and significantly ($P<0.001$) enhanced the glucose tolerance in fructose-fed rats.

The alcoholic root extract of *E. taeckholmiana* exhibited antidiabetic activity through the suppression of α-amylase and α-glucosidase enzymes with IC_{50} values of 54.6 and 60.4 μg/ml, respectively, compared to acarbose with IC_{50} values of 30.57 and 34.71 μg/ml, respectively [53].

Polysaccharide B, another important class of Echinops metabolites with antidiabetic activity, was isolated from *E. latifolius* Tausch and investigated for its antidiabetic activity. It enhanced insulin sensitivity, prevented hepatic metabolic disorders, and increased glycogen synthesis and glucose consumption while decreasing free fatty acids and triglyceride levels in IR-HepG2 cells [53].

DISCUSSION

The echinops genus has a rich collection of bioactive essential oil constituents, primarily found in the roots. For example, the roots of *echinops polycares* available in areas overlooking the Mediterranean Sea identification showed 192 constituents. The main class of compounds detected in these three stages comprised aliphatic hydrocarbons and their derivatives, which amounted to 50.04% (pre-flower), 40.28% (full-flower), and 41.34% (post-flower) of the total composition. The oils also contained appreciable amounts of oxygenated terpenoids, primarily sesquiterpenoids and diterpenoids. The pre-flowering stage was dominated by (2E)-hexenal (8.03%) in addition to the oxygenated diterpene (6E, 10E)-pseudo phytol (7.54%). The full-flowering stage primarily contained (6E, 10E)-pseudo phytol (7.84%), β-bisabolene (7.53%, SH), and the diterpene hydrocarbon dolabradiene (5.50%). The major constituents detected in the EssentialOil obtained at the post-flowering stage included the oxygenated sesquiterpenoid intermedeol (5.53%), the sesquiterpene hydrocarbon (E)-caryophyllene (5.01%), and (6E, 10E)-pseudo phytol (4.47%) [11].

Fresh inflorescences of *E. ritro*GC-MSanalysis resulted in the identification of 34 components representing 93.32 % of the oils these data showed that the most important component of the EO was the presence of oxygenated sesquiterpene by approximately 22.88 %, followed by the oxygenated monoterpenes and sesquiterpene hydrocarbons by approximately 19.86 and 11.49 %, respectively. The dominant components of *Echinops ritro* L. EO are α-pinocarvone, α-terpineol, nerolidol, and machilol [35].

In the oil of *E. kebericho*, 43 compounds representing 92.85% of the total essential oil constituents were identified. Sesquiterpene lactones, monoterpene hydrocarbons, sesquiterpene hydrocarbons, and oxygenated monoterpene structures represented 41.83, 23.97, 14.90, and 2.80%, respectively, of the total essential oil *of E. kebericho.* The main constituents of the oil were dehydrocostus lactone (41.83%), b-phellandrene (10.84%), germacrene B (5.38%), a-selinene (4.13%), a-pinene (3.63%), and b-pinene (3.62%). Qualitatively, these results do not agree with those in previous reports on essential oils of the same species using a similar extraction technique, where eudesm-7(11)-en-4-ol (14.3%), caryophyllene oxide (9.7%), and t-cadinol (8.3%) were reported as main constituents [28]. The difference in % oil yield and chemical composition of *E. kebericho* could be due to the fact of changing between dry and fresh samples [34].

Essential oils analyses from the root of *E. bannaticus and E. sphaerocephalus* that are mainly available in the Mediterranean regionenabling the identification of 81 and 106 components, accounting for 98.0 and 97.9% of the detected GC peak areas, respectively. Generally, two compound classes dominated the composition of the oils: S-containing Polyacetylene Compounds (SPA) (with 65.5 and 64.1%, resp.) and sesquiterpenoids (with 30.9 and 26.9%, respectively), with 5-(3-buten-1-ynyl)-2,2'-bithienyl and α-terthienyl as their major constituents, along with triquinane sesquiterpenoids [8].

Also, twenty compounds were identified in the essential oils of *Echinops spinosus,* representing 97.470% of the total oil, growing in the South of Tunisia roots. According to research. γ-cadinene, 5-(3-buten-1-ynyl)-2,2'-thienyl, and 2,2',5', 2'-terthiophene are the most prevalent compounds. Caryophyllene oxide, agarospirol, alpha caryophyllene, thujone, and 1,8-cineole were also discovered. The monoterpenoid compounds constituted were mostly α-Pinene was the main compound in this series followed by camphor (0.862%) [33].

As regards previous investigations on *E. grijsii* essential oil GC-MS analyses revealed the presence of 31 components, with 5-(3-buten-1-yn-1-yl)-2,2′-bithiophene (5-BBT, 27.63%), α-terthienyl (α-T, 14.95%), 1,8-cineole (5.56%) and cis-β-ocimene (5.01%) being the four major constituents [55].

A study done in 2022 showed that the essential oils of fresh and dried *E. adenocaulos* identified 46 and 75 compounds, respectively. The major constituent classes in the fresh aerial part are oxygenated diterpenes (76.92%) and oxygenated sesquiterpenes (10.78%), followed by aliphatic compounds (10.12%). However, in the dried aerial part, the main classes are oxygenated diterpene (74.47%) and aliphatic compounds (13.34%). Heyderiol was the most abundant constituent (44.96%), followed by bis(2-ethylhexyl) phthalate (20.12%) and *trans*-ferruginol (3.14%). Bis(2-ethylhexyl) phthalate (52.51%), followed by heyderiol (21.60%) and (Z)-ternine (8.81%) are the major compounds of the fresh aerial part [36].

Finally, the essential oil of *E. latifolius* aerial parts at the flowering stage was obtained by hydrodistillation and analyzed by Gas Chromatography-Mass Spectrometry (GC-MS). 35 components of the essential oil of *E. latifolius* aerial parts were identified. The major compounds in the essential oil were 1,8-cineole (19.63%), (Z)-⍰-ocimene (18.44%), and ⍰-pinene (15.56%) followed by ⍰-myrcene (4.75%) and carvone (4.39%) [9].

Research also showed that the most abundant compounds in *E. giganteus* are tricyclic sesquiterpenoids like silphiperfol-6-ene and presilphiperfolan-8-ol, followed by presilphiperfol-7-ene, cameroonan-7-α-ol, and (E)-caryophyllene [28].

Different percentages and numbers of compounds are revealed in the essential oils of each species where *echinops polycares* was the most dominant one<*echinops adenocualus<e. phaerocephalus<e. bannaticus<e. kebericho<e. latifolus<e. ritro<e. spinosus*.

As for the changes in the essential oil composition, they might arise from several environmental factors such as climate, geographic origin, organ used, dried or fresh harvesting time, method of extraction of the samples as well as genetic factors [33]. After extraction of essential oils of fresh and dry *echinops adenacaulos* it was dominated by oxygenated diterpenes compounds. The amount of aliphatic diterpenes in the essential oil from dried *E. adenocaulos* was higher by 3.22% compared to the essential oil obtained from fresh material, while the amount of oxygenated sesquiterpenes dropped by 6.15%. In the essential oil from dried *E. adenocaulos*, 75 compounds were identified. The main components were heyderiol (44.96%), bis(2-ethylhexyl) phthalate (20.12%), and *trans*-ferruginol (3.14%). In the essential oil from fresh *E. adenocaulos*, 46 compounds were identified.

Such composition differences between the essential oil extracted from the dryplant and that extracted from the fresh plant have been explained because drying may have activated the hydrolase enzymes, which probably led to changes in the proportion of volatile compounds. Drying also resulted in the formation of new compounds that were not detected in the essential oil from fresh material such as *trans*-ferruginol, *n*-nonane, N, Ndimethylpalmitamide, and bis(2-ethylhexyl), which has been reported to be of great antibacterial activity [36].

Temperature changes can affect the synthesis and accumulation of essential oils in plants. Higher temperatures can lead to an increase in the concentration of certain compounds, while others may decrease. In a way to mimic the rise in temperature and its effect on essential oil composition, a study done in Iran in 2019 on echinops persicus where the researchers extracted the essential oil by hydro-distillation and microwave-assisted hydro-distillation where this method extracted more compounds and yielded more essential oils from Echinops persicus than conventional hydrothermal method covering 98.2% of their compositions and thus exhibits considerable antioxidant and antimicrobial properties [56].

Another factor that affects essential oil yield is the methods of extraction. Solvent extraction is considered the most important way to extract both polar and non-polar compounds. Polar solvents will extract polar substances, while non-polar solvents will extract non-polar material. A 2018 experiment demonstrated the significance of this factor, where several solvents such as water, methanol, ethanol, chloroform, and ethyl acetate were used in both hot and cold extraction atmospheres to extract the active constituents of Echinops persicus. Among the extracts and methods tested, the methanol/ethyl acetate extract obtained through the hot extraction method showed the highest number of active compounds. Significant differences were found in the contents of the differently processed extracts, with methanol remaining the dominant solvent [56].

The study also revealed that the extraction method affected the antioxidant activity. The extracts obtained through the hot methanol/ethyl acetate method exhibited the most potent antioxidant properties. This is likely due to the increased solubility and extraction efficiency of the bioactive phytochemicals using this solvent combination under elevated temperature conditions [57].

Many studies have investigated the effect of elevated CO_2 levels on the constituents of plants that are adapted to harsh climates, including the genus Echinops. A recent article published in 2024 revealed that adaptation to harsh climates can increase the production of secondary metabolites, which are crucial in protecting plants from environmental stresses.

After exposing these plants to increased CO_2 levels and higher temperatures, the researchers measured the levels of primary and secondary metabolites, as well as antioxidant activity. Gas Chromatography-Mass Spectrometry (GC-MS) analysis showed a decrease in monoterpene compounds in the plants subjected to the CO_2 and temperature treatments. However, the responses of some sesquiterpenes were more varied, with both increases and decreases observed.

These findings suggest that changes in climatic conditions can alter the composition of secondary metabolites in alpine herbs, potentially affecting their therapeutic properties and suitability for use in herbal medicine. The elevated CO_2 and temperature levels also stimulated the plants' antioxidant activities and influenced the composition of secondary metabolites, including the yield and concentration of essential oils and volatile compounds.

The impact of climate change on essential oils in plants is complex and can vary significantly depending on the plant species, the specific environmental changes, and the interactions between different factors. Researchers continue to study these effects to better understand how to manage and adapt essential oil production in the face of changing climate conditions. These results highlight the importance of understanding climate change's impact on medicinal plants' chemical profiles, as it may have significant implications for their therapeutic applications and the development of effective herbal remedies. The combination of these two paragraphs provides a more comprehensive understanding of the challenges and importance of studying the effects of climate change on essential oils in medicinal plants, which is crucial for maintaining the efficacy and availability of herbal remedies in the future [58].

As for its pharmacological activity, most of these activities were related to the species constituents. *E. tournefortii and E. ritro* possess high antioxidant activity, and after measuring the phenolic content as well as mono and sesquiterpenes. The amounts of total phenolic contents ranged from 31.54 to 92.24 (GAE mg/100g) for extracts.

And it showed that higher antioxidant activity came from high phenolic content. The dH2O extract had higher antioxidant capacity and free radical scavenging activity than other extract at the same concentrations. This also shows that different solvents as well affected the total phenolic content [7].

The essential oil of *E. spinosus* roots was dominated by sesquiterpenoids compounds which represent 42.245% of the total essential oil. γ-Cadinene (27.224 %) was the main component of this fraction followed by caryophyllene oxide (5.217%) and β-caryophyllene (2.736%). The monoterpenoid compounds constitute only 4.005 %. α-Pinene was the main compound in this series followed by camphor (0.862%) and these components were the main reason for antioxidant activity [12].

Different species of the genus Echinops have shown antimicrobial activity against different Gram+ and Gram – bacteria and different types of fungi. Considering all the collected data about the antimicrobial activity of different species of genus Echinops and the isolated compounds, we can deduce that this activity is related to their polyphenolic content such as flavonoids mainly (Apigenin and its glucoside derivatives), lignans, phenolic acids which act by changing cell membrane permeability, thiophenes such as (α-terthiophene), and sesquiterpenes consequently, this genus become an excellent natural source of antimicrobial metabolites [3, 17, 38].

Furthermore, several species within the Echinops genus have demonstrated potent antiproliferative activity against various cancer cell lines, including HepG2, HeLa, and HT-29. This suggests that the Echinops genus is a valuable natural source for anti-tumor secondary metabolites, such as flavonoids, monoterpenes, and sesquiterpenes, which have exhibited strong cytotoxic activity with IC50 values comparable to or better than the standard drug doxorubicin [52, 3, 38].

The possible anti-inflammatory effect of Echinops is due to sesquiterpene lactones and flavonoids acting as synthesis and release inhibitors of mediators of inflammation [43]. The anti-inflammatory action of *E. kebericho* extract can be supported by previous reports from scientific journals that stated that other species of echinops as well that contain mainly alkaloids, flavonoids, saponin, and tannins phenolic compounds, glycosides, coumarins, and sesquitriterpenoid chemical constituents showed strong anti-inflammatory effects. So, it can be deduced that the anti-inflammatory effect of *E. kebericho* extract in the present study may be due to the presence of alkaloids, flavonoids, saponin, tannin, and triterpenoids [43].

Finally, flavonoids were isolated from the root of *E. grijsii* and the whole plant of *E. echinatus*. These might be responsible for the hepatoprotective effects of the extracts and further investigations are required on the phytoconstituents of the plants [28].

CONCLUSION

This review of the genus echinops highlights the diversity of the bioactive compounds present in its plants and provides scientific evidence for its various medicinal uses. it also highlights the diversity of essential oils that differs according to several changes like climate, soil, temperature, and methods of extraction of this oil. The diverse species of Echinops demonstrate a remarkable array of essential oils, each contributing significantly to the pharmacological potential of this genus. The unique chemical compositions of these essential oils not only highlight the ecological and biochemical diversity within Echinops but also underscore their therapeutic relevance. Research indicates that the bioactive compounds found in these oils exhibit a range of pharmacological activities, including anti-inflammatory, antimicrobial, and antioxidant properties, which can be harnessed for medicinal purposes. As the demand for natural products in healthcare continues to rise, further exploration of Echinops essential oils could lead to the development of novel therapeutic agents. Thus, emphasizing the importance of conserving these species is crucial, as they hold promise for future pharmacological advancements and the sustainable utilization of natural resources.

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AUTHORS CONTRIBUTIONS

GAM, MAH, AL, MA, made a significant contribution to the work reported, whether that is in the conception, the acquisition, analysis, or interpretation of data, or all the areas; took part in drafting, revising, or critically reviewing the article; and gave final approval of the version to be published. All have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

Declared none

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