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An Updated Review of the Ethnopharmacological Uses, Phytochemistry, And Selected Biological Activities of Genus *Echinops* L.

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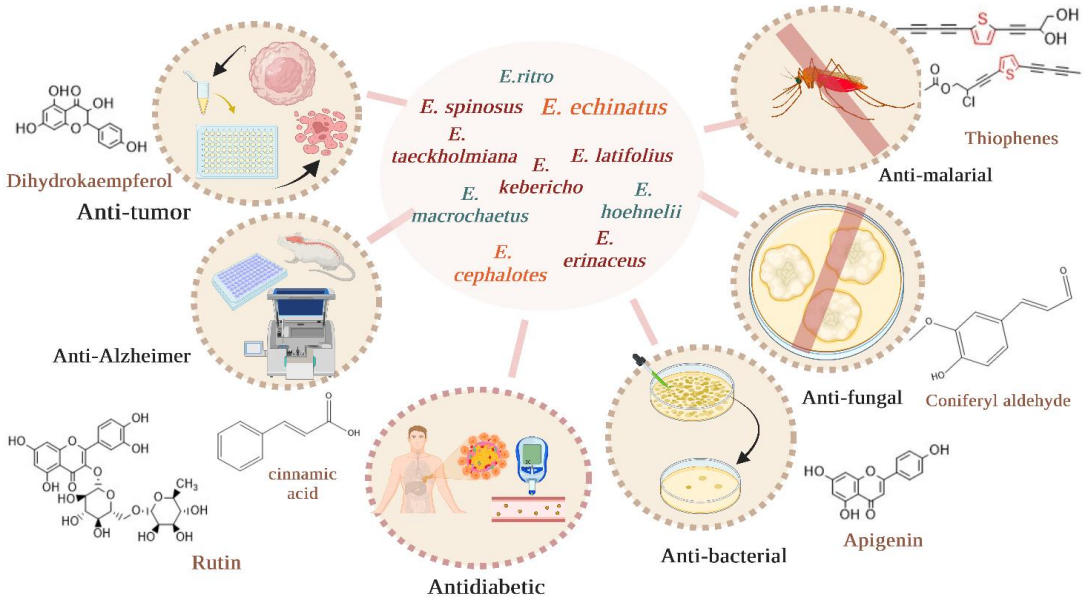
Abstract

The genus *Echinops* is one of the members of the Asteraceae family, which includes about 130 species. It contains a variety of secondary metabolites including thiophenes, alkaloids, essential oils, flavonoids, other phenolics, and terpenes. Numerous *Echinops* species have historically been utilized as medicines, primarily in Africa and Asia, which are traditionally used to treat pain, inflammation, respiratory conditions, and illnesses caused by various germs, as an aphrodisiac, and to remove kidney stones. The biological effects of diverse extracts, essential oils, and isolated chemicals from this genus's members are mostly anti-microbial, cytotoxic, and anti-diabetic. However, few species belonging to this genus are reported to have historical medicinal uses, but their biological effects have not been examined yet. This review aims to assess the most recent data from several scientific research and studies that are accessible regarding the phytoconstituents and selected biological activities which involve the anti-diabetic, anti-malarial, anti-Trypanosoma, anti-microbial, cytotoxicity, and anti-Alzheimer activities of this genus as they may serve as a good source for new lead compounds that can be used in therapy.

Keywords: Asteraceae; *Echinops* L.; (Globe thistle); Ethnopharmacological uses; Thiophenes; Echinopsine; Anti-malarial.

Graphical abstract



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1. Introduction

Phytotherapy has gained a special interest as an integral part of the traditional medicinal in a variety of medical sectors around the world. According to recent estimations of World Health Organization,80% of the worldwide population depends on plant remedies [1]. In this sense, the development of phytotherapy offers a useful, efficient, and secure strategy for therapy. Since ancient times, herbal medicine has been extensively utilized as complementary medicine. Many researchers have been conducted to confirm the ancient use of plant materials and to study their mechanism of action. Recently, the growing need for discovery of drugs from natural sources has driven scientific interest towards the Asteraceae family which distributed throughout the world.

Asteraceae or Aster family has the highest rank in the plant kingdom with worldwide distribution depending on the ecological habitats [2]. It is a monophyletic taxon divided into three subfamilies and 17 tribes and consists of roughly 1600-1700 genera and about 24000-30000 species of herbaceous plants, shrubs, and trees. Morphologically, the presence of head-like inflorescence called capitulum surrounded

by involucre of bracts is the unique feature of the family [2,3]. Plants belong to Asteraceae are considered as good source of several secondary metabolites such as sesquiterpene lactones, flavonoids, phenolics, alkaloids, and triterpenes; The main biological activities that are reported to family Asteraceae include anti-inflammatory, antioxidant, anti-ulcer and antiproliferative activities [4].

Echinops L. is one of the most important genera from the family Asteraceae, it includes more than 130 species [2], Globe thistle is the common name of the genus *Echinops* [5]. There are 120 species in the genus, which have been distributed in northern and tropical Africa, Central Asia, Europe, and the Mediterranean area. Recently, another species has been identified in India [2,3].

Traditionally different species of genus *Echinops* are used as bitter stomachic, antitumor, hepatoprotective, anti-ulcer, anti-inflammatory, fungicidal, insecticides, and antioxidant. Importantly, thiophenes and terpenes are among the main secondary metabolites of the genus. In addition, other phytoconstituents had been reported *viz*, alkaloids, flavonoids, phenolics, lignans, sterols, and volatile oils with multiple pharmacological activities. [2,6,7]

This review will summarize the recent reported data about the phytochemical investigations and isolated compounds from different species of genus *Echinops* as well as it will highlight the selected biological importance of different species as anti-Alzheimer, anti-diabetic, anti-malarial, anti-microbial, anti-Trypanosoma, and cytotoxic activities.

2. Search strategy

To conduct this literature search, several search engines were used, including PubMed, Google Scholar, Springer Nature, Scopus, Medline, Science Direct and Elsevier using keywords like anti-Alzheimer, anti-diabetic, anti-malarial, anti-microbial, anti-Trypanosoma, cytotoxicity, *Echinops*, globe thistle, phytochemistry, traditional uses. The research articles served as the primary sources for the structures of isolated compounds, and PubChem was used to verify these. Our search strategy included the recent accessible published data. Publications that were written in languages other than English were not included in this review.

3. Geographical distribution

Based on the geographic distribution of taxa, number of *Echinops* species have been identified in eight geographic regions include Middle Asia, East Asia, Irano-Turanian Region, Eastern Europe, Western Europe, North Africa, Tropical Africa and the Arabian Peninsula which are represented in fig. 1. [8].

Eight taxa are listed as existing in Italy. Only *E. albidus* Boiss. & Spruner (*E. sphaerocephalus* L. and *E. spinosissimus* Turra have been documented from the Ionian Islands. Currently, 7 taxa recorded from Albania and 12 from Greece. [9]. *E. glaberrimus* DC., *E. hussoni* Boiss., *E. macrochaetus* Fresen., *E. spinosissimus* Turra (*Echinops spinosus* L.) *E.*

galalensis Schweinf and *E. taeckholmiana* Amin are six Egyptian species; the latter is endemic to the Northwest Nile Delta.[10]. *E. longisetus, E. ellenbeckii, E. kebericho and E. buhaitensis* are endemic in Ethiopia [11].

Fig. 1. Distribution of genus *Echinops* (Map is not to scale). Adapted of GBIF-Global Biodiversity Information Facility. [12]

4. Botanical description

Genus *Echinops* is spiny, perennial herbs with undivided simple leaves, serrate or entire margins to three pinnatisect, net-veined or rarely parallel-veined and sessile or petiolate. Synflorescence of the genus is axillary, terminal, compound, single flowered capitula which is aggregated into a globose synflorescence on a swollen common receptacle. Each capitulum sessile, subtended by small, concealed bracts and falling apart at maturity. The capitula consist of outer series of simple or branched extraphyllary white bristles and an inner series of imbricate, rigid, free or partly fused phyllaries.[13,14]

The corolla of the genus may be white to cream, yellow, pink to red or pale to deep blue, rarely violet, monomorphic, tubular, glandular or glabrous tube, with five lobes. Florets are bisexual and tubular. Anthers are purplish or violet. Stigma purple or white. Achenes elongate, oblong or obovate, densely appressed-pilose. Pappus persistent, crown-like, free, or short connate scale like bristles. The unit of dispersal is deciduous, one seeded capitulum.[13,14]

5. Taxonomic classification [15]

Kingdom: Plantae – plant

Phylum: Magnoliophyta -Angiosperm Flowering plants

Class: Magnoliopsida - Dicotyledons

Subclass: Asteridae

Order: Asterales

Family: Asteraceae (Compositae)

Genus: *Echinops* L

6. Synonymus of different species [8,16]

E. spinosissimus *(E. spinosus L.).*

E.jesdianus *(E. laricus, E. lalesarensis and E. austro-iranicus).*

E. polygamus *(E. ecbatanus).*

E. avajensis *(E. leiopolyceroides).*

E. chorassanicus *(E. haussknechtii).*

E. ceratophorus *(E. keredjensis).*

E. khansaricus *(E. elymaiticus, E. erioceras).*

E. spiniger *(E. nizvanus)*

7. Ethnopharmacological uses

Echinops species have historically been used to 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. Many of ethnopharmacological uses of different species in African countries are listed in table.1.

In addition, some species are nutrient-rich, the bulb of the *E. viscidulus* Mozaff plant is eaten as a vegetable in Iran. In Morocco and Cameroon, the roots of *E. giganteus* A. Rich. and *E. spinosus*, respectively are used as spices, the use of *E. giganteus* may be explained by the herb's nutrient content which includes iron, phenols, carotenoids, and vitamins E and C. [3]

Table (1) list of different species of genus *Echinops* that have been cited in ethnomedicine of African countries

Name of species	Region	Part used	Indication	References
E. spinosus	**Algeria**	Roots Inflorescences	Hemorrhoids and hypertension	[17]
		Roots Flower Fruits Aerial parts	Urinary system disorders, neuralgia, eye complaints, digestive diseases, and fever.	[16]
	Egypt	Whole plant	Nerve tonic, cough suppressant, and diuretic drug	[18]
	North African	Stems Leaves Roots	Diuretic drug	[16]
	Morocco	Roots Aerial parts Flowers Seeds Rhizomes Whole plant	Diuretic drug, antidiabetic, stomachic, liver disorders, post-partum care.	[16,19,20]
E. kebericho	**Ethiopia**	Whole plant	Fever, headache, stomachache, malaria, cough, diarrhea, typhus, taenicide, fumigant for mosquitoes, and snake repellent.	[21,22]
		Roots Stem	Liver disease, respiratory diseases, malaria, vomiting, gonorrhea, trypanosomiasis fever, and headache.	[3]
		Roots	Migraine, fumigant, intestinal diseases, heart pain, typhus.	[23]
E. hoehnelii		Roots	Antimalarial, for internal parasite, snakebite, and common cold.	[3,11]
E. echinatus		Whole plant	Stomachic, stimulates the liver, treating worms, hemorrhoids, chronic fever, migraines, joint problems, urinary disorders and infections.	[24]

***E. amplexicaulis* Oliv.**	Root	Liver diseases, trypanosomiasis, stomachache.	[25]
***E. longifolius* A. Rich.**	Root bark	Rheumatism, dry cough, and headache.	[3]
***E. macrochaetus* Fresen.**	Roots Seeds	Headache, toothache, and abdominal colics.	
***E. giganteus* A. Rich**	Roots	Anti-hemorrhoids.	

8. Phytoconstituents

To date, several bioactive metabolites such as flavonoids, triterpenes, phenols, terpenes, thiophenes, alkaloids, lipids, and phenylpropanoids have been detected in *Echinops*. Thiophenes are the primary phytoconstituent detected in roots. Whereas most terpenes and flavonoids were found in the aerial parts or entire plant. Essential oils were the most abundant components in many species of *Echinops*. [3]

The current review summarizes most of the reported phytoconstituents separated and identified from the genus *Echinops*.

8.1. Thiophenes

The primary bioactive components of the genus *Echinops*, thiophenes, are produced synthetically from fatty acids and reduced Sulphur. Structurally, most thiophenes consist of two thiophene rings with acetylenic functional group. Several thiophenes were isolated and identified from *Echinops* species listed in table (2) and their structures have been summarized in fig. 2. Some of thiophenes had multiple pharmacological activities such as antimalarial, insecticidal and fungicidal.[26]. From nine species, α-terthiophene **(20)** and 5-(but-3-en-1-ynyl)-2,2'-bithiophene **(6)** were the two most prevalent thiophenes, the later one was essential oil isolated from the roots of *E. grijsii*, *E. bannaticus*, and *E. sphaerocephalus* L**.** [3]**.**

Table (2) list of the most abundant thiophenes identified from genus *Echinops* L.

No.	Name of compound	Species and part used	Method of isolation or identification	Biological activities	References
1.	**Arctinal**	*E. ritro* (WP)	Medium-Pressure Liquid Cchromatography (MPLC) then Sephadex LH-20 Column Chromatography	Antibacterial	**[3,27]**
2.	**Arctinol**	*E. latifolius* (R), *E. ritro* (WP)	(MPLC)	Anti-inflammatory	**[3,27,28]**
3.	**Arctinol-A**	*E. ritro* (WP)		Antibacterial	**[3,27]**
4.	**Arctinol-b**	*E. grijsii*, *E. latifolius* (R), *E. ritro* (WP)	(MPLC) then Sephadex LH-20 Column Chromatography Column Chromatography Then Preparative High Performance Liquid Chromatography (HPLC**)**	Antibacterial Antifungal Anti-inflammatory Cytotoxic against HL60 and K562 cell lines	**[3,27–29]**
5.	**5-acetyl-2,2'-bithiophene**		(MPLC)	−	**[3,27]**
6.	**5`-(3-buten-1-ynyl)-2,2'-bithiophene**	*E. grijsii*, *E. bannaticus*, *E. nanus Bunge*, *E. sphaerocephalus* L., *E. pappii Chiov.*, *E.latifolius*, *E. maeruchaetu*, *E. transiliensis*, *E. ellenbeckii* (R),	Vaccum Liquid Chromatography (VLC) then Column Chromatography (CC) Preparative silica gel Column Chromatography (PTLC)	Antifungal Termicidal Cytotoxic against K562, HL60 cell lines larvicidal	**[3,11,26,29–33]**

		E. spinosissimus (WP), *E. albicaulis* (WP) (AP) (R), *E. ritro* (R) (AP)			
7.	**5-chloro-*α*-terthiophene**	*E. grijsii* (R)	CC and (PTLC)	−	**[3,34]**
8.	**Cardopatine**	*E. latifolius*, *E. grijsii* (R), *E. ritro* (Rd) (AP)	(VLC) then CC (PTLC)	Termicidal Antifungal	**[3,26,31,34]**
9.	**Echinoynethiophene A**	*E. grijsii* (R)	Column Chromatography then HPLC	−	**[3,34]**
10.	***Echinops*acetylenes A**	*E. transiliensis* (R)			**[3,35]**
11.	***Echinops*acetylenes B**				
12.	**Echinothiophenegenol**	*E. nanus*, *E. grijsii* (R)	CC then Reversed Phase HPLC (RP-HPLC)	Cytotoxic against HL60 and K562 cell lines	**[3,29]**
	Table (2) continued				
13.	**Grijisyne A**	*E. grijsii* (R)	CC	Cytotoxic against HL60, K562, and MCF-7 cell lines	**[3,36]**
14.	**Grijisone A**			Cytotoxic against HL60 and K562 celll lines	
15.	**Isocardopatine**	*E. grijsii*, *E. ritro* (R)	(VLC) then CC Preparative HPLC (PTLC)	Antifungal	**[3,26,31,32,34]**
16.	**Junipic acid**	*E. ritro* (WP)	(MPLC)	−	**[3,27]**
17.	**6-Methoxy-arctinol-b**	*E. latifolius* (R)	−	Anti-inflammatory	**[3,28]**
18.	**5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene**	*E. transiliensis*, *E. ellenbeckii*, *E.hoehnelii* (R), *E. albicaulis* (WP)	CC	Termicidal Antimalarial Larvicidal	**[3,11,31]**
19.	**5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene**	*E. grijsii*, *E. hoehnelii*, *E. transiliensis* (R), *E. ritro* (WP), *E. giganteus* (Rz)	(MPLC) then Sephadex LH-20 CC CC Then Preparative HPLC	Antifungal Cytotoxic against HL60 and K562 cell lines, leukemia Antimalarial Larvicidal	**[3,11,27]**
20.	***α*- terthiophene (*α*- terthienyl)**	*E.sphaerocephalus*, *E. pappii*, *E. ellenbecki*, *E. latifolius*, *E. macrochaetus*, *E. nanus*, *E. transiliensis*, *E.grijsii*, *E.bannaticus*, *E.spinosus*, *E. taeckholmiana* (R), *E. ritro* (R) (Rd) (AP), *E. albicaulis* (R) (WP) (AP)	(VLC) then CC (PTLC)	Antifungal Termicidal Cytotoxic against HepG2, MCF-7, K562 cell lines larvicidal	**[3,10,17,26,29–34]**

R: root; AP: aerial parts; WP: whole plant; Rd: radix; Rz: rhizome

8.2. Flavonoids and other phenolics

Numerous medicinal plants contain therapeutic levels of flavonoids, which are used to treat many disorders such as anti-inflammatory, antispasmodic, and anti-allergic medications. Wide range of pharmacological effects of flavonoids are related to their potent antioxidant and free radical scavenger activity, ability to chelate metals, and interactions with enzymes, adenosine receptors, and bio membranes. Some of them are also capable of wounds healing [37].

Flavonoids from the genus *Echinops* were predominantly flavones and isolated from the whole plant and aerial parts of different species of the genus. The most prevalent flavonoidal aglycone is Apigenin **(21)**, was found in the whole plant and

flower of *E. niveus, E. echinatus, E. integrifolius,* and *E. albicaulis* Kar. & Kir [6] **.** Structures of the most abundant flavonoids from genus *Echinops* are represented in fig. 3. and listed in table (3).

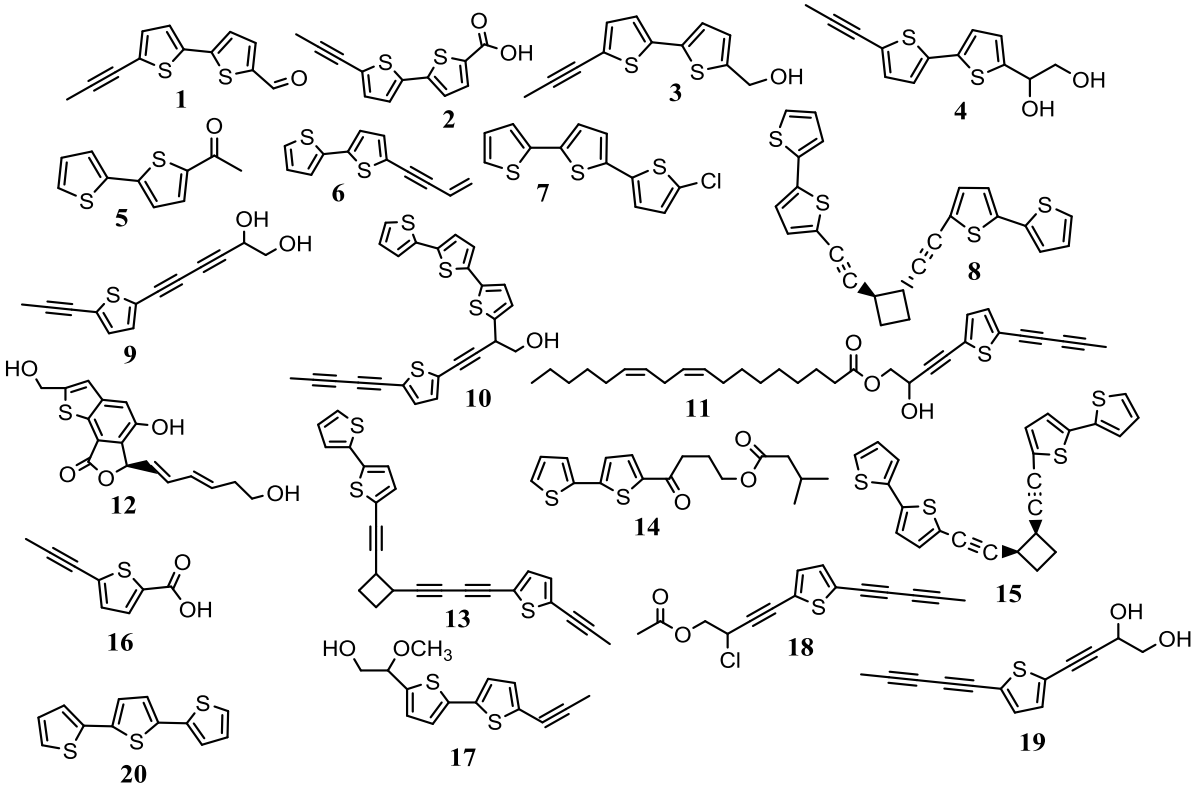


Fig. 2. The most abundant thiophenes identified from genus *Echinops* L.

Table (3) list of the most abundant flavonoids and other phenolics identified from genus *Echinops* L.

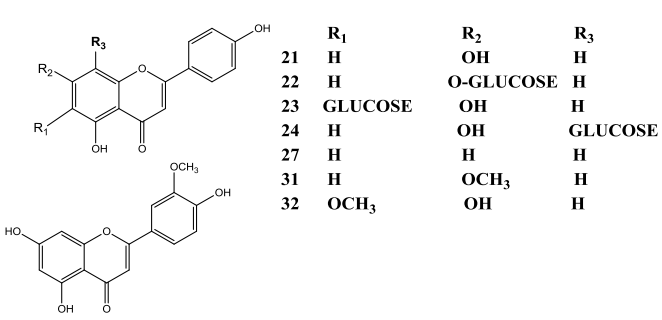
No.	Name of compound	Species and Plant part	Method of isolation or identification	Biological activities	References
			Flavones		
21.	**Apigenin**	*E. echinatus* (WP) (AP) (F), *E. niveus* (WP), *E.integrifolius* *E. albicaulis*, *E. lanceolatus* (AP), *E. spinosus* (AP)(R)(F)	Isolated by Sephadex LH-20 CC then Flash CC	Wound-healing, antimicrobial, antioxidant, anti-Inflammatory, Antiviral, Analgesic, Antiproliferative	**[3,17,24,30,38,39]**
			Identified by HPLC UV-chromatograms, ultra-performance liquid chromatography–electrospray ionization tandem mass spectrometry (UPLC–ESI–MS/MS)	Hepatoprotective	
22.	**Apigetrin (Cosmosiin)**	*E. echinatus (*F) (WP) (AP), *E.spinous (*AP)(R), *E. orientalis* (Sd)(L), *E. lanceolatus* (AP)			**[3,17,24,38]**
23.	**Apigenin-6-C-glucoside**	*E.spinosissimus* (R)	Identified by HPLC		**[17]**

24.	**Apigenin-8-C-glucoside**		UV-chromatograms		
25.	**Apigenin-7-O-(6`-*trans*-*p*-coumaroyl-*β*-*D*-glucopyranoside**	*E. orientalis* (Sd)(L), *E. spinosus* (AP)	CC, PTLC	Antioxidant	**[3,17,40]**
26.	**Chrysoeriol**	*E. integrifolius* (WP)	Isolated by Sephadex LH-20 CC then Flash CC then crystallization		**[3,39]**
27.	**5,4`-dihydroxy flavone**	*E.spinosus* (AP)	CC		**[41]**
28.	**Echinacin**	*E. echinatus* (AP) (WP)	–		**[24]**
29.	**Echinaticin**			–	
30.	**Echitin**	*E. echinatus* (F)			**[3,24]**
	Table (3) continued				
31.	**Genkwanin**	*E. albicaulis* (AP)	VLC then Sephadex LH-20 CC		**[3,30]**
32.	**Hispidulin**	*E. integrifolius* (WP)	Isolated by Sephadex LH-20 CC then Flash CC then semi-preparative HPLC		**[3,39]**
33.	**Luteolin**	*E. niveus* (WP), *E. grijisii*, *E.taeckholmiana* (R), *E.spinosus* (AP)	Identified by HPLC		**[3,10,41]**
34.	**Rhoifolin**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS)	Antimicrobial, Antiproliferative	**[38]**
			Isoflavone		
35.	**Echinoside**	*E. echinatus* (WP)	CC	–	**[3,24,42]**
36.	**7-hydroxyisoflavone**				
			Flavonols		
37.	**Axillarin**	*E. integrifolius* (WP)	Isolated by Sephadex LH-20 CC then Flash CC then semi-preparative HPLC	–	**[3,39]**
38.	**Centaureidin**				
39.	**Isorhamnetin**	*E.taeckholmiana* (C)	Identified by UPLC-ESI-MS/ MS		**[10]**
40.	**Isorhamnetin-3-O-rutinoside**	*E.spinosissimus* (R)	Identified by HPLC UV-chromatograms	–	**[17]**
41.	**Jaceidin**	*E. integrifolius* (WP)	Isolated by Sephadex LH-20 CC then Flash CC		**[3,39]**
42.	**Kaempferol**	*E. echinatus* (WP), *E.spinosissimus* (AP), *E.taeckholmiana* (R)	Preparative paper Then Sephadex LH-20 CC, CC	Wound-healing	**[3,10,17,24,41,42]**
43.	**Kaempferol methyl ether derivatives**	*E. echinatus* (WP), *E.taeckholmiana* (R)	CC		**[3,10,24,42]**
44.	**Kaempferol-7-O-rhamnosyl-glucoside**	*E.spinosissimus* (R)	Identified by HPLC UV-chromatograms		**[17]**
45.	**Kaempferol-*p*-coumaroyl-diglycosided**				

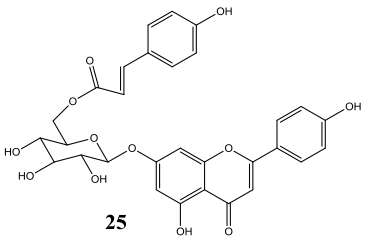
46.	**Myrecetin-3-O-*α*-*L*-rhamnoside**	*E. echinatus* (WP)	CC		**[3,24,42]**
47.	**Quercetin**	*E.taeckholmiana* (R)(C)	Identified by HPLC		**[10,41]**
48.	**Quercetin-3-O-methyl ether**	*E.taeckholmiana* (R)	Identified by UPLC-ESI-MS/ MS		
49.	**Quercetin-3-O-galactoside**		Identified by HPLC UV-chromatograms	–	**[17]**
50.	**Quercetin-3-O-rhamnoside**	*E.taeckholmiana* (C)	Identified by UPLC-ESI-MS/ MS		**[10]**
51.	**Rutin**	*E. heterophyllus*, *E. albicaulis*, *E.spinosus* (AP), *E.taeckholmiana* (R)	Preparative paper Then Sephadex LH-20 CC Identified by HPLC VLC then Sephadex LH-20 CC		**[3,10,30,41]**
			Flavanones		
52.	**Candidone**	*E. giganteus* (Rz)	CC	Cytotoxic against HL60	**[3,43]**
	Table (3) continued				
53.	**Eriodictyol-4'-O-neohesperidoside-7-O-glucoside**	*E.spinosissimus* (R)	Identified by HPLC UV-chromatograms	–	**[17]**
54.	**Hesperetin**	*E.spinosissimus* (AP)	Preparative paper Then Sephadex LH-20 CC Identified by HPLC		**[17,41]**
55.	**Hesperidin**				
56.	**Naringin**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS), HPLC	Antimicrobial, Antiproliferative	**[38,41]**
57.	**Naringenin-7-O-glucoside (Prunin)**				
58.	**5,7,3′,5′-tetrahydroxy flavanone**	*E.erinaceus* (F)	CC	Antioxidant	**[4]**
			Flavanonols		
59.	**Dihydroquercetin-4`-methyl ether**	*E.echinatus* (L)	CC	−	**[24,44]**
60.	**Dihydrokaempferol**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS)	Antimicrobial, Antiproliferative	**[38]**
61.	**Taxifolin**	*E.taeckholmiana* (C)		−	**[10]**
			Flavan-3-ol		
62.	**Epicatechin**	*E.taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)	−	**[10]**
63.	**Epigallocatechin**				
			Neoflavonoids		
64.	**Nivegin**	*E. niveus* (WP)	CC	−	**[3,45]**
65.	**Nivetin**	*E. niveus* (AP)			
			Other phenolics		
			Coumarins		
66.	**Esculetin-6-O-glucoside**	*E. taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)	−	**[10]**
67.	**Umbelliferone**	*E. integrifolius* (WP)	Isolated by Sephadex LH-20 CC then Flash CC then semi-preparative HPLC		**[3,39]**

		Lignans			
68.	**(-)-Secoisolariciresinol**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS)	Antimicrobial, Antiproliferative	**[38]**

R: root; AP: aerial parts; WP: whole plant; Sd: seed; F: flower; L: leaves; C: callus; Rz: rhizome



	R_1	R_2	R_3
21	H	OH	H
22	H	O-GLUCOSE	H
23	GLUCOSE	OH	H
24	H	OH	GLUCOSE
27	H	H	H
31	H	OCH_3	H
32	OCH_3	OH	H



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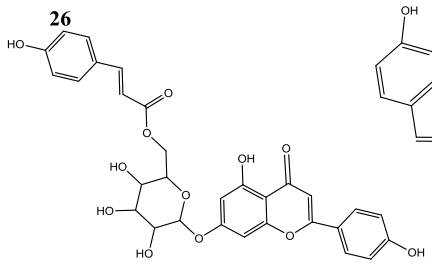

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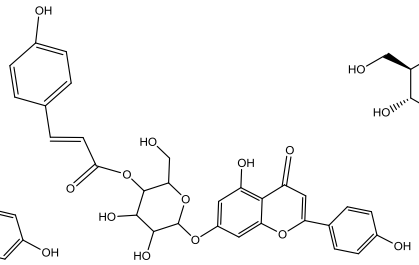

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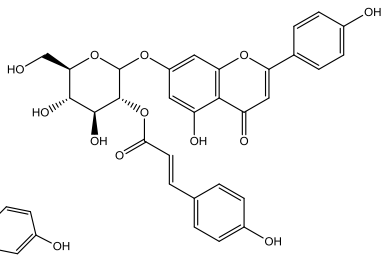

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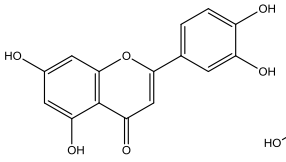

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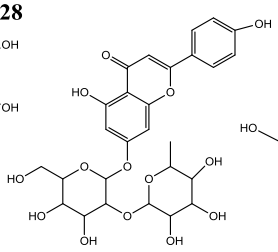

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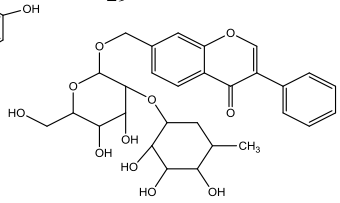

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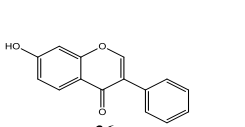

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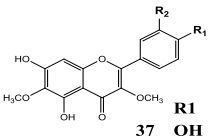
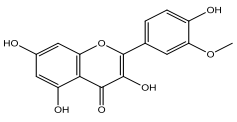


	R1	R2
37	OH	OH
38	OCH_3	OH
41	OH	OCH_3



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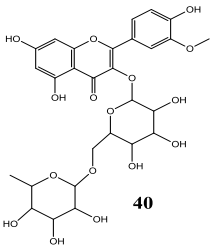

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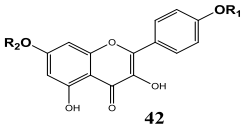
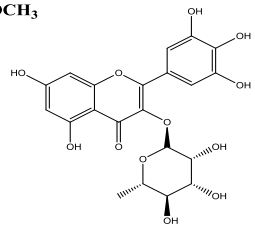


	R1	R2
42	H	H
43 4` O-methyl ether	CH_3	H
7 O-methyl ether	H	CH_3



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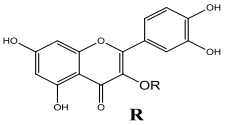
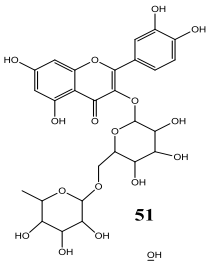


	R
47	H
48	CH_3
49	GALACTOSE
50	RHAMNOSE



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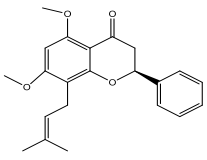

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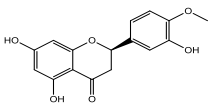

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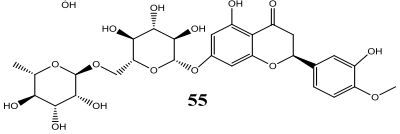

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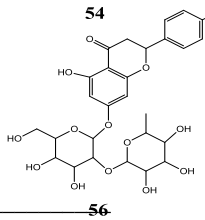

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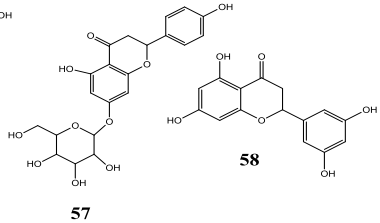

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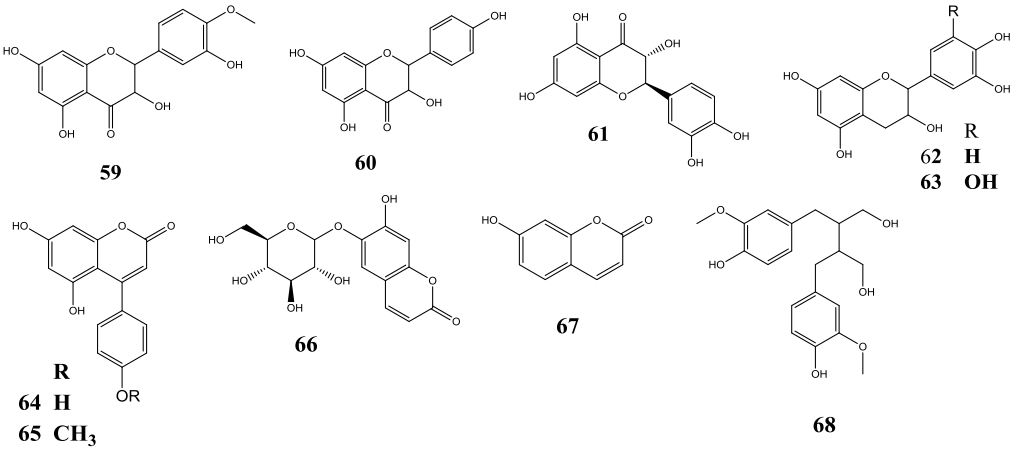


Fig. 3. The most abundant flavonoids and other phenolics identified from genus *Echinops* L.

8.3. Phenolic acids

The most prevalent phenolic acids identified from genus *Echinops* are summarized in fig. 4. and listed in Table (4)

Table (4) list of the most abundant phenolic acids identified from genus *Echinops* L.

No.	Name of compound	Species and Plant part	Method of isolation or identification	Biological activities	References
69.	**Caffeic acid and its derivative**	*E.spinosissimus*, *E.taeckholmiana* (R)	Identified by HPLC UV-chromatograms		**[10,17]**
70.	**Chlorogenic acid**	*E.taeckholmiana* (R)(C), *E. grijisii*, *E. spinosissimus* (R)		–	**[3,10,17]**
71.	**Caffeoylglucaric acid**	*E.taeckholmiana* (C)	Identified by (UPLC–ESI–MS/MS)		**[10]**
72.	**Caftaric acid**	*E.taeckholmiana* (R)(C)			
73.	**Cinnamic acid**	*E.spinosissimus* (R)	Identified by HPLC UV-chromatograms, (UPLC–ESI–MS/MS)		**[17]**
74.	**Coumaric acid**	*E.taeckholmiana* (R)(C), *E. lanceolatus* (AP), *E.erinaceus* (F)	Identified by (UPLC–ESI–MS/MS) Isolated by CC	–	**[4,10,38]**
75.	**5-*P*-Coumaroylquinic acid**	*E.taeckholmiana* (C), *E. lanceolatus* (AP)			**[10]**
76.	**Coniferyl aldehyde**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS)	Antimicrobial, Antiproliferative	**[38]**
77.	**Cynarine**	*E. grijisii* (R)	–	–	**[3]**
78.	**Dicaffeoylquinic acid derivatives**	*E. galalensis* (AP), *E.taeckholmiana* (R)(C)	Hepatoprotective VLC then CC		**[3,10,46]**
79.	**Ethyl caffeate**	*E.taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)		**[10]**
80.	**Ferulic acid**	*E.spinosissimus* (AP), *E.taeckholmiana* (R)	Preparative paper Then Sephadex LH-20 CC		**[10,41]**
81.	**5-Feruloyl quinic acid**	*E. lanceolatus* (AP)	Identified by (UPLC–ESI–MS/MS)	–	**[38]**
	Table (4) continued				
82.	**Gallic acid**	*E.spinosissimus* (AP)	Preparative paper Then Sephadex LH-20 CC		**[41]**

83.	**3-O-Galloylquinic acid**	*E. taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)		**[10]**
84.	**1-O-*D*-Glucopyranosyl sinapate**	*E. taeckholmiana* (C)			
85.	**3-Hydroxybenzoic acid**	*E. lanceolatus* (AP)			**[38]**
86.	**Quinic acid**	*E. lanceolatus* (AP), *E.taeckholmiana* (R)(C)	Identified by (UPLC–ESI–MS/MS)	Antimicrobial, Antiproliferative	**[10,38]**

R: root; AP: aerial parts; F: flower; C: callus

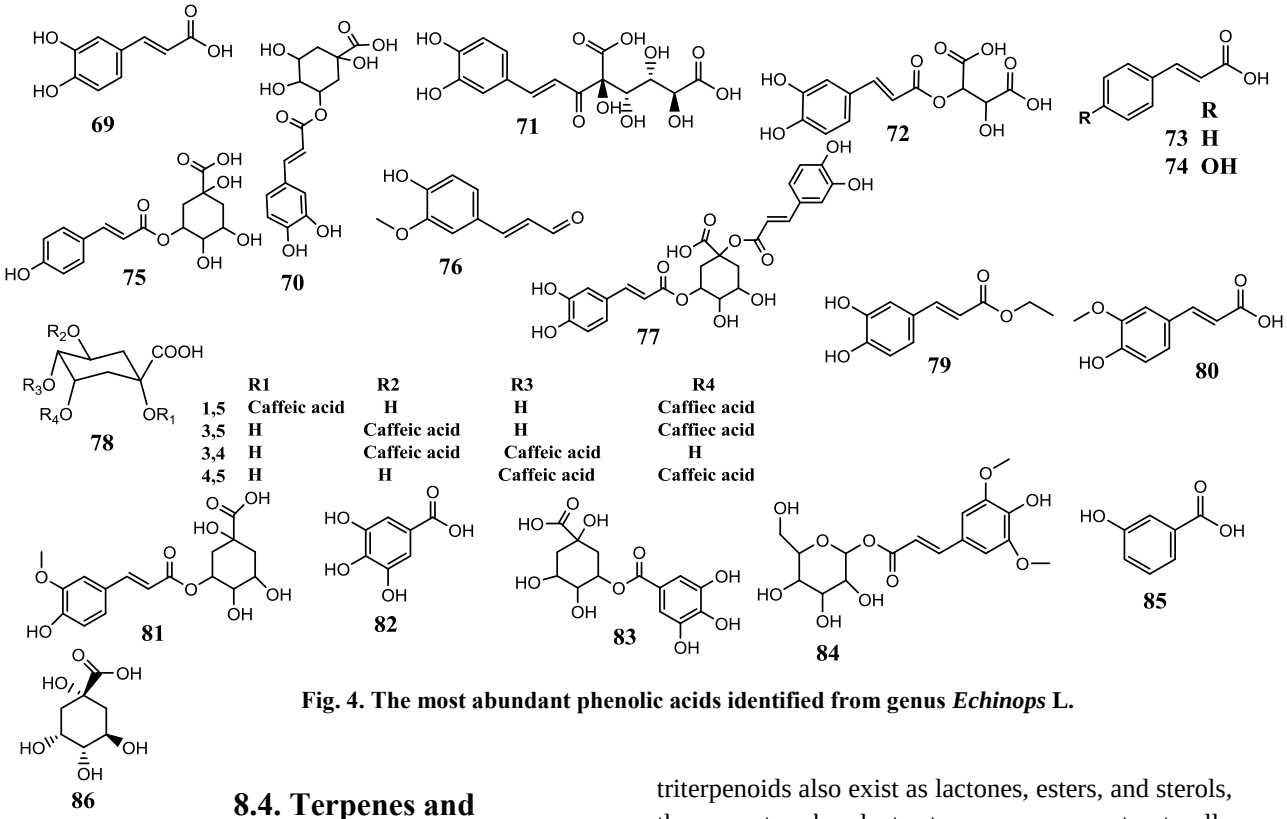


Fig. 4. The most abundant phenolic acids identified from genus *Echinops* L.

8.4. Terpenes and Phytosterols

Sesqui- and triterpenoids were primarily found in the aerial parts and whole plants of the genus *Echinops* and listed in table (5). Lactones are included in the majority of sesquiterpenoids. In addition to triterpenoids glycosides, the majority of triterpenoids also exist as lactones, esters, and sterols, the most abundant terpenes are structurally represented in fig. 5. Lupeol **(93)** and lupeol acetate **(95)** were the prevalent triterpenoids, while costunolide **(107)** a common sesquiterpenoid was isolated from three species. The essential oils of the genus also contained many sesquiterpenoids [3].

Table (5) list of the most abundant terpenes identified from genus *Echinops* L.

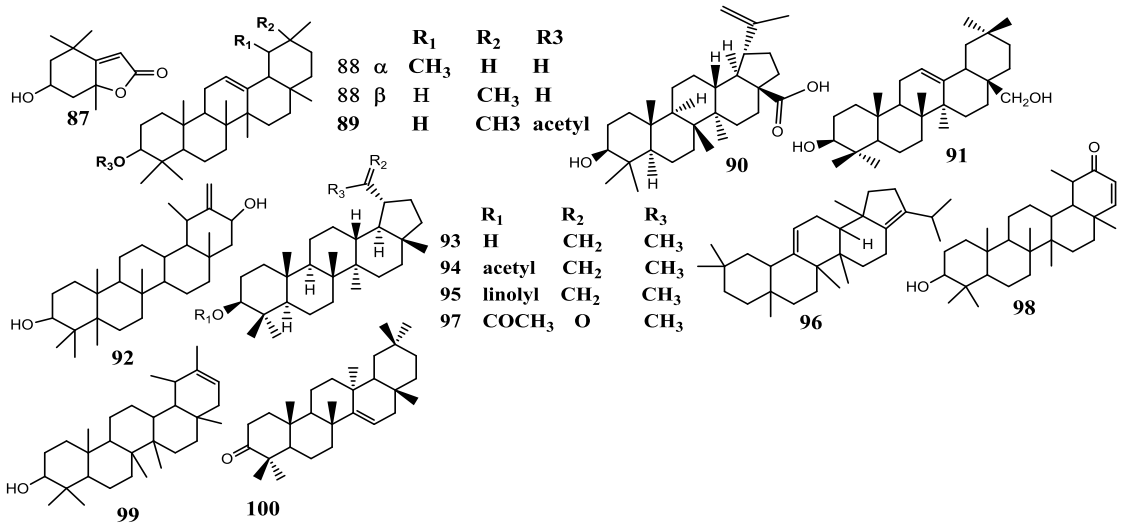
No.	Name of compound	Species and Plant part	Method of isolation or identification	Biological activities	References
			Monoterpenoids		
87.	**Loliolide**	*E.erinaceus* (F)	CC	–	**[4]**
			Triterpenoids		

Table (5) continued

88.	***α and β* -amyrin**	*E.galalensis* (Rz)(AP), *E. niveus* (WP), *E.spinosus* (F)	VLC then CC	Hepatoprotective	**[3,46,47]**
89.	***β*-amyrin acetate**	*E. giganteus* (Rz)	CC	−	**[3,48]**
90.	**Betulinic acid**	*E. niveus* (WP)	−		**[3]**
91.	**Erythrodiol**	*E.galalensis* (Rz)(AP)	VLC then CC	Hepatoprotective	**[3,46]**
92.	**Gmeliniin A**	*E. gmelinii* (AP)	CC then recrystallizatio		**[3,49]**
93.	**Lupeol**	*E. niveus* (WP), *E. giganteus* (R)(AP), *E.integrifolius*(WP)(AP), *E. echinatus* (R), *E.Spinosissimus* (AP)	Isolated by Sephadex LH-20 CC then Flash CC CC then MPLC then PTLC		**[3,7,24,39]**
94.	**Lupeol acetate**	*E. albicaulis* (AP)	VLC then Sephadex LH-20 CC		**[30,39]**
95.	**Lupeol linoleate**	*E. integrifolius* (WP), *E. echinatus* (R), *E. albicaulis* (AP)	VLC then Sephadex LH-20 CC		**[3,30]**
96.	**A-neooleana-3(5),12-diene**	*E.spinosus* (F)	CC then PTLC then identified by Gas chromatography−mass spectroscopy (GC-MS)		**[17,47]**
97.	**29-norlupan-20-one-3*β*-yl-acetate**	*E.Spinosissimus* (AP)	CC then MPLC then PTLC	−	**[7]**
98.	**20-oxo-30-nortaraxast-21-en-3*β*-ol**		CC then MPLC		
99.	**Pseudotaraxasterol**	*E.spinosus* (F)	CC then PTLC then identified by Gas chromatography−mass spectroscopy (GC-MS)		**[47]**
100.	**Taraxerone**	*E. taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)		**[10]**
101.	**Taraxasterol**	*E. niveus* (WP), *E.spinosus* (F)	CC then PTLC then identified by Gas chromatography−mass spectroscopy (GC-MS)		**[3,47]**
102.	**Taraxasterol acetate**	*E. niveus* (WP), *E. echinatus* (WP)(AP)	CC then recrystallization	Anti-Inflammatory	**[3,24,47]**
103.	**Ursolic acid**	*E. giganteus* (Rz)	CC	Cytotoxic	**[3,43]**
			Sesquiterpenoids		
104.	**Atractylenolide-II**	*E. latifolius* (R)	−	Anti-Inflammatory	**[3,28]**
105.	**Caryophyllene epoxide**	*E. giganteus*, *E. hispidus* (R)	Microcolumn chromatography	−	**[50]**
106.	**Costunolide**	*E.amplexicaulis*, *E. kebericho*, *E. pappii* (R)	Percolation with petrol forming pure crystals of the compounds	Antitumor	**[3,21,50]**
107.	**Dehydrocostus lactone**	*E. amplexicauli*, *E. kebericho* (R)	CC	Antibacterial	
108.	**Dihydrocostunolide**	*E. amplexicaulis* (R)	Microcolumn chromatography		**[50]**
109.	**Echusoside**	*E. hussoni Boiss* (AP)	−	−	**[3]**
	Table (5) continued				
110.	**Echinopines A**	*E. spinosus* (R)	CC then RP-HPLC		**[3,17]**
111.	**Echinopines B**				
112.	**Erinaceosin**	*E.erinaceus* (F)	CC	Cytotoxic against HCT-116, CACO2	**[4]**

				cell lines	
113.	**11-Hydroxyisocom-2-en-5-one**	*E.spinosus* (R)	CC then preparative HPLC		**[17,51]**
114.	**jatamol A**	*E. taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)	–	**[10]**
115.	**Latifolanone A**	*E. latifolius* (R)	–		**[3,28]**
116.	**Macrochaetosides A**	*E. macrochaetus* (AP)	CC	Cytotoxic against MCF-7, $HepG_2$, HCT-116	**[52]**
117.	**Macrochaetosides B**			Cytotoxic against MCF-7	
118.	**Reynosin**	*E. pappii* (R)	(VLC) then CC		**[50]**
119.	**Santamarin**	*E. ritro* (WP), *E. pappii* (R)		–	**[3]**
120.	**Vulgarin**	*E. ritro* (WP)	CC		
			Phytosterols		
121.	**Ajugasterone C**	*E. grijisii* (R)	–	–	**[3]**
122.	***β*-sitosterol**	*E. niveus* (WP), *E. transiliensis* *E. taeckholmiana* (R), *E. giganteus* (Rz), *E. orientalis* (Sd), *E.spinosus* (F), *E.galalensis* (AP)	CC, PTLC	Hepatoprotective	**[3,10,17,46,47]**
123.	***β*-sitosterol glucoside**	*E. niveus*, *E. integrifolius* (WP), *E. giganteus* (R), *E. albicaulis* (AP)	VLC then Sephadex LH-20 CC	–	**[3,30,39]**
124.	**Stigmasterol**	*E. transiliensis* (R), *E. macrochaetus* (AP), *E. integrifolius* (WP), *E. giganteus* (Rz), *E.spinosus* (F) (AP), *E. taeckholmiana* (R)	Sephadex LH-20 CC then Flash CC CC CC then MPLC then PTLC	–	**[3,7,10,17,39,43,52]**
125.	**Stigmasterol-3-*β*-*D*-glucoside**	*E. taeckholmiana* (R)	Identified by (UPLC–ESI–MS/MS)		**[10]**

R: root; AP: aerial parts; WP: whole plant; Rz: rhizome; Sd: seed; F: flower



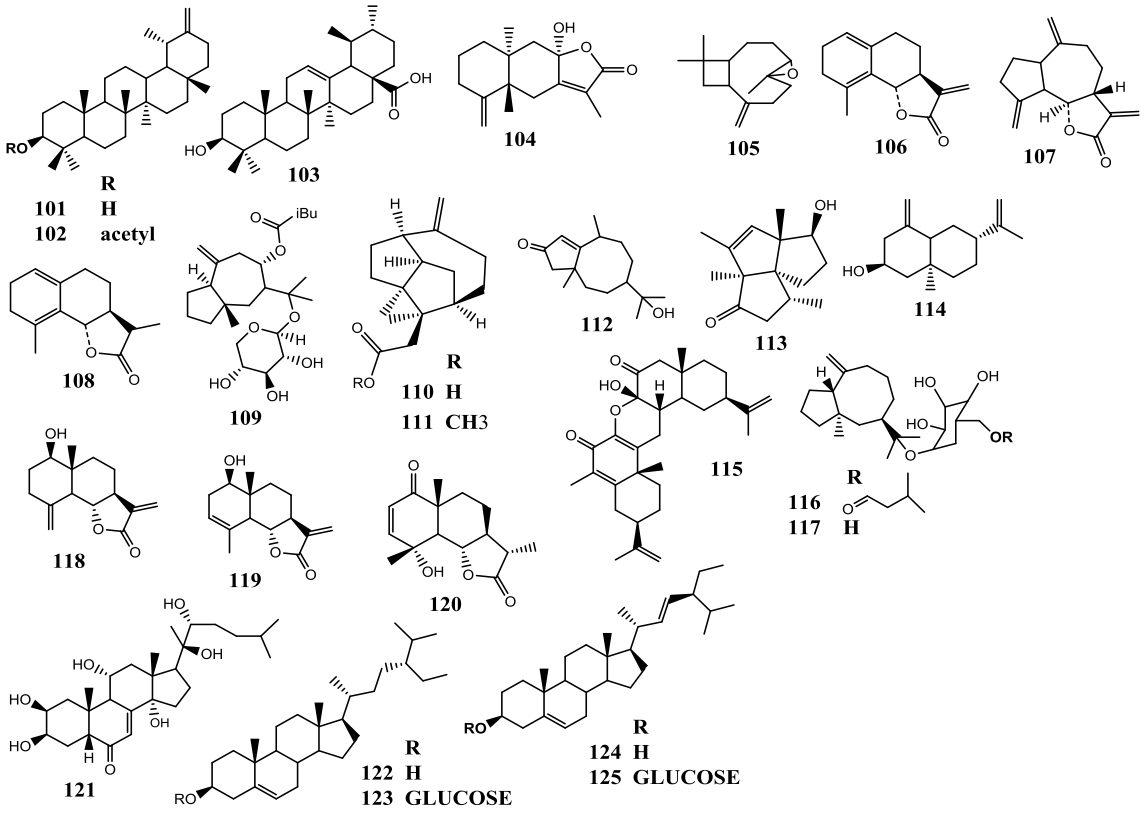


Fig. 5. The most abundant terpenes identified from genus *Echinops* L.

8.5. Essential oils: -

Bioactive essential oil constituents are abundant in the genus *Echinops* and primarily detected in the roots. Forty-two distinct constituents produced from *E. kebericho* M. tubers during hydrodistillation and listed in table (6), The most prevalent compound (12.64%) was isoshyobunone **(152)**, which was followed by modephene **(157)** (10.41%), isocomene **(150)** (8.42%), *β*-phellandrene **(164)** (7.00%), *α*-pinene **(165)** (6.96%), dehydrocostuslactone **(140)** (6.52%), *β*-pinene **(166)** (6.29%), and *β*-isocomene **(151)** (6.08%) which are represented in fig. 6. [21]

Table (6) list of the most abundant Essential oils identified from genus *Echinops* L

No.	Name of compound	Species and Plant part	Method of isolation or identification	Biological activities	References
126.	**Aromandendrene**	*E. kebericho Mesfin* (R)	Identified by (GC-MS)	–	[21]
127.	**Aromadendrene oxide-(1)**				
128.	**Bicyclogermacren**				
129.	**Bornyl acetate**				
	Table (6) continued				
130.	***α*-cadinol**	*E. kebericho Mesfin* (R)	Identified by (GC-MS)		[21]
131.	***γ*-cadinene**				
132.	**Camphene**				
133.	**Caryophyllene**				
		E. giganteus (R)		Anti-Protozoal	[3]
134.	**Caryophyllene oxide**	*E.ellenbeckii* (R)(S)(L)(F)			[3,53]

		E. kebericho Mesfin (R)		–	[21]
135.	**1,8-Cineole**	*E. graecus, E.ritro* (F)	Identified by (GC-MS)		[3,54]
136.	**Costol**	*E. kebericho Mesfin* (R), *E. graecus, E.ritro* (F)			[21]
137.	**Cubebol**				
138.	***P and α*-cymene**				
139.	**Cyperene**	*E.ellenbeckii* (R)(S)(L)(F), *E. kebericho Mesfin* (R)			[3,21,53]
140.	**Dehydrocostuslactone**			Antibacterial	[21]
141.	**Dihydrodehydrocostus lactone**				
142.	***β*-elemen**	*E. kebericho Mesfin* (R)			
143.	**Endo-borneol**				
144.	**Germacrene-*D*-4-ol**				
145.	***α*-guaiene**			–	
146.	**Heptacosane**				
		E. integrifolius (R)	CC then identified by GC/MS		[3,55]
147.	**(*E*)-2-hexenal**	*E. graecus, E.ritro* (F)			[[3,54]
148.	**Humulene**		Identified by (GC-MS)		
149.	***trans*- *β* -ionone**	*E. kebericho Mesfin* (R)			[21]
150.	**Isocomene**				
151.	***β*-Isocomene**				
152.	**Isoshyobunone**				
153.	**Lignoceric acid**	*E. integrifolius* (R)	CC then identified by GC/MS		[3,55]
154.	***β*–maaliene**	*E.ellenbeckii* (R)(S)(L)(F)	Identified by (GC-MS)		[3,53]
155.	**Methyleugenol**	*E. kebericho Mesfin* (R)			[21]
156.	**Methyl chavicol**	*E. graecus, E.ritro* (F)		–	[3]
157.	**Modephene**				
158.	***β*-myrcene**	*E. kebericho Mesfin* (R)			[21]
159.	**(-)-Myrtenol**				
	Table (6) continued				[21]
160.	***trans-β*-ocimene**	*E. kebericho Mesfin* (R)	Identified by (GC-MS)		
161.	**Octacosane**				
162.	**Pentadecanal**				
163.	***α*-phellandrene**				

164.	***β* -phellandrene**			
165.	***α*-pinene**			
166.	***β*- pinene**			
167.	**Ritroyne A**	*E. ritro* (R)	Isolated by Sephadex LH-20 CC then (MPLC)	[3,27,53]
168.	***β*-selinene**	*E.ellenbeckii* (R)(S)(L)(F)		
169.	**Silphiperfol-5ene**	*E. giganteus* (R)	Identified by (GC-MS)	
		E. kebericho Mesfin (R)		[21]
170.	**Terpinen-4-ol**			
171.	**Triacontane**	*E. integrifolius* (R)		[3]
172.	***trans*-verbenol**	*E. kebericho Mesfin* (R)		[21]

R: root; S: stem; F: flower; L: leaves

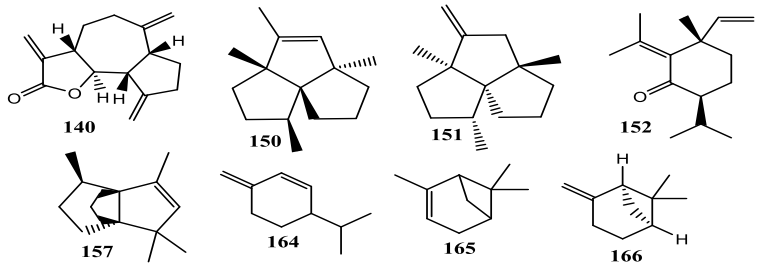


Fig. 6. The most abundant essential oils identified from genus *Echinops* L

8.6. Alkaloids

Reviewing the current literature, alkaloids isolated from different species of genus *Echinops* were limited and summarized in fig. 7. The choloroform and *n*-butanol extracts of the aerial parts of *Echinops echinatus* contained Echinopsine (1-methyl-4-quinolone) (1- methoxycarbonylindole) **(173)**, echinozolinone **(174)**, and Echinopsidine **(175)** respectively. As they were the first alkaloids isolated from the genus *Echinops*. Echinopsine the predominant alkaloid is also isolated from the choloroform fraction of the root of *E. nanus*, methanolic extract of aerial parts of *E. albicaulis*, and seeds of *E. orientalis Trauv* by column chromatography, preparative TLC and also VLC then Sephadex LH-20 CC [3,24,30] and the chloroform extract of inflorescences of *E. spinosus* [17]. A novel minor alkaloid called 7-hydroxy-echinozolinone **(176)**, was isolated from the methanolic extract and the chloroform fraction of flowers of *E. echinatus* [24,56]. 1-methyl-4(1H)-quinolinone **(177)** was isolated from the seeds of *E. heterophyllus*. 1-methyl-4-methoxy-8-(*β-D*-glucopyranosyloxy)-2(1H)-quinolinone **(178)** and 4-methoxy-8-(-*D*-glucopyranosyloxy)-2(1H)-quinolinone **(179)** were isolated from the *n*-butanol extract of aerial parts of. *E. gmelinii Turcz.* Echinorine **(180)** was isolated from the methanolic extract of aerial parts of *E. albicaulis* by VLC then Sephadex LH-20 CC [3,30] and acidulated methanol extract of inflorescences of *E. spinosissimus* [17].

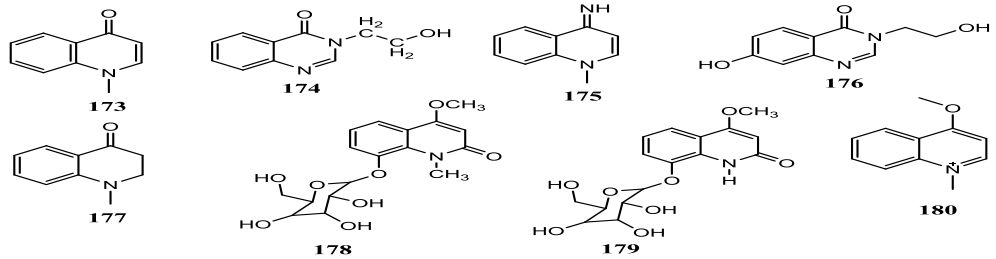


Fig. 7. The most abundant alkaloids identified from genus *Echinops* L.

9. Pharmacological activities

Extracts and chemical constituents isolated from the different species of this genus possess a wide spectrum of biological effects; Fig. 8. summarized the most important recent pharmacological activities of the most abundant species of genus *Echinops*.

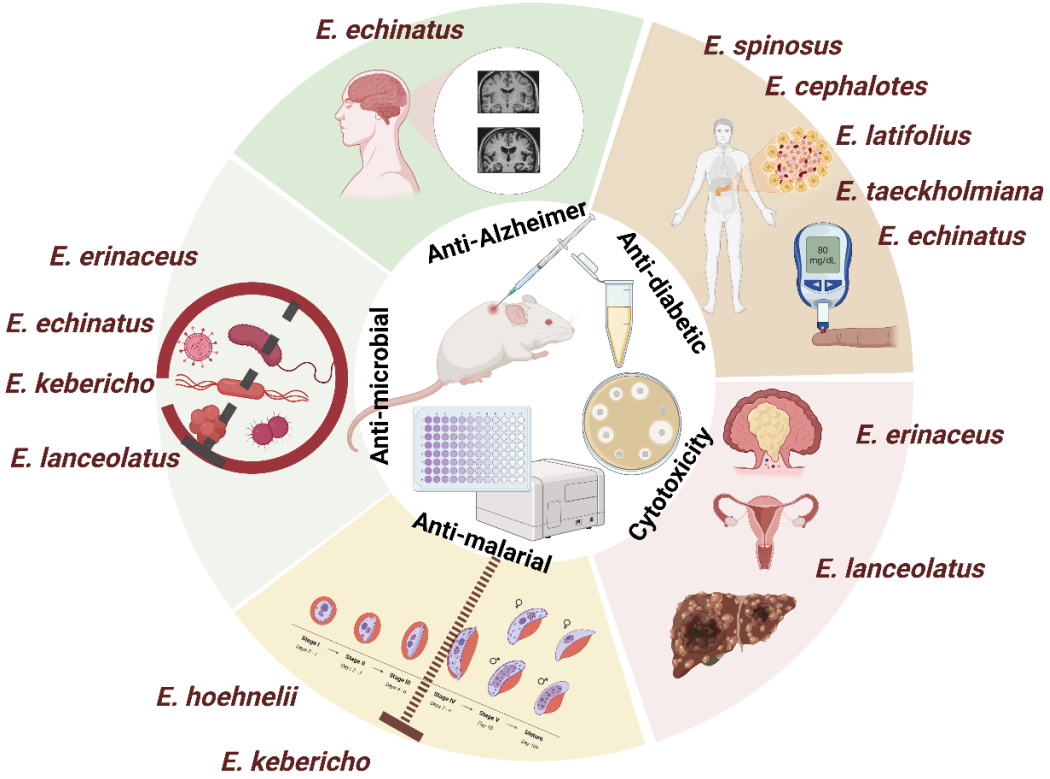


Fig. 8. The most important recent Pharmacological activities of the most abundant species of genus *Echinops* L.

9.1. Anti-Diabetic

Type 2 diabetes is a complex metabolic disorder that has multiple contributing factors. According to the World Health Organization (WHO), there are more than 422 million individuals affected by this condition, and it causes approximately 1.6 million deaths annually. The prevalence of type 2 diabetes is estimated to be eight out of every 1000 people, and the risk of developing it increases with age. In recent years, there has been a rise in the number of children and adolescents who are being diagnosed with this condition [57] .In developing countries, herbal traditional medicine is relied upon by roughly four billion people for the treatment of metabolic diseases like diabetes mellitus. This is due to a wide range of bioactive phytochemical compounds in plants, which are believed to have beneficial effects on health. Several natural compounds have antidiabetic activity and summarized in fig. 9. [58,59]

E. spinosus total extract and its flavonoid fraction showed a promising anti-diabetic activity in streptozotocin (STZ) induced diabetic rats. Either flavonoidal fraction or total extract were significantly increase the serum levels of insulin, marked reduction in blood glucose levels, increase in glycogen levels and insulin receptor (IR) gene expression rates compared with both streptozotocin and metformin groups ($P < 0.05$). The flavonoidal fraction was more potent than total extract. Importantly, the reduction in the diabetic complications of the liver and the kidney was mediated through decreasing the oxidative stress, suppressing the apoptotic cascade, modulating inflammatory mediators, and correcting diabetic dyslipidemia. [58]

K. Benrahou *et al.,* [20] evaluated the antidiabetic enzymatic activity of aqueous and ethanolic extract of roots of *E. Spinosus* using three *invitro* assays and *ex-vivo* oral starch tolerance study. The results were *α*-amylase, *α*-glucosidase and lipase inhibited effectively by the macerated ethanolic extract, with IC_{50} values of 371 ±0.62, 18.6 ±1.2, and 10.44 ±1.08 µg /mL, respectively. While 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. Moreover, both aqueous and ethanolic extracts significantly (p<0.05) lowered blood sugar to 0.96 g/L and 0.93 g/L, respectively after 90 minutes.

The terpenoidal compounds of *E. Spinosus* showed insulin like action and caused promotion in the intracellular glycogen deposition through the stimulation of glycogen synthesis and inhibition of glycogen phosphorylase. It also enhanced glycogen metabolism when hepatic glycogen levels were low. Importantly, rutin inhibited tissue gluconeogenesis, reduced the amount of carbohydrates absorbed from the small intestine, and suppressed the production of precursors for advanced glycation end products, sorbitol, and reactive oxygen species. Cinnamic acid and its derivatives were well-known antioxidants because of their role in scavenging free radicals, increasing the expression of glucose transporters (GLUT), controlling or inhibiting enzymes involved in glucose metabolism, and restoring beta cell function**.** [20]

Evaluation of antidiabetic potential of aqueous extract of *E. cephalotes (EC)* at doses (75, 150, and 300 mg/kg) administered orally to diabetic male Wistar albino rats, using glibenclamide (Glbn) as standard. The extract treated group was significantly but not dose-dependently changed metabolic biomarkers in comparison to standard and control groups. Doses 300 and 150 mg/kg were significantly (P < 0.01) more potent than Glbn treated groups as serum glucose levels were 81.83 ± 6.945, 114.7±8.429 and 130.1 ± 8.19 mg/dl ,respectively [60]

The alcoholic root extract of *E. taeckholmiana* exhibited an antidiabetic activity through suppression of *α*-amylase and *α*-glucosidase enzymes with IC_{50} (54.6 and 60.4 µg/mL, respectively) compared to acarbose IC_{50} (30.57 and 34.71µg/mL, respectively). [10]

Polysaccharide B is another important class of *Echinops* metabolites with antidiabetic activity which was isolated from *E. latifolius* Tausch and investigated for its antidiabetic activity. It enhanced insulin sensitivity, prevented hepatic metabolic disorders, increased glycogen synthesis and glucose consumption, while decreased free fatty acids and triglycerides levels in IR-HepG2 cells**.** [61]

The antidiabetic effect of the methanolic extract of different parts of *E. echinatus* was evaluated using *α*-glucosidase inhibition assay. All extracts showed maximum % enzyme inhibition for *α*-glucosidase. Interestingly, the root extract exhibited the highest percent of inhibition (75.3±1.5% at 1 mg/ml) with an IC_{50} value of (207.3±1.3 µg/mL), followed by stem (62.4±1.5% at 1 mg/ml) with an IC_{50} of (302.7±1.2 µg/mL) then leaves and flowers showed no inhibitory activity (45.2±1.2% , 28.5±1.2% at 1 mg/ml), the demonstrated enzyme inhibition. [62]

Similarly, ethyl acetate and methanolic extracts of leaves, stem, flowers, and seeds of *E. echinatus* demonstrated inhibitory activity against *α* -glucosidase and *α* -amylase. Both ethyl acetate and methanolic extracts of all parts had the greatest *α* -amylase inhibitory effect in a dose dependent activity compared to the standard acarbose with IC_{50} 516.9, 489.1, 592.8 and 619.3 µg/mL, respectively for ethyl acetate and 571.3, 473.4, 627.9 and 699.5 µg/mL, respectively for methanolic extract. The methanolic extract of the leaves and stem showed the greatest significant *α*-glucosidase inhibitory effect compared to acarbose with IC_{50} 371.4 and 368.6 µg /mL, respectively. [5]

S. R. Y. Chaudhry *et al.,* [63] 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) taken orally at doses 100, 300 and 500mg/kg. The extract significantly(P<0.001) lowered the fasting blood glucose levels in a dose-dependent pattern in the both diabetic models and significantly (P<0.001) enhanced the glucose tolerance in fructose-fed rats.

Similarly, another study examined the methanolic extract of *E. echinatus* root at doses (100 and 200mg/kg) demonstrated a significant(p<0.001) antidiabetic effect in alloxan induced diabetes rats and normoglycemic rats. The extract lowered the

blood glucose level in both normal and diabetic rats by stimulating insulin release from β cells of Langerhans islet. [64]

S. Fatima *et al.*, [65] highlighted the antidiabetic effect of hydro-alcoholic root extract of *E. echinatus* using alloxan-induced diabetic rats' model. The extract reduced blood glucose levels (164 mg/dL) after 21 days of treatment at a dose (200 mg/kg) compared to the untreated rats (277.6 mg/dL). Additionally, the extract being able to regenerate renal proximal and distal convoluted tubules, glomeruli, and pancreatic islet cells.

Overall, the crude methanolic extract and isolated compounds from several species of genus *Echinops* showed potential antidiabetic activity through several *invivo* and *invitro* studies. The terpenoidal and flavonoidal content are the main active constituents attributed to the activity through different mechanisms. [20,58]

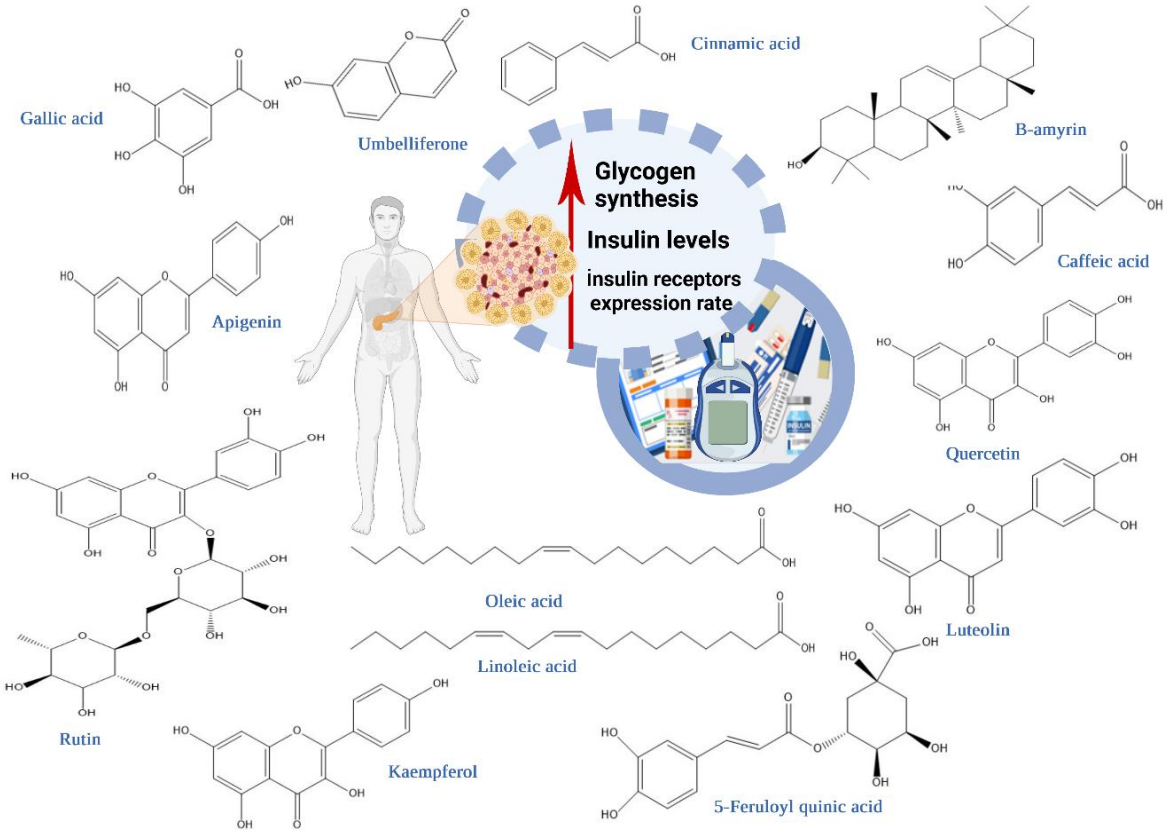


Fig. 9. Structures of some secondary metabolites that were reported to have anti-diabetic activity

9.2. Anti-Alzheimer's disease

Alzheimer's disease is the most common life-threatening age-related neurodegenerative disease and one of the most prevalent forms of dementia affecting the older population worldwide. According to estimates, Alzheimer's disease affects roughly 13% of those over 65 years and 45% of those over 85 years.[66,67] One of the mechanisms of anti-alzheimer's drugs is acetylcholinesterase (AChE) inhibitory which is illustrated in fig. 10.

In a study to investigate the anti-cholinesterases (acetyl-cholinesterase (AChE) and butyryl-cholinesterase (BChE)) activity of extracts of *E.ritro* by different methods of extraction include homogenizer-assisted extraction (HAE) and maceration (MAC). The galantamine equivalent value of AChE inhibitory effect of HAE extract was

2.41± 0.04 GALAE/g. The HAE and MAC extracts showed the strongest BChE inhibitory activity (0.80 ± 0.10 and 0.87 ± 0.11 mg GALAE/g, respectively).[68]

N. Jamila *et al.*, [5] examined the (AChE and BChE) inhibitory activity of different extracts of leaves, stems, flowers, and achenes of *E. echinatus* compared to galanthamine and physostigmine as standards. The methanol and ethyl acetate extracts were the strongest AChE and BChE inhibitors, ethyl acetate extract of stem and leaves was strongly inhibited AChE with IC_{50} 15.3 and 15.8 µg/mL, respectively compared to physostigmine and galanthamine with IC_{50} 0.05 and 2.1 µM/mL, respectively. Moreover, the ethyl acetate extract of the leaves and stem was the most potent inhibitor of BChE with IC_{50} 17.5 and 16.3 µg/mL, respectively, compared to physostigmine and galanthamine (IC_{50} 0.08 and 19.3 µM/mL, respectively).

The anti-Alzheimer's activity of genus *Echinops* needs further examination to proof the responsible active constituents and isolated compounds.

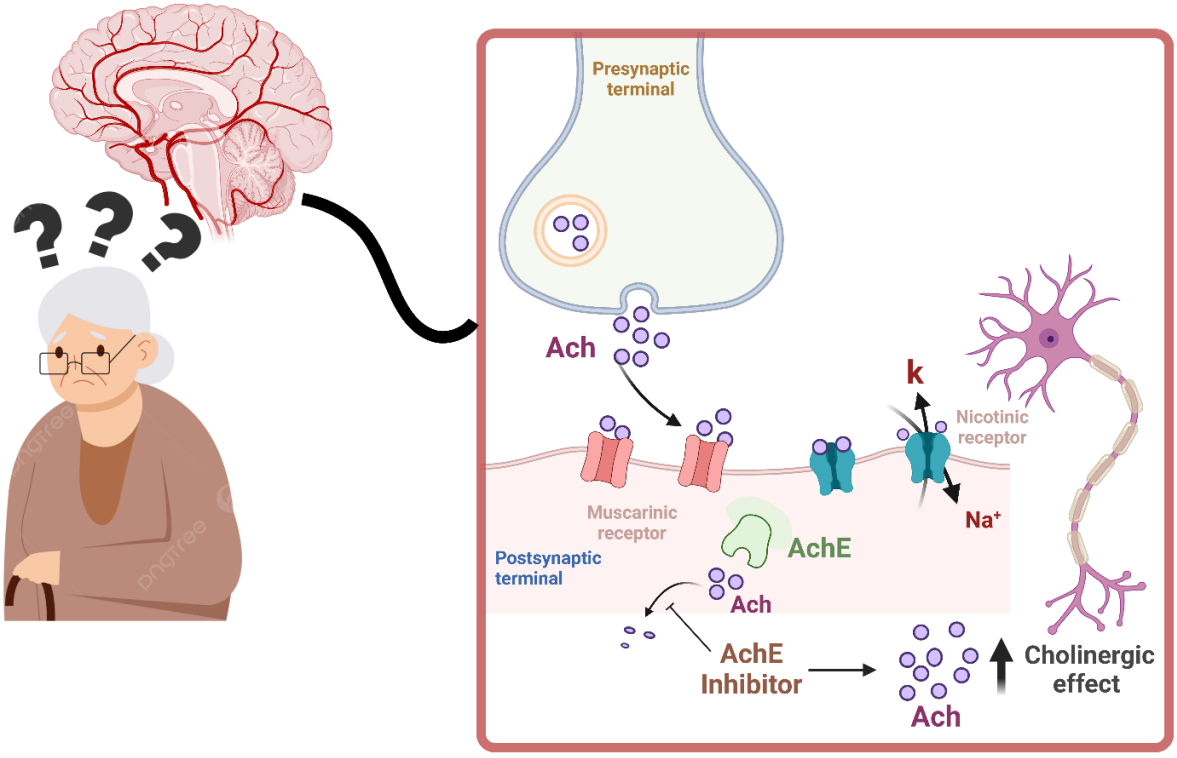


Fig. 10. Representative AchE inhibitory mechanism of alzheimer's disease

9.3. Anti-protozoal

9.3.1 Anti-malaria

Interestingly, the methanolic extract of rhizomes of *E. kebericho* Mesfin showed antiplasmodial activity against rodent malaria parasite, *P. berghei*, at oral doses 1000, 500 and 250 mg/kg/day. The extract had significant dose-dependent chemo-suppressions compared to the negative control with parasitemia-suppressing levels 49.53±1.90, 34.66±0.76, and 22.13±0.87 for dosages of 1000, 500, and 250 mg/kg, respectively. The extract treated mice at all doses had dose-dependently longer lives than the negative control and protect against the reduction in Packed Cell Volum compared to the control groups. The activity could mainly attributed to the presence of Sesquiterpenes as an antiplasmodial agent.[69]

A similar study evaluated the crude extract and its different fractions of roots of *E. Kebericho* against *Plasmodium berghei* infected mice at oral doses 200, 350 and 500 mg/kg body weight. The *n*-butanol and aqueous fractions showed significant ($P < 0.001$) and dose dependent parasitemia suppression at doses 350 and 500 mg/kg (range from 31 to 36% and 27 to 36%, respectively) compared to negative control. Additionally, the extract treated groups showed significant percentage of mice that survived on the 10th day ($P < 0.05$). [70]

H. Bitew *et al.*, [11] investigated antimalarial activity of the crude extract, four different fractions and two isolated thiophenes from the roots of *E. hoehnelii* against *Plasmodium berghei* infected mice at doses 50, 100, 200, and 400 mg/kg. The methanolic extract showed % parasitaemia suppression (4.6%, 27.8%, 68.5%, and 78.7%, respectively). The dichloromethane fraction demonstrated % suppression 24.9%, 33.5%, and 43.0% at doses 100, 200, and 400 mg/kg body weight, respectively. Moreover, the two acetylenicthiophenes 5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene **(18)** and 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene **(19)** showed % suppression 18.8%, 32.7% and 43.2%, 50.2%, respectively at 50 and 100 mg/kg, respectively**.**

Similarly, the antimalarial activity of the hydroethanolic extract *of E. kebericho* roots against a chloroquine sensitive strain of *Plasmodium berghei infected mice* was evaluated at oral doses 200, 350 and 500 mg/kg. The extract showed significant (P<0.001) % parasitemia suppression at doses 350 and 500 mg/kg compared to the negative control, the maximum % suppression was 57.29 ±1.76% at dose 500 mg/kg. The oral LD_{50} showed that the extract of *E.kebericho* is safe. [22]

The investigation of the effectiveness of many species of genus *Echinops* against malarial still requires further examination. The limited data available about the antimalarial activity of genus *Echinops* indicate that thiophenes compounds such as **(18)** and **(19)** are related to the activity but the mechanism of action still need to be proof.[11]

9.3.2. Anti-Trypanosoma

D. Abdeta *et al.*, [71] investigated the anti-trypanosomal effect of the hydro-methanolic extract of *E. kebericho* Mesfin roots against *Trypanosoma congolense*. The extract inhibited the motility of trypanosomes within 40 min at 4 and 2 mg/mL. The oral extract treated groups at doses 200 and 400 mg/kg showed significant (p < 0.05) reduction in parasitemia and improvement in Packed Cell Volume measurement in blood compared to control groups**.**

The anti-trypanosoma activity could be attributed to presence of flavonoids, alkaloids by DNA intercalation and inhibition of protein synthesis and Phenolics by inhibiting the trypanosome alternative oxidase. [71]

9.3.3. Insect Repellent

In Ethiopia, the smoke produced by burning the dry roots of *E. kebericho* acts directly as a natural insect repellent to protect against mosquitoes and other harmful arthropods. Accordingly, in a study using human volunteer to investigate the repellent activity of *E. kebericho* root essential oil against *A. arabienses* at concentrations 125, 250, 500, and 1000 ppm., the mean percentage of repellent activities is used as an indicator parameter. The mean percentage of repellent activities was in range 90.31 ± 4.34 and 93.16 ± 2.62 at 125 and 1000 ppm respectively. the LC_{50} and LC_{90} values were calculated to be 0.28 and 0.71 ppm, respectively. Results of the chi-square analysis revealed a statistically significant difference at the 5% level (P <0.05; χ^2 = 71.58). [72]

9.4 . Anti-microbial

Interestingly, the antimicrobial activity of the methanolic extract of flowering aerial parts of *E. erinaceus* Kit Tan and the subsequent partition fractions was evaluated against six micro-organisms (*Bacillus subtilus*, *Methicillin-resistant Staphylococcus aureus (MRSA)*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida albicans* and *Asperigllus niger*). The methanolic extract exhibited the greatest antibacterial activity against all tested bacteria except for *MRSA*, compared to streptomycin. It showed significant antibacterial activity against *B. subtilus with diameter of inhibition zone* (27.5±0.7 mm), and it also showed a strong antifungal activity against *C. albicans* (26±1.41 mm). The *n*-hexane and ethyl acetate extracts were the second most potent fractions as they exhibited potent antibacterial and antifungal properties. However, none of the examined extracts showed any antibacterial activity against *MRSA*. The chloroform extract was active effectively against *B. subtilis* (20.5±1.41 mm), *P. aeruginosa* (17.5±1.41 mm), and *E. coli* (18 ±1.41 mm), but it had no activity against the fungal strains**.** [4]

Similarly, M. Rafay *et al.*, [62] investigated the anti-bacterial activity of the methanolic extract of different parts of *E. echinatus* against different strains of bacteria include *Gram*-positive bacteria (*S. aureus*) and *Gram*-negative bacteria (*P. aeruginosa, K.*

pneumoniae and E. coli). The greatest inhibition zone exhibited by methanolic extract of leaves was against *K. pneumoniae* (10 mm), whereas methanolic extract of flowers had strong sensitivity to *Staphylococcus aureus* with an inhibition zone (19 mm). Moreover, the greatest zone of inhibition of methanolic root extract was against *S. aureus* (18mm).

The antibacterial effect of the ethanolic extract of the tuber of *E. kebericho* Mesfin and its fractions as well as the essential oils extracted from the herb was examined. The essential oils were active against *methicillin-resistant Staphylococcus aureus* (*MRSA)* with MIC ranging from 78.125 to 625µg/ml. The ethyl acetate fraction showed the highest activity against *MRSA* with MIC 39.075µg/ml followed by *Enterococcus faecalis* and *Klebsiella pneumoniae* with MIC 78.125µg/ml and 1,250µg/ml, respectively. *E. fecalis* had the maximum sensitivity for the hexane fraction with MIC 156.2 µg/ml, whereas the chloroform fraction had the maximum activity against *S. aureus* with MIC of 312.5 µg/ml. The *n*-butanol fraction was pharmacologically ineffective with MIC of 2,500 µg/ml for all species and without significant activity against *E. coli*. [21]

The antimicrobial activity of the methanolic extract of the aerial parts of *E. lanceolatus* and its fractions was examined against eight bacterial strains include *Gram*-positive (*S. aureus and E. faecalis*) and *Gram*-negative bacteria (*K. pneumoniae, E. coli, A. baumannii, S. enterica, E. cloacae* and *P. aeruginosa*). The methanolic extract and its fractions showed weak to moderate antibacterial activity. The ethyl acetate fraction showed the highest activity followed by dichloromethane fraction then other *n*-hexane, butanol fractions and methanol extract. MIC values were ranged from 256 to 1024 µg/mL, where the methanolic extract was the least active than other fractions. However, all extracts were effective against *S. enterica, S. aureus and E. cloacae*. [38]

Different species of genus *Echinops* shown antimicrobial activity *against different Gram + and Gram* – bacteria and different types of fungus. 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 drevatives), lignans, phenolic acids which act by changing cell membrane permeability, thiophenes such as (α-terthiophene), and sesquiterpenes. consequently, this genus become excellent natural source of antimicrobial metabolites [3,17,38]

9.5. Cytotoxicity

Several studies showed anti-cancer activity of different species of genus *Echinops* against different cancer cell lines, the most prevalent activity is against colorectal carcinoma which is One of the most dangerous and prevalent illnesses, particularly in developed nations. It is anticipated that colorectal cancer has a global impact, affecting around 1.9 million individuals and resulting in the mortality of approximately 900,000 individuals. Colorectal cancer accounts for 3.47% of cancer cases in males and 3% of cancer cases in females[73]. Many species of genus *Echinops* showed significant activity against it and summarized in fig. 11.

S. H. Sweilam *et al.*, [4] evaluated the potential cytotoxic activity of the methanolic extract of *E. erinaceus* and its fractions by viability assay using HCT-116 cells (human colon cancer cell line), and CACO2 cells (human colorectal intestinal carcinoma). The chloroform extract showed the greatest activity among other fractions. It had a moderate cytotoxic effect against HCT-116 and CACO2 with IC_{50} 67.30±4.87 and 81.95±4.63 µg/mL, respectively. Compounds (methyl oleate / ethyl oleate) exhibited substantial activity against the examined cells with IC_{50} 24.95±1.23 and 19.74±1.94 µg/mL, respectively.

Similarly, the antiproliferative properties of the methanolic extract and its fractions of aerial parts of *E. lanceolatus* was investigated towards 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 and other fractions showed antiproliferative activity at a fixed dose of 100 µg/mL. The most effective fraction was ethyl acetate, which significantly inhibited HepG2 and A549 cells by 72% and 71%, respectively. At concentrations ranging from 0.82 to 200 µg/mL of ethyl acetate fraction, the results showed that cancer cell proliferation was inhibited in a dose-dependent manner. The strong cytotoxicity was against A549 (IC_{50} 8.27 µg/mL) and the moderate cytotoxicity was against HeLa (IC_{50} 28.27 µg/mL). [38]

The cytotoxic activity of metabolites of *E. macrochaetus* was evaluated towards MCF-7 (human breast cancer cell line), HepG2, and HCT-116 cancer cell lines. cyclostenol and macrochaetosides A showed a potent cytotoxic activity with IC_{50}s 2.1, 2.9, and 3.6 µM and 1.9, 3.3, and 2.3 µM, respectively compared to doxorubicin (IC_{50} 0.18, 0.60, and 0.20 µM, respectively). [52]

Substantially, several species of Genus *Echinops* have potential antiproliferative activity against several cancer cell lines viz (HepG2, HeLa, HT-29, etc.) which indicate that genus *Echinops* is a good natural source for anti-tumor secondary metabolites such as flavonoids (Apigenin), terpenes (Macrochaetosides (A and B), Cyclostenol, Erinaceosin) and thiophenes (α- terthiophene). Further investigation is necessary to assess the safety and efficacy of secondary metabolites that are responsible for the observed *in-vitro* effects of extracts/fractions using *in-vivo* models.[3,38,52]

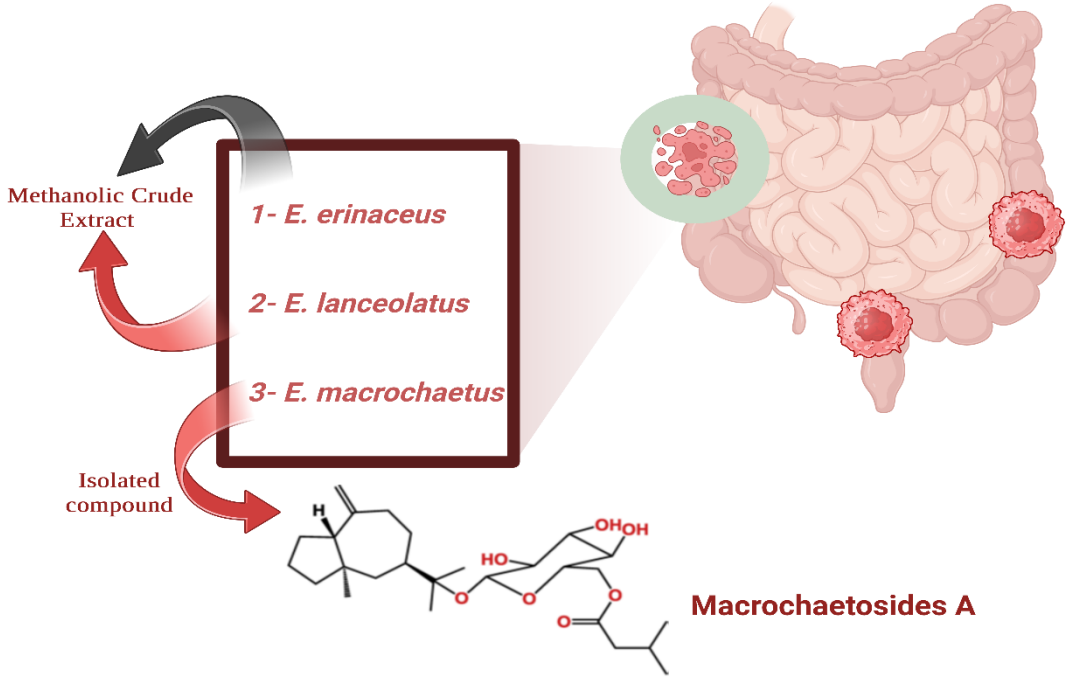


Fig. 11. Some of *Echinops* species demonestrate colon cancer antiproliferative activity

10. Conclusion

The *Echinops* genus is widely recognized for its ethnopharmacological use in the treatment of pain and respiratory symptoms. The traditional arguments were substantiated through several biological assessments. The results obtained from *in-vitro* investigations suggest that species belonging to the genus has the ability to potentially combat various types of cancer cells, microbial strains, and insects. Additionally, they demonstrated noteworthy *in- vivo* efficacy against malaria, insect repellent, and anti-diabetic properties.

Several of the extracts and isolated chemicals had positive findings. This includes the anticancer action of compounds 6,20,52,116 and 117, anti-microbial activity of compounds 20, 21,76, and 107 and the larvicidal effect of compound 18,19.

Further investigation is necessary to assess the safety and efficacy of secondary metabolites that are responsible for the observed *in-vitro* effects of extracts/fractions using *in-vivo* models. Thiophenes and terpenoids are the predominant bioactive secondary metabolites found in the genus. These

compounds have been attributed in the observed cytotoxic effects.

The scope of research on the therapeutic potential of isolated compounds in terms of their anti-malarial, anti-Alzheimer, and anti-microbial properties appears to be constrained and need further examination. It is anticipated that this review will offer a concise and current compilation of data to the scientific researchers interested in research on the genus.

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13. Declaration of competing interest

All authors declare that there is no competing interest in the manuscript.

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