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REVIEW
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The Genus *Echinops*: Phytochemistry and Biological Activities: A Review

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The genus *Echinops* belongs to the family of Asteraceae and comprises about 130 species. Many species belonging to the genus *Echinops* are traditionally used as medicinals mainly in Africa and Asia. The genus is reported to contain diverse secondary metabolites. The aim of this review is to critically evaluate the available research reports on the genus and systematically organize the findings. Information for this study was obtained using various search engines including PubMed and Google Scholar. This review revealed that the genus is used traditionally to treat pain, inflammation, respiratory diseases, diseases caused by different microorganisms, as an aphrodisiac, to fasten expulsion of placenta, and for removal of renal stones. More than 151 secondary metabolites have been reported from the genus in which thiophenic compounds held the biggest share. Various extracts, essential oils, and isolated compounds from members of this genus are shown to exhibit different biological effects mainly anti-microbial, anti-proliferative, and anti-inflammatory. However, there are a number of species in this genus that are claimed to have traditional medicinal uses but their biological effect not yet been evaluated.

Keywords: *Echinops*, thiophene, phytochemistry, Asteraceae, pharmacological activity, traditional use

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INTRODUCTION

Echinops L., belongs to the family of Asteraceae, a family which is distributed all over the world except in Antarctica. Asteraceae is a monophyletic taxon distinguished by florets arranged on a receptacle in centripetal heads and bounded by bracts. It comprises 1,600–1,700 genera and 24,000–30,000 species (Funk et al., 2005). The genus *Echinops* belongs to the tribe Cardueae and is recognized by the presence of uniflowered capitula aggregated into second-order spherical or oval heads. This feature makes it unique within the tribe (Garnatje et al., 2005; Sánchez-Jiménez et al., 2010). It contains 120–130 species distributed across north and tropical Africa, the Mediterranean Basin, and central Asia. Members of this genus are mostly perennial with few annuals (Hedberg et al., 2004; Sánchez-Jiménez et al., 2010).

Many members of this genus are traditionally used to treat different diseases. Some are scientifically investigated for various biological activities and phytoconstituents. Previously, reviews that focus on single species, *Echinops spinosus* L. and *E. echinatus* Roxb. have been conducted (Bouzabata et al., 2018; Maurya et al., 2015). To the authors' knowledge, there is no study that reviewed the traditional use, phytochemistry, and biological activities of the whole genus. This review is aimed to critically evaluate available research reports on the genus and systematically organize and present the findings. It is attempted to include all articles published from 1990–2018 while some articles published before 1990 were included considering their significance. This review excluded unpublished findings and

publications which were not available online and articles written in languages other than English. Chemical structures of only isolated and characterized compounds were provided while structures of compounds identified from essential oils and other chemical analysis were not. The main sources of the structures of isolated compounds were the research articles and these were confirmed using PubChem. Structures that were not available in the articles were obtained from theses, books, PubChem, and other reliable sources. Different search engines including PubMed and Google Scholar were employed to search literature using searching words such as *Echinops*, plant, phytochemical, phytochemistry, pharmacological activity, biological effect, and traditional use.

TRADITIONAL USES

Ethnomedicinal claims on the genus *Echinops* to treat a number of ailments are depicted in **Table 1**. The common traditional uses can fall into three general groups. The frequently described application is to treat symptoms like inflammation, pain, and fever (Regassa, 2013; Rathore et al., 2015). The other common traditional use was to treat ailments related to respiratory tract including cough and sore throat (Ghasemi Pirbalouti et al., 2013; Sajjad et al., 2017). Members of the genus have been used as an aphrodisiac (Hamayun et al., 2006), facilitation of expulsion of retained placenta and delivery (Okello and Ssegawa, 2007; Qureshi and Bhatti, 2008), as an abortifacient (Abouri et al., 2012), treatment of uterus tumor (Abderrahim et al., 2013), and leucorrhoea (Wagh and Jain, 2018). Three species (*E. bannaticus* Rochel ex Schrad*, E. cornigerus* D.C., and *E. polyceras* Boiss.) reported to have been employed in the managment of kidney stones (Mustafa et al., 2012; Nawash et al., 2013; Kumar et al., 2018).

In addition to the traditional medicnal applications described in **Table 1**, the plants have nutritional value. In Iran, the bulb of *E. viscidulus* Mozaff is consumed as a vegetable (Ghasemi Pirbalouti et al., 2013). The roots of *E. giganteus* A. Rich. and *E. spinosus* are used as a spice in Morocco and Cameroon, respectively (Pavela et al., 2016; Tbatou et al., 2016). The use of *E. giganteus* might be attributed to the presence of nutrients including iron, phenols, carotenoids, and vitamins E and C in the plant (Abdou Bouba et al., 2012).

PHYTOCHEMICALS

As presented in **Table 2** and **Figure 1**, 151 compounds have been isolated and characterized using different spectroscopic/spectrometric techniques. Members of the genus *Echinops* contain primarily thiophenes and terpenes. Flavonoids and other phenolic compounds, alkaloids, lipids, and phenylpropanoids were also reported. The root of the plant is the main source of the thiophenes while most of the terpenes and flavonoids were isolated from the aerial part/the whole plant. The genus is also known for essential oil content and all morphological parts of the plants are reported to contain some of the essential oils. Around 53 of the isolated and characterized compounds are reported to have different biological activities. The structural formulae of isolated and characterized compounds are given in **Figure 1**.

Thiophenes

Thiophenes, the main bioactive constituents of the genus *Echinops*, are biosynthetically derived from fatty acids and reduced sulphur (Arroo et al., 1997). Majority of the thiophenic compounds comprise an acetylenic functional group and most of the thiophenes comprised two thiophene rings in their structure. The most abundant thiophenes which were reported from nine species were 5-(but-3-en-1-ynyl)-2,2'-bithiophene (**1**) and α-terthiophene (**2**). 5-(4-hydroxybut-1-ynyl)- 2-(pent-1,3-diynyl)-thiophene (**5**), 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (**14**), and 5-(4-hydroxy-1-butynyl)-2,2'-bithiophene (**31**) were isolated from five species. Thiophenes were detected in essential oils obtained from the different plants of this genus. 5-(3-buten-1-ynyl)-2,2'-bithienyl was detected in essential oils obtained from the roots of *E. grijsii* Hance, *E. bannaticus*, and *E. sphaerocephalus* L.

The biological activities of thiophenes were evaluated mainly *in vitro* and they have an insecticidal, anti-proliferative, and anti-fungal potential effects.

Terpenoids

Sesqui- and triterpenoids were reported mainly from the whole plant and aerial parts of the genus *Echinops*. Most of the sesquiterpenoids contain lactones. Sesquiterpene lactones are also the most prevalent secondary metabolites in the family of Asteraceae (Chadwick et al., 2013). Most triterpenoids exist in various forms including lactones, esters, and sterols along with their glycosides. The common sesquiterpenoid reported was costunolide (**61**), which was isolated from three species whereas lupeol (8**6**) and lupeol acetate (**94**) were the common triterpenoids. Many sesquiterpenoids were also detected from the essential oils of the genus.

Flavonoids and Other Phenolic Compounds

Flavonoids from the genus *Echinops* were mainly flavones and mostly isolated from the whole plant and aerial parts of the members. Apigenin (**105**) is the most common flavonoidal aglycone and it was isolated from the flower and whole plant of *E. niveus* Wall., *E. echinatus, E. integrifolius* Kar. & Kir., and *E. albicaulis* Kar. & Kir. (**Table 2**). In addition to flavonoids, phenolic compounds including coumarins, phenylpropanoids, and lignans were reported (Tene et al., 2004; Dong et al., 2008a; Senejoux et al., 2013).

Alkaloids

The first alkaloids isolated from the genus *Echinops* were echinopsine (**139**), echinozolinone (**140**), and echinopsidine (**141**) from the aerial parts of *E. echinatus* (Chaudhuri, 1987). Later on, another alkaloid, 7-hydroxyechinozolinone (**142**), was isolated from the flowers of the same plant (Chaudhuri, 1992). Additional four alkaloids of which two were in glycosidic form were reported (**Table 2**). The alkaloids were mainly isolated from the aerial parts of the plants. The predominant alkaloid, which was isolated from four different species, was 1-methyl-4-quinolone (139).

TABLE 1 | Traditional uses of members of the genus *Echinops*.

Species	Part used	Indication	Country	Ref.
E. amplexicaulis Oliv.	R	HIV/AIDS	Uganda	Lamorde et al., 2010
	R	Ulcerative lymphagitis (LS)	Ethiopia	Fenetahun and Eshetu, 2017
		Stomachache	Ethiopia	Regassa et al., 2017
	R	Trypanosomiasis, liver disease, pasteurellosis	Ethiopia	Kitata et al., 2017
	R	Hydrocele	Uganda	Kamatenesi et al., 2011
	R	Fasten expulsion of placenta, hernia	Uganda	Okello and Ssegawa, 2007
	R	Ulcerative lymphagitis (LS)	Ethiopia	Tekle, 2014
E. bannaticus Rochel ex Schrad	R	Kidney stones	Kosovo	Mustafa et al., 2012
E. bovei (Boiss.) Maire.	AP	Eye complaints, trachoma, sores, inflammation, digestive diseases	Central Sahara	Hammiche and Maiza, 2006
E. cornigerus D.C.	R	Urinary problems mainly caused by kidney stones	India	Kumar et al., 2018
	WP	Insanity	India	Tiwari et al., 2010
	R	Removal of kidney stones	Pakistan	Jabeen et al., 2015
	R	Urinary complaints, fever	India	Dangwal et al., 2011
	WP	Cough, emergence of teeth in infants, fever, urinary trouble, tonic, sepsis, food poisoning	India	Sharma et al., 2012
	R	Urinary disorder, fever	India	Kumar and Pandey, 2015
	VP	Diuretic, aphrodisiac, fever, pain, chronic fever	Pakistan	Hamayun et al., 2006
	R	Fever, emergence of teeth in infants	India	Rathore et al., 2015
E. echinatus Roxb.	R	To treat hernia	India	Shende et al., 2018
	L	Earache	India	Maru et al., 2018
	R	Leucorrhoea	India	Wagh and Jain, 2018
	R, L	Joint pain	Pakistan	Malik et al., 2018
		Aphrodisiac, to facilitate the delivery process, abortifacient, leucorrhea, diabetes, eczema, heatstroke, wounds of cattle for killing maggots, liver disorders, cough, malarial fever, renal colic, lice, polyuria, appetite stimulant		Maurya et al., 2015
E. giganteus A. Rich	R	Anti-hemorrhoidal	Ethiopia	Desta, 1995
	R	Flatulence and bloody stool	Cameroon	Tacham et al., 2015
		Stomache, asthma attacks, as carminative	Cameroon	Menut et al., 1997
E. hispidus Fresen.	R and S	Sunstroke	Ethiopia	Meragiaw et al., 2016
E. hoehnelii Schweinf.	R	Internal parasite, amoebae, common cold	Ethiopia	Tekle, 2014
	R	Malaria, snakebite	Ethiopia	Giday et al., 2010
E. kebericho Mesfin	R	Black leg, respiratory manifestations, liver disease (LS)	Ethiopia	Yigezu et al., 2014
	Bl	Cough, headache	Ethiopia	Mesfin et al., 2014
	R	Scabies	Ethiopia	Amsalu et al., 2018
	R	Toothache, stomachache, common cold, sunstroke, tonsillitis, acute sickness, snake bite	Ethiopia	Regassa, 2013
	S	Fever, headache	Ethiopia	Gari et al., 2015
	R	Malaria, common cold	Ethiopia	Mekuanent et al., 2015
	R	Dislocated bone (LS)	Ethiopia	Teklay et al., 2013
	R	Toothache, vomiting, headache	Ethiopia	Abera, 2014
	R	Trypanosmiasis	Ethiopia	Shilema et al., 2013
	R	Gonorrhea	Ethiopia	Bizuayehu and Garedew, 2018
E. longifolius A. Rich.	RB	Headache, rheumatism, dry cough	Ethiopia	Suleman and Alemu, 2012
	R	Scorpion sting	Sudan	Issa et al., 2018
E. macrochaetus Fresen.	R	Toothache	Ethiopia	Belayneh and Bussa, 2014
	R	Headache	Ethiopia	Moravec et al., 2014
	Sd	Abdominal colic	Ethiopia	Gabriel and Guji, 2014
E. niveus Wall.	R	• Diuretic, nerve tonic, cough, indigestion, ophthalmia. • Applied to wounds in cattle to destroy maggots	India	Sharma et al., 2004
E. polyceras Boiss.	R	Kidney stones	Jordan	Nawash et al., 2013
E. ritrodes L.	S	Chronic cough	Urmia	Asadbeigi et al., 2014
	WP	Skin diseases, prevention of cough	Iran	Farouji and Khodayari, 2016
E. sphaerocephalus L.	R, S, L	Typhoid	Kenya	Nyang'au et al., 2017
E. spinosissimus Turra.	WP	Splenic diseases, sore throat	Saudi Arabia	El-Ghazali et al., 2010
	WP	Nerve tonic, diuretic, cough suppressant	UAE	Sajjad et al., 2017
	WP	Diuretic, nerve tonic, cough suppressant	Egypt	Mahmoud and Gairola, 2013
E. spinosissimus subsp. fontqueri (Pau) Greuter	R	Rheumatism, colds, uterus pains, uterus tumor	Morocco	Abderrahim et al., 2013
E. spinosissimus subsp. macroplepis (Boiss.) Greuter	S,R, L	Renal disorders	Lebanon	Baydoun et al., 2015
E. spinosus L.	R	As hypoglycaemic, decoction is drunk.	Morocco	Merzouki et al., 2000

(Continued)

TABLE 1 | Continued

Species	Part used	Indication	Country	Ref.
	R	Appetite stimulant, cold, diabetes, renal stones	Morocco	El Abbouyi et al., 2014
	L, S, R	Hepatoprotective, abortifacient	Morocco	Akdime et al., 2015
	R	Diabetes	Morocco	Katiri et al., 2017
	FAP	Colds, kidney stones, diuretic, hypoglycemic	Morocco	Abouri et al., 2012
	Br, R	Abortifacient, labor pain	Morocco	Abouri et al., 2012
	F	Neuralgia, tiredness	Morocco	Abouri et al., 2012
E. spinosus L. subsp Bovei (Boiss). Maire	R-Fr	Labor pains, abortifacient, neuralgia	Algeria	Chermat and Gharzouli, 2015
E. viscidulus Mozaff.	Bl	Cough, cold, sore throat	Iran	Ghasemi Pirbalouti et al., 2013
E. viscosus DC.	C	Boil	Turkey	Bulut et al., 2017

AP, Aerial part; B, Bark; Bl, Bulb; Br, Branch; C, Capitulum; F, Flower; FAP, Flowered aerial part; Fr, Fruit, L, Leaf; LS, Livestock; R, Root; RB, Root bark; S, Stem; Sd, Seed; VP, Vegetative part; WP, Whole plant.

Essential Oils and Lipids

The genus *Echinops* is rich in bioactive essential oil constituents, which were mainly found in the roots. Various reports indicated the presence of terpenoids and thiophenes.

The root of *E. grijisii* was found to contain *cis*-β-farnesene and 5-(3-buten-1-ynyl)-bithiophene as main components (Guo et al., 1994). Essential oils from root, stem, leaf, and flowers of *E. ellenbeckii* comprised mainly β-maaliene, cyperene, caryophyllene oxide, and β-selinene from the respective plant parts (Hymete et al., 2004). The fresh inflorescences of *E. graecus* and *E. ritro* yielded methyl chavicol and (*E*)-2-hexenal, 1,8-cineole, and *p*-cymene as major constituents, respectively (Papadopoulou et al., 2006).

Essential oils from the root of *E. bannaticus* and *E. sphaerocephalus* were reported to contain 5-(3-buten-1-ynyl)-2,2'-bithienyl and α-terthienyl as major constituents, and also triquinane sesquiterpenoids (Radulović and Denić, 2013). The most abundant compounds from *E. giganteus* have been reported to be tricyclic sesquiterpenoids such as silphiperfol-6-ene and presilphiperfolan-8-ol followed by presilphiperfol-7-ene, cameroonan-7-α-ol, and (*E*)-caryophyllene (Pavela et al., 2016).

Ceramides, sulf-polyacetylene ester, and simple hydrocarbons were the nonpolar constituents from the genus (**Figure 1**). The ethyl acetate extract of *E. integrifolius* contained lupeolacetate, 1,3-butadiene-1-carboxylic acid, lupeol, (1*R*,3*R*,4*R*,5*R*)-(–)-quinic acid, palmitic acid, and D-*threo*-*O*-ethylthreonine as the main constituents (Karimov and Aisa, 2012). In a related study, GS-MS analysis of petroleum ether extract of the aerial part of *E. integrifolius* indicated the presence of methyl esters of fatty acids as well as saturated hydrocarbons such as octacosane, hentriacontane, hexacosane, tetratetraacontane, eicosane, and nonadecane. Trace amount of 2-octanone and 4,8,12,16-tetramethyl heptadecan-4-olide were also detected in *E. integrifolius* (Karimov and Aisa, 2013).

BIOLOGICAL ACTIVITIES

Anti-Microbial Activity

The genus *Echinops* is traditionally used to treat different infectious diseases including trachoma, sepsis, typhoid, gonorrhea, and ulcerative lymphangitis. It is also used to treat different ailments that might be caused by bacterial/fungal infections including fever, respiratory diseases, toothache, leucorrhoea, and earache. Thus, they have been investigated for their anti-microbial activities. Anti-bacterial and anti-fungal activities of extracts from the genus with their respective minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBI), minimum fungicidal concentration (MFC), and zone of inhibitions are presented in **Table 3**. These studies showed that both Gram-positive and Gram-negative bacteria were sensitive to the extracts/isolated compounds obtained from the genus.

Out of the tested strains, *M. tuberculosis* (H37Rv) showed higher sensitivity to the ether root extract of *E. giganteus* and methanolic extract of *E. amplexicaulis* Oliv. with MIC of 12 μg/mL and 32 μg/mL, respectively (Tekwu et al., 2012; Kevin et al., 2018). The methanolic root extract of *E. amplexicaulis* also showed a promising effect against a multidrug-resistant strain of *M. tuberculosis* with a MIC of 50 μg/mL (Kevin et al., 2018). The ethanolic root extract and essential oils obtained from *E. kebericho* Mesfin showed relatively strong effect against *Staphylococcus aureus* (Ameya et al., 2016) and *Klebsiella pneumoniae* (Belay et al., 2011). These results might justify the traditional application of *E. kebericho* in treating respiratory disease, toothache, and fever. The essential oil from *E. ritro* L. exhibited anti-bacterial effect and antibiofilm and disruption of the bacterial membrane were suggested as mechanisms of actions (Jiang et al., 2017).

Different extracts from members of the genus having anti-bacterial effect were analyzed for their chemical constituents. The unsaponifiable matter from the hexane extract of *E. spinosissimus* contained mainly taraxasterol, lupeol, pseudotaraxasterol, α-amyrin, β-amyrin, pseudotaraxasteryl acetate, lup-22(29)-en-3-yl acetate, β–sitosterol, and stigmasterol. The hexane extract showed anti-bacterial activity with MIC values of less than 125 μg/mL against different bacterial strains (*Bacillus amyloliquefaciens*, *Micrococcus luteus*, *Bacillus subtilis*, and *Salmonella enteric*) (Bouattour et al., 2016). Thiophens (**31**, **46**, **54**, and **59**) isolated from the root of *E. ritro* possessed anti-bacterial effect against *S. aureus* with a MIC value of 8 μg/mL. This was similar to the effect observed for the positive control, levofloxacin. The anti-bacterial effects of thiophenes **31**, **46**, **55**, **57**, and **59** against *Escherichia*

TABLE 2 | Secondary metabolites isolated from members of the genus *Echinops*.

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Thiophenes					
1.	5-(but-3-en-1-ynyl)-2,2'-bithiophene	*E. macrochaetus*	R		Abegaz et al., 1991
		E. pappii Chiov.	R		Abegaz et al., 1991; Abegaz, 1991
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP		
		E. latifolius	R		Wang et al., 2006
		E. grijsii	R		Zhang and Ma, 2010; Chang et al., 2015
		E. grijsii	R	Cytotoxic	Jin et al., 2008
		E. grijsii	R	Insecticidal	Zhao et al., 2017
		E. nanus Bunge	R		Nakano et al., 2012
		E. albicaulis	AP		Kiyekbayeva et al., 2017
		E. albicaulis	WP	Termicidal	Fokialakis et al., 2006b
		E. spinosissimus subsp. spinosissimus	WP	Termicidal	Fokialakis et al., 2006b
2.	α-terthiophene	*E. ellenbeckii*	R		Abegaz et al., 1991
		E. pappii	R		Abegaz et al., 1991
		E. macrochaetus	R		
		E. grijsii	R	Cytotoxic	Jin et al., 2008
		E. grijsii	R		Liu et al., 2002; Zhang and Ma, 2010; Chang et al., 2015
		E. grijsii	R	Insecticidal	Zhao et al., 2017
		E. latifolius	R		Wang et al., 2006
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
		E. nanus	R		Nakano et al., 2012
		E. albicaulis	R		Kiyekbayeva et al., 2017
		E. albicaulis	WP	Termicidal	Fokialakis et al., 2006b
		E. albicaulis	WP	Termicidal	Fokialakis et al., 2006b
		E. albicaulis	WP	Termicidal	Fokialakis et al., 2006b
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
3.	5-(penta-1,3-diynyl)-2-(3-chloro-4-hydoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Abegaz et al., 1991
		E. giganteus	R		
		E. hispidus Fresen.	R		
		E. longisetus	R		
		E. macrochaetus	R		
4.	Cis or trans-2-(pent-3-en-1-ynyl)-5-(4-hydroxybut-1-ynyl)-thiophenes	*E. pappii*	R		Abegaz, 1991
5.	5-(4-hydroxybut-1-ynyl)-2-(pent-1,3-diynyl)-thiophene	*E. pappii*	R		Abegaz, 1991
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
		E. grijsii	R		Chang et al., 2015
		E. grijsii	R	Cytotoxic	Zhang et al., 2009;
		E. grijsii	R	NQO1-inducing	Zhang and Ma, 2010
		E. giganteus	Rz	Cytotoxic	Kuete et al., 2013
		E. giganteus	Rz	Cytotoxic	Sandjo et al., 2016
6.	5-(penta-1,3-diynyl)-2-(but-3-en-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
7.	5-(penta-1,3-diynyl)-2-(4-acetoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
8.	5-(penta-1,3-diynyl)-2-(3-hydroxy-4-acetoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
		E. hoehnelii	R		Bitew et al., 2017
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
9.	5-(penta-1,3-diynyl)-2-(3,4-diacetoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005a
		E. grijsii	R		Jin et al., 2008
		E. grijsii	R	NQO1-inducing	Zhang and Ma, 2010
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
10.	5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
		E. albicaulis	WP	Termicidal	Fokialakis et al., 2006b

(Continued)

TABLE 2 | Continued

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Thiophenes					
		E. hoehnelii	R	Anti-malarial	Bitew et al., 2017
11.	5-(penta-1,3-diynyl)-2-(3,4-epoxy-but-1-ynyl)-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
12.	5-[-(5-acetoxymethyl-2-trienyl)-2-(but-3-ene-1-ynyl)]-thiophene	*E. ellenbeckii*	R		Hymete et al., 2005b
13.	5-(5,6-dihydroxy-hexa-1,3-diynyl)-2-(prop-1-ynyl)-thiophene (echinoynethiophene A)	*E. grijsii*	R		Liu et al., 2002; Dong et al., 2008a
		E. grijsii	R	Cytotoxic	Zhang et al., 2009
14.	5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene	*E. grijsii*	R		Liu et al., 2002; Dong et al., 2008a; Chang et al., 2015
		E. ritro	WP		Li et al., 2019
		E. grijsii	R	NQO1-inducing	Shi et al., 2010; Zhang and Ma, 2010
		E. grijsii	R	Cytotoxic	Zhang et al., 2009
		E. giganteus	Rz	Cytotoxic	Sandjo et al., 2016
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
		E. hoehnelii	R	Anti-malarial	Bitew et al., 2017
15.	5-(3,4-dihydroxybut-1-ynyl)-2,2′-bithiophene	*E. grijsii*	R		Liu et al., 2002; Dong et al., 2008a; Zhang et al., 2009; Zhang and Ma, 2010; Chang et al., 2015
		E. ritro	WP		Li et al., 2019
		E. latifolius	R	Cytotoxic	Wang et al., 2007
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
16.	2,2'-bithiophene-5-carboxylic acid	*E. grijsii*	R		Liu et al., 2002; Chang et al., 2015
		E. ritro	WP		Li et al., 2019
17.	5-(3-buten-1-ynyl)-2,2'-bithiophene	*E. grijsii*	R		Liu et al., 2002
18.	5-(4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene	*E. grijsii*	R		Liu et al., 2002; Chang et al., 2015
		E. grijsii	R		Wang et al., 2006
		E. grijsii	R	Cytotoxic	Jin et al., 2008
		E. grijsii	R	Insecticidal	Zhao et al., 2017
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
19.	5-chloro- α-terthiophene	*E. grijsii*	R		Liu et al., 2002
20.	5-acetyl α-terthiophene	*E. grijsii*	R		Liu et al., 2002
21.	5,5'-dichloro-α-terthiophene	*E. grijsii*	R		Liu et al., 2002
22.	Cardopatine	*E. grijsii*	R		Liu et al., 2002; Chang et al., 2015
		E. latifolius	R		Wang et al., 2006
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
23.	Isocardopatine	*E. grijsii*	R		Liu et al., 2002; Zhang and Ma, 2010; Chang et al., 2015
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. grijsii	R	Cytotoxic	Jin et al., 2008
24.	Grijisyne A	*E. grijsii*	R		Zhang et al., 2008
25.	Grijisone A	*E. grijsii*	R		Zhang et al., 2008
26.	5-(4-hydroxy-3-methoxy-1-butyny)-2,2'-bithiophene	*E. grijsii*	R		Chang et al., 2015
27.	5-acetyl-2,2'-bithiophene	*E. latifolius*	R		Wang et al., 2008
		E. grijsii	R		Chang et al., 2015
		E. ritro	WP		Li et al., 2019
28.	5-formyl-2,2'-bithiophene	*E. grijsii*	R		Chang et al., 2015
29.	Methyl 2,2'-bithiophene-5-carboxylate	*E. grijsii*	R		Chang et al., 2015
30.	5-(3-hydroxymethyl-3-isovaleroyloxyprop-1-ynyl)-2,2'-bithiophene	*E. latifolius*	R		Wang et al., 2006
		E. grijsii	R		Chang et al., 2015
31.	5-(4-hydroxy-1-butynyl)-2,2'-bithiophene	*E. latifolius*	R		Wang et al., 2008
		E. ritro	Rd	Antifungal	Fokialakis et al., 2006a
		E. latifolius	R	Cytotoxic	Wang et al., 2007

(Continued)

TABLE 2 | Continued

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Thiophenes					
		E. grijsii	R		Zhang et al., 2009; Chang et al., 2015
		E. ritro	WP	Antibacterial, Antifungal	Li et al., 2019
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
32.	5-(4-acetoxy-1-butynl)-2,2'-bithiophene	*E. grijsii*	R		Chang et al., 2015
33.	5-(3-hydroxy-4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene	*E. latifolius*	R		Wang et al., 2006
34.	5-(3-acetoxy-4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene	*E. latifolius*	R		Wang et al., 2006
		E. grijsii	R	Cytotoxic	Jin et al., 2008
35.	Echinopsacetylenes A	*E. transiliensis*	R		Nakano et al., 2011
36.	Echinopsacetylenes B	*E. transiliensis*	R		Nakano et al., 2011
37.	Echinothiophenegenol	*E. grijsii*	R		Zhang et al., 2009
		E. nanus	R		Nakano et al., 2012
38.	5-(4-acetoxy-3-chlorobut-1-ynyl)-2-(pent-1,3-diynyl)-thiophene	*E. ritro*	Rd	Antifungal	Fokialakis et al., 2006a
39.	5-(3,4-diacetoxybut-1-ynyl)-2,2′-bithiophene	*E. ritro*	Rd	Antifungal	Fokialakis et al., 2006a
		E. ritro	AP	Termicidal	Fokialakis et al., 2006b
		E. grijsii	R		Zhang and Ma, 2010
		E. grijsii	R	Cytotoxic	Jin et al., 2008
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
40.	5-{4-[4-(5-pent-1,3-diynylthiophene-2-yl)-but-3-yny}-2,2'-bithiophene	*E. latifolius*	R	Cytotoxic	Wang et al., 2007
41.	5-(4-hydroxybut-1-one)-2,2'-bithiophene	*E. latifolius*	R	Cytotoxic	Wang et al., 2007
		E. ritro	WP		Li et al., 2019
42.	5-(prop-1-ynyl)- 2-(3,4-diacetoxybut-1-ynyl)-thiophene	*E. latifolius*	R		Wang et al., 2007
		E. grijsii	R	Cytotoxic	Jin et al., 2008
43.	5-(1,2-dihydroxy-ethyl)-2-(*Z*)-hept-5-ene-1,3-diynylthiophene	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
44.	5-(1,2-dihydroxyethyl)-2-(*E*)-hept-5-ene-1,3-diynylthiophene	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
45.	6-Methoxy-arctinol-b	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
46.	Arctinol-b	*E. grijsii*	R		Zhang et al., 2009
		E. latifolius	R	Anti-inflammatory	Jin et al., 2016
		E. ritro	WP	Antibacterial, Antifungal	Li et al., 2019
47.	Arctinol	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
		E. ritro	WP		Li et al., 2019
		E. ritro	WP		Li et al., 2019
48.	Methyl [5'-(1-propynyf)-2,2'-bithienyl-5-yl] carboxylate	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
49.	5-(penta-1,3-diynyl)-2-(3-methoxy-4-hydroxy-but-1-ynyl)-thiophene	*E. hoehnelii*	R		Bitew et al., 2017
50.	5-(penta-1,3-diynyl)-2-(3-methoxy-4-acetoxy-but-1-ynyl)-thiophene	*E. hoehnelii*	R		Bitew et al., 2017
51.	5-(3-hydroxy-4-acetoxybut-1-ynyl)-2,2′-bithiophene	*E. transiliensis*	R		Nakano et al., 2014
		E. transiliensis	R	Insecticidal	Nakano et al., 2014
52.	5-(penta-1,3-diynyl)-2-(3-acetoxy-4-hydroxy-but-1-ynyl)-thiophene	*E. transiliensis*	R	Insecticidal	Nakano et al., 2014
53.	5'-(3,4-dihydroxybut-1-yn-1-yl)-[2,2'-bithiophene]-5-carbaldehyde.	*E. ritro*	WP		Li et al., 2019
54.	5'-(3,4-dihydroxybut-1-yn-1-yl)-[2,2'-bithiophene]-5-carboxylic acid	*E. ritro*	WP	Antibacterial	Li et al., 2019
55.	4-hydroxy-1-(5'-methyl-[2,2'-bithiophen]-5-yl)butan-1-one	*E. ritro*	WP	Antibacterial, Antifungal	Li et al., 2019
56.	Junipic acid	*E. ritro*	WP		Li et al., 2019
57.	Arctinal	*E. ritro*	WP	Antibacterial	Li et al., 2019
58.	4-(5'-methyl-[2,2'-bithiophen]-5-yl)but-3-yn-1-ol	*E. ritro*	WP		Li et al., 2019
59.	Arctinol A	*E. ritro*	WP	Antibacterial	Li et al., 2019
Terpenes					
60.	Dehydrocostus lactone	*E. amplexicauli* *E. kebericho*	R		Abegaz et al., 1991
61.	Costunolide	*E. amplexicaulis*, *E. kebericho*, *E. pappii*			Abegaz et al., 1991Abegaz, 1991
62.	Dihydrocostunolide	*E. amplexicaulis*	R		Abegaz et al., 1991
63.	Echinopines A	*E. spinosus*	R		Dong et al., 2008b
64.	Echinopines B	*E. spinosus*	R		Dong et al., 2008b

(Continued)

TABLE 2 | Continued

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Terpenes					
65.	(3α,4α,6α)-3,13-dihydroxyguaia-7(11),10(14)-dieno-12,6-lactone)	*E. ritro*	WP		Li et al., 2010
66.	(3α,4α,6α,11β)-3-hydroxyguai-1(10)-eno-12,6-lactone)	*E. ritro*	WP		Li et al., 2010
67.	(11α)-11,13-dihydroarglanilic acid methyl ester	*E. ritro*	WP		Li et al., 2010
68.	Vulgarin	*E. ritro*	WP		Li et al., 2010
69.	(3*R*,3a*S*,6a*R*,9*S*,9a*R*,9b*S*)-octahydro-3,9-dimethyl-6-methyleneazuleno[4,5-b]furan2,8(3*H*,9b*H)*-d ione	*E. ritro*	WP		Li et al., 2010
70.	(3a*S*,6a*R*,8*S*,9*S*,9a*R*,9b*R*)-decahydro-8-hydroxy-9-methyl-3,6 dimethyleneazuleno[4,5-b]furan-2(9b*H*)-one	*E. ritro*	WP		Li et al., 2010
71.	(3a*S*,6a*R*,8*R*,9*R*,9a*R*,9b*R*)-decahydro-8-hydroxy-3,3,9-trimethyl-6-methyleneazuleno[4,5-b]furan-2(9b*H*)-one	*E. ritro*	WP		Li et al., 2010
72.	(3*R*,3a*S*,6a*R*,8*S*,9*S*,9a*R*,9b*S*)-decahydro-8-hydroxy-3,9-dimethyl-6-methyleneazuleno[4,5-b]furan-2(9b*H*)-one	*E. ritro*	WP		Li et al., 2010
73.	Santamarin	*E. pappii*			Abegaz, 1991
		E. ritro	WP		Li et al., 2010
74.	Reynosin	*E. pappii*	R		Abegaz, 1991
75.	Caryophyllene epoxide	*E. giganteus*	R		Abegaz et al., 1991
		E. hispidus			
76.	Echusoside	*E. hussoni* Boiss.	AP		Ka, 2001
77.	(3*S*,3a*S*,5a*R*,6*R*,8*R*,9b*S*)-decahydro-6,8-dihydroxy-3,5a-dimethyl-9-methylenenaphtho[1,2-b]furan-2(*9bH*)-one	*E. ritro*	WP		Li et al., 2010
78.	(3*S*,3a*S*,5a*R*,6*S*,9b*S*)-3,3a,4,5,5a,6-hexahydro-6-hydroxy-3,5a,9-trimethylnaphtho[1,2-b]furan-2,7(9a*H*,9b*H*)-dione	*E. ritro*	WP		Li et al., 2010
79.	2,6,10-trimethyldodeca-2,6,10-triene	*E. albicaulis*	AP		Kiyekbayeva et al., 2017
80.	Macrochaetosides A	*E. macrochaetus*	AP	Cytotoxic	Zamzami et al., 2019
81.	Macrochaetosides B	*E. macrochaetus*	AP	Cytotoxic	Zamzami et al., 2019
82.	Latifolanone A	*E. latifolius*	R		Jin et al., 2016
83.	Atractylenolide-II	*E. latifolius*	R	Anti-inflammatory	Jin et al., 2016
84.	β-amyrin	*E. niveus*	WP		Singh et al., 1990
85.	Betulinic acid	*E. niveus*	WP		
86.	Lupeol	*E. niveus*	WP		Singh et al., 1990
		E. giganteus	R		Tene et al., 2004
		E. integrifolius	WP		Senejoux et al., 2013
		E. echinatus	R		Patel, 2016
87.	Taraxasterol	*E. niveus*	WP		Singh et al., 1990
88.	Taraxasterol acetate	*E. niveus*	WP		Singh et al., 1990
		E. echinatus	WP	Anti-inflammatory	Singh et al., 1989
89.	β-sitosterol	*E. niveus*	WP		Singh et al., 1990
		E. transiliensis	R		Nakano et al., 2012
		E. giganteus	Rz		Kuete et al., 2013
		E. orientalis	Sd	Antioxidant	Erenler et al., 2014
90.	β-sitosterol glucoside	*E. niveus*	WP		Singh et al., 1990
		E. giganteus	R		Tene et al., 2004
		E. integrifolius	WP		Senejoux et al., 2013
		E. albicaulis	AP		Kiyekbayeva et al., 2017
91.	Reynosin	*E. pappii*	R		Abegaz, 1991
92.	Gmeliniin A	*E. gmelinii*	AP		He et al., 2000
93.	Stigmasterol	*E. transiliensis*	R		Nakano et al., 2012
		E. macrochaetus	AP		Zamzami et al., 2019
		E. integrifolius	WP		Senejoux et al., 2013
		E. giganteus	Rz		Kuete et al., 2013
94.	Lupeol acetate	*E. integrifolius*	WP		Senejoux et al., 2013
		E. echinatus	R		Patel, 2016
		E. albicaulis	AP		Kiyekbayeva et al., 2017
95.	Lupeol linoleate	*E. albicaulis*	AP		Kiyekbayeva et al., 2017
96.	Ajugasterone C	*E. grijisii*	R		Dong et al., 2008a
97.	Ursolic acid	*E. giganteus*	Rz	Cytotoxic	Kuete et al., 2013
98.	Echinopsolide A (3β-acetoxy-15α-bromoolean-13β,28-olide)	*E. giganteus*	Rz	Cytotoxic	Sandjo et al., 2016
99.	β-amyrin acetate	*E. giganteus*	Rz		Sandjo et al., 2016
100.	3β-acetoxy-taraxast-12,20(30)-diene-11α-21α-diol	*E. galalensis*	AP	Hepato-protective	Abdallah et al., 2013
101.	α-amyrin	*E. galalensis*	Rz	Hepato-protective	
102.	Erythrodiol	*E. galalensis*	Rz	Hepato-protective	

(Continued)

TABLE 2 | Continued

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Terpenes					
103.	Lup-20(29)-ene-1,3-diol	*E. galalensis*	Rz	Hepato-protective	
104.	Cyclostenol	*E. macrochaetus*	AP	Cytotoxic	Zamzami et al., 2019
Flavonoids and other phenolic compounds					
105.	Apigenin	*E. niveus*	WP		Singh et al., 1990
		E. echinatus			Ram et al., 1995
		E. integrifolius	AP		Senejoux et al., 2013
		E. spinosus	AP		Boumaraf et al., 2016
		E. albicaulis	AP		Kiyekbayeva et al., 2017
106.	Luteolin	*E. niveus*	WP		Singh et al., 1990
		E. grijisii	R		Dong et al., 2008a
107.	Nivegin	*E. niveus*	WP		Singh et al., 1990
108.	Nivetin	*E. niveus*	AP		Singh and Pandey, 1990
109.	Apigenin 7-*O*-glucoside	*E. echinatus*	F		Ram et al., 1995
		E. spinosus	AP		Boumaraf et al., 2016
		E. orientalis	Sd	Antioxidant	Erenler et al., 2014
110.	Echitin	*E. echinatus*	F		Ram et al., 1995
111.	Echinoside	*E. echinatus*	WP		Singh et al., 2006
112.	7-hydroxyisoflavone	*E. echinatus*	WP		Singh et al., 2006
113.	Kaempferol	*E. echinatus*	WP		Singh et al., 2006
114.	Kaempferol-4'-methylether	*E. echinatus*	WP		Singh et al., 2006
115.	Kaempferol-7-methylether	*E. echinatus*	WP		Singh et al., 2006
116.	Kaempferol-3-*O*-α-L-rhamnoside	*E. echinatus*	WP		Singh et al., 2006
		E. heterophyllus	AP		Mahmood and Khadeem, 2013
117.	Myrecetin-3-*O*-α-L-rhamnoside	*E. echinatus*	WP		Singh et al., 2006
118.	Chrysoeriol	*E. integrifolius*	WP		Senejoux et al., 2013
119.	Hispidulin	*E. integrifolius*	WP		Senejoux et al., 2013
120.	Jaceidin	*E. integrifolius*	WP		Senejoux et al., 2013
121.	Centaureidin	*E. integrifolius*	WP		Senejoux et al., 2013
122.	Axillarin	*E. integrifolius*	WP		Senejoux et al., 2013
123.	Genkwanin	*E. albicaulis*	AP		Kiyekbayeva et al., 2017
124.	Apigenin-7-*O*-(6"-trans-pcoumaroyl- β -D-glucopyranoside	*E. orientalis*	L	Antioxidant	Erenler et al., 2014
		E. spinosus	AP		Boumaraf et al., 2016
125.	5,7-dihydroxy-8,4'-dimethoxyflavanone-5-*O*-α-L-rhamno-pyranosyl-7-*O*-β-D-arabinopyranosyl (1→4)-*O*-β-D-glucopyranoside	*E. echinatus*	WP	Anti-inflammatory	Yadava and Singh, 2006
126.	Candidone	*E. giganteus*	Rz	Cytotoxic	Kuete et al., 2013
127.	Chlorogenic acid	*E. grijisii*	R		Dong et al., 2008a
128.	Cynarin	*E. grijisii*	R		Dong et al., 2008a
129.	Rutin	*E. heterophyllus*	AP		Mahmood and Khadeem, 2013
		E. albicaulis	AP		Kiyekbayeva et al., 2017
130.	(+)-4-(3-methylbutanoyl)-2,6-di(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane	*E. giganteus*	R		Tene et al., 2004
131.	(+)-4-hydroxy-2,6- di(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane	*E. giganteus*	R		Tene et al., 2004
		E. giganteus	Rz		Sandjo et al., 2016
		E. giganteus	Rz	Cytotoxic	Kuete et al., 2013
132.	Hexacosyl-(*E*)-ferulate	*E. nanus*	R		Nakano et al., 2012
133.	Umbelliferone	*E. integrifolius*	WP		Senejoux et al., 2013
134.	Syringin	*E. grijisii*	R		Dong et al., 2008a
135.	1,5-dicaffeoylquinic acid	*E. galalensis*	AP	Hepato-protective	Abdallah et al., 2013
136.	3,5-dicaffeoylquinic acid			Hepato-protective	
137.	3,4-dicaffeoylquinic acid			Hepato-protective	
138.	4,5-dicaffeoylquinic acid			Hepato-protective	
Alkaloids					
139.	Echinopsine (1-methyl-4-quinolone)	*E. echinatus*	AP		Chaudhuri, 1987
		E. nanus	R		Nakano et al., 2012
		E. albicaulis	AP		Kiyekbayeva et al., 2017
		E. orientalis	Sd	Antioxidant	Erenler et al., 2014
140.	Echinozolinone	*E. echinatus*	AP		Chaudhuri, 1987

(Continued)

TABLE 2 | Continued

No.	Name of secondary metabolites	Species	Plant part	Pharmacological activity	Ref.
Alkaloids					
141.	Echinopsidine	*E. echinatus*	AP		Chaudhuri, 1987
142.	7-hydroxyechinozolinone	*E. echinatus*	F		Chaudhuri, 1992
143.	1-Methyl-4(*1H*)-quinolinone	*E. heterophyllus*	Sd		Khadim et al., 2014
144.	1-methyl-4-methoxy-8-(β-D-glucopyranosyloxy)-2(*1H*)-quinolinone	*E. gmelinii Turcz.*	AP		Su et al., 2004
145.	4-methoxy-8-(-D-glucopyranosyloxy)-2(*1H*)-quinolinone	*E. gmelinii*	AP		Su et al., 2004
146.	Echinorine	*E. albicaulis*	AP		Kiyekbayeva et al., 2017
Lipids					
147.	Triacontane	*E. integrifolius*	R		Karimov and Aisa, 2013
148.	Heptacosane	*E. integrifolius*	R		Karimov and Aisa, 2013
149.	Lignoceric acid	*E. integrifolius*	R		Karimov and Aisa, 2013
150.	Tetrahydrofurano-ceramide	*E. giganteus*	Rz	Cytotoxic	Sandjo et al., 2016
151.	Ritroyne A	*E. ritro*	R		Li et al., 2019

AP, Aerial part; F, Flower; L, Leaf; R, Root; Rd, Radix; Rz, Rhizome; Sd, Seed; WP, Whole plant.

coli with a MIC of 64, 32, 64, 64, and 8 μg/mL, respectively, were also described (Li et al., 2019).

In addition to those described in **Table 3**, the root extract of *Echinops* spp from Ethiopia showed anti-bacterial activity through growth inhibition (Ashebir and Ashenafi, 1999). The study did not delineate the specific name of the plant, MIC/MBC, and zone of inhibitions which makes it challenging to compare with other study results. Methanolic extract of the whole plant of *E. polyceras* improved the effect of tetracycline on resistant strains of *Pseudomonas aeruginosa* (Aburjai et al., 2001). The effect of the plant without tetracycline however was not studied. The leaf and flower extracts of *E. viscosus* subsp. bithynicus were described to have anti-bacterial properties against *E. coli*, *Micrococcus luteus*, *S. aureus*, *Mycobacterium smegmatis*, *P. aeruginosa*, *Enterobacter cloacae*, and *Bacillus megaterium*. Even though the concentration of the extracts is not well defined in the study, the flower extract of *E. microcephalus* has been reported to have greater zone of inhibition than the standard drug, vancomycin (30 μg/disc) (Toroğlu et al., 2012).

Most of the anti-fungal studies on the genus revealed that the extracts/isolated compounds were effective mainly against *Candida albicans* with the most potent effect observed for the root methanolic extract of *E. kebericho* (MIC = 3.12 μg/mL) (Ameya et al., 2016).

Thiophenes (**1**, **2, 5**, **18**, **22**, **23**, **31**, **38**, and **39**) from *E. ritro* have been described to possess significant anti-fungal activity against different fungal isolates. The most active thiophenes were **1** (IC_{50} = 4.2 μM) against *Colletotrichum gloeosporioides*, **2** (IC_{50} = 1.9 μM), and 5 (IC_{50} = 1.1 μM) against *C. fragariae* (Fokialakis et al., 2006a). A recent study also showed that thiophenes (**31**, **46**, and **55)** isolated from *E. ritro* exhibited anti-fungal effect against *C. albicans* with the MIC of 64, 32, and 64 μg/mL, respectively (Li et al., 2019). The anti-fungal activity of extracts obtained from *E. viscosus* subsp. bithynicus and *E. microcephalus* leaves and flowers were found to be active against *Saccharomyces cerevisiae*, *Rhodotorula rubra*, *Mucor pusillus*, and *Kluyveromyces fragilis* (Toroğlu et al., 2012).

Effect on Cancer Cell Lines

The traditional use of the genus *Echinops* in the treatment of cancer is not common nevertheless the species in this genus were explored for cytotoxic activity. The methanolic extract of *E. kotschyi* Boiss. against MOLT-4 and K562 cancer cell lines (Afshaki et al., 2012) and essential oils obtained from *E. kebericho*, which consist of 43 compounds predominantly dehydrocostus lactone, showed cytotoxic activity against human monocytic leukemia cell line (THP-1) with an IC_{50} value of 0.4 μg/L (Tariku et al., 2011).

Four thiophens isolated from *E. latifolius* Tausch., 5-(3,4-dihydroxybut-1-ynyl)-2,2'-bithiophene (**15**), 5-(4-hydroxy-1-butynyl)-2,2'-bithiophene (**31**), 5-{4-[4-(5-pent-1,3-diynylthiophene-2-yl)-but-3-yny}-2,2'-bithiophene (**40**), and 5-(4-hydroxybut-1-one)-2,2'-bithiophene (**41**) were tested against human malignant melanoma (A375-S2) and human cervical carcinoma (HeLa) cell lines. The four compounds displayed cytotoxic activity and the effect was more when the mixture of cell lines and compounds were exposed to ultraviolet A (UVA) light for 30 min. The effects of the four compounds were higher against HeLa cell line with IC_{50} values of 5.2, 10.2, 3.1, and 6.5 μmol/L, respectively (Wang et al., 2007).

Jin et al. (2008) illustrated the *in vitro* cytotoxic activity of the dichloromethane fraction of the crude ethanolic root extract of *E. grijisi* and thiophenes (**1**, **2**, **9**, **18**, **23**, **34**, **39**, and **42**) isolated from this fraction. The fraction, as well as the isolated compounds showed different effects towards human hepatocarcinoma (HepG2 and MFC-7), human acute myeloid leukemia (HL-60), and human chronic myelogenous leukemia (K562) cell lines. The highest activities were observed for the dichloromethane fraction against HL-60 (IC_{50} = 5 μg/mL), 5-(4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene (**18**) against HepG2 (IC_{50} = 2 μg/mL), 5-(3-acetoxy-4-isovaleroyloxybut-1-ynyl)-2,2′-bithiophene (**34**) against HepG2 and K562 (IC_{50} = 1.8 and 7 μg/mL), and 5-(prop-1-ynyl)-2-(3,4-diacetoxybut-1-ynyl)-thiophene (**42**) against HL-60 (IC_{50} = 8 μg/mL). The dichloromethane fraction was tested in mice and did not show anti-tumor effect.

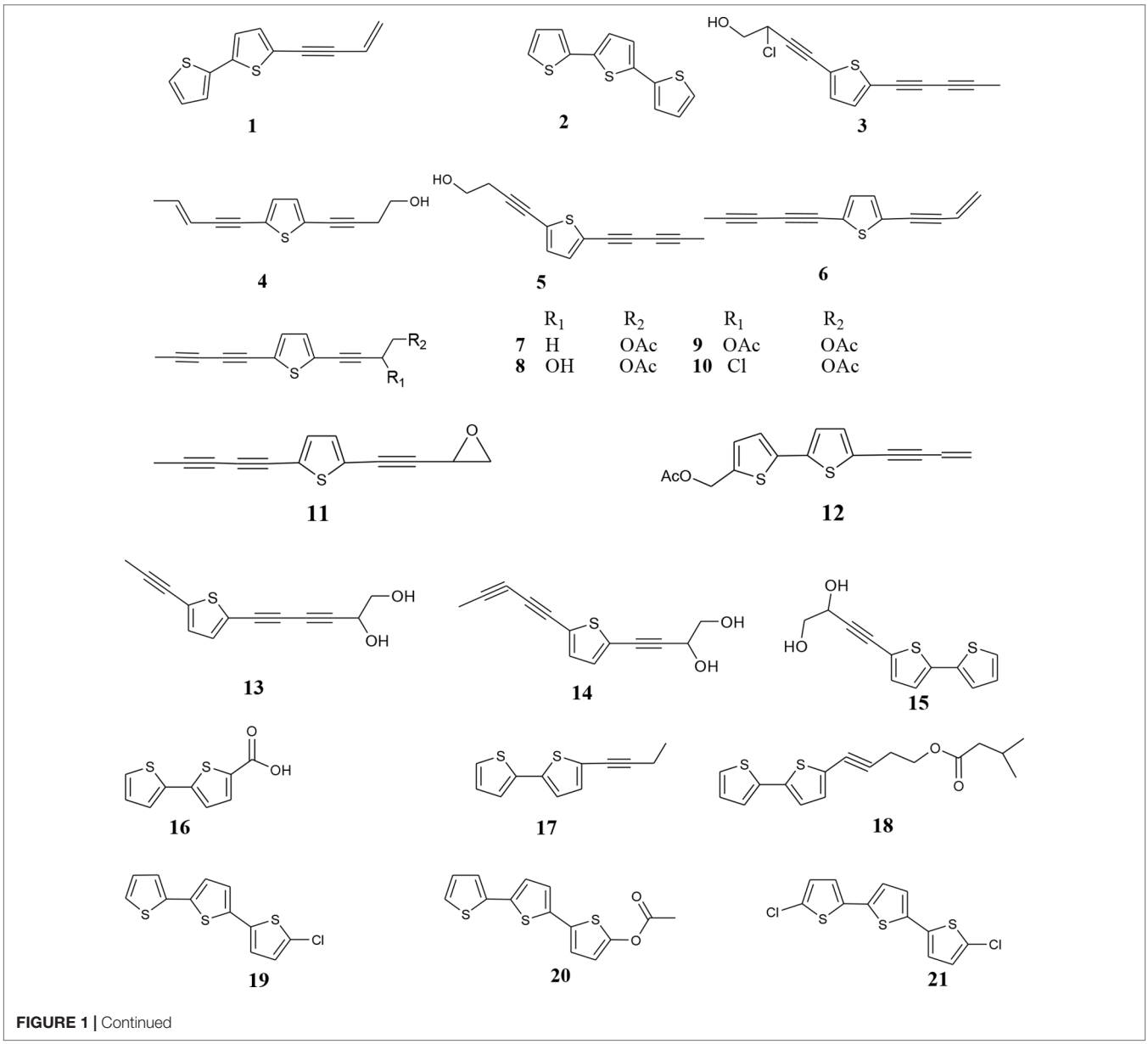

FIGURE 1 | Continued

Similarly, Zhang et al. (2009) evaluated the cytotoxic effect of thiophenes isolated from *E. grijisii* on human cancer cell lines, HL60 and K562. Significantly potent effect was achieved with **5** (IC_{50} = 0.23 and 0.47 μg/mL) and **14** (IC_{50} = 0.27 and 0.43 μg/mL) against HL60 and K562, respectively. The thiophenes showed better activity against HL-60. A compound isolated from the root of *E. grijsii*, 5-(5,6-dihydroxy-hexa-1,3-diynyl)-2-(prop -1-ynyl)-thiophene (**13**), possessed anti-proliferative activity against human colon cancer cells, SW620, SW480, and HCT116 with IC_{50} values of 19.5 μM, 10.5 μM, and 27.7 μM, respectively, at 24 h. The proposed mechanism of action for the thiophene (**13**) was mitochondrial-mediated apoptosis (Zhang and Ma, 2010; Xu et al., 2015).

The methanolic extract from the underground part of *E. giganteus* also exhibited cytotoxic activity with an IC_{50} values of 9.84, 6.68, and 7.96 μg/mL against prostate cancer (Mia PaCa2) and two leukemia cells (CCRF-CEM and CEM/ADR5000), respectively (Kuete et al., 2011). In addition, the crude extract showed strong activity against breast cancer (MDA-MB-231-pcDNA3) with an IC_{50} value of 4.17 μg/mL. The secondary metabolites (**5**, **97**, **126**, and **131**) from the methanolic extract of this plant were tested for their cytotoxic effect and showed lower effect than that of the crude extract (Kuete et al., 2013). In continuation of this study, 5-(3,4-dihydroxybut-1-ynyl)-2-(penta-1,3-diynyl)-thiophene (**14**), echinopsolide A (**98**), and tetrahydrofurano-ceramide (**150**) were isolated from *E. giganteus*. These three compounds tested against leukemia showed the highest activity on CCRF-CEM (IC_{50} values of 46.96, 36.78, and 9.83 μM, respectively) and CEM/ADR5000 (IC_{50} values of 21.09, 38.57, and 6.12 μM, respectively) cell lines (Sandjo et al., 2016).

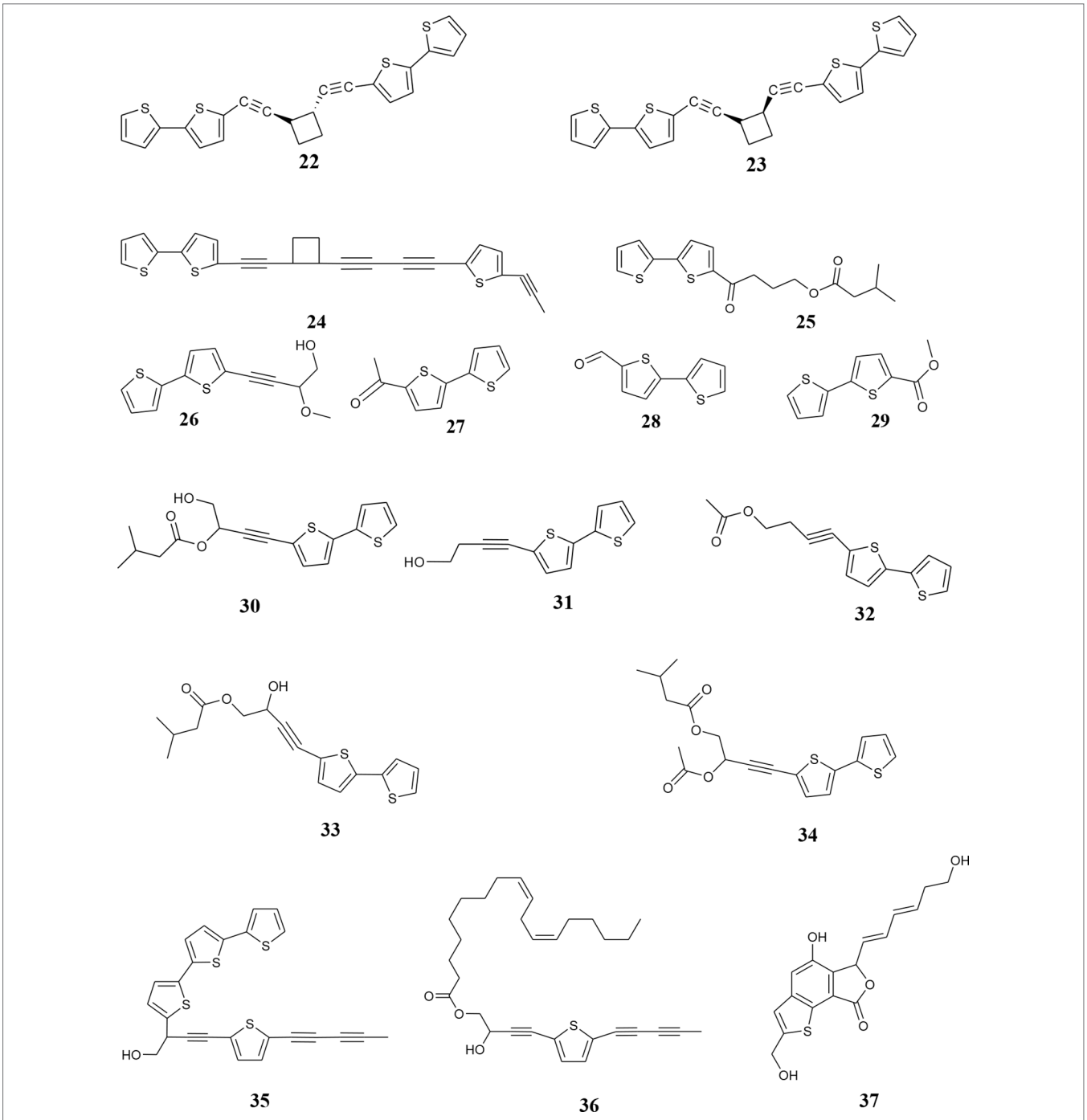

FIGURE 1 | Continued

Macrochaetosides A and B (**80** and **81**) and cyclostenol (**104**), isolated from aerial parts of *E. macrochaetus* Boiss., were tested for their cytotoxic activity. The activity was observed on cell lines of breast adenocarcinoma (MCF-7) (IC_{50} = 2.1 and 0.18 μM), human hepatocellular carcinoma (HepG2) (IC_{50} = 2.9 and 3.3 μM), and colorectal adenocarcinoma (HCT-116) (IC_{50} = 3.6 and 2.3 μM) for cyclostenol and macrochaetosides A, respectively. Macrochaetoside B only showed a cytotoxic activity against MCF-7 with an IC_{50} of 6.9 μM (Zamzami et al., 2019).

The vehicle used to dissolve the compounds for the cytotoxicity study is not mentioned in some of the reports (Sandjo et al., 2016; Zamzami et al., 2019). In one study, α-terthiophene (**2**) was used as a positive control against A375-S2 (IC_{50} = 10.6 μmol/L) and HeLa (IC_{50} = 6.3 μmol/L) cell lines (Wang et al., 2007). Similarly

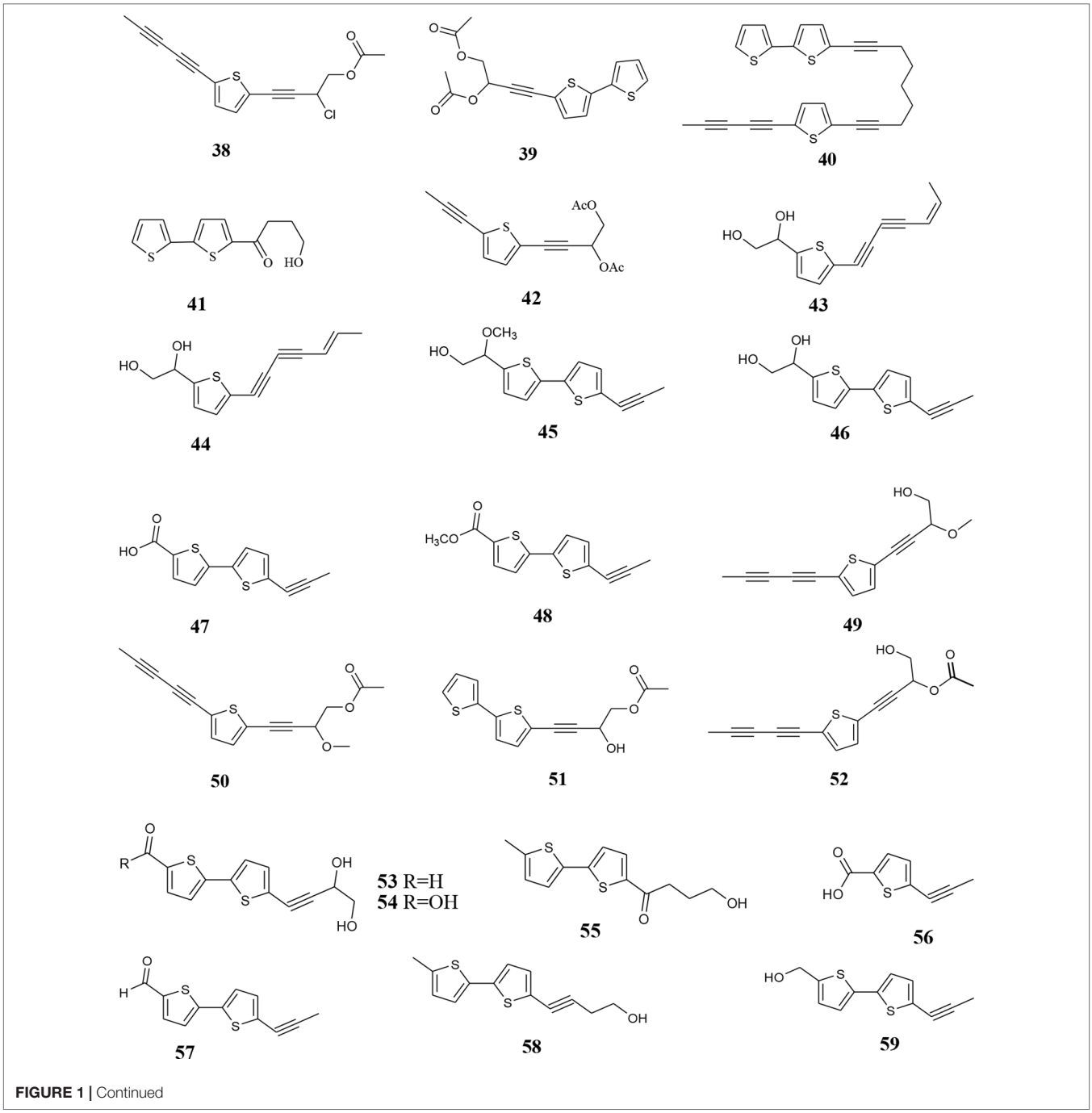

FIGURE 1 | Continued

α-terthiophene showed cytotoxic effect towards K562 (IC_{50} = 50 μg/mL) and HepG2 (IC_{50} = 10μg/mL) (Jin et al., 2008).

The above-described effects on cancer cell lines could be mainly due to thiophenes. Terpenoids and ceramides were the other secondary metabolites having a cytotoxic effect. Among the cell lines tested, leukemia cell lines were comparatively more sensitive in which 5-(4-hydroxybut-1-ynyl)-2-(pent-1,3-diynyl)-thiophene (**5**) showed the most potent effect.

Even though the extracts and isolated compound from the genus showed promising effects against different cancer cell lines, the effects are ought to be further investigated using *in vivo* models.

Hepato-Protective and Anti-Oxidant Activities

Members of the genus *Echinops* were also shown to have hepatoprotective and anti-oxidant activities. Most of the studies were conducted in carbon tetrachloride (CCl_4)-induced liver damage, in which biomarkers of liver function like aspartate

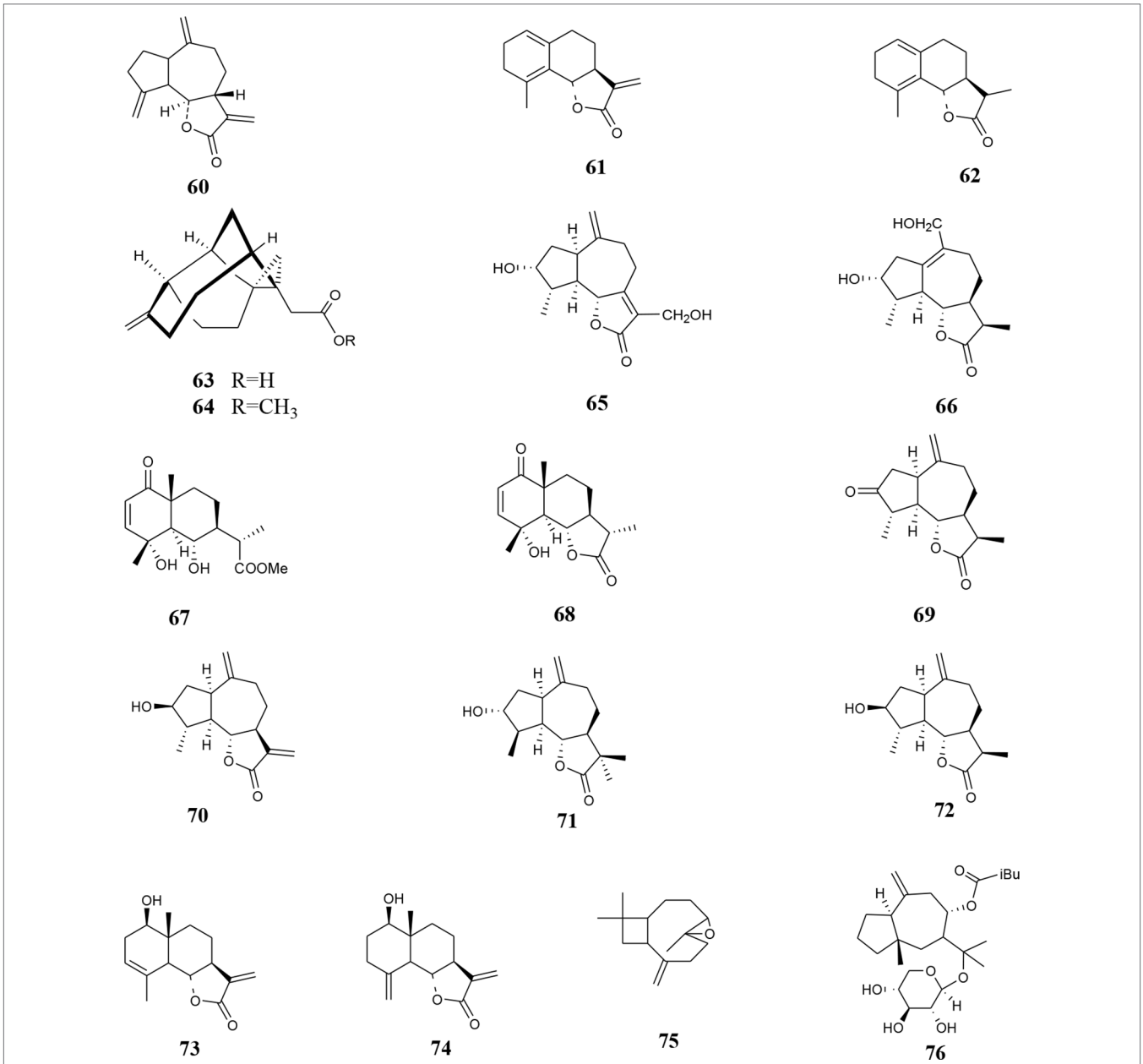

FIGURE 1 | Continued

aminotransferase (AST) and alanine aminotransferase (ALT) were measured.

The methanolic root extract, as well as *n*-butanol and aqueous fractions of *E. grijsii, showed* hepatoprotective activity in CCl_4-induced liver damage in rats. The effect was prominent in the aqueous and butanol fractions, at a dose of 300 mg/kg, that markedly decreased AST and ALT levels (Lin et al., 1993). A study conducted by Eram et al. (2013) in CCl_4-intoxicated rabbits justified the traditional claim of *E. echinatus* to treat jaundice (Gupta et al., 2010). The ethanolic aerial parts extract of *E. echinatus* at 500 and 750 mg/kg resulted in a significant decrease of ALT and AST, of which the lower dose (500 mg/kg) showed a higher effect (Eram et al., 2003). As presented in **Table 1**, 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 (Wang et al., 2015; Zang et al., 2017) and further investigations are required on phytoconstituents of the plants.

The hepatoprotective effect of compounds isolated from members of the genus *Echinops* was also investigated along with crude extracts. The protective effects of *E. galalensis* Schweinf. as well as isolated compounds β-sitosterol (**89**), apigenin-7-*O*-β-D-glucoside (**109**), 3β-acetoxy-taraxast-12,20(30)-diene-11α-21α–diol (**100**), α-amyrin (**101**), erythrodiol (**102**),

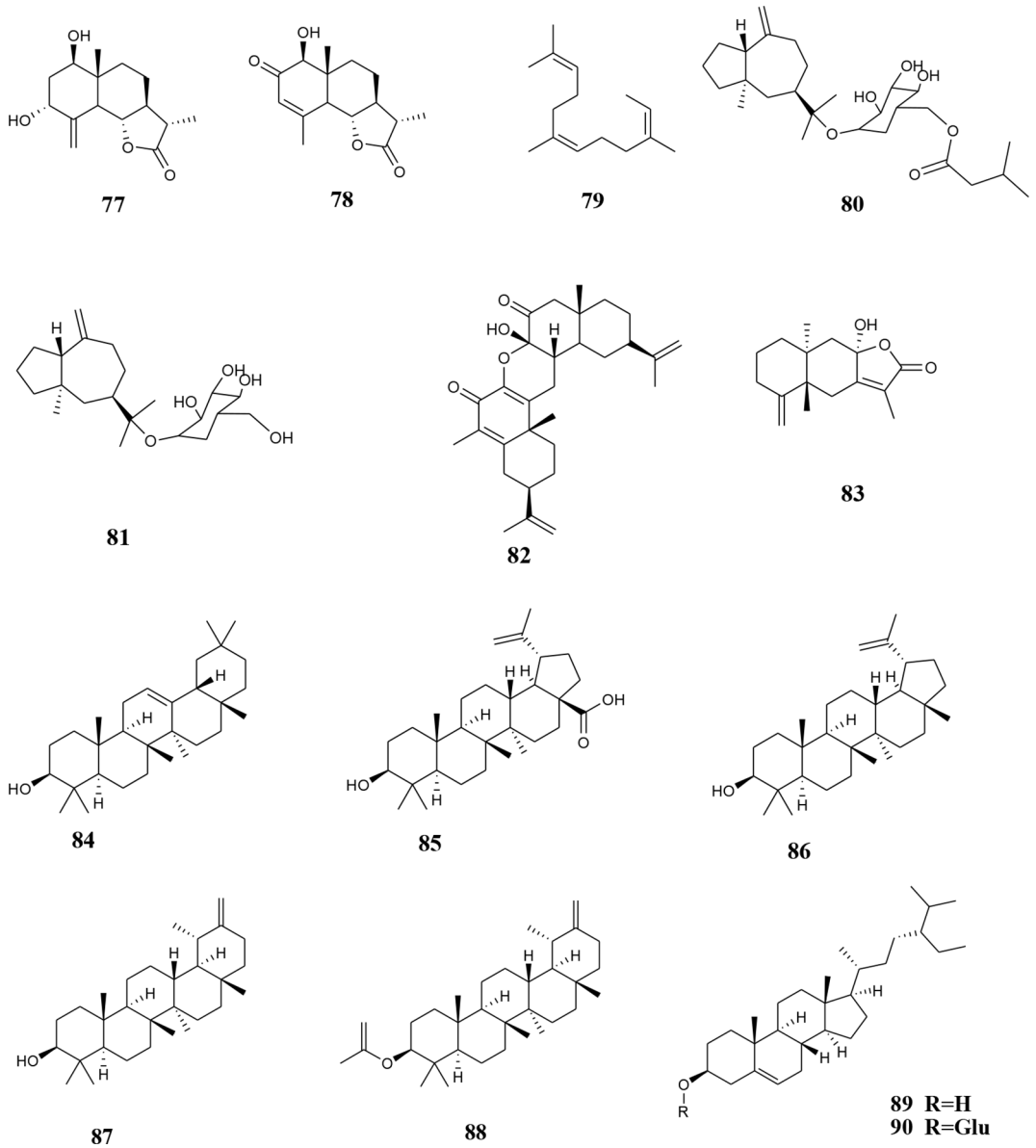

FIGURE 1 | Continued

lup-20(29)-ene-1,3-diol (**103**), and dicaffeoyl-quinic acid derivatives (**135-138**) on human hepatoma cell line (Huh7) have also been established. The highest protection was exhibited by **100**, **102**, and **103** and they significantly decreased the level of ALT. Except for the crude extract, all the tested samples decrease the level of AST and **89**, **101**, and **135** showed the highest effect (Abdallah et al., 2013). According to Abdallah et al. (2013), the protective effect of the extract and isolated compounds was suggested to be partly due to anti-oxidant effects of the samples.

Methotrexate-induced hepatotoxicity was also used to evaluate the hepatoprotective effect of some of the plants. Using this model, the protective effect of ethanolic aerial part extract and flavonoid fraction of *E. heterophyllus* P.H. Davis was established in rabbits. The crude ethanolic extract (250 mg/kg) significantly decreased the serum proteins, liver enzymes, and oxidative stress markers than the flavonoid fraction (Abdulmohsin et al., 2019).

In liver diseases, excessive oxidative stress undoubtedly contributes to the progression and pathological expression of the disease and serves as a prognostic indicator (Zhu et al., 2012). The methanolic root extract of *E. giganteus* showed *in vitro* free radical scavenging effect with 12.54 mg equivalent weight of trolox per 100 g (Bouba et al., 2010). The aqueous extracts of *E. ritro*, *E. tournefortii* Ledeb. possessed 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging effect with inhibitions more than 80% and 70%, respectively, at 1 mg/mL (Aydın et al., 2016). A study that compared different types of extraction methods on antioxidant

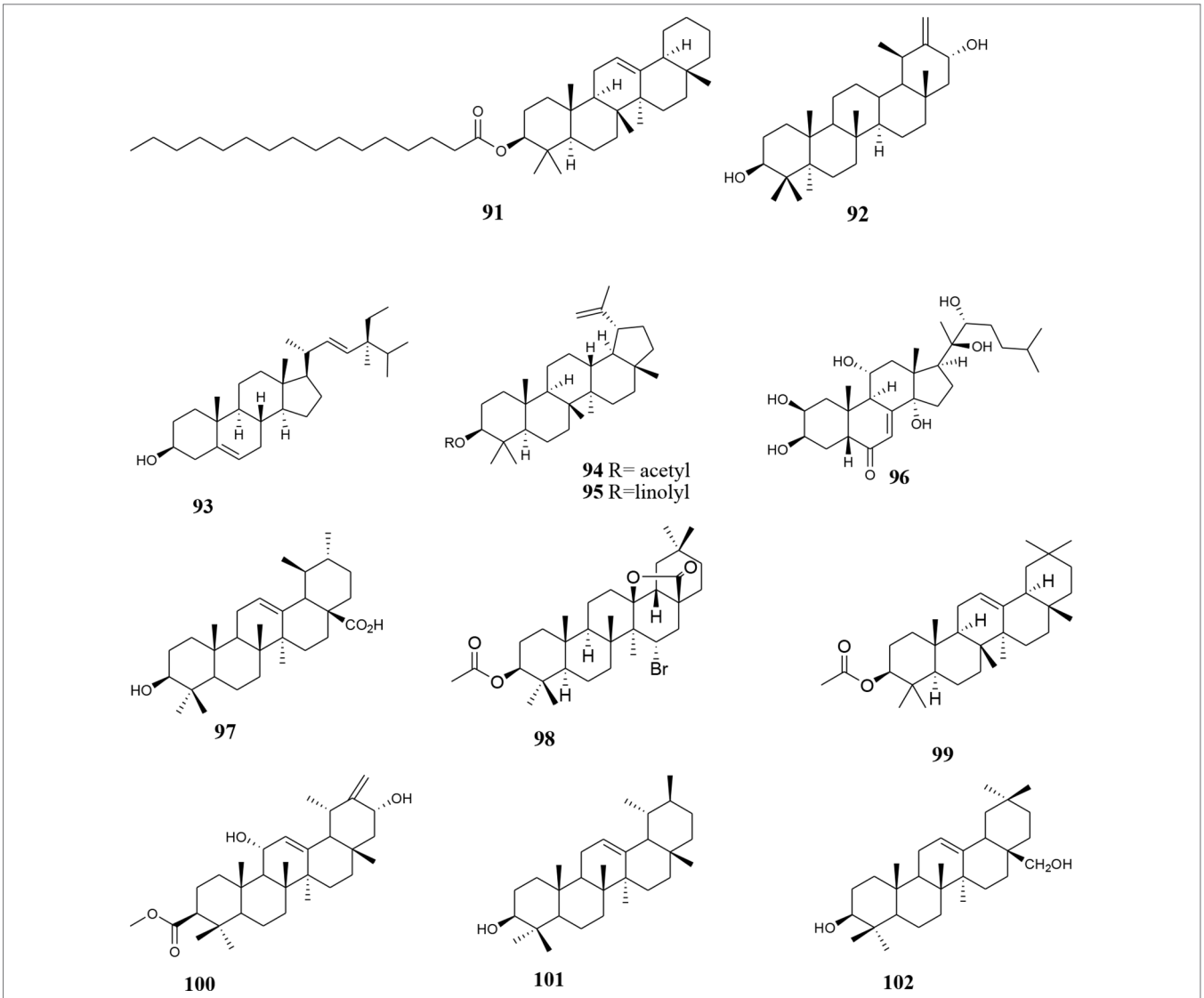

FIGURE 1 | Continued

activity reported that hot extraction using methanolic-ethyl acetate of *E. persicus* showed higher *in vitro* free radical scavenging effect (89.14%) against DPPH (Mohseni et al., 2017). The free radical scavenging effect of crude seed and leaf extracts *E. orientalis* Trautv. as well as isolated compounds β-sitosterol (**89**) and 1-methylquinolin-4(*1H*)-one (**139**) from seeds and apigenin-7-*O*-β-D-glucoside (**109**) and apigenin-7-*O*-(6"-trans-*p*-coumaroyl-β-D-glucopyranoside (**124**) from leaf methanolic extract was demonstrated. The extracts showed a significant effect (> 60% at 40 μg/mL) while the effect of the isolated compounds was not significant against 2,2-diphenyl-1-picrylhydrazyl (DPPH). However, the two flavonoids (**109** and **124**) showed better scavenging effect towards 3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical cation than the extracts and the other two compounds (**89** and **139**), with IC_{50} of 3 and 5 μg/mL (Erenler et al., 2014).

Active cell cultures of human peripheral blood mononuclear cells were also used to evaluate the anti-oxidant effect of aqueous methanolic extract of *E. albicaulis* aerial parts. The study showed that the active oxygen species (ROS) generation in the cells was significantly reduced at concentrations of 1, 20, and 50 mg/mL of the extract; however, the extract induced overproduction ROSs at higher concentrations (Kiyekbayeva et al., 2017).

Regardless of the effects described, the anti-oxidant activity evaluations are not still sufficient. In most of the reports the IC_{50} value for the *in-vitro* anti-oxidant effect are not mentioned. No single *in vivo* anti-oxidant model was employed. In some of the hepatoprotective effect studies standard drugs were not utilized and comparison was made only with the negative control (**Table 5**). The hepatoprotective effect of traditionally used plant, *E. spinosus* L. (Akdime et al., 2015), has not been scientifically investigated yet.

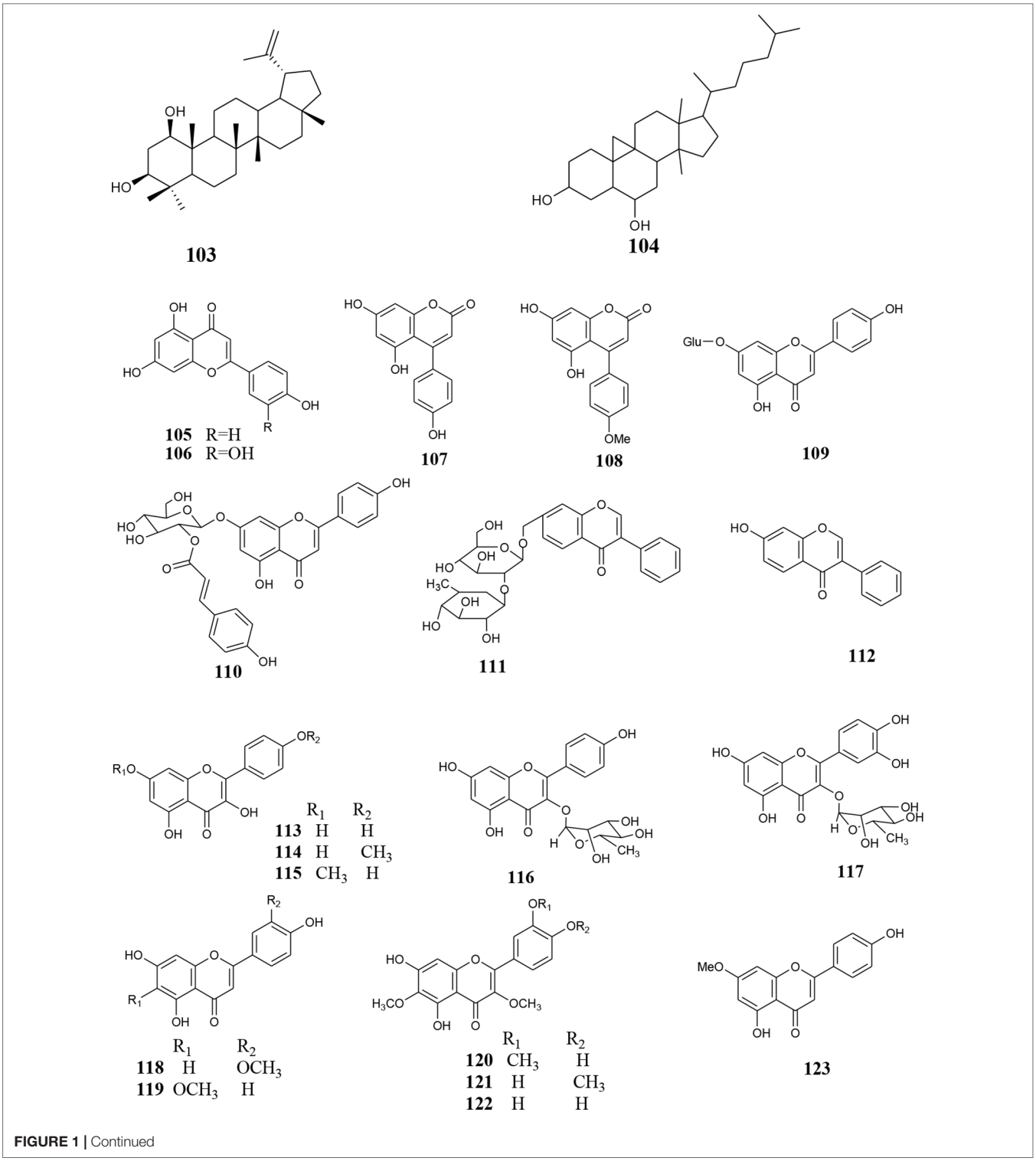

FIGURE 1 | Continued

Anti-Inflammatory, Analgesic, Anti-Pyretic, and Wound Healing Activities

Traditionally, members of the genus *Echinops* are documented to have been used to treat inflammation, pain, and fever. Accordingly, several species have been explored for anti-inflammatory, analgesic, and anti-pyretic activities.

The whole plant ethanolic extract of *E. echinatus* showed anti-inflammatory activity against carrageenan and formaldehyde

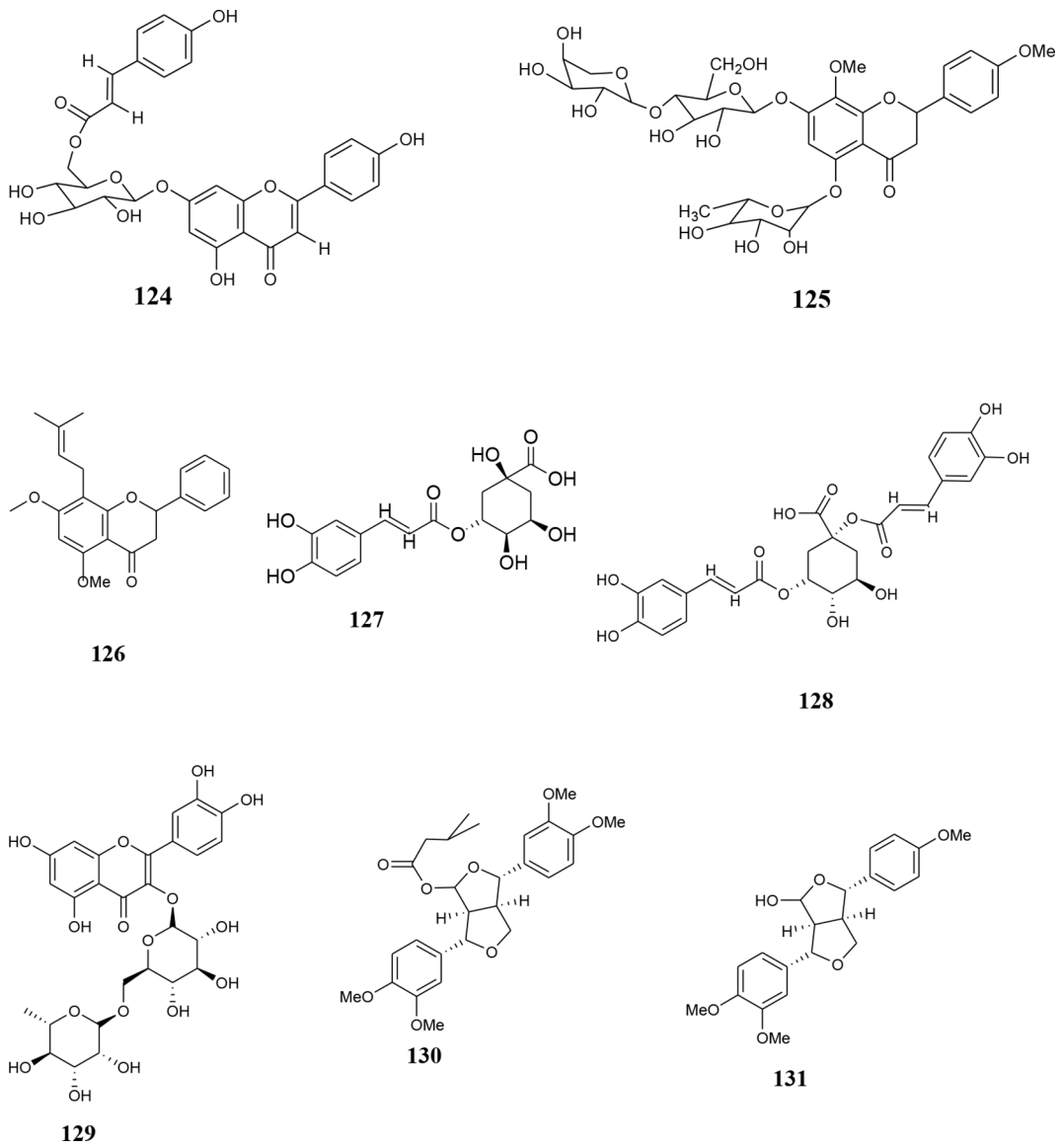

FIGURE 1 | Continued.

induced edema in rats with inhibitions of 67.5% and 51.8% at a dose of 800 mg/kg administered intraperitoneally and orally, respectively (Singh et al., 1989). A triterpenoid isolated from this plant, taraxasterol acetate (**88**), showed anti-inflammatory activity on carrageenan-induced pedal edema in rats with the highest inhibition of 68.3% and 63.2% at 200 mg/kg administered by the intraperitoneal and oral route, respectively (Sing et al., 1991). Flavanone glycoside, 5,7-dihydroxy-8,4'-dimethoxyflavanone-5-O-α-L-rhamno-pyranosyl-7-O-β-D-arabinopyranosyl (1→4)-O-β-D-glucopyranoside (**125**) isolated from *E. echinatus*, showed anti-inflammatory activity (Yadava and Singh, 2006). The methanolic root and aerial part extract of the plant showed analgesic properties in both hotplate and tail immersion models. The aerial part exhibited the highest activity by increasing the reaction time in both models to 7.99 and 7.77 sec, respectively, at 500 mg/kg, and it was comparable with the standard drug, pentazocine (Patel et al., 2011b). The ethanolic leaf and stem extract of *E. echinatus* showed antipyretic effect at a dose of 750 mg/kg in rabbits (Alam et al., 2016).

The methanolic root extracts of *E. spinosus*, *E. grijissi*, and *E. latifolius* exhibited significant anti-inflammatory activity (Lin et al., 1992; Rimbau et al., 1999). The ethyl acetate, chloroform, and n-hexane fractions obtained from the crude extract of *E. grijissi* showed significant anti-inflammatory activities in carrageenan-induced edema in rats, of which the chloroform fraction, at a dose of 300 mg/kg, exhibited inhibitory effect (56.7%) higher than that of indomethacin (Lin et al., 1992). Flavonoids, extracted from *E. latifolius*, were tested on rheumatoid arthritis using rats and inhibited the synovium proliferation through fibroblast-like synoviocytes apoptosis at 150 mg/kg (Miao et al., 2015).

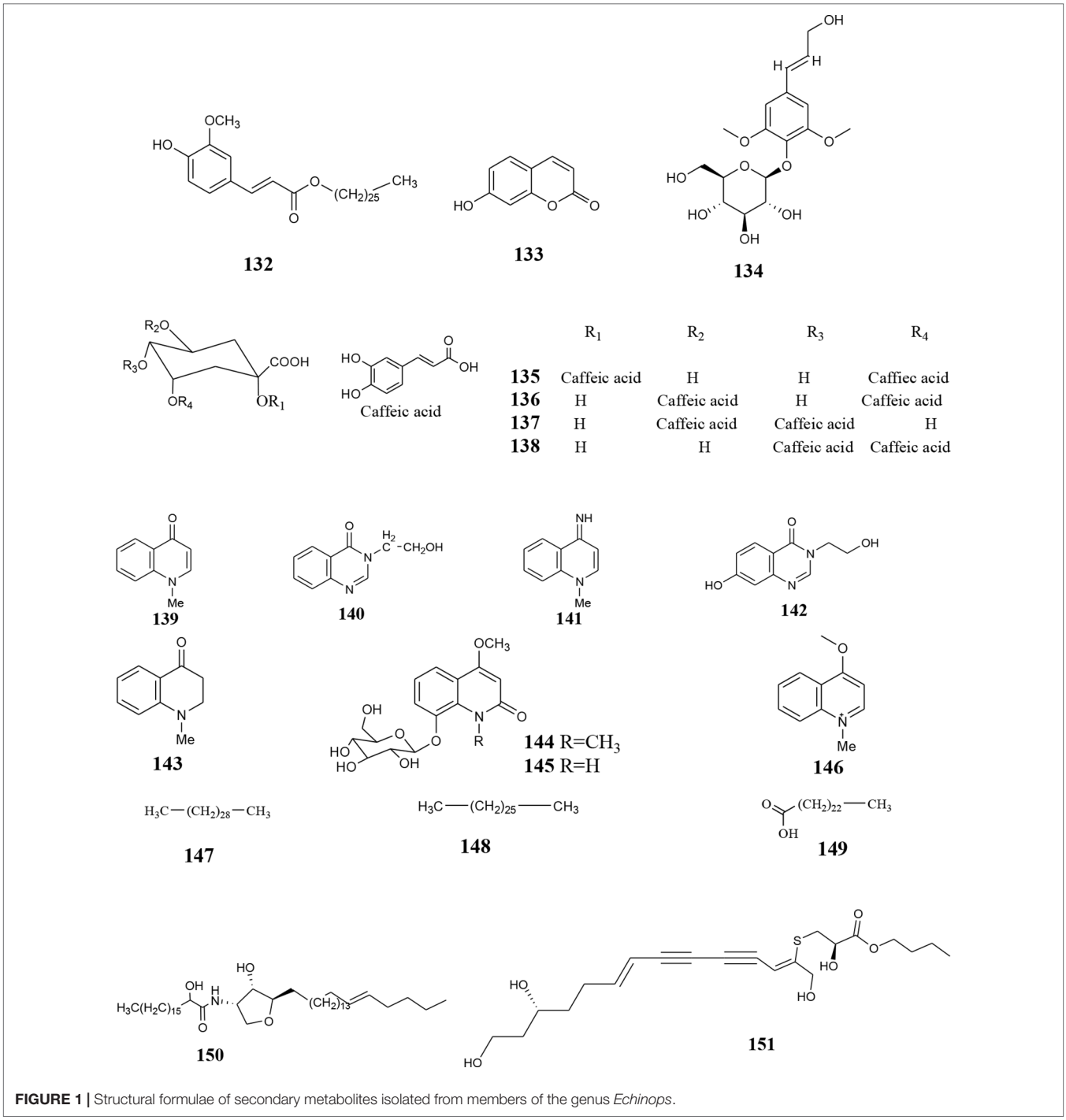

FIGURE 1 | Structural formulae of secondary metabolites isolated from members of the genus *Echinops*.

A study was conducted to evaluate the anti-inflammatory activity of compounds isolated from *E. latifolius*, 5-(1,2-dihydroxy-ethyl)-2-(*Z*)-hept-5-ene-1,3-diynylthiophene (**43**), 5-(1,2-dihydroxyethyl)-2-(*E*)-hept-5-ene-1,3-diynylthiophene (**44**), 6-methoxy-arctinol-b (**45**), arctinol-b(**46**),latifolanoneA(**82**),arctinol(**47**),methyl[5'-(1-propynyf)-2,2'-bithienyl-5-yl] carboxylate (**48**), and atractylenolide-II (**83**) on inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) production. In the order of presented compound names, thiophenic compounds numbered **43**-**46** inhibited the NO production with IC_{50} ranging from 12.8–42.7 μM, whereas the IC_{50} of **47**, **48**, and **83** were reported to be more than 100 μM (Jin et al., 2016).

The whole plant extract of *E. heterophyllus* and the alkaloidal faction facilitated epithelialization and left no scars in rabbits (Abdulrasool et al., 2013). This is the only wound healing activity reported on members of this genus although the dose, vehicle, and the standard drug are not described.

TABLE 3 | *In vitro* antibacterial and antifungal activities of some *Echinops* species.

Echinops species	Extract(Plant part)	Strain (ID)	Type	MIC	MBC	Zone of inhibition (mm) (Conc.) (mg/mL)	Ref.
E. adenocaulos Bioss.	Zamzam water	*Streptococcus pneumonia* (MDR)	I	780 µg/mL	–	–	Saleh Fares et al., 2013
E. amplexicaulis	Ether (R)	*Mycobacterium tuberculosis* (MDR)	I	50 µg/mL	50 µg/mL	41.0 (50)	Kevin et al., 2018
		M.tuberculosis (H37Rv)	S	12 µg/mL	10 µg/mL	40.3 (50)	
		M. bovis (BCG strain)	S	45 µg/mL	50 µg/mL	40. 7 (50)	
E. echinatus	70% Ethanol (AP)	*Bacillus subtilis*	S			14.7 (0.8)	Ahmad, 2012
		S. aureus	S			12.7 (0.8)	
		Pseudomonas aeruginosa	S			20.7 (0.8)	
		Salmonella typhi	S			27.3 (0.8)	
		Shigella sonnei	S			17.3 (0.8)	
		Escherichia coli	S			24 (0.8)	
E. ellenbeckii	80% Methanol (L)	*S. aureus* (ATCC 6538)	S	–	–	23.0 (10)	Hymete et al., 2005a
E. giganteus	Methanol (R)	*Klebsiella pneumonia* (K24)	LC	32 µg/mL	–	–	Fankam et al., 2011
		M. tuberculosis (H37Rv)	CC	32 µg/mL	128 µg/mL		Tekwu et al., 2012
		M. tuberculosis (H37Ra)	CC	16 µg/mL	128 µg/mL		
E. kebericho	Water/Ethanol/ Methanol (R)	*S. aureus*	S	100/3.1/3.1 µg/mL	> 100/6.3/9.4 µg/mL	8.3/19.3/18(0.08)	Ameya et al., 2016
	Ethanol/Methanol (R)	*E. fecalis*	S	12.5/12.5 µg/mL	18.75/18.75 µg/mL	11.66/14.1(0.08)	
		E. coli	S	25/25 µg/mL	37.5/37.5 µg/mL	9.66/8.66 (0.08)	
	Essential oils (R)	*Listeria monocytogenes*	S	0.2 µL/mL	0.4 µL/mL	–	Belay et al., 2011
		S. aureus		0.2 µL/mL	0.4 µL/mL		
		S. pyogenes		0.2 µL/mL	0.8 µL/mL		
		P. aeruginosa		0.2 µL/mL	0.4 µL/mL		
		Shigella dysenteriae		6.3 µL/mL	6.3 µL/mL		
		K. pneumonia		0.1 µL/mL	0.2 µL/mL		
		Proteus mirabilis		25 µL/mL	25 µL/mL		
		Bacillu scereus		0.4 µL/mL	0.8 µL/mL		
E. longisetus	80% Methanol (L)	*S. aureus* (ATCC 6538)	S	–	–	23.0 (10)	Hymete et al., 2005a
	80% Methanol (St)	*S. aureus* (ATCC 6538)	S	–	–	23.3 (10)	
E. ritro	Essential oil (AP)	*S. aureus* (ATCC 25923)	S	150 µg/mL			Jiang et al., 2017
		Salmonella Enteritidis (CICC21513)	S	600 µg/mL			
E. spinosissimus	Methanol (AP)	*B. cereus*	I	–	–	12 (6)	Rahman et al., 2011
	Methanol (AP)	*S. aureus*	I	–	–	12 (6)	
	Methanol (AP)	*S. aureus*	I	–	–	10 (6)	
	Methanol (AP)	*S. aureus*	I	–	–	32 (6)	
	Hexane (AP)	*S. sepidermis*	I	–	–	16 (6)	
	Methanol (AP)	*E. coli*	I	–	–	11 (6)	
	Methanol (AP)	*Klebsiella oxytoca*	I	–	–	12(6)	
	Hexane (AP)	*Yersinia enterocolitica ss. Entero colitica* (ATCC 23715)	CC			20 (6)	
***Echinops* species**	**Extract(plant part)**	**Strain (ID)**	**Type**	**MIC**	**MFC**	**Zone of inhibition (mm) (Conc.) (mg/mL)**	**Ref.**
E. cephalotes	Ethanol/Methanol/ Water	*C. albicans*	I			18.9/16.3/18(7.8)	Heshmati et al., 2016
	Ethanol	*C. glabrata*	I			15.7(7.8)	
E. ellenbeckii	80% Methanol (L)	*C. albicans*	I	–	–	18.9 (10)	Hymete et al., 2005a
E. kebericho	Ethanol/methanol (R)	*A. flavus*	I	12.5/6.25 µg/mL	22.92/12.5 µg/mL	17.33/18.66 (0.08)	Ameya et al., 2016
		C. albicans	I	6.25/3.12 µg/mL	12.5/6.25 µg/mL	18.66/20.33 (0.08)	
E. pinosissimus	Methanol (AP)	*C. albicans*	S	–	–	18 (23)	Abd-Ellatif et al., 2011

AP, Aerial part; F, Fruit; L, Leaf; R, Root; St, Stem; WP, Whole plant; MDR, Multidrug resistant; I, Isolate; S, Standard. All studies resulting in MIC values over 1 mg were not included as such dosages cannot be applied in vivo.

The *in vivo* anti-inflammatory effects of the genus seemed to be not promising since the plants resulted in an inhibition of edema at higher doses. In spite of the studies stated above, scientific data justifying the traditional claim of *E. bovei* (Boiss.) Maire., *E. cornigerus*, *E. kebericho*, *E. longifolius* A. Rich., *E. macrochaetus*, and *E. spinosissimus* to treat rheumatism and pain are not provided yet.

TABLE 4 | *In vitro* cytotoxic effect of members of the genus *Echinops*.

Plant/fraction/compound name (Plant)	Cell line	Positive control	Negative control	IC_{50}	References
Essential oils(*E. kebericho*)	Human monocytic leukemia (THP-1)	Amphotericin B	1% DMSO	0.4 µg/mL	Tariku et al., 2011
15 (*E. latifolius*)	Human cervical carcinoma (HeLa)	α-terthienyl	DMSO	5.2 µmol/L	Wang et al., 2007
31 (*E. latifolius*)	HeLa	α-terthienyl	DMSO	10.2 µmol/L	Wang et al., 2007
40 (*E. latifolius*)	HeLa	α-terthienyl	DMSO	3.1 µmol/L	Wang et al., 2007
41 (*E. latifolius*)	HeLa	α-terthienyl	DMSO	6.5 µmol/L	Wang et al., 2007
Dichloromethane fraction (*E. grijisi*)	Human acute myeloid leukemia (HL-60)	Platinol	DMSO	5 µg/mL	Jin et al., 2008
18 (*E. grijisi*)	Human hepatocarcinoma (HepG2)	Adriamycin	DMSO	2 µg/mL	Jin et al., 2008
34 (*E. grijisi*)	HepG2	Adriamycin	DMSO	1.8 µg/mL	Jin et al., 2008
34 (*E. grijisi*)	Human chronic myelogenous leukemia (K562)	Adriamycin	DMSO	7 µg/mL	Jin et al., 2008
42 (*E. grijisi*)	HL-60	Platinol	DMSO	8 µg/mL	Jin et al., 2008
5 (*E. grijisi*)	HL-60	Platinol	DMSO	0.23 µg/mL	Zhang et al., 2009
5 (*E. grijisi*)	K562	Adriamycin	DMSO	0.47µg/mL	Zhang et al., 2009
14 (*E. grijisi*)	HL-60	Platinol	DMSO	0.27 µg/mL	Zhang et al., 2009
14 (*E. grijisi*)	K562	Adriamycin	DMSO	0.43 µg/mL	Zhang et al., 2009
13 (*E. grijisi*)	Colon cancer (SW480)	4′-Bromoflavone	DMSO	19.5 µM	Zhang and Ma, 2010
13 (*E. grijisi*)	Colon cancer (SW480)	4′-Bromoflavone	DMSO	10.5 µM	Zhang and Ma, 2010
13 (*E. grijisi*)	Colon cancer (HCT116)	4′-Bromoflavone	DMSO	27.7µM	Zhang and Ma, 2010
E. giganteus	Prostate cancer (Mia PaCa2)	Doxorubicin	DMSO	9.84 µg/mL	Kuete et al., 2011
E. giganteus	Leukemia (CCRF-CEM)	Doxorubicin	DMSO	6.68 µg/mL	Kuete et al., 2011
E. giganteus	Leukemia (CEM/ADR5000)	Doxorubicin	DMSO	7.96 µg/mL	Kuete et al., 2011
14 (*E. giganteus*)	CCRF-CEM	Doxorubicin	NM	46.96 µM	Sandjo et al., 2016
14 (*E. giganteus*)	CEM/ADR5000	Doxorubicin	NM	21.09 µM	Sandjo et al., 2016
98 (*E. giganteus*)	CCRF-CEM	Doxorubicin	NM	36.78 µM	Sandjo et al., 2016
98 (*E. giganteus*)	CEM/ADR5000	Doxorubicin	NM	38.57 µM	Sandjo et al., 2016
150 (*E. giganteus*)	CCRF-CEM	Doxorubicin	NM	9.83 µM	Sandjo et al., 2016
150 (*E. giganteus*)	CEM/ADR5000	Doxorubicin	NM	6.12 µM	Sandjo et al., 2016
80 (*E. macrochaetus*)	Breast adenocarcinoma (MCF-7)	Doxorubicin	NM	0.18 µM	Zamzami et al., 2019
80 (*E. macrochaetus*)	HepG2	Doxorubicin	NM	3.3 µM	Zamzami et al., 2019
80 (*E. macrochaetus*)	MCF-7	Doxorubicin	NM	2.1 µM	Zamzami et al., 2019
104 (*E. macrochaetus*)	HepG2	Doxorubicin	NM	2.9 µM	Zamzami et al., 2019
104 (*E. macrochaetus*)	MCF-7	Doxorubicin	NM	6.9 µM	Zamzami et al., 2019

DMSO, Dimethyl sulfoxide; NM, Not mentioned.

Anti-Protozoal and Anti-Helmentic Activities

As presented in **Table 3,** *E. hoehnelii* Schweinf. and *E. kebericho* have been used in traditional treatment of malaria. These plants along with other species showed anti-malarial activity.

Aqueous extract of the aerial parts of *E. polyceras* exhibited strong (96%) *in vitro* growth inhibitory activity against *Plasmodium falciparum*. Nevertheless, the concentration of the extract used for the test and the standard drug used as positive control has not been reported (Sathiyamoorthy et al., 1999). A study on 70% ethanolic root extract *E. kebericho* resulted in an inhibition of parasitemia by 57.3% at a dose of 500 mg/kg in mice against *Plasmodium berghei* (Toma et al., 2015). A recent study conducted on the 70% methanolic extract from roots of *E. kebericho* exhibited 49.5% of inhibition at 1000 mg/kg in mice (Biruksew et al., 2018). This might suggest that the potency of *E. kebericho* extract could be dependent on the extraction solvent.

Dichloromethane faction of the 80% methanolic extract of *E. hoehnelii*, and thiophens (5-(penta-1,3-diynyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene (**10**), and 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (**14**)) possessed anti-malarial activity. The two compounds showed parasitemia inhibition of 32.7% and 50.2% at a dose of 100 mg/kg, respectively, against *P. berghei* in mice (Bitew et al., 2017).

Different studies showed that essential oils possess strong anti-protozoal effects. The essential oil isolated from *E. kebericho* displayed a strong activity against two *Leishmania* strains (*L. aethiopica* and *L. donovani)* with an EC_{50} values of 0.24 and 0.5 µg/mL (Tariku et al., 2011). Essential oil obtained from *E. giganteus* had anti-protozoal effect against *Trypanosoma brucei* with an IC_{50} of 10.5 µg/mL and GC-MS analysis of the oil revealed the presence of modheph-2-ene, presilphiperfolan-8-ol, presilphiperfol-7-ene, cameroonan-7-α-ol, and (*E*)-caryophyllene as the main constituents of the oil (Kamte et al., 2017).

The anti-helminthic effects of members of the genus were also described. The root 80% methanolic extract of *E. kebericho* showed higher anti-helmentic effect (LD_{50} = 57µg/mL) than niclosamide (LD_{50} = 84.5 µg/mL) against earthworms (Hymete and Kidane, 1991). The root 80% methanolic extracts of *E. ellenbeckii* as well as *E. longisetus* A. Rich. were active against earthworms with 100% mortality at 500 µg/mL (Hymete et al., 2005a). Essential oil from the root of *E. kebericho* showed lethal effect (81.8%) at a concentration of 1% (v/v) towards *Haemonchus contortus* (Hussien et al., 2011).

Effects on Insects and Termites

The leaves of *Echinops* spp, which are commonly known as "Kebericho" in Ethiopia, had a mosquito repellant effect against

TABLE 5 | Other biological effects of members of the genus *Echinops*.

Plant/compound name (Plant)	Effects [Model]	Positive control	Negative control	Dose/Concentration (Rout of administration)	Activity	References
Hepatoprotective and antioxidant activities						
100, **102**, and **103** (*E. galalensis*)	Hepatoprotective [2]	Silymarin	PBS	100 mg/ml	↓ ALT	Abdallah et al., 2013
100, **102**, and **103** (*E. galalensis*)	Hepatoprotective [2]	Silymarin	PBS	100 mg/ml	↓ AST	Abdallah et al., 2013
109 (*E. orientalis*)	Anti-oxidant [2]	Trolox	NM		IC_{50} = 3 µg/mL	Erenler et al., 2014
131 (*E. orientalis*)	Anti-oxidant [2]	Trolox	NM		IC_{50} = 5 µg/mL	Erenler et al., 2014
E. albicaulis	Anti-oxidant [2]	N-acetylcysteine	NM	1, 20, and 50 mg/mL	↓ Generation of ROSs	Kiyekbayeva et al., 2017
E. echinatus	Hepatoprotective [1]	Silymarin	Normal saline	500 mg/kg (p.o.)	↓ AST and ALT	Eram et al., 2013
E. giganteus	Anti-oxidant [2]	Trolox	Distilled water		12.54 mg equivalent weight of trolox per 100 g	Bouba et al., 2010
E. grijsii	Hepatoprotective [1]	NM	Normal saline	300 mg/kg (p.o.)	↓ AST and ALT	Lin et al., 1993
E. heterophyllus	Hepatoprotective [1]	NM	Distilled water	250 mg/kg (p.o.)	↓ AST, ALT, and Aalkaline phosphatase(ALP)	Abdulmohsin et al., 2019
E. orientalis	Anti-oxidant [2]	Trolox	NM	40 µg/mL	> 60%	Erenler et al., 2014
E. persicus	Anti-oxidant [2]	NM	Methanol		89.1%	Mohseni et al., 2017
E. ritro	Anti-oxidant [2]	BHT (Dibutylhydroxytoluene)	Distilled water	1 mg/mL	> 80%	Aydın et al., 2016
E. tournefortii	Anti-oxidant [2]	BHT	Distilled water	1 mg/mL	> 70%	Aydın et al., 2016
Anti-inflammatory, analgesic, anti-pyretic and wound healing activities						
132 (*E. echinatus)*	Anti-inflammatory [1]	Phenylbutazone	1% gumacacia	200 mg/kg (i.p.)	Inh = 68.3%	Singht et al., 1991
43 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = 12.8 µM	Jin et al., 2016
44 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = 28.2 µM	Jin et al., 2016
45 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = 30.9 µM	Jin et al., 2016
46 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = 48.6 µM	Jin et al., 2016
47 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = > 100 µM	Jin et al., 2016
48 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and Indomethacin	NM		IC_{50} = > 100 µM	Jin et al., 2016
83 (*E. latifolius*)	Inhibition of LPS-induced NO production [2]	Aminoguanidine and indomethacin	NM		IC_{50} = > 100 µM	Jin et al., 2016
Chloroform fraction (*E. grijissi*)	Anti-inflammatory	Indomethacin	Normal saline	300 mg/kg (i.p.)	Inh = 56%	Lin et al., 1992
E. echinatus	Anti-inflammatory [1]	Phenylbutazone	1% gumacacia	800 mg/kg (i.p.)	Inh = 67.5%	Singh et al., 1989
E. echinatus	Analgesic [1]	Pentazocine	Distilled water	500 mg/kg (p.o)	↑ Reactionary time	Patel et al., 2011b
E. echinatus	Antipyretic [1]	Paracetamol	NM	750 mg/kg	↓ Rectal temperature	Alam et al., 2016
E. heterophyllus	Wound healing [1]	NM	NM	NM	Facilitated epithelialization	Abdulrasool et al., 2013
Flavonoids (*E. latifolius*)	Inhibition of rheumatoid arthritis [1]	NM	Phosphate-buffered saline (PBS)	50, 100 and 150 mg/kg	↓ Arthritis and paw swelling score	Miao et al., 2015
Anti-protozoal and anti-helmentic activities						
10 (*E.hoehnelii*)	Anti-malarial [1]	Chloroquine	7% Tween 80/3% ethanol	100 mg/kg	Inh = 32.7%	Bitew et al., 2017
14 (*E.hoehnelii*)	Anti-malarial [1]	Chloroquine	7% Tween 80/3% ethanol	100 mg/kg	Inh = 50.2%	Bitew et al., 2017
E. ellenbeckii	Anti-helmentic [2]	Niclosamide	Tap water	500 µg/mL	Mortality rate = 100%	Hymete et al., 2005a
E. kebericho	Anti-malaria [1]	Chloroquine	(3% of Tween 80	500 mg/kg	Inh = 57.3%	Toma et al., 2015
E. kebericho	Anti-helmentic [2]	Niclosamide	Tap water		LD_{50} = 57 µg/mL	Hymete and Kidane 1991

(Continued)

TABLE 5 | Continued

Plant/compound name (Plant)	Effects [Model]	Positive control	Negative control	Dose/Concentration (Rout of administration)	Activity	References
E. longisetus	Anti-helmentic [2]	Niclosamide	Tap water	500 µg/mL	Mortality rate = 100%	Hymete et al., 2005a
E. polyceras	Anti-malarial [2]	NM	Distilled water	0.2% (w/v)	Inh = 96%	Sathiyamoorthy et al., 1999
Essential oil (*E. giganteus*)	Anti-trypanosomal [2]	Suramin	DMSO		IC_{50} = 10.5 µg/mL	Kamte et al., 2017
Essential oil (*E. kebericho*)	Anti-leishmanial [2]	Amphotericin B	1% DMSO		EC_{50} = 0.24 µg/mL	Tariku et al., 2011
Essential oil (*E. kebericho*)	Anti-helmentic [2]	Thiabendazole	0.5% Tween 80 in PBS	1% (v/v)	Inh = 81.8%	Hussien et al., 2011
Effects on insects and termites						
1 (*E. grijsii*)	Larvicidal [2]	Rotenone	0.25% Tween 40		LC_{50} = 0.12 µg/mL	Zhao et al., 2017
1, **2** (*E. ritro* and *E. spinosissimus*)	Termicidal [2]	NM	Distilled water	1% (w/w)	Mortality rate = 100%	Fokialakis et al., 2006b
10 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 14.71 µg/mL	Nakano et al., 2014
14 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 12.45 µg/mL	Nakano et al., 2014
15 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 9.89 µg/mL	Nakano et al., 2014
18 (*E. grijsii*)	Larvicidal [2]	Rotenone	0.25% Tween 40		LC_{50} = 0.33 µg/mL	Zhao et al., 2017
2 (*E. grijsii*)	Larvicidal [2]	Rotenone	0.25% Tween 40		LC_{50} = 1.38 µg/mL	Zhao et al., 2017
2 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 0.16 µg/mL	Nakano et al., 2014
39 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 4.22 µg/mL	Nakano et al., 2014
51 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 7.45 µg/mL	Nakano et al., 2014
52 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 19.97 µg/mL	Nakano et al., 2014
8 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 18.55 µg/mL	Nakano et al., 2014
9 (*E. transiliensis*)	Larvicidal [2]	Permethrin	DMSO		LC_{50} = 17.95 µg/mL	Nakano et al., 2014
Butanol fraction (*E. echinatus*)	Anti- hyperplasia [1]	Finasteride	2% Tween 80	50, 100, and 200 mg/kg (p.o.)	↓ Prostatic/body weight ratio	Agrawal et al., 2012
Butanol fraction (*E. echinatus*)	5α-reductase inhibitory effect [2]	Finasteride	Ethanol		IC_{50} = 0.22 mg	Agrawal et al., 2012
E. echinatus	Anti-fertility [1]	NM	Distilled water	50, 100, and 200 mg/kg	↓ sizes of testes, epididymis, ventral prostate, vas deferens, and seminal vesicle	Chaturvedi et al., 1995
Essential oil (*E. giganteus*)	Larvicidal [2]	NM	DMSO		LC_{50} = 227.4 µL/L	Pavela et al., 2016
Effects on the reproductive system						
Terpenoidal fraction (*E. echinatus*)	Effect on male reproductive parameters [1]	NM	1% Tween 80	60 mg/kg (p.o.)	↓ Seminiferous tubular diameter and germinal epithelial cell thickness	Padashetty and Mishra, 2007
Other activities						
14 (*E. grijsii*)	NQO1 inducing activity [2]	4'-Bromoflavone	NM	40 µM	Induction = 3.1X of the control	Shi et al., 2010
14 (*E. grijsii*)	NQO1 inducing activity [2]	4'-Bromoflavone	NM	2.87 µg/mL	Induction = 2X of the control	Zhang and Ma, 2010
5 (*E. grijsii*)	NQO1 inducing activity [2]	4'-Bromoflavone	NM	1.86 µg/mL	Induction = 2X of the control	Zhang and Ma, 2010
9 (*E. grijsii*)	NQO1 inducing activity [2]	4'-Bromoflavone	NM	2.58 µg/mL	Induction = 2X of the control	Zhang and Ma, 2010
E. echinatus	Anti-diabetic [1]	Sitagliptin	Normal saline	200 mg/kg (p.o.)	↓ Blood glucose level	Fatima et al.2017
E. echinatus	Anti-diabetic [1]	MetforminHCl	1% Tween 80 in saline	200 mg/kg (p.o.)	↓ Blood glucose level	Sarvaiya et al., 2017
E. echinatus	Diuretic	Furosemide	Normal saline	500 mg/kg (p.o.)	↑ Urine volume and electrolyte excretion	Patel et al., 2011a
E. ellenbeckii	Molluscicidal [2]	NM	De-chlorinated tap water	20.25 µg/mL	Mortality rate = 100%	Hymete et al., 2005a
E. giganteus	Amylase inhibitory [2]	NM	Distilled water	NM	> 75%	Etoundi et al., 2010
E. lasiolepis	Immunomodulating activity	NM	DMSO	1 µg/mL	Inhibited PBMCs proliferation	Asadi et al., 2014
E. longisetus	Molluscicidal [2]	NM	De-chlorinated tap water	45 µg/mL	Mortality rate = 100%	Hymete et al., 2005a
E. persicus	Anti-ulcer	NM	Distilled water	500 mg/kg (p.o./i.p.)	↓ Number and level of stomach ulcer	Rad et al., 2010

DMSO, Dimethyl sulfoxide; NM, Not mentioned; p.o., Per os (Oral); i.p., intraperitoneal; [1], In vivo; [2], In vitro.

Anopheles arabiensis with the effectiveness of 92.47% as a smoke (Karunamoorthi et al., 2008).

The activity of thiophenes (**2**, **8**, **9**, **10**, **14**, **15, 39**, **51**, and **52**) isolated from *E. transiliensis* Golosk. against *Aedes aegypti* was reported and the toxic effect increased with the number of thiophene moieties in the molecule. Strong activity was observed for 2''-terthiophene (**2**) with an LC_{50} value of 0.16 µg/mL (Nakano et al., 2014). Similarly, the root extract of *E. grijsii* possessed significant larvicidal activity against *Aedes albopictus*, *Anopheles sinensis*, and *Culex pipienspallens* with LC_{50} values of 2.65, 3.43, and 1.47 µg/mL, respectively.

Bioactivity-directed chromatographic separation of the essential oil obtained from *E. grijsii* led to the isolation of thiophenes. The larvicidal effects of the isolated compounds, 5-(3-buten-1-yn-1-yl)-2,2' -bithiophene (**1**) (LC_{50} 0.34, 1.36, and 0.12 µg/mL), α-terthienyl (**2**) (LC_{50} 1.41, 1.79, and 1.38 µg/mL), and 5-(4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene (**18**) (LC_{50} 0.45, 5.36, and 0.33 µg/mL) against the three organisms mentioned above was described (Zhao et al., 2017). On the contrary, the larvicidal activity of essential oils from *E. giganteus* against *Culex quinquefasciatus* was relatively low (LC_{50} = 227.4 µL/L) (Pavela et al., 2016).

Fokialakis et al. (2006b) evaluated the termicidal effect of eight thiophenes (**1**, **2**, **5**, **10**, **18**, **23**, **31**, and **39**) isolated from *E. ritro*, *E. spinosissimus*, *E. albicaulis*, and *E. transiliensis* on *Coptotermes formosanus*. The study revealed that all the thiophenes showed termicidal activity and 100% morality was observed after application of 5-(3-buten-1-ynyl)-2,2-bithiophene (**1**) and 2''-terthiophene (**2**) for 9 days at 2% and 1% (w/w), respectively. However, the exact concentrations of the compounds were not mentioned.

Effects on the Reproductive System

A number of species have been used for the management of various reproductive health problems (**Table 1**). In spite of the traditional claims, only *E. echinatus* has been evaluated for these biological activities.

Corresponding to its traditional use, the terpenoidal fraction from *E. echinatus* displayed anti-fertility properties at doses of 30 and 60 mg/kg in male rats (Padashetty and Mishra, 2007). Earlier studies also indicated that the root ethanolic extract of *E. echinatus* has anti-fertility properties through decrement in sizes of testes, epididymis, ventral prostate, vas deferens, and seminal vesicle at doses of 50, 100, and 200 mg/kg. In addition, the extract also decreased sperm motility and density with an inhibition of sepermatogenesis in rats (Chaturvedi et al., 1995). The butanol fraction of the root extract demonstrated a protective effect on testosterone-induced prostatic hyperplasia at a dose of 100 mg/kg in rats. The butanol fraction also showed better 5α-reductase inhibitory effect (IC_{50} = 0.22 mg/mL) than of the crude extract and other fractions followed by the water soluble fraction (IC_{50} = 0.43 mg/mL) (Agrawal et al., 2012). Similarly, the root petroleum ether extract of *E. echinatus* inhibited 5α-reductase. The enzyme plays an important role in the pathogenesis of benign prostatic hyperplasia (BPH), prostatic cancer, acne, alopecia, baldness in men, and hirsutism in women (Nahata and Dixit, 2014).

Other Activities

A study showed that 5-(penta-1,3-diynyl)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (**14**), isolated from the root of *E. grijsii*, has an induction effect on nicotinamide adenine dinucleotide phosphate (NAD(P)H): quinone oxidoreductase1 (NQO1), an enzyme that is involved in detoxification of toxic quinones. The induction effect was dose-dependent and the maximum effect was observed at a concentration of 40 µM and it was 3.1 folds of the control, 4'-bromoflavone (Shi et al., 2010). Similarly, compounds **5**, **9**, and **14**, from the root of *E. grijsii*, had a strong NQO1-inducing effect and the concentrations that caused a twofold induction were 1.86, 2.58, and 2.87 µg/mL, respectively. Compounds **5** and **14** were found to have an alkylating effect on cysteine residues in NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) (Zhang and Ma, 2010).

The 70% hydro-alcoholic root extract of *E. echinatus* was reported to have significant anti-diabetic activity on alloxan-induced diabetic rats. The the extract treated animals (200 mg/kg) showed lower blood glucose level (164 mg/dL) compared to the negative control (277.6 mg/dL) after 21 days of treatment. In addition, the extract exhibited the ability to regenerate pancreatic islet cells and normal structure of glomeruli and proximal and distal convoluted tubules in kidneys (Fatima et al., 2017). Similarly, the methanolic root extract of *E. echinatus* exhibited a significant anti-diabetic effect at doses of 100 and 200 mg/kg on alloxan induced diabetic rats. The extract was also able to decrease serum cholesterol, serum triglyceride, serum low-density lipoprotein, serum very low-density lipoprotein, and serum alkaline phosphate significantly while it increased high-density lipoproteins (Sarvaiya et al., 2017).

The molluscicidal activities of 80% methanolic root extracts of *E. ellenbeckii* and *E. longisetus* with a 100% mortality rate at 20.25 and 45 µg/mL, respectively, was described (Hymete et al., 2005a). The pancreatic amylase inhibitory activity (> 75%) of aqueous root extract of *E. giganteus* was reported although the exact concentration of the extract was not mentioned (Etoundi et al., 2010). The latex of *E. persicus* at 500 mg/kg resulted in lower number and level of stomach ulcer compared to the negative control in rats (Rad et al., 2010). The methanolic extract of root and aerial parts of *E. echinatus* significantly increased urine volume and excretion at doses of 250 and 500 mg/kg (Patel et al., 2011a). The immunomodulating activity of aerial parts methanolic extract of *E. lasiolepis* Bunge has been reported. The extract at different concentrations (0.1, 1, 10, 100, and 200 µg/mL) inhibited peripheral blood mononuclear cells (PBMCs) proliferation of which 1 µg/mL showed optimum proliferation (30.66%) (Asadi et al., 2014).

Biological effects evaluated on genus *Echinops* and the doses with maximum effect are summarized in **Tables 3–5**.

CONCLUSION

The genus *Echinops* is well known for its use to treat pain and respiratory manifestations. The traditional claims were justified by different biological evaluations. Findings from *in vitro* studies indicated that members of the genus have a potential

effect against different cancer lines, microbial strains, and insects. They also showed significant *in vivo* anti-inflammatory, analgesic, and hepatoprotective activities. Some of the extracts and isolated compounds showed promising effects. This includes the anticancer activity of compounds **5** and **14**, antioxidant potential of **109**, anti-leishmanial and anti-helmentic effects of *E. kebericho*, and the larvicidal effect of compound **1**. The safety and efficacy of secondary metabolites responsible for the *in vitro* effects of extracts/fractions should further be investigated in *in vivo* models. The most abundant bioactive secondary metabolites in members of the genus are thiophenes and terpenoids which are also mentioned as responsible for the cytotoxic effect observed. In the current review, it has been observed that the potential uses of the species in the removal of kidney stones and use to solve nerve-related problems have not been scientifically addressed yet. Investigation of the anti-microbial activity of isolated compounds seems to be limited. We believe this review will provide summarized information to the scientific community working on the genus.

AUTHOR CONTRIBUTIONS

HB developed concept of the review, conducted the literature review, extracted relevant information to the study, and drafted the manuscript. AH guided the literature search and edited the manuscript. Both authors have read and approved the manuscript.

REFERENCES

Abdallah, H. M., Ezzat, S. M., Dine, R. S., Abdel-Sattar, E., and Abdel-Naim, A. B. (2013). Protective effect of *echinops galalensis* against CCl_4-induced injury on the human hepatoma cell line (Huh7). *Phytochem. Lett.* 6, 73–78. doi: 10.1016/j.phytol.2012.10.01

Abd-Ellatif, S., Abdel Rahman, S. M., and Deraz, S. F. (2011). Promising antifungal effect of some folkloric medicinal plants collected from El-Hammam habitat, Egypt against dangerous pathogenic and toxinogenic fungi. *J. Agric. Biol. Sci.* 6, 25–32.

Abderrahim, O., Martin, G. J., and Abdelaziz, A. (2013). Botanical identification and ethno-medicinal uses of some underground part of medicinal plants collected and traded in Marrakech region. *J. Med. Plants. Res.* 7, 2165–2169. doi: 10.5897/JMPR11.1597

Abdulrasool, A. A., Fahmi, Z. M., and Khadeem, E. J. (2013). Relative assess on wound healing and anti scar activity of crude *Echinops heterophyllus* extract and some of its bioactive fractions. *Int. J. Pharm. Pharm. Sci.* l5, 468–475.

Abdou Bouba, A., Njintang Yanou, N., Foyet, H., Scher, J., Montet, D., and Mbofung, C. M. (2012). Proximate composition, mineral and vitamin content of some wild plants used as spices in Cameroon. *Food Nutr. Sci.* 3, 423–432. doi: 10.4236/fns.2012.34061

Abdulmohsin, H., Raghif, A. A., and Manna, M. J. (2019). The protective effects of *echinops heterophyllus* extract against methotrexate-induced hepatotoxicity in rabbits. *Asian. J. Pharm. Clin. Res.* 12, 384–390. doi: 10.22159/ajpcr.2019.v12i1.30213

Abegaz, B. M. (1991). Polyacetylenic thiophenes and terpenoids from the roots of *echinops pappii*. *Phytochemistry* 30, 879–881. doi: 10.1016/0031-9422(91)85271-Z

Abegaz, B. M., Tadesse, M., and Majinda, R. (1991). Distribution of sesquiterpene lactones and polyacetylenic thiophenes in *Echinops*. *Biochem. Syst. Ecol.* 19, 323–328. doi: 10.1016/0305-1978(91)90021-Q

Abera, B. (2014). Medicinal plants used in traditional medicine by oromo people, ghimbi district, southwest ethiopia. *J. Ethnobiol. Ethnomed.* 10, 40. doi: 10.1186/1746-4269-10-40

Abouri, M., Mousadik, A. E., Msanda, F., Boubaker, H., Saadi, B., and Cherifi, K. (2012). An ethnobotanical survey of medicinal plants used in the Tata Province, Morocco. *Int. J. Med. Plant. Res.* 1, 99–123.

Aburjai, T., Darwish, R. M., Al-khalil, S., Mahafzah, A., and Al-abbadi, A. (2001). Screening of antibiotic resistant inhibitors from local plant materials against two different strains of *Pseudomonas aeruginosa*. *J. Ethnopharmacol.* 76, 39–44.

Afshaki, S., Jafari, A., Javidnia, K., and Firuzi, O. (2012). Antioxidant and cytotoxic activities of four plant extracts from dena region of Iran. *Res. Pharm. Sci.* 7, S853.

Agrawal, M., Nahata, A., and Dixit, V. K. (2012). Protective effects of *echinops echinatus on* testosterone-induced prostatic hyperplasia in rats. *Eur. J. Integr. Med.* 4, 177–185. doi: 10.1016/j.eujim.2012.01.004

Ahmad, M., Ghafoor, N., and Aamir, M. N. (2012). Antibacterial activity of mother tinctures of cholistan desert plants in Pakistan. *Indian. J. Pharm. Sci.* 74, 465–468. doi: 10.4103/0250-474X.108429

Akdime, H., Boukhira, S., Mansouri, L. E. L., El, A. H., and Bousta, D. (2015). Ethnobotanical study and traditional knowledge of medicinal plants in ain leuh region (Middle-Atlas of Morocco). *Am. J. Adv. Drug. Deliv.* 3, 248–263.

Alam, M. K., Ahmed, S., Anjum, S., Akram, M., Shah, S. M., Wariss, H. M., et al. (2016). Evaluation of antipyretic activity of some medicinal plants from Cholistan desert Pakistan. *Pak. J. Pharm. Sci.* 29, 529–533.

Ameya, G., Gure, A., and Dessalegn, E. (2016). Antimicrobial activity of *echinops kebericho* against human pathogenic bacteria and fungi. *Afr. J. Tradit. Complement. Altern. Med.* 13, 199–203.

Amsalu, N., Bezie, Y., Fentahun, M., Alemayehu, A., and Amsalu, G. (2018). Use and conservation of medicinal plants by indigenous people of gozamin wereda, east gojjam zone of amhara region, ethiopia: an ethnobotanical approach. *evidence-based. complement. altern. Med.* 2018, 1–23. doi: 10.1155/2018/2973513

Arroo, R. R., Jacobs, J. J., Van Gestel, J. A., Kenkel, H., Jannink, W., Croes, A. F., et al.. (1997). Regulation of thiophene biosynthesis by sulphate in roots of marigolds. *New. Phytol.* 135, 175–181.

Asadbeigi, M., Mohammadi, T., Rafieian-Kopaei, M., Saki, K., Bahmani, M., and Delfan, M. (2014). Traditional effects of medicinal plants in the treatment of respiratory diseases and disorders: an ethnobotanical study in the Urmia. *Asian. Pac. J. Trop. Med.* 7, S364–S368.

Asadi, M., Hadinedoushan, H., Mirghanizadeh, S. A., Karimollah, A., Dashti, F., and Malek-hosseini, S. (2014). The effect of *echinops lasiolepis* extracts, native plant of yazd province, on peripheral blood mononuclear cellproliferation and IFN-γ Secretion. *Int. J. Med. Lab.* 1, 7—14.

Ashebir, M., and Ashenafi, M. (1999). Evaluation of the anibactrtial activity of crude preparation of *zingiber officinale* (zinjibl) *echinops* spp. (kebericho), *coriandrum sativum* (dimbilal), and *cymbopogan citraus* (tej sar) on some food-borne pathogens. *Ethiop. J. Hlth. Sci.* 9, 33–39.

Aydın, Ç., Özcan, G. T., Turan, M., and Mammadov, R. (2016). Phenolic contents and antioxidant properties of *echinops ritro* L. and *E. tournefortii* Jaup. Et. Spach extract. *Int. J. Sec. Metabolite.* 3, 74–81.

Baydoun, S., Chalak, L., Dalleh, H., and Arnold, N. (2015). Ethnopharmacological survey of medicinal plants used in traditional medicine by the communities of mount hermon, Lebanon. *J. Ethnopharmacol.* 173, 139–156. doi: 10.1016/j.jep.2015.06.052

Belay, G., Tariku, Y., Kebede, T., Hymete, A., and Mekonnen, Y. (2011). Ethnopharmacological investigations of essential oils isolated from five ethiopian medicinal plants against eleven pathogenic bacterial strains. *Phytopharmacology* 1, 133–143.

Belayneh, A., and Bussa, N. F. (2014). Ethnomedicinal plants used to treat human ailments in the prehistoric place of harla and dengego valleys, eastern ethiopia. *J. Ethnobiol. Ethnomed.* 1, 18. doi: 10.1186/1746-4269-10-18

Biruksew, A., Zeynudin, A., Alemu, Y., Golassa, L., Yohannes, M., Debella, A., et al. (2018). *Zingiber Officinale* Roscoe and *Echinops Kebericho* Mesfin showed antiplasmodial activities against *Plasmodium berghei* in a dose-dependent manner in Ethiopia. *Ethiop. J. Health. Sci.* 28, 655. doi: 10.4314/ejhs.v28i5.17

Bitew, H., Mammo, W., Hymete, A., and Yeshak, M. Y. (2017). Antimalarial activity of acetylenic thiophenes from *echinops hoehnelii* schweinf. *Molecules* 22, 1965. doi: 10.3390/molecules22111965

Bizuayehu, B., and Garedew, B. (2018). A review on the ethnobotanical study of medicinal plants used for the treatment of gonorrhea disease in Ethiopia. *Indian. J. Nat. Prod. Resour.* 9, 183–193.

Bouattour, E., Fakhfakh, J., Dammak, F., Jabou, K., and Damak, M. (2016). Hexane extract of *echinops spinosissimus* turra subsp. spinosus from tunisia: a potential source of acetylated sterols – investigation of its Biological Activities. *Chem. Biodivers.* 13, 1674–1684. doi: 10.1002/cbdv.2016001182016;1674–84

Bouba, A., Njintang, Y. N., Scher, J., and Mbofung, C. M. F. (2010). Phenolic compounds and radical scavenging potential of twenty cameroonian spices. *Agric. Biol. J. N. Am.* 1, 213–224.

Boumaraf, M., Benyahia, S., Mekkiou, R., Benayache, S., and Benayache, F. (2016). Flavonoids from ethyl acetate extract of *echinops spinosus* (Asteraceae). *Der Pharma. Chemica.* 8, 158–160.

Bouzabata, A., Mahomoodally, F., and Tuberoso, C. (2018). Ethnopharmacognosy of Echinops spinosus L. in North Africa: a mini review. *J. Complement. Med. Res.* 8, 40–52. doi: 10.5455/jcmr.20180318051853

Bulut, G., Haznedaroğlu, M. Z., Doğan, A., Koyu, H., and Tuzlacı, E. (2017). An ethnobotanical study of medicinal plants in acipayam (Denizli-Turkey). *J. Herb. Med.* 10, 64–81. doi: 10.1016/j.hermed.2017.08.001

Chadwick, M., Trewin, H., Gawthrop, F., and Wagstaff, C. (2013). Sesquiterpenoids lactones: benefits to plants and people. *Int. J. Mol. Sci.* 14, 12780–12805. doi: 10.3390/ijms140612780

Chang, F. P., Chen, C. C., Huang, H. C., Wang, S. Y., Chen, J. J., Yang, C. S., et al. (2015). A new bithiophene from the root of *echinops grijsii*. *Nat. Prod. Commun.* 12, 2147–2149.

Chaturvedi, M., Mali, P. C., and Dexit, V. P. (1995). Antifertility effects of the roots of *echinops echinatus* (Roxb.) in male rats. *J. Phytol. Res.* 8, 115–118.

Chaudhuri, P. K. (1987). Echinozolinone, an alkaloid from *echinops echinatus*. *Phytochemistry* 26, 587–589.

Chaudhuri, P. K. (1992). 7-hydroxyechinozolinone, a new alkaloid from the flowers of *Echinops echinatus*. *J. Nat. Prod.* 55, 249–250. doi: 10.1021/np50080a019

Chermat, S., and Gharzouli, R. (2015). Ethnobotanical study of medicinal flora in the north east of algeria - an empirical knowledge in djebel zdimm (Setif). *J. Mater. Sci. Eng. A* 5, 50–59.

Dangwal, L. R., Rana, C. S., and Sharma, A. (2011). Ethno-medicinal plants from transitional zone of nanda devi biosphere reserve, district chamoli, uttarakhand (India). *Indian. J. Nat. Prod. Resour.* 2, 116–120.

Desta, B. (1995). Ethiopian traditional herbal drugs. Part I: studies on the toxicity and therapeutic activity of local taenicidal medications. *J. Ethnopharmacol.* 45, 27–33.

Dong, L. I., Ning, L. I., Wan, X. I., Peng, Z. H., Zhong-jun, M. A., and Xian, L. I. (2008a). Chemical constituents of the root of *echinops grijisii* Hance. *Shenyang. Yao. Ke. Da. Xue. Xue. Bao.* 8, 007.

Dong, M., Cong, B., Yu, S. H., Sauriol, F., Huo, C. H., Shi, Q. W., et al. (2008b). Echinopines A and B: sesquiterpenoids possessing an unprecedented skeleton from *Echinops spinosus*. Org. *Lett.* 10, 701–704. doi: 10.1021/ol702629z

El Abbouyi, P. A., Ansari, N. F., Khyari, P. S. E., and Loukili, H. (2014). Inventory of medicinal plants prescribed by traditional healers in El Jadida city and suburbs (Morocco). *Int. J. Green Pharm.* 8, 242–251.

El-Ghazali, G. E., Al-Khalifa, K. S., Saleem, G. A., and Abdallah, E. M. (2010). Traditional medicinal plants indigenous to Al-Rass province, Saudi Arabia. *J. Med. Plants. Res.* 4, 2680–2683. doi: 10.5897/JMPR09.556

Eram, S., Ahmad, M., and Arshad, S. (2013). Experimental evaluation of *echinops echinatus* as an effective hepatoprotective. *Sci. Res. Essays.* 8, 1919–1923. doi: 10.5897/SRE2012.0766

Erenler, R., Yilmaz, S., Aksit, H., Sen, O., Genc, N., Elmastas, M., et al. (2014). antioxidant activities of chemical constituents isolated from *echinops orientalis* Trauv. *Rec. Nat. Prod.* 8, 32–36.

Etoundi, C. B., Kuaté, D., Ngondi, J. L., and Oben, J. (2010). Anti-amylase, anti-lipase and antioxidant effects of aqueous extracts of some cameroonian spices. *J. Nat. Prod.* 3, 165–171.

Fankam, A. G., Kuete, V., Voukeng, I. K., Kuiate, J. R., and Pages, J. (2011). Antibacterial activities of selected cameroonian spices and their synergistic effects with antibiotics against multidrug-resistant phenotypes. *BMC Complement. Altern. Med.* 11, 104. doi: 10.1186/1472-6882-11-104

Farouji, A. E., and Khodayari, H. (2016). Ethnomedicinal plants of Farouj district, north khorasan province, Iran. *J. Herbal. Drugs.* 7, 21–36.

Fatima, S., Afroz, S., and Qureshi, A. S. (2017). Anti-diabetic activity of hydro-alcoholic root extract of *echinops echinatus* and its beneficial effects on nephropathy in experimental rats. *Indian. J. Res. Pharm. Biotechnol.* 5, 19–27.

Fenetahun, Y., and Eshetu, G. (2017). A review on ethnobotanical studies of medicinal plants use by agro-pastoral communities in, Ethiopia. *J. Med. Plants. Stud.* 5, 33–44.

Fokialakis, N., Cantrell, C., Duke, S. O., Skaltsounis, A. L., and Wedge, D. E. (2006a). Antifungal activity of thiophenes from *echinops ritro*. *J. Agric. Food Chem.* 54, 1651–1655.

Fokialakis, N., Osbrink, W. L. A., Mamonov, L. K., Gemejieva, N. G., Mims, A. B., Skaltsounis, A. L., et al. (2006b). Antifeedant and toxicity effects of thiophenes from four *echinops* species against the formosan subterranean termite, *coptotermes formosanus*. *Pest. Manag. Sci.* 62, 832–838. doi: 10.1002/ps.1237

Funk, V. A., Bayer, R. J., Keeley, S., Chan, R., Watson, L., Gemeinholzer, B., et al.., (2005). Everywhere but antarctica: using a super tree to understand the diversity and distribution of the compositae. *Biol. Skr.* 55, 343–374.

Gabriel, T., and Guji, T. (2014). Ethnopharmacological survey of medicinal plants in Agaro district, Jimma zone, South West Ethiopia. *Int. J. Pharm. Sci. Res.* 5, 3551. doi: 10.13040/IJPSR.0975-8232.5(8).3551-59

Gari, A., Yarlagadda, R., and Wolde-Mariam, M. (2015). Knowledge, attitude, practice, and management of traditional medicine among people of Burka Jato Kebele, West Ethiopia. *J. Pharm. Bioall. Sci.* 7, 136–144. doi: 10.4103/0975-7406.148782

Garnatje, T., Susanna, A., Garcia-Jacas, N., Vilatersana, R., and Vallès, J. (2005). A first approach to the molecular phylogeny of the genus *Echinops* (Asteraceae): Sectional delimitation and relationships with the genus *Acantholepis*. *Folia. Geobot.* 40, 407–419.

Ghasemi Pirbalouti, A., Momeni, M., and Bahmani, M. (2013). Ethnobotanical study of medicinal plants used by Kurd tribe in Dehloran and Abdanan districts, Ilam province, Iran. *Afr. J. Tradit. Complement. Altern. Med.* 10, 368–385. doi: 10.4314/ajtcam.v10i2.24

Giday, M., Asfaw, Z., and Woldu, Z. (2010). Ethnomedicinal study of plants used by Sheko ethnic group of Ethiopia. *J. Ethnopharmacol.* 132, 75–85. doi: 10.1016/j.jep.2010.07.046

Guo, D. A., Lou, Z. C., and Liu, Z. A. (1994). Chemical components of volatile oil from *Echinops grijisii* Hance. *Zhongguo. Zhong. Yao. Za. Zhi.* 19, 100–101.

Gupta, R., Vairale, M. G., Deshmukh, R. R., Chaudhary, P. R., and Wate, S. R. (2010). Ethnomedicinal uses of some plants used by Gond tribe of Bhandara district, Maharashtra. *Indian J. Tradit. Knowl.* 9, 713–717.

Hamayun, M., Khan, M. A., Chudhary, M. F., and Ahmad, H. (2006). Studies on traditional knowledge of medicinal herbs of swat kohistan, District Swat, Pakistan. *J. Herbs. Spices. Med. Plants.* 12, 11–28. doi: 10.1300/J044v12n04_02

Hammiche, V., and Maiza, K. (2006). Traditional medicine in central sahara: pharmacopoeia of tassili n'ajjer. *J. Ethnopharmacol.* 105, 358–367. doi: 10.1016/j.jep.2005.11.028

He, L., Chao, Q., Li, R., Lin, G., and Huang, H. (2000). A new pentacyclic triterpene, gmeliniin A, from *Echinops gmelinii* Turcz. *Chin. J. Chem.* 18, 112–114.

Hedberg, I., Friis, I., and Edwards, S. (2004). "Vol. 4, part 2'," in *Flora of Ethiopia and Eritrea* (Addis Ababa: Addis Ababa University), 15–23.

Heshmati, S., Madani, M., and Amjad, L. (2016). Study of inhibitory effect of *echinops cephalotes on candida* spp isolated from vulvovaginal candidiasis Patients in Isfahan. *J. Res. Med. Sci.* 18, e7355. doi: 10.17795/zjrms-7355

Hussien, J., Urgessa, K., Regassa, F., Jemal, A., Abajebel, S., and Hussien, N. (2011). Antihelmentic effects of the essential oil extracts of selected plants against *Haemonchus contortus*. *Int. J. Agric. Res.* 6, 290–298.

Hymete, A., and Kidane, A. (1991). Screening for anthelmintic activity in two *Echinops* spp. Ethiop. *Pharm. J.* 9, 67–71.

Hymete, A., Iversen, T. H., Rohloff, J., and Erko, B. (2005a). Screening of *echinops ellenbeckii* and *echinops longisetus* for biological activities and chemical constituents. *Phytomedicine* 12, 675–679. doi: 10.1016/j.phymed.2004.01.013

Hymete, A., Rohloff, J., and Iversen, T. H. (2004). Chemical constituents of volatile fractions from *echinops ellenbeckii* O. Hoffm. *J. Essent. Oil. Bear Pl.* 7, 9–15. doi: 10.1080/0972-060X.2004.10643359

Hymete, A., Rohloff, J., Kjosen, H., and Iversen, T. H. (2005b). Acetylenic thiophenes from the roots of *echinops ellenbeckii* from Ethiopia. *Nat. Prod. Res.* 19, 755–761. doi: 10.1080/1478641012000301711

Issa, T. O., Mohamed, Y. S., Yagi, S., Ahmed, R. H., Najeeb, T. M., Makhawi, A. M., et al. (2018). Ethnobotanical investigation on medicinal plants in Algoz area

(South Kordofan), Sudan. *J. Ethnobiol. Ethnomed.* 14, 1–22. doi: 10.1186/s13002-018-0230-y

Jabeen, N., Ajaib, M., Siddiqui, M. F., Ulfat, M., and Khan, B. (2015). A survey of ethnobotanically important plants of District Ghizer, Gilgit-Baltistan. *FUUAST. J. Biol.* 5, 153–160.

Jiang, B., Wang, F., Liu, L., Tian, S., Li, W., Yang, X., et al. (2017). Antibacterial activity and action mechanism of the *echinops ritro* L. essential oil against foodborne pathogenic bacteria. *J. Essent. Oil Bear. Pl.* 20, 1172–1183. doi: 10.1080/0972060X.2017.1399090

Jin, Q., Lee, J. W., Jang, H., Choi, J. E., Kim, H. S., and Lee, D. (2016). Dimeric sesquiterpene and thiophenes from the roots of *Echinops latifolius.* Bioorg. *Med. Chem. Lett.* 26, 5995–5998. doi: 10.1016/j.bmcl.2016.10.017

Jin, W., Sh, , i Q., Hong, C., Cheng, Y., Ma, Z., and Qu, H. (2008). Cytotoxic properties of thiophenes from *echinops grijissi* Hance. *Phytomedicine* 15, 768–774. doi: 10.1016/j.phymed.2007.10.007

Ka, S. (2001). A pseudoguaiane sesquiterpene xylopyranoside *from Echinops hussoni*. *Pharmazie* 56, 415–417.

Kamatenesi, M. M., Acipa, A., and Oryem-Origa, H. (2011). Net medicinal plants of otwal and ngai sub counties in oyam district, northern uganda. *J. Ethnobiol. Ethnomed.* 7, 1–14. doi: 10.1186/1746-4269-7-7

Kamte, S. L. N., Ranjbarian, F., Campagnaro, G. D., Nya, P. C. B., Woguem, V., Womeni, H. M., et al. (2017). *Trypanosoma brucei* Iinhibition by essential oils from medicinal and aromatic plants traditionally used in cameroon (*Azadirachta indica*, *Aframomum melegueta*, *Aframomum daniellii*, *Clausena anisata*, *Dichrostachys cinerea* and *Echinops giganteus*). *Int. J. Environ. Res. Public. Health.* 14, 737. doi: 10.3390/ijerph14070737

Karimov, U. T., and Aisa, H. A. (2012). Phytochemical study of the plant Echinops integrifolius growing in the Altai (XUAR PRC). *Chem.Nat. Compd.* 48, 903–905

Karimov, U. T., and Aisa, H. A. (2013). Hydrocarbons and fatty acids from *echinops integrifolius*. *Chem. Nat. Compd* 49, 920–921. doi: 10.1007/s10600-013-0778-7

Karunamoorthi, K., Mulelam, A., and Wassie, F. (2008). Laboratory evaluation of traditional insect/mosquito repellent plants against anopheles arabiensis, the predominant malaria vector in ethiopia. *Parasitol. Res.* 103, 529–534. doi: 10.1007/s00436-008-1001-9

Katiri, A., Barkaoui, M., Msanda, F., and Boubaker, H. (2017). Ethnobotanical survey of medicinal plants used for the treatment of diabetes in the tizi n' test region (Taroudant Province, Morocco). *J. Pharmacogn. Nat. Prod.* 03, 1–10. doi: 10.4172/2472-0992.1000130

Kevin, K., John, K., Carolyn, N., Derrick, S., and Lubega, A. (2018). *In* vitro anti-tuberculosis activity of total crude extract of *echinops amplexicaulis* against multi-drug resistant *Mycobacterium tuberculosis*. *J. Health. Sci* 6, 296–303. doi: 10.17265/2328-7136/2018.04.008

Khadim, E. J., Abdulrasool, A. A., and Awad, Z. J. (2014). Phytochemical investigation of alkaloids in the iraqi *echinops heterophyllus* (Compositae). *Iraqi J. Pharm. Sci.* 23, 26–34.

Kitata, G., Abdeta, D., and Amante, M. (2017). Ethnoknowledge of plants used in veterinary practices in midakegn district, west showa of oromia region, Ethiopia. *J. Med. Plants. Stud.* 5, 282–288.

Kiyekbayeva, L., Mohamed, N. M., Yerkebulan, O., Mohamed, E. I., Ubaidilla, D., Nursulu, A., et al. (2017). Phytochemical constituents and antioxidant activity of *echinops albicaulis*. *Nat. Prod. Res.* 32, 1203–1207. doi: 10.1080/14786419.2017.1323213

Kuete, V., Krusche, B., Youns, M., Voukeng, I., Fankam, A. G., Tankeo, S., et al. (2011). Cytotoxicity of some cameroonian spices and selected medicinal plant extracts. *J. Ethnopharmacol.* 134, 803–812. doi: 10.1016/j.jep.2011.01.035

Kuete, V., Sandjo, L. P., Wiench, B., and Efferth, T. (2013). Cytotoxicity and modes of action of four cameroonian dietary spices ethno-medically used to treat cancers: *echinops giganteus*, *xylopia aethiopica*, *imperata cylindrica* and *piper capense*. *J. Ethnopharmacol.* 149, 245–253. doi: 10.1016/j.jep.2013.06.029

Kumar, H., Khajuria, A. K., and Bisht, N. S. (2018). Traditional phytoremedies used to treatment urolithiasis in Pauri (Garhwal) Uttarakhand India. *J. Pharmacogn. Phytochem.* 7, 2941–2944.

Kumar, S., and Pandey, S. (2015). An ethnobotanical study of local plants and their medicinal importance in tons river area, dehradun, uttarakhand. *Indian. J. Trop. Biodivers.* 23, 227–231.

Lamorde, M., Tabuti, J. R. S., Obua, C., Kukunda-Byobona, C., Lanyero, H., Byakika-Kibwika, P., et al. (2010). Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda. *J. Ethnopharmacol.* 130, 43–53. doi: 10.1016/j.jep.2010.04.004

Li, L., Ren, J., Cheng, Z., and Zhu, H. (2010). Three new sesquiterpenoids from *echinops ritro* L. *Helve. Chimica. Acta.* 93, 1344–1349.

Li, L. B., Xiao, G. D., Xiang, W., Yang, X., Cao, K. X., and Huang, R. S. (2019). Novel substituted thiophenes and sulf-polyacetylene ester from *Echinops ritro* L. *Molecules* 24, 805. doi: 10.3390/molecules24040805

Lin, C. C., and Lin, C. H. (1993). Pharmacological and pathological studies on taiwan folk medicine (IX): the heptoprotective effect of the methanolic extract of *Echinops grijissi*. *Am. J. Chin. Med. XXI*, 21, 33–34.

Lin, C. C., Lin, C. H., Chiu, H. F., and Hu, M. F. (1992). Pharmacological and pathological studies on taiwan folk medicine (VII): the anti-inflammatory effect of *Echinops grijissi*. *Am. J. Chin. Med. XX*, 20, 127–134.

Liu, Y., Ye, M., Guo, H. Z., Zhao, Y. Y., and Guo, D. A. (2002). New thiophenes from *echinops grijisii*. *J. Asian. Nat. Prod. Res.* 4, 175–178. doi: 10.1080/1028602021000000071

Mahmood, A. A. R., and Khadeem, E. J. (2013). Phytochemical investigation of flavonoids glycoside in the Iraqi *Echinops heterophyllus* (Compositae). *Pharm. Glob.* 4, 1.

Mahmoud, T., and Gairola, S. (2013). Journal of medicinal plants studies traditional knowledge and use of medicinal plants in the eastern desert of egypt : a case study from Wadi El-Gemal National Park. *J. Med. Plants. Stud.* 1, 10–17.

Malik, K., Ahmad, M., Zhang, G., Rashid, N., Zafar, M., Sultana, S., et al. (2018). Traditional plant based medicines used to treat musculoskeletal disorders in Northern Pakistan. *Eur. J. Integr. Med.* 19, 17–64. doi: 10.1016/j.eujim.2018.02.003

Maru, R. N., Patel, H. R., and Patel, R. S. (2018). Some plants used for the treatment of eye and earche from forest areas of Jhalod Taluka, Dahod District, Gujarat, India. *Int. J. S. Res. Sci. Tech.* 4, 578–581.

Maurya, S. K., Kushwaha, A. K., and Seth, A. (2015). Ethnomedicinal review of Usnakantaka (*Echinops echinatus* Roxb.). *Pharmacogn. Rev.* 9, 149–154. doi: 10.4103/0973-7847.162138

Mekuanent, T., Zebene, A., and Solomon, Z. (2015). Ethnobotanical study of medicinal plants in chilga district, northwestern ethiopia. *J. Nat. Remedies.* 15, 88–112. doi: 10.18311/jnr/2015/476

Menut, C., Lamaty, G., Weyerstahl, P., Marschall, H., Seelmann, I., and Amvam Zollo, P. H. (1997). Aromatic plants of tropical Central Africa. Part XXXI. Tricyclic sesquiterpenes from the root essential oil of Echinops giganteus var. lelyi CD Adams. Flavour. *Frag. J.* 12, 415–421

Meragiaw, M., Asfaw, Z., and Argaw, M. (2016). The status of ethnobotanical knowledge of medicinal plants and the impacts of resettlement in Delanta, northwestern Wello, northern Ethiopia. *Evid. Based. Complement. Alternat. Med.* 2016, 24. doi: 10.1155/2016/5060247

Merzouki, A., Ed-derfoufi, F., and Mesa, J. M. (2000). Contribution to the knowledge of Rifian traditional medicine. II: folk medicine in Ksar Lakbir district (NW Morocco). *Fitoterapia.* 71, 278–307.

Mesfin, F., Seta, T., and Assefa, A. (2014). An ethnobotanical study of medicinal plants in Amaro Woreda Ethiopia. *Ethnobot. Res. Appl.* 12, 341–354.

Miao, C. G., Zhou, G. L., Qin, M. S., Chen, J. Z., Li, C. F., and Zhang, B. (2015). Treatment of rheumatoid arthritis with flavonoids of *echinps latifolius* tausch in rat model. *Zhejiang. Da. Xue. Xue. Bao. Yi. Xue. Ban.* 44, 43–48.

Mohseni, S., Sani, A. M., Tavakoli, M., and Raoufi, A. M. (2017). Effect of extraction conditions on antioxidant activities of *echinops persicus*. *J. Essent. Oil. Bear. Pl.* 20, 1633–1644. doi: 10.1080/0972060X.2017.1399088

Moravec, I., Fernández, E., Vlkova, M., and Milella, L. (2014). Ethnobotany of medicinal plants of northern ethiopia. *Bol. Latinoam. Caribe. Plantas. Me. Aromát.* 13, 126–134.

Mustafa, B., Hajdari, A., Krasniqi, F., Hoxha, E., Ademi, H., Quave, C. L., et al. (2012). Medical ethnobotany of the albanian alps in kosovo. *J. Ethnobiol. Ethnomed.* 8, 1–14. doi: 10.1186/1746-4269-8-6

Nahata, A., and Dixit, V. K. (2014). Evaluation of 5α-reductase inhibitory activity of certain herbs useful as antiandrogens. *Andrologia.* 46, 592–601. doi: 10.1111/and.12115

Nakano, H., Ali, A., Rehman, J. U., Mamonov, L. K., Cantrell, C. L., and Khan, I. A. (2014). Toxicity of thiophenes from *echinops transiliensis* (Asteraceae) against *a aegypti* (Diptera: Culicidae) larvae. *Chem. Biodivers.* 11, 1001–1009.

Nakano, H., Cantrell, C. L., Mamono, L. K., Osbrink, W. L. A., and Ross, S. A. (2011). Echinopsacetylenes A and B, new thiophenes from *Echinops transiliensis*. *Org. Lett.* 13, 6228–6231. doi: 10.1021/ol202680a

Nakano, H., Cantrell, C. L., Mamonov, L. K., Kustova, T. S., Fronczek, F. R., and Ross, S. A. (2012). Chemical constituents from *Echinops nanus* and *Echinops transiliensis*. *Biochem. Syst. Ecol.* 45, 127–129. doi: 10.1016/j.bse.2012.07.008

Nawash, O., Shudiefat, M., Al-Tabini, R., and Al-Khalidi, K. (2013). Ethnobotanical study of medicinal plants commonly used by local bedouins in the badia region of Jordan. *J. Ethnopharmacol.* 148, 921–925. doi: 10.1016/j.jep.2013.05.044

Nyang'au, H. O., Maingi, J., Kebira, A., Muriithi, I. A., Muthoni, N. P., Ntarara, M. G., et al. (2017). The efficacy of some medicinal plants used locally within Transmara west, Narok County, Kenya against selected *Enterobacteria* and *Candida*. *Infection* 11, 13.

Okello, J., and Ssegawa, P. (2007). Medicinal plants used by communities of Ngai Subcounty, Apac District, northern Ugand. *Afr. J. Ecol.* 45, 76–83.

Padashetty, S. A., and Mishra, S. H. (2007). Effect of terpenoidal fraction of *Echinops echinatus* roots on reproductive parameters of male rats. *J. Nat. Med.* 61, 452–457. doi: 10.1007/s11418-007-0173-4

Papadopoulou, P., Couladis, M., and Tzakou, O. (2006). Essential Oil Composition of two Greek *Echinops* species: *E. graecus* Miller and *E. ritro* L. *J. Essent. Oil. Res.* 18, 242–243. doi: 10.1080/10412905.2006.9699076

Patel, A. J. (2016). Isolation and characterization of lupeol from *Echinops echinatus* Roxb. *Root. Eur. J. Pharm. Med. Res.* 3, 385–387.

Patel, A. J., Patel, N. M., Patel, A. A., Patel, J., and Patel, S. (2011b). Comparative analgesic activity of root and aerial part methanolic extracts of *Echinops echinatus* Roxb. *Int. J. Pharm. Innov.* 1, 23–29.

Patel, A. J., Patel, N. M., Patel, A. A., Patel, J., and Patel, S. (2011a). Comparative diuretic activity of root and aerial part methanolic extracts of *Echinops echinatus* Roxb. *Pharm. Lett.* 3, 168–172.

Pavela, R., Maggi, F., Mbuntcha, H., Woguem, V., Fogang, H. P. D., Womeni, H. M., et al. (2016). Traditional herbal remedies and dietary spices from cameroon as novel sources of larvicides against filariasis mosquitoes? *Parasitol. Res.* 115, 4617–4626. doi: 10.1007/s00436-016-5254-4

Qureshi, R., and Bhatti, G. R. (2008). Ethnobotany of plants used by the Thari people of Nara Desert, Pakistan. *Fitoterapia.* 79, 468–473. doi: 10.1016/j.fitote.2008.03.010

Rad, A. A., Najafzadeh-Varzi, H., and Farajzadeh-Sheikh, A. (2010). Evaluation of anti-ulcer activity of *echinops persicus* on experimental gastric ulcer models in rats. *Vet. Res. Forum.* 1, 188–189.

Radulović, N. S., and Denić, M. S. (2013). Essential oils from the roots of *echinops bannaticus* rochel ex schrad. and *echinops sphaerocephalus* L.(Asteraceae): chemotaxonomic and biosynthetic aspects. *Chem. Biodivers.* 10, 658–676. doi: 10.1002/cbdv.201200330

Rahman, S. M., Abd-Ellatif, S. A., Deraz, A. F., and Khalil, A. A. (2011). Antibacterial activity of some wild medicinal plants collected from western mediterranean coast, Egypt: natural alternatives for infectious disease treatment. *Afr. J. Biotechnol.* 10, 10733–10743. doi: 10.5897.AJB11.007

Ram, S. N., Roy, R., Singh, B., Singh, R. P., and Pandey, V. B. (1995). An acylfiavone glucoside of *echinops echinatus* flowers. *Planta. Med.* 62, 187.

Rathore, S., Tiwari, J. K., and Malik, Z. A. (2015). Ethnomedicinal survey of herbaceous flora traditionally used in health care practices by inhabitants of dhundsir gad watershed of garhwal himalaya, India. *Global. J. Res. Med. Plants. Indigen. Med.* 4, 65–78.

Regassa, R. (2013). Assessment of indigenous knowledge of medicinal plant practice and mode of service delivery in Hawassa city, southern Ethiopia. *J. Med. Plants.* 7, 517–535.

Regassa, R., Bekele, T., and Megersa, M. (2017). Ethnobotonical study of traditional medicinal plants used to treat human ailments by halaba people, southern Ethiopia. *J. Med. Plants. Stud.* 36, 36–47.

Rimbau, V., Cerdan, C., Vila, R., and Iglesias, J. (1999). Antiinflammatory activity of some extracts from plants used in the traditional medicine of North-African countries (II). *Phytother. Res.* 13, 128–132.

Sajjad, A., Adnan, S., Hasnain Alam, H., and Mohamed, E. A. R. (2017). Ethno botanical study of traditional native plants in Al Ain UAE. *Int. J. Adv. Res. Biol. Sci.* 4, 165–174. doi: 10.22192/ijarbs.2017.04.02.020

Saleh Fares, G. O., Abdallah, L., Almasri, M., Slaileh, A., and Zurba, Z. (2013). Antibacterial activity of selected palestinian wild plant extracts against multidrug-resistant clinical isolate of *streptococcus pneumoniae*. *JPR : BioMedRx: Int J.* 1, 963–969.

Sánchez-Jiménez, I., Lazkov, G. A., Hidalgo, O., and Garnatje, T. (2010). Molecular systematics of *Echinops* L. (Asteraceae, Cynareae): A phylogeny based on ITS and trnL-trnF sequences with emphasis on sectional delimitation. *Taxon.* 59, 698–708.

Sandjo, L. P., Kuete, V., Siwe, X. N., and Poumale, H. M. P. (2016). Cytotoxicity of an unprecedented brominated oleanolide and a new furoceramide from the Cameroonian spice, *Echinops giganteus*. *Nat. Prod. Res.* 30, 2529–2537. doi: 10.1080/14786419.2015.1120724

Sarvaiya, D. D., Sheth, N. R., and Dudhrejiya, A. V. (2017). Antidiabetic and antioxidant activity of roots of *Echinops echinatus* Roxb. *Pharmacologyonline.* 2, 10–39.

Sathiyamoorthy, P., Lugasi-Evgi, H., Schlesinger, P., Kedar, I., Gopas, J., Pollack, Y., et al. (1999). Screening for cytotoxic and antimalarial activities in desert plants of the negev and bedouin market plant products. *Pharm. Biol.* 37, 188–195.

Senejoux, F., Demougeot, C., Karimov, U., Muyard, F., Kerram, P., Aisa, H. A., et al. (2013). Chemical constituents from *echinops integrifolius*. *Biochem. Syst. Ecol.* 47, 42–44. doi: 10.1016/j.bse.2012.10.013

Sharma, J., Gairola, S., Gaur, R. D., and Painuli, R. M. (2012). The treatment of jaundice with medicinal plants in indigenous communities of the sub-himalayan region of uttarakhand, India. *J. Ethnopharmacol.* 143, 262–291. doi: 10.1016/j.jep.2012.06.034

Sharma, P. K., Chauhan, N. S., and Lal, B. (2004). Observations on the traditional phytotherapy among the inhabitants of Parvati valley in western Himalaya, India. *J. Ethnopharmacol.* 92, 167–176. doi: 10.1016/j.jep.2003.12.018

Shende, A. N., Mohture, V. M., and Korpenwar, A. N. (2018). Traditional medicinal plants used against various diseases in Nagbhid tahsil, Chandrapur (MS) India. *Int. J. Life. Sci. A* 12, 135–142.

Shi, J., Zhang, X., and Jiang, H. (2010). 2-(Penta-1,3-diynyl)-5-(3,4-dihydroxybut-1-ynyl)thiophene, a novel NQO1 inducing agent from *Echinops grijsii* Hance. *Molecules* 15, 5273–5281. doi: 10.3390/molecules15085273

Shilema, A., Zerom, K., and Mussa, A. (2013). Ethnoveterinary practices against animal trypanosomosis in Amaro district, Southern Ethiopia. *Int. J. Med. Plants Res.* 2, 238–241.

Sing, B., Ram, S. N., Pandeys, V. B., Joshis, V. K., and Gambhir, S. S. (1991). Studies on antiinflammatory activity of taraxasterol acetate from *echinops echinatus* in rats and mice. *Phytother. Res.* 5, 103–106.

Singh, B., Gambhir, S. S., Pandjwb, V. B., and Joshf, V. K. (1989). Anti-inflammatory activity of *Echinops echinatus*. *J. Ethnopharmacol.* 25, 189–199.

Singh, R. P., and Pandey, V. B. (1990). Nivetin, a neoflavonoid from *Echinops niveus.* Phytochemistry. *Phytochemistry* 29, 680–681.

Singh, R. P., Singh, K. N., and Pandey, V. B. (1990). Constituents of *echinops niveus*. *Fitoterapia.* 61, 279.

Singh, S., Upadhyay, R. K., Pandey, M. B., Singh, J. P., and Pandey, V. B. (2006). Flavonoids from Echinops echinatus. *J Asian Nat Prod Res.* 8, 197–200.

Su, Y. F., Luo, Y., Guo, C. Y., and Guo, D. A. (2004). Two new quinoline glycoalkaloids from *Echinops gmelinii*. *J. Asian. Nat. Prod. Res.* 6, 223–227. doi: 10.1080/10286020310001653327

Suleman, S., and Alemu, T. (2012). A survey on utilization of ethnomedicinal plants in Nekemte town, East Wellega (Oromia), Ethiopia. *J. Herbs. Spices. Med. Plants.* 18, 34–57. doi: 10.1080/10496475.2011.645188

Tacham, W. N., Fonge, B. A., and Fonkou, T. (2015). Traditional medicine and ethnobotanical use of wild plants by the Mundani people of Wabane, South West Region, Cameroon. *J. Ethnobiol. Tradit. Med. Photon.* 125, 1060–1080.

Tariku, Y., Hymete, A., Hailu, A., and Rohloff, J. (2011). *In vitro* evaluation of antileishmanial activity and toxicity of essential oils of *artemisia absinthium* and *echinops kebericho*. *Chem. Biodivers.* 8, 614–623.

Tbatou, M. A., Belahyan, A. B., and Belahsen, R. E. (2016). Wild edible plants traditionally used in the countryside of El Jadida, coastal area in the Center of Morocco. *Life. Sci. Leafl.* 75, 28–48.

Teklay, A., Abera, B., and Giday, M. (2013). An ethnobotanical study of medicinal plants used in Kilte Awulaelo District, Tigray Region of Ethiopia. *J. Ethnobiol. Ethnomed.* 9, 65. doi: 10.1186/1746-4269-9-65

Tekle, Y. (2014). An ethno-veterinary botanical survey of medicinal plants in Kochore district of Gedeo Zone, Southern Nations Nationalities and Peoples Regional State (SNNPRs), Ethiopia. *J. Sci. Innov. Res.* 3, 433–445.

Tekwu, E. M., Askun, T., Kuete, V., Nkengfack, A. F., Nyasse, B., Etoa, F. X., et al. (2012). Antibacterial activity of selected cameroonian dietary spices ethnomedically used against strains of *Mycobacterium tuberculosis*. *J. ethnopharmacol.* 142, 374–382. doi: 10.1016/j.jep.2012.05.003

Tene, M., Tane, P., Sondengam, B. L., and Connolly, J. D. (2004). Lignans from the roots of *echinops giganteus*. *phytochemistry* 65, 2101–2105. doi: 10.1016/j.phytochem.2004.05.014

Tiwari, J. K., Ballabha, R., and Tiwari, P. (2010). Ethnopaediatrics in garhwal Himalaya, Uttarakhand, India (Psychomedicine and Medicine). *N. Y. Sci. J.* 3, 123–126.

Toma, A., Deyno, S., Fikru, A., Eyado, A., and Beale, A. (2015). *In vivo* antiplasmodial and toxicological effect of crude ethanol extract of *Echinops kebericho* traditionally used in treatment of malaria in Ethiopia. *Malar. J.* 14, 196. doi: 10.1186/s12936-015-0716-1

Toroğlu, S., Keskin, D., Vural, C., Kertmen, M., and Cenet, M. (2012). Comparison of antimicrobial activity of *echinops viscosus* subsp. *bithynicus* and *E. microcephalus* leaves and flowers extracts from turkey. *Int. J. Agric. Biol.* 14, 637–640.

Wagh, V. V., and Jain, A. K. (2018). Status of ethnobotanical invasive plants in western Madhya Pradesh, India. *S. Afr. J. Bot.* 114, 171–180. doi: 10.1016/j.sajb.2017.11.008

Wang, Y., Li, X., Meng, D., Li, N., and Zhang, Y. (2008). Chemical constituents of thiophenes from *Echinops latifolius* Tausch. *Shenyang. Yao. Ke. Da. Xue. Xue. Bao.* 8.

Wang, Y., Li, X., Li, L., Meng, D., Li, Z., and Li, N. (2007). Two new thiophenes from *Echinops latifolius* and their phototoxic activities. *Planta. Med.* 73, 696–698. doi: 10.1055/s-2007-981541

Wang, Y., Li, X., Meng, D.-L., Li, Z.-L., Zhang, P., and Xu, J. (2006). Thiophenes from *Echinops latifolius*. *Nat. Prod. Res.* 8, 585–588. doi: 10.1080/10286020500176724

Wang, M., Sun, J., Jiang, Z., Xie, W., and Zhang, X. (2015). Hepatoprotective effect of kaempferol against alcoholic liver injury in mice. *Am. J. Chin. Med.* 43, 241–254.

Xu, D. G., Lv, W., Dai, C. Y., Zhu, F. F., Xu, G. H., Ma, Z. J., et al. (2015). 2 2-(Pro-1-ynyl)-5-(5,6-dihydroxypenta-1,3- diynyl) thiophene induces apoptosis through reactive oxygen species-mediated JNK activation in human colon Cancer SW620 Cells. *Anat. Rec.* 298, 376–385. doi: 10.1002/ar.23045

Yadava, R. N., and Singh, S. K. (2006). New anti-inflammatory active flavanone glycoside from the *Echinops echiantus* Roxb. *Indian. J. Chem.* 45, 1004–1008.

Yigezu, Y., Haile, D. B., and Ayen, W. Y. (2014). Ethnoveterinary medicines in four districts of jimma zone, Ethiopia: cross sectional survey for plant species and mode of use. *BMC. Vet. Res.* 10, 1–12. doi: 10.1186/1746-6148-10-76

Zamzami, T. A., Abdallah, H. M., Shehata, I. A., Mohamed, G. A., Alfaifi, M. Y., Elbehairi, S. E. I., et al. (2019). Macrochaetosides A and B, new rare sesquiterpene glycosides from *Echinops macrochaetus* and their cytotoxic activity. *Phytochem. Lett.* 30, 88–92. doi: 10.1016/j.phytol.2019.01.025

Zhang, P., Jin, W. R., Shi, Q., He, H., Ma, Z. J., et al. (2008). Two novel thiophenes from *Echinops grijissi* Hance. *J. Asian. Nat. Prod. Res.* 10, 977–981. doi: 10.1080/10286020802240467

Zhang, P., Liang, D., Jin, W., Qu, H., Cheng, Y., L, i X., et al. (2009). Cytotoxic thiophenes from the root of *Echinops grijisii* Hance. *Zeitschrift für. Naturforschung C.* 1, 193–196.

Zhang, X., and Ma, Z. (2010). Characterization of bioactive thiophenes from the dichloromethane extract of *Echinops grijisii* as Michael addition acceptors. *Anal. Bioanal. Chem.* 39, 1975–1984. doi: 10.1007/s00216-010-3729-1

Zhang, H., Tan, X., Yang, D., Lu, J., Liu, B., Baiyun, et al. (2017). Dietary luteolin attenuates chronic liver injury induced by mercuric chloride via the Nrf2/NF-κB/P53 signaling pathway in rats. *Oncotarget.* 8, 40982. doi: 10.18632/oncotarget.17334

Zhao, M. P., Liu, Q. Z., Liu, Q., and Liu, Z. L. (2017). Identification of Larvicidal Constituents of the Essential Oil of *Echinops grijsii* Roots against the three species of mosquitoe. *Molecules* 22, 205. doi: 10.3390/molecules2202020

Zhu, R., Wang, Y., Zhang, L., and Guo, Q. (2012). Oxidative stress and liver disease. *Hepatol. Res.* 42, 741–749. doi: 10.1111/j.1872-034X.2012.00996.x

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