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

**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 management of kidney stones (Mustafa et al., 2012; Nawash et al., 2013; Kumar et al., 2018).

In addition to the traditional medicinal applications described in Table 1, the plants have nutritional value. In Iran, the bulb of E. viscidulus Moazzaf 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 Bouha 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/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-butylnyl)-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'-bithieryl 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 (86) 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 glycone 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 echinopside (139), echinozolinone (140), and echinopside (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 lymphangitis (LS)                                                | Ethiopia     | Fenetahun and Eshetu, 2017 |
|                          | R         | Stomachache                                                                  | Ethiopia     | Regassa et al., 2017    |
|                          | R         | Typhoonsis, liver disease, pasteurellosis                                   | Ethiopia     | Kitata et al., 2017    |
|                          | R         | Hydrocele                                                                    | Uganda       | Kamatenesi et al., 2011 |
|                          | R         | Fasten expulsion of placenta, hernia                                         | Uganda       | Okeillo and Szegawa, 2007   |
|                          | R         | Ulcerative lymphangitis (LS)                                                | Ethiopia     | Teké, 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    |
|                          | WP        | Cough, emergence of teeth in infants, fever, urinary trouble, colic          | India        | Sharma et al., 2012    |
|                          | R         | Urinary disorder, fever                                                      | Pakistan     | Rathore et al., 2015   |
|                          | WP        | Diuretic, aphrodisiac, fever, pain, chronic fever                            | India        | Hamayun et al., 2006   |
|                          | R         | Fever, emergence of teeth in infants                                         | India        | Maru et al., 2018      |
|                          | WP        | Cough, emergence of teeth, fever, urinary trouble, colic, pain              | Pakistan     | Wagh and Jain, 2018    |
| *E. echinatus* Roxb.    | R         | To treat hernia                                                              | India        | Maurya et al., 2015    |
|                          | L         | Earache                                                                      | India        | Maru et al., 2018      |
|                          | R         | Leucorrhoea                                                                  | Pakistan     | Malik et al., 2018     |
|                          | R         | Aphrodisiac, to facilitate the delivery process, abortifacient,              | Pakistan     | Malik et al., 2018     |
|                          | L         | Joint pain                                                                    | Pakistan     | Malik et al., 2018     |
|                          | R         | Leucorrhoea                                                                  | Pakistan     | Malik et al., 2018     |
| *E. giganteus* A. Rich. | R         | Anti-hemorrhoidal                                                            | Ethiopia     | Desta, 1995            |
|                          | R         | Flatulence and bloody stool                                                  | Cameroon     | Tacham et al., 2015    |
|                          | R         | Stomachache, asthma attacks, as carminative                                  | Cameroon     | Menut et al., 1997     |
| *E. hispidus* Fresen.   | R and S   | Sunstroke                                                                     | Ethiopia     | Meragia et al., 2016   |
| *E. hoehnelii* Schweinf. | R         | Internal parasite, amoebae, common cold                                       | Ethiopia     | Teké, 2014            |
| *E. kebericho* Mesfin    | R         | Black leg, respiratory manifestations, liver disease (LS)                    | Ethiopia     | Yigezu et al., 2014    |
|                          | S         | Cough, headache                                                              | Ethiopia     | Berhanu et al., 2014   |
| *E. kebericho* Mesfin    | R         | Scabies                                                                      | Ethiopia     | Berhanu et al., 2014   |
|                          | R         | Toothache, stomachache, common cold, sunstroke, tonsillitis, acute           | Ethiopia     | Regassa, 2013          |
|                          | S         | Fever, headache                                                              | Ethiopia     | Gari et al., 2015      |
|                          | R         | Malaria, common cold                                                         | Ethiopia     | Mekuanent et al., 2015  |
|                          | R         | Dislocoted bone (LS)                                                         | Ethiopia     | Teké, 2013            |
|                          | R         | Toothache, vomiting, headache                                                | Ethiopia     | Abeera, 2014          |
|                          | R         | Typhoonsis                                                                   | Ethiopia     | Shilema et al., 2013   |
|                          | R         | Gonorhea                                                                     | Ethiopia     | Bizuayehu and Garedew, 2018 |
| *E. longifolius* A. Rich. | RB       | Headache, rheumatism, dry cough                                              | Ethiopia     | Suleman and Alemu, 2012 |
| *E. macrochaetus* Fresen. | R         | Scorpion sting                                                               | Sudan        | Issa et al., 2018      |
| *E. niveus* Wall.        | R         | Diuretic, nerve tonic, cough, indigestion, ophthalmia.                        | India        | Sharma et al., 2004    |
| *E. nitrodes* Boiss.     | R         | Kidney stones                                                                 | Jordan       | Nawash et al., 2013    |
| *E. polyceras* Boiss.    | S         | Chronic cough                                                                | Urmia        | Asadbeigi et al., 2014 |
| *E. sphaerocephalus* L. | WP        | Skin diseases, prevention of cough                                           | Iran         | Farouji and Khodayari, 2016   |
| *E. spinicosissimus* Turra. | R, S, L | Typhoid                                                                      | Kenya        | Nyang‘au et al., 2017 |
| *E. spinicosissimus* subsp. fontqueri (Pau) Greuter | R | Rheumatism, colds, uterine pains, uterus tumor                               | Saudi Arabia | El-Ghazali et al., 2010 |
|                         | S, R, L   | Renal disorders                                                              | Egypt        | Mahmoud and Gairoia, 2013 |
| *E. spinicosissimus* subsp. macroplepis (Boiss.) Greuter | R | As hypoglycaemic, decocition is drunk.                                       | Lebanon      | Merzouki et al., 2000  |
| *E. spinosus* L.        | R         | • Diuretic, nerve tonic, cough, indigestion, ophthalmia.                      | India        | Sharma et al., 2004    |
|                         |           | • Applied to wounds in cattle to destroy maggots                             | Jordan       | Nawash et al., 2013    |
|                         |           |                                                                           | Urmia        | Asadbeigi et al., 2014 |
|                         |           |                                                                           | Iran         | Farouji and Khodayari, 2016   |
|                         |           |                                                                           | Kenya        | Nyang‘au et al., 2017 |
|                         |           |                                                                           | Saudi Arabia | El-Ghazali et al., 2010 |
|                         |           |                                                                           | Egypt        | Mahmoud and Gairoia, 2013 |
|                         |           |                                                                           | Morocco      | Abderrahim et al., 2013 |
|                         |           |                                                                           | Lebanon      | Baydoun et al., 2015    |
|                         |           |                                                                           | Morocco      | Merzouki et al., 2000    |

(Continued)
TABLE 1 | Continued

| Species | Part used | Indication | Country | Ref. |
|---------|-----------|------------|---------|------|
| E. spinosus L. subsp Bovei (Boiss). Maire | 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 | Katri 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 |
| | 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. viscous DC. | C | Boll | Turkey | Bulut et al., 2017 |

AR: Aerial part; B: Bark; Bl: Bulb; Br: Branch; C: Capitolium; 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, dihydrocarveol, 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 (Papadopoulos 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 presilphiperfol-8-ol followed by presilphiperfol-7-ene, cameroonan-7-α-ol, and (E)-caryophyllene (Pavela et al., 2016).

Ceramides, sulfonylacetone ester, and simple hydrocarbons were the nonpolar constituents from the genus (Figure 1). The ethyl acetate extract of E. integrifolius contained lupeolacetate, 1,3-butanediene-1-carboxylic acid, lupeol, (1R,3R,4R,5R)-(−)-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, tetratriacontane, 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 (MBC), 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 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 enterica) (Bouattour et al., 2016). Thioephens (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
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**TABLE 2** | Secondary metabolites isolated from members of the genus *Echinops*.

| No. | Name of secondary metabolites | Species | Plant part | Pharmacological activity | Ref. |
|-----|-------------------------------|---------|------------|--------------------------|------|
| **Thiophenes**<br>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. latifolius* | R | | Wang et al., 2006 |
| | | *E. grijisi* | R | | Zhang and Ma, 2010; Chang et al., 2015 |
| | | *E. grijisi* | R | Cytotoxic | Fokialakis et al., 2006a |
| | | *E. ritro* Bunge | Rd | Antifungal | Abegaz, 1991 |
| | | *E. ritro* AP | AP | Antifungal | Fokialakis et al., 2006a |
| | | *E. nanus* | R | Termicidal | Kiyekbayeva et al., 2017 |
| | | *E. albicaulis* WP | WP | Termicidal | Fokialakis et al., 2006b |
| | 2. | α-terthiophene | *E. ellenbeckii* | R | Cytotoxic | Abegaz et al., 1991 |
| | | *E. pappii* | R | | Abegaz et al., 1991 |
| | | *E. macrochaetus* | R | | Jin et al., 2008 |
| | | *E. grijisi* | R | | Liu et al., 2002; Zhang and Ma, 2010; Chang et al., 2015 |
| | | *E. grijisi* | R | | Zhao et al., 2017 |
| | | *E. latifolius* | R | | Wang et al., 2006 |
| | | *E. ritro* AP | AP | Antifungal | Fokialakis et al., 2006b |
| | | *E. nanus* | R | Termicidal | Nakano et al., 2012 |
| | | *E. albicaulis* WP | WP | Termicidal | Kiyekbayeva et al., 2017 |
| | | *E. transiliensis* | R | Insecticidal | Abegaz et al., 1991 |
| | 3. | 5-(penta-1,3-diynyl)-2-(3-chloro-4-hydroxy-but-1-ynyl)-thiophene | *E. ellenbeckii* | R | | Hymete et al., 2005b |
| | | *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 | Cytotoxic | Abegaz, 1991 |
| | 5. | 5-(4-hydroxybut-1-ynyl)-2-(pent-1,3-diynyl)-thiophene | *E. pappii* | R | Antifungal | Fokialakis et al., 2006a |
| | | *E. ritro* AP | AP | Termicidal | Fokialakis et al., 2006b |
| | | *E. grijisi* | R | Cytotoxic | Chang et al., 2015 |
| | | *E. grijisi* | R | NQO1-inducing | Zhang et al., 2009; Zhang and Ma, 2010 |
| | | *E. grijisi* | R | | Sandjo et al., 2016 |
| | | *E. grijisi* | R | | Hymete et al., 2005b |
| | | *E. grijisi* | R | | Hymete et al., 2005b |
| | | *E. grijisi* | R | | Hymete et al., 2005b |
| | 6. | 5-(pent-1,3-diynyl)-2-(but-3-en-1-ynyl)-thiophene | *E. ellenbeckii* | R | | Hymete et al., 2005b |
| | 7. | 5-(pent-1,3-diynyl)-2-(4-acetoxyl-buty-1-ynyl)-thiophene | *E. ellenbeckii* | R | | Hymete et al., 2005b |
| | 8. | 5-(pent-1,3-diynyl)-2-(3-hydroxy-4-acetoxyl-buty-1-ynyl)-thiophene | *E. ellenbeckii* | R | | Hymete et al., 2005b |
| | 9. | 5-(pent-1,3-diynyl)-2-(3,4-diacetoxyl-buty-1-ynyl)-thiophene | *E. ellenbeckii* | R | | | |
| | | *E. transiliensis* | R | | | |
| | | *E. grijisi* | R | | | |
| | | *E. grijisi* | R | | | |
| | | *E. transiliensis* | R | | | |
| | | *E. transiliensis* | R | | | |
| | 10. | 5-(pent-1,3-diynyl)-2-(3-chloro-4-acetoxyl-buty-1-ynyl)-thiophene | *E. ellenbeckii* | R | | | |
| | | *E. transiliensis* | R | | | |
| | | *E. albicaulis* WP | WP | Termicidal | Fokialakis et al., 2006b |

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

(Continued)
| No. | Name of secondary metabolites                             | Species       | Plant part | Pharmacological activity                          | Ref.                              |
|-----|----------------------------------------------------------|---------------|------------|--------------------------------------------------|-----------------------------------|
| 32. | 5-(4-acetoxy-1-butynyl)-2,2'-bithiophene                | E. grijsii    | R          | Antibacterial, Antifungal                         | Zhang et al., 2009; Chang et al., 2015 |
| 33. | 5-(3-hydroxy-4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene | E. latifolius  | R          | Termicidal                                       | Wang et al., 2006                 |
| 34. | 5-(3-acetoxy-4-isovaleroyloxybut-1-ynyl)-2,2'-bithiophene | E. latifolius  | R          | Termicidal                                       | Wang et al., 2006                 |
| 35. | Echinopsacetylenes A                                     | E. transiliensis | R        | Cytotoxic                                        | Jin et al., 2008                  |
| 36. | Echinopsacetylenes B                                     | E. transiliensis | R        | Insecticidal                                     | Nakano et al., 2014               |
| 37. | Echinothiophenegenol                                     | E. grijsii    | R          | Cytotoxic                                        | Jin et al., 2008                  |
| 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. latifolius  | R          | Antifungal                                       | Wang et al., 2007                 |
| 40. | 5-{4-[4-(5-pent-1,3-diynylthiophene-2-yl)-but-3-ynyl]-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                 |
| 42. | 5-[(prop-1-ynyl]-2-(3,4-diacetoxybut-1-ynyl)-thiophene   | E. latifolius  | R          | Cytotoxic                                        | Wang et al., 2007                 |
| 43. | 5-(1,2-dihydroxy-ethyl)-2-(2,3-diyndiythiophene)         | E. latifolius  | R          | Anti-inflammatory                                | Jin et al., 2016                  |
| 44. | 5-(1,2-dihydroxyethyl)-2-(E)-hept-5-ene-1,3-diyndiythiophene | 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. latifolius  | R          | Anti-inflammatory                                | Jin et al., 2016                  |
| 47. | Arctinol                                                 | E. latifolius  | R          | Anti-inflammatory                                | Jin et al., 2016                  |
| 48. | Methyl [5'-(1-propynyf)-2,2'-bithienyl-5-yl] carboxylate  | E. latifolius  | R          | Anti-inflammatory                                | Jin et al., 2016                  |
| 49. | 5-(pent-1,3-diyndiythiophene-2-yl)-but-3-ynyl-2,2'-bithiophene | E. hoehnelii | R          | Anti-inflammatory                                | Bitew et al., 2017                |
| 50. | 5-(pent-1,3-diyndiythiophene-2-yl)-but-3-ynyl-2,2'-bithiophene | E. hoehnelii | R          | Anti-inflammatory                                | Bitew et al., 2017                |
| 51. | 5-(3-hydroxy-4-acetoxybut-1-ynyl)-2,2'-bithiophene       | E. transiliensis | R        | Insecticidal                                     | Nakano et al., 2014               |
| 52. | 5-(pent-1,3-diynyl)-2-(3-acetoxy-4-hydroxybut-1-ynyl)-thiophene | E. transiliensis | R        | Insecticidal                                     | Nakano et al., 2014               |
| 53. | 5'-(3,4-dihydroxybut-1-ynyl)-5-carboxaldehyde            | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 54. | 5'-(3,4-dihydroxybut-1-ynyl)-5-carboxaldehyde            | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 55. | 4-hydroxy-1-(5'-methyl-[2,2'-bithiophen]-5-yl)-butan-1-one | E. nitro      | WP         | Antibacterial, Antifungal                        | Li et al., 2019                   |
| 56. | Junipic acid                                             | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 57. | Arctinol                                                 | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 58. | 4-(5'-methyl-[2,2'-bithiophen]-5-yl)-but-3-yn-1-ol        | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 59. | Arctinol A                                               | E. nitro      | WP         | Antibacterial                                     | Li et al., 2019                   |
| 60. | Dehydrocostus lactone                                   | E. amplexicaul | R          | Antibacterial                                     | Abegaz et al., 1991               |
| 61. | Costunolide                                              | E. kebericho, E. amplexicaul, | R          | Antibacterial                                     | Abegaz et al., 1991 | 1991 | Abegaz, 1991 |
| 62. | Dihydrocostunolide                                       | E. amplexicaul | R          | Antibacterial                                     | Abegaz et al., 1991               |
| 63. | Echinopines A                                            | E. spinosus    | R          | Antibacterial                                     | Dong et al., 2008b                 |
| 64. | Echinopines B                                            | E. spinosus    | R          | Antibacterial                                     | 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. nitro | WP | Cytotoxic | Li et al., 2010 |
| 66. | (3α,4α,6α,11β)-3-hydroxyguaia-1(10)-en-12,6-lactone | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 67. | (1α,11,13-dihydroxy)-E. niveus | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 68. | Vulgarin | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 69. | (3β,5α,6α,9α,9β,9β)-octahydro-3,9-dimethyl-6-methyleneazulenol(4,5-b)furane2,3(9b)H-1one | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 70. | (3α,6α,8β,9α,9β,9β)-decahydro-8-hydroxy-9-methyl-3,6 dimethylenazulenol(4,5-b)furane2,9(9h)-1one | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 71. | (3α,6α,8β,9α,9β,9β)-decahydro-3,3,9-trimethyl-6-methyleneazulenol(4,5-b)furane-2,9(h)-1one | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 72. | (3α,5α,6α,8β,9α,9β)-decahydro-3,9-dimethyl-6-methyleneazulenol(4,5-b)furane-2,9(h)-1one | E. nitro | WP | Cytotoxic | Li et al., 2010 |
| 73. | Santamarin | E. pappi | WP | Anti-inflammatory | Abegaz, 1991 |
| 74. | Reynosin | E. pappi | R | Anti-inflammatory | Abegaz, 1991 |
| 75. | Caryophyllene epoxide | E. giganteus | R | Anti-inflammatory | Lebedeva et al., 1991 |
| 76. | Echusoside | E. hussoni Bois. | AP | Anti-inflammatory | Ka, 2001 |
| 77. | (3S3αS,5αR,6β,8β)-decahydro-6,8-dihydroxy-3,5a-dimethyl-9-methyleneazulenophthal(1,2-b)furane-2,9(h)-1one | E. nitro | WP | Anti-inflammatory | Li et al., 2010 |
| 78. | (3S3αS,5αR,6β,8β,9βS)-hexahydro-3,5,9-trimethylhexahydro-2,9(9b)-1one | E. ritro | WP | Anti-inflammatory | Li et al., 2010 |
| 79. | 2,6,10-trimethylidodeca-2,6,10-triene | E. albaicus | AP | Antioxidant | Kiyekbayeva et al., 2017 |
| 80. | Macrochaetosides A | E. macrochaetus | AP | Antioxidant | Zamzami et al., 2019 |
| 81. | Macrochaetosides B | E. macrochaetus | AP | Antioxidant | Zamzami et al., 2019 |
| 82. | Latifolanone A | E. latifolius | R | Anti-inflammatory | Jin et al., 2016 |
| 83. | Atractylenolide-II | E. latifolius | R | Anti-inflammatory | Jin et al., 2016 |
| 84. | β-amyrin | E. niveus | WP | Anti-inflammatory | Singh et al., 1990 |
| 85. | Betulinic acid | E. niveus | WP | Anti-inflammatory | Singh et al., 1990 |
| 86. | Lupeol | E. niveus | WP | Anti-inflammatory | Tene et al., 2004 |
| 87. | Taraxasterol | E. niveus | WP | Anti-inflammatory | Patel et al., 2016 |
| 88. | Taraxasterol acetate | E. niveus | WP | Anti-inflammatory | Patel et al., 2016 |
| 89. | β-sitosterol | E. niveus | WP | Anti-inflammatory | Patel et al., 2016 |
| 90. | β-sitosterol glucoside | E. niveus | WP | Anti-inflammatory | Patel et al., 2016 |
| 91. | Reynosin | E. pappi | R | Anti-inflammatory | Abegaz, 1991 |
| 92. | Cnelminin A | E. gmelini | AP | Anti-inflammatory | He et al., 2000 |
| 93. | Stigmasterol | E. transiliensis | R | Anti-inflammatory | Nakano et al., 2012 |
| 94. | Lupeol acetate | E. integrifolius | WP | Anti-inflammatory | Senegueju et al., 2013 |
| 95. | Lupeol linoeleate | E. albaicus | AP | Anti-inflammatory | Kiyekbayeva et al., 2017 |
| 96. | Ajugasterone C | E. albaicus | AP | Anti-inflammatory | Kiyekbayeva et al., 2017 |
| 97. | Ursolic acid | E. giganteus | Rz | Anti-inflammatory | Dong et al., 2008a |
| 98. | Echinopsolid A (3β-acetoxy-15α-bromoolean-13β,28-olide) | E. giganteus | Rz | Anti-inflammatory | Kiyekbayeva et al., 2017 |
| 99. | β-amyrin acetate | E. giganteus | Rz | Anti-inflammatory | Kiyekbayeva et al., 2017 |
| 100. | 3β-acetoxy-12,20(30)-diene-11α-21α-diol | E. galalensis | AP | Anti-inflammatory | Senegueju et al., 2013 |
| 101. | α-amyrin | E. galalensis | Rz | Anti-inflammatory | Abdallah et al., 2013 |
| 102. | Erythrodial | E. galalensis | Rz | Anti-inflammatory | Abdallah et al., 2013 |
| No. | Name of secondary metabolites | Species | Plant part | Pharmacological activity | Ref. |
|-----|-------------------------------|---------|------------|--------------------------|------|
| 103. | Lup-20(29)-ene-1,3-diol | E. galalensis | Rz | Hepato-protective | Zaman et al., 2019 |
| 104. | Cycloartenol | E. macrochaetus | AP | Cytotoxic | Zamzami et al., 2019 |
| 105. | Apigenin | E. niveus | WP | Singh et al., 1990 |
| 106. | Luteolin | E. niveus | R | Singh et al., 1990 |
| 107. | Nivegin | E. niveus | WP | Singh et al., 1990 |
| 109. | Apigenin 7-O-glucoside | E. echinatus | F | Singh et al., 1995 |
| 110. | Echitin | E. echinatus | F | Ram et al., 1995 |
| 111. | Chrysoeriol | E. integrifolius | WP | Senejoux et al., 2013 |
| 112. | Myrecetin-3-O-α-L-rhamnoside | 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 |
| 117. | Myricetin-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 | Singh et al., 2006 |
| 121. | Centaureidin | E. integrifolius | WP | Singh et al., 2006 |
| 122. | Axillarin | E. integrifolius | WP | Singh et al., 2006 |
| 123. | Genkwanin | E. albicaulis | AP | Singh et al., 2006 |
| 124. | 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 | Singh et al., 2006 |
| 125. | (+)-4-(3-methylbutanoyl)-2,6-di(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane | E. giganteus | R | Tene et al., 2004 |
| 126. | Candidone | E. giganteus | Rz | Cytotoxic | Kuete et al., 2013 |
| 127. | Chlorogenic acid | E. grijisi | R | Dong et al., 2008a |
| 128. | Cyanarin | E. grijisi | R | Dong et al., 2008a |
| 129. | Rutin | E. heterophyllus | Rz | Mhamood and Khaideem, 2013 |
| 130. | (+)-4-(3-methylbutanoyl)-2,6-di(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane | E. echinatus | WP | Singh et al., 2006 |
| 131. | (+)-4-hydroxy-2,6-di(3,4-dimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane | E. echinatus | WP | Singh et al., 2006 |
| 132. | Hexacosyl-(E)-ferulate | E. nanus | R | Kaideem and Mhamood, 2013 |
| 133. | Umbelliferone | E. integrifolius | WP | Senejoux et al., 2013 |
| 134. | Syringin | E. grijisi | R | Dong et al., 2008a |
| 135. | 1,5-dicaffeoylquinic acid | E. galalensis | AP | Hepato-protective | Abdallah et al., 2013 |
| 136. | 3,5-dicaffeoylquinic acid | E. orientalis | L | Antioxidant | Erener et al., 2014 |
| 137. | 3,4-dicaffeoylquinic acid | E. integrifolius | WP | Senejoux et al., 2013 |
| 138. | 4,5-dicaffeoylquinic acid | E. echinatus | AP | Singh et al., 2006 |
| 139. | Echinopsine (1-methyl-4-quinolone) | E. echinatus | AP | Chaudhuri, 1987 |
| 140. | Echinozolinone | E. echinatus | AP | Chaudhuri, 1987 |
coliforms with a MIC of 64, 32, 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 zones of inhibitions which makes it challenging to compare with other study results. Methanolic extract of the whole plant of *E. polyceras* has been reported to have greater zone of inhibition than the standard drug, vancomycin (30 µg/disc) of *E. polyceras* (Aburjai et al., 2001). The effect of the plant without tetracycline however was not studied. The leaf and flower extracts of *E. echinatus* subsp. bithynicus were described to possess significant anti-fungal activity against *C. albicans* and *M. grisea* (Khadim et al., 2014) with the MIC = 3.12 µg/mL) against *C. albicans* and *M. grisea* (Khadim et al., 2014).

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 I (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 activity 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-butyryl)-2,2′-bithiophene (31), 5-[4-(5-pent-1,3-diylnylthiophene-2-yl)-but-3-ynyl]-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)-bithiophene (42) against HL-60 (IC$_{50}$ = 8 µg/mL). The dichloromethane fraction was tested in mice and did not show anti-tumor effect.
Similarly, Zhang et al. (2009) evaluated the cytotoxic effect of thiophenes isolated from *E. grijissi* 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. grijissi*, 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).
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...
α-terthiophene showed cytotoxic effect towards K562 (IC\text{50} = 50 µg/mL) and HepG2 (IC\text{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\textsubscript{4})-induced liver damage, in which biomarkers of liver function like aspartate

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**FIGURE 1** | Continued

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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 CCl₄-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 CCl₄-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),
Phytochemistry and Biological Activities of Echinops Bitew and Hymete

lup-20(29)-ene-1,3-diol (103), and dicafeoyl-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 of *E. orientalis* Traut. 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.
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...
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).
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.
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 3** | In vitro antibacterial and antifungal activities of some *Echinops* species.

| *Echinops* species | Extract(Plant part) | Strain (ID) | Type | MIC (µg/mL) | MBC (µg/mL) | Zone of inhibition (mm) (Conc.) (mg/mL) | Ref. |
|--------------------|------------------|-------------|------|-------------|-------------|--------------------------------|------|
| *E. adenocaulos* | Biosk. Zamzam water | *Streptococcus pneumonia* (MDR) | I | 780 | – | – | Saleh Fares et al., 2013 |
| *E. amplexicaulis* | Ether (R) | *Streptococcus pneumonia* (MDR) | I | 50 | 50 | 41.0 (50) | Kevin et al., 2018 |
| *E. echinatus* | 70% Ethanol (AP) | Bacillus subtilis | S | – | – | – | Ahmed, 2012 |
| *E. longisetus* | 80% Methanol (L) | *Aerococcus viridans* (ATCC 6538) | S | – | – | 23.0 (10) | Hymete et al., 2005a |
| *E. longifolius* | 80% Methanol (St) | Meloidogyne incognita | L | 10 | 5 | 127 (40) | Rahman et al., 2011 |
| *E. pinosissimus* | Methanol (AP) | C. albicans | I | 12.5/12.5 | 18.75/18.75 | 11.66/14.10 (0.08) | Belay 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.
**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 monocyctic leukemia (THP-1) | Amphotericin B | DMSO | 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)** | K562 | Platinol | DMSO | 0.23 µg/mL | Zhang et al., 2009 |
| 14 **(E. grijisi)** | HL-60 | Platinol | DMSO | 0.27 µg/mL | Zhang et al., 2009 |
| 14 **(E. grijisi)** | K562 | Platinol | DMSO | 0.47 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 | 27.7 µM | 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 | DMSO | 46.96 µM | Sandjo et al., 2016 |
| 14 **(E. giganteus)** | CEM/ADR5000 | Doxorubicin | DMSO | 21.09 µM | Sandjo et al., 2016 |
| 98 **(E. giganteus)** | CCRF-CEM | Doxorubicin | DMSO | 36.78 µM | Sandjo et al., 2016 |
| 98 **(E. giganteus)** | CEM/ADR5000 | Doxorubicin | DMSO | 38.57 µM | Sandjo et al., 2016 |
| 150 **(E. giganteus)** | CCRF-CEM | Doxorubicin | DMSO | 9.93 µM | Sandjo et al., 2016 |
| 150 **(E. giganteus)** | CEM/ADR5000 | Doxorubicin | DMSO | 6.12 µM | Sandjo et al., 2016 |
| 80 **(E. macrochaetus)** | Breast adenocarcinoma (MCF-7) | Doxorubicin | DMSO | 0.18 µM | Zamzami et al., 2019 |
| 80 **(E. macrochaetus)** | DMSO | Doxorubicin | DMSO | 3.3 µM | Zamzami et al., 2019 |
| 80 **(E. macrochaetus)** | DMSO | Doxorubicin | DMSO | 2.1 µM | Zamzami et al., 2019 |
| 104 **(E. macrochaetus)** | DMSO | Doxorubicin | DMSO | 2.9 µM | Zamzami et al., 2019 |
| 104 **(E. macrochaetus)** | DMSO | Doxorubicin | DMSO | 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. polycears* 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). 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 fraction of the 80% methanolic extract of *E. hoehnelii*, and thiophens (5-(penta-1,3-diylnyl)-2-(3-chloro-4-acetoxy-but-1-ynyl)-thiophene (10), and 5-(penta-1,3-diylnyl)-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, presilipherpofuran-8-ol, presilipherpof-7-en, cameroon-7-α-ol, and (E)-caryophyllene as the main constituents of the oil (Kamte et al., 2017).

The anti-helmentic effects of members of the genus were also described. The root 80% methanolic extract of *E. kebericho* showed higher anti-helmentic effect (LD$_{50} = 57 µg/mL$) 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.

### Hepatoprotective and antioxidant activities

| Plant/compound name (Plant) | Effects Model | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|---------------|------------------|------------------|---------------------------------------------|----------|------------|
| E. echinatus                | Hepatoprotective 1 | Silymarin         | Normal saline    | 500 mg/kg (p.o.)                            | ↓ ALT    | Eram et al., 2013 |
| E. giganteus               | Anti-oxidant 1   | Trolox            | Distilled water  | 1% gumacacia                                | Inh = 68.3% | Singht et al., 1991 |
| E. grijsii                  | Hepatoprotective 1 | NM               | Normal saline    | 300 mg/kg (p.o.)                            | ↓ ALT    | Lin et al., 1993 |
| E. heterophyllus            | Hepatoprotective 2 | NM               | Distilled water  | 250 mg/kg (p.o.)                            | ↓ AST, ALT, and Asialine 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%                                       | > 80%    | Mohseni et al., 2017 |
| E. nitro                   | Anti-oxidant 2   | BHT (Dibutylhydroxytoluene) | Distilled water | 1 mg/mL                                     | > 70%    | Aydin et al., 2016 |

### Anti-inflammatory, analgesic, anti-pyretic and wound healing activities

| Plant/compound name (Plant) | Anti-inflammatory 1 | Inhibition of LPS-induced NO production 2 | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|----------------------|------------------------------------------|------------------|------------------|---------------------------------------------|----------|------------|
| E. echinatus                | Anti-inflammatory 1 | Phenylbutazone                            | 1% gumacacia     | NM               | 200 mg/kg (p.o.)                            | Inh = 68.3% | Singht et al., 1991 |
| E. latifolius               | Inhibition of LPS-induced NO production 2 | Aminoguanidine and Indomethacin | NM               | 12.8 µM          | IC50 = 12.8 µM                              | Jin et al., 2016 |
| E. latifolius               | Inhibition of LPS-induced NO production 2 | Aminoguanidine and Indomethacin | NM               | IC50 = 28.2 µM   | Jin et al., 2016 |
| E. latifolius               | Inhibition of LPS-induced NO production 2 | Aminoguanidine and Indomethacin | NM               | IC50 = 30.9 µM   | Jin et al., 2016 |
| E. latifolius               | Inhibition of LPS-induced NO production 2 | Aminoguanidine and Indomethacin | NM               | IC50 = 48.6 µM   | Jin et al., 2016 |
| E. latifolius               | Inhibition of LPS-induced NO production 2 | Aminoguanidine and Indomethacin | NM               | IC50 = > 100 µM  | Jin et al., 2016 |
| Chloroform fraction (E. grijsii) | Anti-inflammatory 1 | Indomethacin                               | Normal saline    | 300 mg/kg (p.o.) | Inh = 56%                                   | Lin et al., 1992 |

### Anti-protozoal and anti-helmentic activities

| Plant/compound name (Plant) | Anti-malarial 1 | Inhibition of plasmodium falciparum 1 | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|------------------|----------------------------------------|------------------|------------------|---------------------------------------------|----------|------------|
| E. hoehnelii                | Anti-malarial 1 | Chloroquine                             | 7% Tween 80/3%   | NM               | 100 mg/kg                                   | Inh = 32.7% | Bitew et al., 2017 |
| E. hoehnelii                | Anti-malarial 1 | Chloroquine                             | 7% Tween 80/3%   | NM               | 100 mg/kg                                   | Inh = 50.2% | Bitew et al., 2017 |
| E. ellenbeckii              | Anti-helmentic 2 | Niclosamide                            | NM               | 500 µg/mL         | Mortality rate = 100%                       | LD50 = 57 µg/mL | Toma et al., 2015 |

(Continued)
**TABLE 5 | Continued**

| Plant/compound name (Plant) | Effects Mode | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|--------------|-----------------|------------------|---------------------------------------------|----------|------------|
| *E. longisetus*              | Anti-helmentic ² | Nicosamide       | Tap water        | 500 µg/mL                                   | LC₅₀ ₀.12 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             | IC₅₀ 10.5 µg/mL                             |         | Kim et al., 2017 |
| Essential oil (E. kebericho) | Anti-keishmanial ² | Amphotericin B   | 1% DMSO          | EC₂₀ 0.24 µg/mL                             |         | Tariku et al., 2011 |
| Essential oil (E. kebericho) | Anti-helmentic ² | Thiabendazole    | 0.5% Tween 80 in PBS | 1% (w/v)                                   | Inh 81.8% | Hussien et al., 2011 |

**Effects on insects and termites**

| Plant/compound name (Plant) | Effects Mode | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|--------------|-----------------|------------------|---------------------------------------------|----------|------------|
| 1 *E. gnijisi*               | Larvicidal ² | Rotenone        | 0.25% Tween 40   | LC₅₀ ₀.12 µg/mL                             |          | Zhuo et al., 2017 |
| 1, 2 (E. nitro and E. spenosissimus) | Termicidal ² | NM              | Distilled water  | 1% (w/v)                                   |          | Fokialakis et al., 2006b |
| 10 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 14.71 µg/mL                            |          | Nakano et al., 2014 |
| 14 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 12.45 µg/mL                            |          | Nakano et al., 2014 |
| 15 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 9.89 µg/mL                             |          | Nakano et al., 2014 |
| 18 (E. gnijisi)              | Larvicidal ² | Rotenone        | 0.25% Tween 40   | LC₅₀ 1.38 µg/mL                             |          | Zhao et al., 2017 |
| 2 (E. gnijisi)               | Larvicidal ² | Rotenone        | 0.25% Tween 40   | LC₅₀ 1.6 µg/mL                              |          | Nakano et al., 2014 |
| 39 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 4.22 µg/mL                             |          | Nakano et al., 2014 |
| 51 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 7.45 µg/mL                             |          | Nakano et al., 2014 |
| 52 (E. transiliensis)        | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 19.97 µg/mL                            |          | Nakano et al., 2014 |
| 8 (E. transiliensis)         | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 18.55 µg/mL                            |          | Nakano et al., 2014 |
| 9 (E. transiliensis)         | Larvicidal ² | Permethrin      | DMSO             | LC₅₀ 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.)              |          | Agrawal et al., 2012 |
| Butanol fraction (E. echinatus) | Anti-hyperplasia ¹ | Finasteride     | Ethanol          | LC₅₀ 0.22 mg/L                               |          | Agrawal et al., 2012 |
| *E. echinatus*               | Anti-fertility ¹ | NM              | Distilled water  | 50, 100, and 200 mg/kg                     |          | Chaturvedi et al., 1995 |

**Phytochemistry and Biological Activities of *Echinops***

| Plant/compound name (Plant) | Effects Mode | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|--------------|-----------------|------------------|---------------------------------------------|----------|------------|
| Essential oil (E. giganteus) | Larvicidal ² | NM              | DMSO             | LC₅₀ 227.4 µL/L                             |          | Pavela et al., 2016 |

**Effects on the reproductive system**

| Plant/compound name (Plant) | Effects Mode | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|--------------|-----------------|------------------|---------------------------------------------|----------|------------|
| Terpenoidal fraction (E. echinatus) | Effect on male reproductive parameters ¹ | NM | 1% Tween 80 | 60 mg/kg (p.o.) |          | Padashetty and Mishra, 2007 |

**Other activities**

| Plant/compound name (Plant) | Effects Mode | Positive control | Negative control | Dose/Concentration (Route of administration) | Activity | References |
|-----------------------------|--------------|-----------------|------------------|---------------------------------------------|----------|------------|
| 14 (E. gnijisi)             | NQO1 inducing activity ² | 4′-Bromoflavone | NM               | 40 µM                                       | Induction 3.1X of the control | Shi et al., 2010 |
| 14 (E. gnijisi)             | NQO1 inducing activity ² | 4′-Bromoflavone | NM               | 2.87 µg/mL                                  | Induction 2X of the control | Zhang and Ma, 2010 |
| 5 (E. gnijisi)              | NQO1 inducing activity ² | 4′-Bromoflavone | NM               | 1.86 µg/mL                                  | Induction 2X of the control | Zhang and Ma, 2010 |
| 9 (E. gnijisi)              | 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 | Sitaglipin      | 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 | Sarvaya et al., 2017 |
| *E. echinatus*              | Diuretic      | Furosemide      | Normal saline    | 500 mg/kg (p.o.)                            | Blood glucose level | Fatima et al., 2017 |
| *E. ellenbeckii*            | Molluscidaic ² | NM               | De-chlorinated tap water | 20.25 µg/mL | Blood glucose level | Pat et al., 2011a |
| *E. giganteus*              | Amylase inhibitory ² | NM | Distilled water | 75% | Blood glucose level | Hymete et al., 2005a |
| *E. lasiolepis*             | Immunomodulating activity | NM | DMSO | 1 µg/mL | Inhibited PBMC proliferation | Etonuki et al., 2010 |
| *E. longisetus*             | Molluscidaic ² | NM               | De-chlorinated tap water | 45 µg/mL | Blood glucose level | Asadi et al., 2012 |
| *P. persicus*               | Anti-ulcer    | NM               | Distilled water  | 500 mg/kg (p.o. / i.p.)                     | Blood glucose level | Eto et al., 2012 |

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 (Karunamooorthy et al., 2008).

The activity of thiophenes (2, 8, 9, 10, 14, 15, 39, 51, and 52) isolated from E. transiens Golsk. 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. grijisi possessed significant larvicidal activity against Aedes albopictus, Anopheles sinensis, and Culex p. p. 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. grijisi 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-isovaleryloxybut-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 quinqueducatus was relatively low (LC$_{50}$ = 227.4 µL) (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. spinozissimus, E. albicus, and E. transiens on Coptoptermes formosanus. The study revealed that all the thiophenes showed termicidal activity and 100% mortality 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 (Padshetty and Mishra, 2007). Earlier studies also indicated that the root ethanol extract of E. echinatus has anti-fertility properties through decrement in sizes of testes, epididymis, vental 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 spermatogenesis 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 5a-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-diyln)-2-(3,4-dihydroxybut-1-ynyl)-thiophene (14), isolated from the root of E. grijisi, 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. grijisi, 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 alloxa-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 Büngel 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-helmintic 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.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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