Inula helenium: A literature review on ethnomedical uses, bioactive compounds and pharmacological activities

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Abstract
Dynamic growth of antimicrobial and anthelmintic resistance throughout the years has caused increased interest in natural alternatives to synthetic drugs. Elecampane (Inula helenium L.), a widely distributed herbaceous plant, is one of the most researched and well-known member of the genus Inula, family Compositae. I. helenium has been included in the Chinese Pharmacopeia, Russian Pharmacopeia and Pharmacopeias of some European countries. This review is an up-to-date summary of the existing knowledge on Inula helenium's ethnomedicinal uses, secondary metabolites and pharmacological activities. Initially used in the treatment of respiratory and digestive diseases in both humans and animals, the roots of elecampane have been also proven to possess a cytotoxic and antiproliferative effect on cancer cell lines, as well as anti-inflammatory, antioxidant, antibacterial, antifungal and anthelmintic activities. The main bioactive compounds isolated from elecampane roots known to be responsible for their pharmacological activities are inulin, sesquiterpene lactones such as alantolactone and isoalantolactone, thymol derivatives, phenolic acids and flavonoids. This review suggests that I. helenium's secondary metabolites have a strong therapeutic potential. However, further in vitro and in vivo studies of isolated I. helenium bioactive compounds are required in order to understand their mechanism of action, pharmacokinetics and potential adverse effects.
Keywords: *Inula helenium, Chemical composition, Pharmacological activity*

Introduction

Inula helenium L., commonly known as elecampane or horseheal, is an herbaceous perennial that belongs to the family Asteraceae (Compositae), genus *Inula*. Elecampane is believed to be native to West and Central Asia but spread throughout Europe during the Bronze Age, and only recently introduced and naturalized in United States and Canada (Preston et al., 2004; ITIS, 2020).). *I. helenium* grows well in temperate regions with dump, well-drained soil, in full sun or semi-shade habitats, located on the fields and hills near river or forest (Bojor, 2003). Due to its wide distribution and ethnomedicinal uses, elecampane has been included in various pharmacopeias, including the Chinese Pharmacopeia, Ayurvedic Pharmacopeia of India, the State Pharmacopeia of the Russian Federation, the British Herbal Pharmacopeia, and Pharmacopeias of some European countries (Zhao et al., 2015; Stojakowska et al., 2016; Shikov et al., 2017).

Since ancient times, dried roots and rhizome of *I. helenium* have been used for the treatment of respiratory and digestive diseases, but also as anthelmintic, antimicrobial and general tonic herb in both humans and animals (Seca et al., 2014; Shikov et al., 2017). Over the past decades the rapid spreading of antimicrobial resistance, together with continuous development of medical technology, have encouraged the researchers to study bioactive potential of plants and their secondary metabolites, including elecampane. Isolated and purified bioactive compounds as well as the extract of *I. helenium* root have been investigated *in vitro* and *in vivo* for their potential anti-inflammatory, antioxidant, antibacterial, antifungal, anthelmintic, antiproliferative and cytotoxic activity. Most of these biological activities are explained by the presence of sesquiterpene lactones (alantolactone and isoalantolactone), thymol derivatives, polysaccharide inulin, flavonoids (quercetin, kaempferol, catechin gallate and epicatechin) and phenolic acids (chlorogenic, caffeic, hydroxibenzoic) (Yan et al., 2012; Spiridon et al., 2013; Zlatić et al., 2019). In this review, we have compiled the existing data on the ethnomedicinal and modern uses of *I. helenium*, bioactive compounds and their mechanism of action, providing a baseline for the future studies.

Ethnomedical Uses of *Inula helenium*

The information about medicinal properties of *I. helenium* dates back to the ancient Romans and Greeks. It has been described by the ancient herbalist Pedianos Dioscorides in the first Pharmacopoeia entitled *De materia medica* as *oinos nektaries*, used for the treatment of stomach and chest pain, and as a diuretic (Dioscorides et al., 2000). Galen recommended the root of *I. helenium* for alleviation of sciatica symptoms (Castleman, 2017).

According to the Traditional Chinese Medicine (TCM) web platform, *I. helenium* roots (Tu Mu Xiang) shows a tropism for liver, lung and spleen tissues, relieving abdominal pain, treating diarrhoea, emesis and preventing spontaneous abortion (TCM, 2020). In the Chinese Pharmacopeia, dry roots of *I. helenium* are also mentioned as stomachic medicine (Tang and Eisenbrand, 1992). In Tibetan medicine, the roots of elecampane ("Ma Na Ba Zha") are used for the treatment of digestive and circulatory system diseases, and as an expectorant (Pasang, 1999). During the Middle Ages the roots of *I. helenium* were used in preparation of the medieval digestive wine, known as Potio Sancti Pauli (the drink of Saint Paul). In veterinary medicine, elecampane was used in the treatment of psoroptic mange in sheep and for lung disorders in horses, from where the name horseheal and scabwort originated (Wynn and Fougère, 2006).

In Romanian folk medicine, *I. helenium* was used mainly for the cleaning and treatment of wounds (Grințescu, 1945). The rhizome was also used in the mixture with honey for the treatment of tuberculosis; the tea from rhizome was used for the asthma treatment (Grigore, 2008). In Oltenian region, elecampane decoction it is used for its expectorant, anthelmintic and anti-inflammatory properties (Tita et al., 2009). In the folk medicine of Republic of Moldova, *I. helenium* was collected during vernal equinox or summer solstice, when it was considered the most effective, and used to wash the body and especially hair, believed to promote the hair growth (Grădinaru, 2005).

In Hungarian folk medicine, essential oil of elecampane is used in the treatment of digestive and respiratory diseases (Babulka, 2011). In Bulgaria, the infusion of elecampane rhizomes is used as anti-ascaridic, antitussive and in the treatment of bronchial and throat affection (Ivancheva and Stantcheva, 2000). In Montenegro, the roots of *I. helenium* are used in the external treatment of psoriasis (Menkovic et al., 2011). In Serbian folk medicine, the tea of leaves and flowers of *I. helenium* are used internally for the cold treatment, as expectorant and for blood detoxification; and externally as tincture for rheumatism and sciatica pain (Jarić et al., 2015). In Italian traditional medicine, *I. helenium* roots are used internally as infusion and decoction for the treatment of bronchitis, catarrh and coughs; as bitter tonic, diuretic and choleretic. Externally it is applied for pruritus (Leporatti and Ivancheva, 2003). In Moroccan traditional medicine, decoction of leaves and roots of *I. helenium* are used in the treatment of hypertension, and the decoction of leaves of *I. helenium* in combination with *Inula conyza* and *Inula viscosa* is used in diabetes mellitus (Eddouks et al., 2002; Eddouks et al., 2007).

Bioactive compounds isolated from *Inula helenium*

Identification and isolation of bioactive compounds from *I. helenium* roots and rhizomes play an important role in understanding their biosynthetic pathway, biological properties, mechanism of action and potential toxicity. Table 1 summarizes the secondary metabolites identified from the roots of *I. helenium*.

Table 1.

Bioactive compounds isolated from *I. helenium*

Secondary metabolite classification and name	Parts of plant used	References
Terpene compounds:		
Thymol derivatives (Monoterpenes)		
10-isobutyryloxy8,9-epoxy-thymol isobutyrate	Roots	Stojakowska et al. (2006)
10-isobutyryloxy6-methoxy-8,9-epoxy-thymol isobutyrate	Roots	Stojakowska et al. (2006)
10-(2-methylbutyryloxy)-8,9-epoxy-thymol isobutyrate	Roots	Stojakowska et al. (2006)
Eudesmanolides (Sesquiterpenes)		
Alantolactone		
Isoalantolactone	Roots/roots essential oil	Bourrel et al. (1993), Yan et al. (2012)
11α,13-Dihydroalantolactone	Roots/roots essential oil	Bourrel et al. (1993), Yan et al. (2012)
11α*H*,13-Dihydroisoalantolactone	Roots	Konishi et al. (2002)
4α,5α-Epoxyalantolactone	Roots	Yan et al. (2012)
Diplophyllin	Roots	Jiang et al. (2011), Yan et al. (2012)
5α-Epoxyalantolactone	Roots essential oil	Stojanović-Radić et al. (2012)
Macrophyllilactone E	Roots	Konishi et al. (2002)
5α,6α–Epoxyalantolactone	Roots	Yan et al. (2012)
3-Oxo-4(5),11-eudesmadien-8,12-olide	Roots	Yan et al. (2012)
Spiroalanpyrroid A	Roots	Yan et al. (2012)
Spiroalanpyrroid B	Roots	Cai et al. (2020)
Helenalanproline A	Roots	Cai et al. (2020)
Helenalanproline B	Roots	Cai et al. (2020)
	Roots	Cai et al. (2020)
Elemanolides (Sesquiterpenes)		
Elema-1,3,11(13)-trien-12,8b-olide		
	Roots	Konishi et al. (2002)
Germacranolides (Sesquiterpenes)		
Isocostunolide		
	Roots	Chen et al. (2007)
Phenolic compounds:		
Phenolic acid		
Gallic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
2-Hydroxy benzoic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Chlorogenic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Neochlorogenic acid	Roots	Petkova et al. (2017)
Caffeic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
p-Coumaric acid	Roots	Petkova et al. (2017)
Sinapic acid	Roots	Petkova et al. (2017)
Ferulic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
3,4-Dihydroxybenzoic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Vanillic acid	Roots	Petkova et al. (2017)
Cinnamic acid	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Flavonoids		
Quercetin	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Kaempferol	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Myricetin	Roots	Petkova et al. (2017)
Catechin	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Epichatechin	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Quercetin-3-*O*-β-glucopyranoside	Roots	Spiridon et al. (2013), Petkova et al. (2017)
Polysaccharide		
Inulin	Roots	Petkova et al. (2017)

Pharmacological activities of *Inula helenium*

Several *in vitro* and *in vivo* studies (Table 2) have shown that elecampane extracts possess a wide range of pharmacological activities including anti-inflammatory, antioxidant, neuroprotective, anti-proliferative effects on cancer cell lines, antibacterial, antifungal, anthelmintic, insecticidal, prebiotic etc. These activities may be attributed to the main bioactive compounds isolated from *I. helenium*, mainly sesquiterpene lactones (alantolactone, isoalantolactone) and total phenolic compounds (Wang et al., 2015; Peng et al., 2016). In the Table 2 we have included some of the recent studies on elecampane biological activities.

Tabel 2.

Biological activity studies of *I. helenium* extracts

Evaluated pharmacological activity	Plant parts used	Extraction method	Results	References
Anti-inflammatory (*in vitro*)	Roots	Ethanolic extract 60% (v/v, 1:10)	Ethanolic extract of *I. helenium* (20-100 μg/mL) suppressed the neutrophil binding to the epithelium surface (A549), decreasing the expression of β-integrin on neutrophil membrane. It also inhibited IL-8, IL-1β and TNF-α production in lipopolysaccharide-stimulated A549 cells.	Gierlikowska et al. (2020)
Antioxidant and neuroprotective (*in vitro*)	Not identified	Ethanol extract – Total phenolic compounds	Total phenolic compounds (0.5-5 μ g/mL) isolated from *I. helenium* blocked ROS production, inhibited the reduction of SOD, reversed the changes in MMP and increased ATP production.	Wang et al. (2015)
Anti-proliferative (*in vitro*)	Rhizome and roots	Ethyl acetate extract	Ethyl acetate extract of *I. helenium* produced mitochondria-dependent apoptosis of CFPAC-1 cells, IC-50 value being of 4.3 μg/mL.	Zhang et al. (2018)
Antibacterial (*in vitro*)	Not identified	Aqueous extracts	Aqueous extract of *I. helenium* showed antibacterial activity against *Bacillus mycoides* (MIC 5 mg/mL) and synergism with sodium nitrite and potasium sorbate against *Bacillus subtilis* and *Pseudomonas fluorescens*.	Stanojević et al.(2010)
Antimicrobial (*in vitro*)	Roots	Supercritical fluid extraction (SFE)/ Hydrodistilled essential oil (HD)	HD and SFE oil manifested strong antifungal activity against *Candida* spp., MIC values being 0.009-0.6 mg/mL and 0.07-0.12 mg/mL, respectively. HD oil was more active against *Acinetobacter baumannii* (MIC 0.017 mg/mL), both oils showed strong bactericidal effect against *Enterococcus faecium* (MIC 0.12 mg/mL).	Deriu et al. (2008)
Antimicrobial (*in vitro*)	Roots	Ethanolic extracts (50% and 70%)	Extracts exhibited moderate to high antibacterial activity on *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus cereus* and *Bacillus subtilis*. In addition, low to moderate antifungal activity on *Candida albicans*, *C. parapsilosis* and *C. lipolytica*.	Diguță et al. (2014)
Antistaphylococcal (*in vitro*)	Rhizome and roots	Hydroethanolic extract 50%	The extract was 100% effective against 200 clinically isolated antibiotic-resistant	O'Shea et al. (2009)

			and -sensitive strains of *S. aureus*¸ at concentrations between 0.9-9.0 mg/mL.	
Antistaphylococcal (*in vitro*)	Roots	Hydrodistilled essential oil	Manifested a potent but retard antistapylococcal activity, causing membrane damage. The MIC and MBC values were 0.013 µg/mL and 0.02 µg/mL, repectively.	Stojanović-Radić et al. (2012)
Anticandidal (*in vitro*)	Roots	Hydrodistilled essential oil	Showed medium to high anticandidal activity against clinical isolated of *C. albicans* and *C. cruset*, MICs varying between 0.009-0.312 mg/mL.	Stojanović-Radić et al. (2020)
Anthelmintic (*in vitro*)	Rhizome and roots	80% Hydroethanolic extract	Manifested a higher larvicidal effect against *Trichostrongylus colubriformis* in comparison with albendazole (Zentel).	Urban et al. (2008)
Anthelmintic (*in vitro*)	Rhizome and roots	Aqueous extract	Exhibited strong ovicidal and larvicidal activity against donkey strongyles, with LC-50 values of 0.041 mg/mL and 0.41 mg/mL, respectively.	Buza et al. (2020)
Insecticidal (*in vitro*)	Roots	Acetone/methanol 2:1	Reduced the fecundity of *Oncopeltus fasciatus*, had a strong juvenoid and antifeedant effect. Caused shortening of antennae and proboscis.	Alexenizer and Dorn (2007)
Prebiotic and antioxidant (*in vivo*)	Rhizome	Ethanol extract (EE)	1000 mg/kg of EE increased body weight gain and feed conversion ratio of broiler chickens. Decreased *E. coli* and *Clostridium* spp. population, and increased the count of *Lactobacillus* spp. Increased the activity of antioxidant enzymes in jejunal and ileal mucosa.	Abolfathi et al. (2019)

LC-50 - median lethal concentration
MBC - minimum bactericidal concentration
MICs - minimal inhibitory concentrations
MMP – mitochondrial membrane potential
ROS - reactive oxygen species
SOD - superoxide dismutase

Conclusions

We can conclude that *I. helenium* is a promising medicinal plant for both human and veterinary medicine. However, further *in vivo* studies of *I. helenium* extracts and isolated secondary metabolites are needed to prove their safety, bioavailability, pharmacokinetics, potential sites and mechanism of action.

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