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Review

# Locally and traditionally used *Ligusticum* species – A review of their phytochemistry, pharmacology and pharmacokinetics

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ABSTRACT

*Ethnopharmacological relevance:* *Ligusticum* species (Umbelliferae) have been widely used in traditional Chinese medicine, Korean folk medicine and Native American medicine for their medicinal and nutritional value. Decoctions of the rhizomes are used in treatment and prophylaxis of migraine, anemia and cardiovascular conditions including stroke.

*Aim of study:* This review is intended to fully compile the constituents of locally and traditionally used *Ligusticum* species, present their bioactivities and highlight potential leads for future drug design, and thus, provide a reference for further research and application of these species. Emphasis is also placed on current trends in the pharmacokinetic studies of the major constituents.

*Methods:* The literature discussed is derived from readily accessible papers spanning the early 1990 s to the end of 2015. Information was collected from journals, books and online searches (Google Scholar, PubMed, ScienceDirect, SciFinder, Springerlink and CNKI).

*Results:* The major phytoconstituents, 154 of which are presented in this review, include alkaloids, phthalides and phenolic acids. The crude extracts and isolated constituents have exhibited a wide range of *in vitro* and *in vivo* pharmacologic effects, including cardioprotective, antioxidant, anti-inflammatory and neuroprotective activities. The bioactive alkaloid tetramethylpyrazine (TMP) has attracted the most attention for its potent effect on calcium channels, anti-platelet as well as anti-inflammatory effects. Pharmacokinetic studies of major constituents have also been summarized.

*Conclusion:* The pthalides, organic acids and alkaloids of *Ligusticum* species have emerged as a good source of traditional medicines for the management of cardio- and cerebrovascular conditions, inflammation and neurogenerative disorders. The species discussed in this review have demonstrated wide pharmacological actions and have great potential to yield multipotent drugs if challenges such as poor bioavailability, solubility and toxicological profiles are addressed. Apart from the rhizomes, pharmacological activities of other botanical parts also need to be studied further. Expansion of research to cover other species in the *Ligusticum* genus would provide more opportunities for the discovery of new bioactive principles.

## 1. Introduction

The genus *Ligusticum* (Apiaceae) comprises 66 species of flowering plants (She et al., 2005). The species are widely distributed in the Northern Hemisphere of Asia, Europe and North America with about 40 species (35 endemic) in China alone. The species in the genus are characterized as perennial herbs with cylindrical or fusiform roots, erect stems and oblong or oblong-ovoid fruits. The fruit is the main distinguishing feature among closely related genera (www.efloras.org).

The aqueous extracts and essential oils from the rhizomes of the genus *Ligusticum* are used in indigenous medicines for the management of several ailments. The dried rhizome of L. *chuanxiong* Hort. ex

*Abbreviations:* ASR, *Angelica sinensis radix*; BBB, Blood Brain Barrier; BDPH, Butylidenephthalide; CD, circular dichroism; CO, *Cnidium officinale*; EC, endothelial cells; EO, essential oils; FA, ferulic acid; GC/MS, gas chromatography/mass spectroscopy; $H_2O_2$, hydrogen peroxide; iNOS, inducible Nitric Oxide Synthase; LC, *Ligusticum chuanxiong*; LPS, lipopolysaccharide; NE, norepinephrine; PL, Phthalide Lactone; ROS, reactive oxygen species; SEI, scar elevation index; TCM, traditional Chinese medicine; TMP, Tetramethylpyrazine

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S.H. Qiu et al., is a popular medicine in China for the treatment of angina pectoris, cardiac arrhythmias, hypertension and stroke because of its reputation for facilitating blood circulation and dispersing blood stasis (Chinese Pharmacopoeia, 2005). Chunkung, the traditional name for rhizomes of L. *officinale* (Makino) Kitag. in Korea, are particularly useful as a traditional oriental medicine for the treatment of female genital inflammatory diseases whiles its leaves are used in salads and as a condiment (Choi et al., 2002).

*Ligusticum* species have demonstrated remarkable adaptogenic properties as evidenced by their diverse pharmacological activities. Some species have been reported to be useful in managing cardio- and cerebrovascular-related conditions including atherosclerosis (Zhang et al., 2009), thrombus formation (Li et al., 2001b), ischemic stroke (Chen and Chen., 1992; Yang et al., 2010), angina pectoris (Chan et al., 2009), hypertension (Hou et al., 2005, 2004) as well as inducing vasodilatation (Liang et al., 2005). They have also been used to prevent and cure numerous diseases including rheumatic arthralgia, gynecological conditions, pain, migraine and inflammation (Chan et al., 2006; Chinese Pharmacopoeia, 2005; Li et al., 2014; Peng et al., 2009). The broad spectrum of biological activities reported in the genus has been attributed to the complex and varied phytochemical composition. Though their contents may vary significantly due to geographic sources, harvesting and processing, current research indicates that organic acids, phthalides, alkaloids, polysaccharides, ceramides and cerebrosides are present as the major constituents.

Previous reviews on *Ligusticum* species have focused on the general pharmacological effects (Ran et al., 2011) and extraction, isolation and chemical analysis of constituents (Li et al., 2012b). Phthalides occurring in the Apiaceae have been summarized, and the phthalides of *Ligusticum* species were included (Beck and Chou, 2007). This review, however, discusses the traditional uses, pharmacological activities of phytochemical constituents and pharmacokinetic studies of isolates obtained from locally and traditionally used *Ligusticum* species. This review is intended to fully compile the phytochemical constituents, catalogue their bioactivities, and thus, provide a reference for further research and application of this genus. The literature discussed is derived from readily accessible papers spanning the early 1990s to the end of 2015.

## 2. Traditional uses

A list of some *Ligusticum* species including their traditional uses, local names and main pharmacological actions described in literature has been provided in Table 1. Whereas notable species such as L. *chuanxiong*, L. *officinale*, L. *porteri* J.M.Coult. & Rose and L. *jeholense* (Nakai & Kitag.) Nakai & Kitag. are used for their ethnomedicinal value, most of the other species in the genus are used for food and agriculture (Beck and Chou, 2007). A taxonomic framework of the species discussed in this manuscript has been presented in Supplementary data.

*Ligusticum* species represent important crude drugs in traditional Chinese medicine (TCM), Korean folk medicine and Native American medicine (Lee et al., 2010; Scott and Bye, 1980; Wagner et al., 2011). For instance, decoctions of L. *chuanxiong* are used in TCM formulae such as Ding Tong herbal granules for the treatment and prophylaxis of migraine (Fu et al., 2012), Buyang Huanwu decoction to manage stroke (Cai et al., 2007; Sun et al., 2007; Yang et al., 2012a) and Taohong Siwu tang to prevent cardiovascular diseases (Wu et al., 2007). It is usually added to soups, such as LC mutton soup and LC fish head soup, and eaten as a health food (Yuan et al., 2008). It is not only used for medicinal purposes, but also in facial cosmetics, as a forage additive, tobacco flavour additive, natural preservative among others (Wu et al., 2011). L. *officinale* is used in Korean traditional medicine to treat anemia (Jeong et al., 2009; Lee et al., 2007) and also serves as a fumigant (Kwon and Ahn, 2002). Aqueous extracts of the roots and rhizomes of L. *sinense* Oliv. have been widely used in TCM to relieve pain and cure cold. Besides its medicinal value, the species have also been employed as a pesticide and an insecticide (Sanghong et al., 2014; Shan and Yu, 1985). Also known as Senkyu in Japanese, L. *officinale* is one of the most frequently occurring drugs in the prescriptions of Kampo medicine for thousands of years. The Zuni people of North America use an infusion of the roots of L. *porteri* to treat body aches and chew its roots to treat sore throat (Scott and Bye, 1980).

Recognition of the therapeutic and medicinal value of L. *chuanxiong* in TCM dates from the Han Dynasty (200–300 CE) where it was first cited in the Shennong's *Classic of Materia Medica* as “xiongqiong” (Ramalingam and Yong., 2010). Traditional prescriptions of *Ligusticum* species are used in the form of decoction pieces and are always accompanied with other TCMs (Sheng et al., 2004). According to TCM theory, *Ligusticum* species elicit their diverse therapeutic effects by promoting circulation to alleviate blood stasis as well as promoting *qi* in order to activate blood (Li and Liu, 1998).

## 3. Phytochemical constituents

More than 150 isolates from the genus have been identified. A comprehensive structural classification of these constituents has been provided in Fig. 1**a-f**. With respect to the phytochemical aspects of the genus, the following characteristics deserve our full attention: (i) the species of L. *chuanxiong*, L. *officinale*, *L jeholense* and L. *sinense* have received the most phytochemical attention (ii) Phthalides and volatile oils are the most abundant constituents in the genus (iii) the phytochemical diversity in the genus is responsible for the observed wide pharmacologic potential within the genus. The rhizomes but not the leaves, stems or fruits of this genus are the most commonly investigated targets for isolating bioactive compounds.

### 3.1. Phthalides and volatile oils

Phthalides, and their corresponding dihydro, tetrahydro, and dimer analogues, are major constituents of the Apiaceae (Beck and Chou, 2007). They have a lactone that serves as the core chemical structure for a variety of more complex chemical compounds. Studies have reported that Z-ligustilide and butylidenephthalide (BDPH) are the most abundant phthalides in the genus *Ligusticum* (Wu et al., 2011; Yan et al., 2008). Generally, the phthalides contain a skeletal structure of 1(3*H*)-isobenzofuranone, usually butylated at C-3, with a double bond in benzene ring which can be easily oxidized. Phthalides in *Ligusticum* can be divided into two main types: monomeric and dimeric.

#### 3.1.1. Monomeric phthalides

Among *3-butylidene-phthalides*, the highest degree of unsaturation is the most common, and most of them have a hydroxyl group on the benzene ring. The monohydroxy derivatives of 3-butylidene-phthalide (**1**), namely senkyunolide B (**2**), senkyunolide C (**3**), 3-butylidene-7-hydroxyphthalide (**4**) and Z-senkyunolide E (**5**), have the Z-form in 3(10)-ene functional group, while E-senkyunolide E (**6**) has the E-form, which is uncommon in phthalide skeletons. Only three *3-butylphthalides*, namely 3-butylphthalide (**7**), chuanxiongol (**8**) and 4,7-dihydroxy-3-butylphthalide (**9**), have both butyl group and benzene ring. Among these compounds, the butyl side chain is saturated and the benzene ring may be substituted by one or two hydroxyl groups. Two *4,5-dihydro-3-butyilene-phthalides* from the genus, namely Z-ligustilide (**10**) and senkyunolide F **11**, have a 4(5)-ene double bond which is hydrogenated and a butylidene side chain in positions 3 and 10 which take Z-forms. At the same time, E-ligustilide (**12**), the corresponding E-form, has also been identified, but this is quite unstable.

Compounds **13—19** are Z-ligustilide derivatives with different substituent groups in C-6, C-7 and C-11 which belong to the *4,5-dihydro-6,7-dihydroxy-phthalides* group. Senkyunolide H (**13**), senkyunolide I (**14**), ligustilidiol (**15**) and *cis*–6,7-dihydroxy-ligustilide