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Review

Phytochemistry and pharmacology of the genus *Leonurus*: The herb to benefit the mothers and more

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ABSTRACT

Plants belonging to the genus *Leonurus*, also named motherwort, are traditionally used for anti-gynecological disorder in East Asia, and for sedative in Europe. Chemical investigation of the genus *Leonurus* not only enriched the natural products library, but also enlarged the pharmacological application of this traditional herb. In this review, we systematically summarized the structures of 259 compounds isolated from the genus *Leonurus*, featured with 147 labdane diterpenoids. The reported bioactivity studies up to 2017 are presented in the second part, with the main focus on the isolated compounds and also concerning the extracts. In addition to the traditional uterine contraction and sedative activity, recently the cardiovascular protection effect of leonurine has drawn most attention. Other than that, neuroprotection, anti-inflammation, anti-cancer, anti-platelet aggregation and many other activities have been assigned to various compounds from the genus *Leonurus*. Among 70 bioactivity references cited in this review, 57% of them were concentrated on two alkaloids (leonurine and stachydrine), whereas only 20% are about the 147 diterpenoids. Anti-inflammation is the major bioactivity discovered so far for the labdane diterpenoids from the genus *Leonurus*, whose further therapeutic potential still remains for exploration.

1. Introduction

Known as the motherwort, species belonging to the genus *Leonurus* (family Lamiaceae) have been used in folk medicine of Asia, Europe and America with a long history. The dried aerial parts of the herb, “Yi-Mu-Cao”, are one of the most commonly used Chinese medicine materials, and the dried fruits is used as a separate ingredient called “Chong-Wei-Zi”. As indicated by the name “the herb to benefit the mothers”, the motherwort is applied to treat gynecological and obstetrical disorders in China. In European countries, on the other hand, motherwort is used for treatment of anxiety and heart diseases. In fact, the “motherwort” refers to two different species of the genus *Leonurus* in East Asia and Europe, which may explain the different medicinal applications.

The genus *Leonurus* belongs to the family Lamiaceae, natively grows in the temperate zone of Asia and Europe and was latterly naturalized in America and Africa. About 24 species of *Leonurus* have been identified, of which 13 species are distributed in China (WCSP, 2017) (Table 1). *Leonurus japonicus* (also recorded as *Leonurus heterophyllus*) and *Leonurus cardiaca* are the typical species in Eastern Asia and Europe, respectively.

Since around 1930s, intensive studies have been performed to reveal the chemical constituents and pharmacological mechanism of the motherwort. The investigations are mainly focused on *L. japonicus* (East Asia), *L. cardiaca* (Europe), *L. persicus* (Turkey, Iran) and *L. sibiricus* (Mongolia, Siberia), also referred to minor species like *L. macranthus* (Northeast Asia), *L. turkestanicus* (Central and West Asia) and *L. glaucescens* (Northwest Asia). However, a confusion of *L. japonicus* and *L. sibiricus* might exist in literature, a recent study by Pitschmann et al. provided comprehensive characters to identify the species (Pitschmann et al., 2017). Hundreds of specialized metabolites including alkaloids, flavonoids, terpenoids, glycosides and cyclic peptides have been discovered in *Leonurus* (Shang et al., 2014; Wojtyniak et al., 2013). As the major clinical application in folk, the uterotonic activity of motherwort is owed to

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Table 1
Species of the genus *Leonurus*.

L. cardiaca	*L. kuprijanoviae*	*L. pseudomacranthus*[a]	*L. tataricus*
L. chaiturioides[a]	*L. macranthus*[a]	*L. pseudopanzerioides*[a]	*L. tibeticus*[a]
L. deminutus[a]	*L. mongolicus*	*L. pubescens*	*L. turkestanicus*[a]
L. glaucescens[a]	*L. nuristanicus*	*L. quinquelobatus*	*L. villosissimus*[a]
L. incanus	*L. panzerioides*	*L. royleanus*	*L. wutaishanicus*[a]
L. japonicus[a]	*L. persicus*	*L. sibiricus*[a]	*L. urticifolius*[a]

[a] Distributed in China.

the alkaloids: leonurine (**1**) (Kong et al., 1976) and stachydrine (**2**) (Li et al., 2013a). Alkaloids from *Leonurus* also possess other pharmacological effects, with the highlighted cardiovascular protection of leonurine (**1**) (Liu et al., 2010c). Labdane diterpenoids are featured compounds in the genus *Leonurus*, with diverse structures and considerable quantities in the plants. Various pharmacological effects have been identified for the diterpenoids, including anti-inflammatory (Khan et al., 2012), anti-platelet aggregation (Lee et al., 1991) and anti-cholinesterase (Hung et al., 2011).

Although decades have past, the research trend of *Leonurus* never falls. The present reviews on the topic *Leonurus* are either focused on one species (Sayed et al., 2016; Shang et al., 2014; Wojtyniak et al., 2013), one compound (Yang et al., 2016), or a specific pharmacological application (de Boer and Cotingting, 2014; Liu et al., 2012d). During our research of *L. japonicus*, we realized the lack of a systematic summary of the molecule structures discovered from different species of the genus *Leonurus*, as well as the therapeutic potential of the isolated compounds and their protein targets. In this review, we provide an overview of the reported specialized metabolites from different species of the genus *Leonurus*, as well as the biological activity and pharmacological applications exhibited by isolated compounds or crude extracts (Fig. 1). We collected the articles and reviews from Web of Science covering the period 1930–June 2017. For the phytochemistry part, we summarized all reported specialized metabolites isolated from the genus *Leonurus*. For the pharmacological activity part, we preferred the bioactivity reports of the isolated compounds, but to cover all the major pharmacological applications of the *Leonurus*, we also summarized the bioactivity of the crude extracts if the information of compounds were still unclear. In case of multiple articles studying the same pharmacological application of the same compound, we selected the original and (or) the representative work.

2. Phytochemistry

This section summarizes the structures of 259 compounds identified from the root and aerial parts of the herb, with varying scaffolds covering alkaloids, monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, iridoids, flavonoids, sterols, phenylpropanoids and cyclic peptides.

2.1. Alkaloids

The uterotonic effect of the Chinese motherwort was assigned to the alkaloid leonurine (**1**) discovered in *L. sibiricus* (Kubota and Nakashima, 1930) and *L. japonicus* (Yeung et al., 1977) (Fig. 2). However, a recent study showed the absence of leonurine in *L. sibiricus*, and the possible confusion of *L. sibiricus* and *L. japonicus*

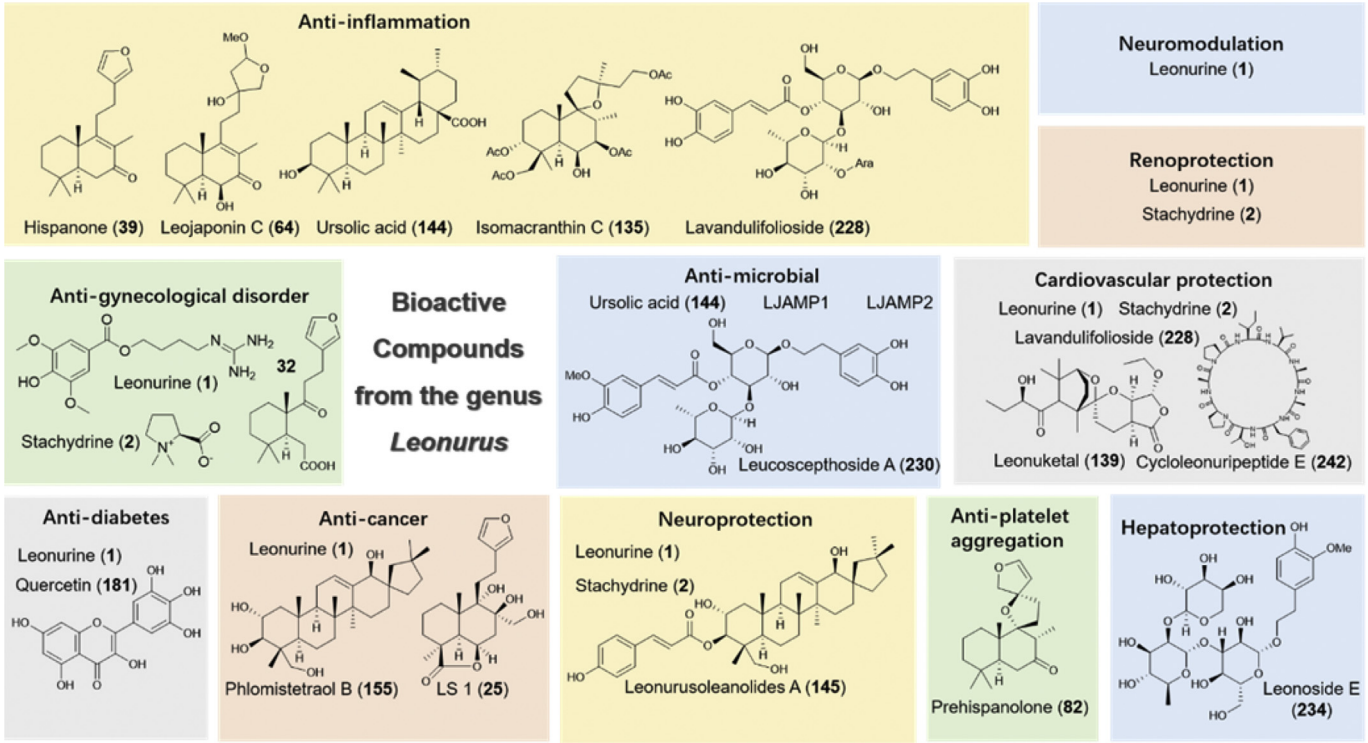

Fig. 1. Representative chemical structures from the genus *Leonurus* with various bioactivities.