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Discovery of Leonuri and therapeutical applications: From bench to bedside

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ABSTRACT

Despite several advances in percutaneous coronary intervention and the discovery of new drugs, the incidence of myocardial infarction and deaths due to cardiovascular diseases (CVD) has not decreased markedly in China. The quality of life is affected seriously, which further results in great social and family burden. Many drugs, from the century-old aspirin to the newly FDA-approved Byvalson, have been proven to be effective in the treatment and prevention of CVD. As clinically reported, those life-saving drugs still have their side effects in regards to the narrow therapeutic indexes influenced by individual genetic variations. *Herba Leonuri*, also known as Chinese Motherwort, which are naturally present in plants and traditionally are used for the uterotonic action, postpartum blood stasis, breast pain as well as other gynecological disorders in China for thousands of years. Since the last two decades, our group has reported leonurine, a unique alkaloid found in *Herba Leonuri*, exhibits various bioactivities such as antioxidant, anti-apoptotic effects, free radical scavenging and anti-inflammatory effects, in addition to improving micro-circulation. These bioactivities are related to the underlying mechanisms of ischemic heart diseases and cardiac fibrosis. Pharmacological studies have proven leonurine to be effective in treating CVD in various ways, particularly ischemic heart diseases. Besides the cardio protective effects, which are similar in the central nervous system, more specifically, inhibited mitochondrial reactive oxygen species production together with the restored mitochondrial function and redox state were observed in middle cerebral artery occlusion rats by leonurine treatment, which strongly reveals its neuroprotective effects and carries a therapeutic potential for recovery and prevention of stroke. Based on their mode of action, we propose that leonurine can be developed as drugs to treat ischemic heart diseases. Taking advantage of the most recent findings in pharmacological research including the effects of low toxicity and good pharmacokinetics characteristics, leonurine has a very attractive prospect of clinical application. Our recent promising pharmacological results may be able to eradicate the barrier hindering its sale on market. In sum, from bench to bedside is no longer a long way for leonurine.

Contents

Abbreviations: CVD, cardiovascular diseases; ROS, reactive oxygen species; MI, myocardial infarction; ECM, extracellular matrix; HIF, hypoxia-inducible factor; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-κB; DOX, doxorubicin; MDA, malondialdehyde; MMPs, metalloproteinases; AngII, angiotensinII; Nox, NADPH oxidase; AD, Alzheimer's disease; Aβ, amyloid-β; CREB, camp-response element-binding protein; BDNF, neurotrophic factor; TrkB, tropomyosin-related kinase B; BBB, blood-brain barrier; BMECs, brain microvascular endothelium cells; tMCAO, transient middle cerebral artery occlusion; OGD/R, oxygen-glucose deprivation and reoxygenation; HDAC, Histone deacetylase; TJs, tight junctional proteins.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide with an estimated 17.5 million deaths annually calculated from the World Health Organization (Khan, Marvel, Wang, and Martin, 2017). People's lifestyles such as alcoholism (Lin et al., 2017), smoking (Wang et al., 2017), obesity (Triggiani et al., 2017), hypertension (Wang et al., 2017), as well as environmental pollution (Feigin et al., 2016) and all those unhealthy factors contribute greatly to the occurrence and development of CVD. Moreover, the incidence of CVD will remain an upward trend in the next few decades (Weiwei et al., 2016). Since the thiazide diuretics used to treat essential hypertension in 1957, the development of anti-cardiovascular drugs has made great strides. The current clinical application of drugs for the treatment of cardiovascular disease is a wide range including calcium antagonists, antiarrhythmic drugs, anti-chronic heart failure drugs, anti-angina drugs, anti-atherosclerosis drugs and antihypertensive diuretics or dehydration drugs. But these drugs are not impeccable, regardless of a hundred years old drug aspirin or the combined drug Byvalson approved newly by FDA, due to the intricate side effects caused by the narrow therapeutic indexes and individual distinction of genotypes. For the past few years, pharmacochemistry and pharmacological studies have made the clinical application of Chinese medicine more objective and scientific. As the thousands of years of gynecological herbal medicine inherited from the Compendium of Materia, herb leonuri also named motherwort is commonly used in Chinese herbal medicine for the treatment of postpartum blood stasis, menorrhagia and menoxenia. Leonurine is the main active compound of motherwort, and first time we had uncovered the cardiovascular protection of leonurine through the anti-apoptotic and anti-inflammatory effects in the past several decades. Furthermore, what excited us is its unique protective effect on central nervous system after stroke. Leonurine can inhibit mitochondrial reactive oxygen species (ROS) production and adenosine triphosphate biosynthesis in rat middle cerebral artery occlusion model. In consideration of its admirable cardiovascular treatment effects, we also innovatively optimized the synthesis route to produce large number of leonurine. As the saying goes, the Great Wall is not built on the day, in spite of the superiorities of leonurine in druggability such as low toxicity and good pharmacokinetics characteristics, the real potential mechanisms for treating cardiovascular disease remain to be tapped, the recent series of encouraging experimental results lend significant therapeutic promise as it translates from bench to beside.

2. History

2.1. Herba Leonuri

Herba Leonuri, also named Chinese Motherwort or Siberian Motherwort, is native to China, central Europe, Scandinavia and Russia, but now it is also popular in Japan, Java, Malaysia and North America. Thousands of years ago, *Leonurus japonicus* has been recorded as "Top grade" in the oldest classical medicinal book Sheng Nong Ben Cao Jing (a bible of Chinese medicine) in China. In Ben Cao Gang Mu (another most famous masterpiece of Chinese medicine), it was considered to be non-toxic and harmless and used for treatment of vaginal bleeding, dystocia, retained fetal membranes, bruising, metrorrhagia, metrostaxis, hemuresis and some other diseases, which has been circulating so far. Since 1990, it also has been listed in the Pharmacopoeia of the People's Republic of China, in which more than 15 kinds of traditional Chinese medicine prescription contain *Leonurus japonicus* as the main active component (Shang, Pan, Wang, He, and Li, 2014). Coincidentally, the description of *Leonurus japonicus* is also emerged in the seventh edition of the European Pharmacopoeia. Since modern times, western researchers seem to have reached an agreement with oriental scholars on the treatment effects of *Leonurus japonicus* on gynecological diseases. Besides, it is applied in nervous conditions as an aid in hyperthyroidism owing to its efficacy to remit the palpitations and tachycardia associated with hyperthyreosis (Wojtyniak, Szymanski, and Matlawska, 2013).

2.2. Leonurine

In 1976, Yeung CH put forward that leonurine extracted from the leaves of *Herba Leonuri* was an uterotonic demonstrated in rat uterus *in vitro*. Results from this study suggested that leonurine is able to develop into a new and effective drug based on ethno-botanical experiment, which is the first scientific description about leonurine to be a drug (Kong et al., 1976). In the following year, Cheng KF further confirmed the structure of leonurine and its uterotonic effect *in vitro* (Yeung, Kong, Lay, and Cheng, 1977). In addition, Kong YC developed a synthetic procedure of leonurine and showed, the chemical synthesized leonurine had the same uterotonic effect compared to natural extraction (Cheng, Yip, Yeung, and Kong, 1979). After entering the 21st century, the number of researches about leonurine was blown up and most of which concerned the protective effects of leonurine on cardiocerebral vascular diseases (Chen and Kwan, 2001; Liu, Xin, Hou, and Zhu, 2009; Loh et al., 2010; Zhang et al., 2017).

3. Active chemical compounds of traditional Chinese medicine *Herba Leonuri*

It has been reported that approximately 140 chemical components had been isolated and identified from *Herba Leonuri* including alkaloids, flavonoid, and diterpenes (Shang et al., 2014). In addition, *Herba Leonuri* also contains plentiful amounts of potassium and vitamins, all of which exert special beneficial effects in CVD and cerebral ischemia. Among these compounds, alkaloids are considered a major class of active ingredients of *Herba Leonuri*. The total amount of alkaloids ranges from 0.1% to 0.2%; higher alkaloids content is found in younger and more succulent plants (Liu, Pan, and Zhu, 2012b).

3.1. Alkaloids

Alkaloids are dominated in *Herba Leonuri*, the main four alkaloids have been identified: leonuridine, leonurine, leonurinine and stachydrine. To date, lots of reports have shown that the alkaloids exert beneficial effects in ischemic cardio-cerebrovascular diseases, fortunately, it also be verified by our recent work on leonurine showing the protective effects on ischemia both *in vivo* and *in vitro via* different mechanisms.

Leonurine, a unique alkaloid, possessing several pharmacological effects, such as an uterotonic action, antiplatelet aggregation and inhibition of vascular contractile responses (Wang, Zhang, and Ju, 2004), has received more attention than any other chemical substances in *Herba*

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