Computational Molecular Biology 2025, Vol.15, No.2, 84-90
http://bioscipublisher.com/index.php/cmb

Research Insight Open Access

The Molecular Mechanisms and Regulatory Network of the Accumulation of *Leonurus japonicus* Alkaloids

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Computational Molecular Biology, 2025, Vol.15, No.2 doi: 10.5376/cmb.2025.15.0008
Received: 27 Jan., 2025
Accepted: 08 Mar., 2025
Published: 29 Mar., 2025

Preferred citation for this article:
Zhong J.L., 2025, The molecular mechanisms and regulatory network of the accumulation of *Leonurus japonicus* alkaloids, Computational Molecular Biology, 15(2): 84-90 (doi: 10.5376/cmb.2025.15.0008)

Abstract This study investigates the molecular mechanisms and regulatory networks that control the accumulation of alkaloids in *Leonurus japonicus,* a medicinal plant widely used in gynecological treatments, recognized for its antioxidant, anti-inflammatory, and anti-melanogenesis properties. Alkaloids such as Leonurine are key active compounds in the plant, playing a crucial role in its medicinal properties. This research explores the biosynthetic pathways of these alkaloids and identifies environmental factors, such as pH and external stresses, that influence their production. By integrating genomic, transcriptomic, and metabolomic analyses, the study aims to deepen the understanding of how these alkaloids contribute to the plant's medicinal characteristics, helping to optimize cultivation and medicinal application strategies, ensuring the sustainability and effectiveness of *Leonurus japonicus* as a medicinal resource.
Keywords *Leonurus japonicus*; Alkaloids; Leonurine; Biosynthesis; Medicinal properties

1 Introduction

Motherwort is a familiar face in traditional Asian medicine. Perhaps everyone is more familiar with its other name-Chinese Motherwort. For gynecological problems like irregular menstruation, veteran traditional Chinese medicine doctors often use it to regulate. However, interestingly, recent research has found that it can also deal with skin pigmentation, which is quite surprising.

When it comes to its active ingredients, alkaloids are definitely the stars. Especially that guy called Leonurine, it's good at both anti-inflammation and anti-oxidation. Of course, there are also flavonoids, phenolic acids and other helpers in plants that work together. But to be honest, although we know it is useful, scientists still haven't fully figured out how these alkaloids accumulate.

Environmental factors have a considerable influence on it. For instance, when the soil pH level changes slightly, the content of alkaloids within it also varies. This phenomenon was noticed in research as early as 2022. What's more complicated is that different components can also influence each other. The synthetic pathway of diterpenoids, for instance, has an ambiguous relationship with the metabolism of alkaloids.

In fact, traditional medication experience tells us that this grass is useful, but modern research is more eager to know why it is useful. At present, to truly make good use of this medicinal plant, it is not enough to merely know what components it contains; it is also necessary to understand where these components come from and what influences them. If we can figure out these problems in the future, perhaps we can grow more useful motherwort.

2 The Types of Alkaloids in Motherwort

2.1 Identification of key alkaloids in *Leonurus japonicus*

One of the most well-known features of motherwort is that it is rich in alkaloids. Among them, Leonurine is the main component confirmed in current research and also the most representative compound. Researchers have been able to successfully isolate and purify Leonurine from *Leonurus japonicus*. This substance can almost be regarded as the unique active ingredient of *Leonurus japonicus* and holds a core position in medicinal value.

In addition to Leonurine, quercetin, an important compound, was also discovered in the research. Its synthesis process is rather complex, requires the participation of nitrogen, and is easily affected by external conditions, such as the pH of the solution (Zhang et al., 2022). The discovery of these components is inseparable from the support of modern analytical methods. For instance, ultra-performance liquid chromatography-mass spectrometry (UPLC-QTRAP®/MS^2) has been employed to detect various alkaloids within mothergrass. With this technology, not only can the contents of Leonurine and quercetin be accurately determined, but also the differences in plants from different parts or different origins can be compared, thereby revealing the influence of environmental and biological factors on the component levels (Tan et al., 2020).

2.2 Medicinal properties and biological activities of key alkaloids in *Leonurus japonicus*

In the efficacy of *Leonurus japonicus*, Leonurine plays a core role. It has a wide range of activities and can regulate physiological processes such as oxidative stress, inflammatory response, fibrosis and apoptosis. Therefore, it is considered to have potential therapeutic effects on many types of diseases (Li et al., 2019b). Meanwhile, extracts containing Leonurine also exhibit good antioxidant and melanin-inhibiting effects, which help reduce the accumulation of reactive oxygen species and inhibit pigmentation, presenting application prospects in the research of skin-related diseases.

As for quercetin, its functions are not limited to human medicinal effects; it is also directly related to the health and growth of plants themselves. In an alkaline environment, the synthesis of quercetin is more active because it is more conducive to the nitrogen addition reaction at this time. By promoting the growth and yield of motherwort, it indirectly increases the content of plant pharmacodynamic components, thereby enhancing the overall medicinal value.

2.3 Comparison with alkaloids in other medicinal plants

By comparing the alkaloids of *Leonurus japonicus* with those of other medicinal plants, the differences between them can be discovered. Many plants also contain common active ingredients such as antioxidants and anti-inflammatory agents. However, Leonurine is special in that it can act on multiple metabolic pathways and has a particularly significant effect in the treatment of gynecological related diseases. This targeting property and broad-spectrum activity make it unique among medicinal plants.

Although quercetin is not unique to motherwort and can be found in many plants, its function is particularly prominent in motherwort. Its sensitivity to environmental conditions, instead, becomes part of the adaptability of motherwort: in a suitable environment, it can promote the synthesis of more active substances in plants, thereby enhancing the overall efficacy (Zhang et al., 2024). In contrast, alkaloids in other plants may not exhibit the same flexibility when the environment changes, and thus there are differences in the stability of application and efficacy.

3 Biosynthesis of *Leonurus japonicus* Alkaloids

3.1 Main synthetic pathways

The alkaloid synthesis pathway in *Leonurus japonicus* is rather complex, involving multiple biochemical processes. Substances like Leonurine are essentially formed by the gradual transformation of primary metabolites into secondary metabolites, and it is precisely these secondary metabolites that endow Leonurine with medicinal value (Liu et al., 2018). This synthetic pathway is not fixed. It is not only restricted by the plant's own genetic background but also influenced by the external environment. Therefore, the content of alkaloids in different parts of motherwort, or even in motherwort from different origins, can vary (Tan et al., 2020).

In motherwort, the formation process of alkaloids is closely related to the synthesis of other secondary metabolites (such as diterpenoids, flavonoids, etc.) (Miao et al., 2019). These metabolic pathways often share precursor substances or enzymes, so multiple metabolites may be produced simultaneously in the same process. It is precisely this interwoven metabolic network that enables motherwort to better adapt to the environment and is also closely related to its pharmacological effects (Wang et al., 2022).

3.2 Key enzymes and genes

The generation of *Leonurus japonicus* alkaloids requires the participation of a series of specific enzymes, which respectively catalyze different reaction links. For instance, during the process of converting primary metabolites into intermediate products, key enzymes play a role. There are usually strictly regulated genes driving behind these enzymes, and external conditions (such as environmental stress or plant hormone signals) often also affect the expression of these genes (Tian et al., 2021).

In recent years, some studies have successively identified some genes that play a core role in the synthesis of *Leonurus japonicus* alkaloids. Most of these genes belong to larger gene families, and these families themselves are related to the synthesis of multiple types of secondary metabolites. It is worth noting that the activity of these genes is often not controlled in isolation; they are regulated by transcription factors. Transcription factors regulate transcriptional levels by binding to promoter regions of genes, thereby affecting the synthetic efficiency of alkaloids (Li et al., 2019a).

3.3 Mechanisms affecting synthesis

The formation of motherwort alkaloids is not determined by a single factor, but is the result of the combined effects of genetics, environment and biochemical mechanisms. At the genetic level, the presence of different alleles and the expression levels of genes related to synthesis will both have an impact on the final yield. Some genotypes may promote synthesis, while others may have an inhibitory effect.

The external environmental conditions should also not be ignored. For instance, changes in light intensity, temperature and soil nutrients can affect the accumulation of alkaloids by altering the metabolic state of plants (Du et al., 2020).

At the biochemical level, the supply of substrates and the activity of key enzymes are important links that determine the amount of products. There is often a substrate competition relationship among different metabolic pathways, which also affects the final yield of alkaloids. Furthermore, some signaling molecules (such as jasmonic acid substances) can induce the expression of related genes, enabling plants to accelerate the accumulation of alkaloids when facing environmental stress or developmental regulation (Jiao et al., 2022).

4 The Regulatory Network of *Leonurus japonicus* Alkaloid Accumulation

4.1 The role of transcription factors in the synthesis of *Leonurus japonicus* alkaloids

In motherwort, transcription factors (TFs) play a key role in regulating the synthesis of alkaloids. Studies have shown that many transcription factors related to jasmonic acid, especially members from the AP2/ERF, bHLH, MYB and WRKY families, can promote the generation of various secondary metabolites including alkaloids by initiating specific metabolic pathways. Among them, the bHLH transcription factor has been verified in the synthesis of cyanogenic glycosides in *Lotus japonicus*, and this pathway is closely related to the formation of alkaloids (Chen et al., 2022). These transcription factors can activate the expression of key enzyme genes, thereby promoting the accumulation of alkaloids within the plant.

It is worth noting that transcription factors do not "fight alone" among themselves. They often form more complex regulatory networks through interaction. For instance, the WRKY transcription factor has been confirmed to promote the synthesis of phenylisoquinoline alkaloids in Nelumbo nucifera (Li et al., 2022). Furthermore, they may also interact with jasmonic acid-Zirm domain proteins, etc., further increasing the levels and flexibility of regulation. This means that the regulation of alkaloids in motherwort may also follow a similar pattern.

4.2 The influence of plant hormones on the accumulation of alkaloids in *Leonurus japonicus*

The role of plant hormones in the accumulation of *Leonurus japonicus* alkaloids cannot be ignored. Jasmonic acid (JAs) is one of the most deeply studied ones. It can induce the synthesis of multiple secondary metabolites by activating specific transcription factors (Zhou and Memelink, 2016). For instance, in *Leonurus japonicus*, jasmonic acid has been proven to regulate cyanoglycoside synthesis, suggesting that it may also play a similar role in the alkaloid metabolism of *Leonurus japonicus*. Functionally speaking, this regulation is not only for the accumulation of products, but also closely related to the plant's resistance to external stress.

In addition to jasmonic acid, hormones such as abscisic acid (ABA) and ethylene (ET) are also involved in the regulation of secondary metabolites. Studies have found that some transcription factors of the AP2/ERF family are activated under the regulation of these hormones, thereby affecting the synthesis of metabolites including alkaloids (Xie et al., 2019). Therefore, the synergistic relationship between hormones and transcription factors enables motherwort to flexibly adjust the accumulation of metabolites to better adapt to environmental changes (Zhang et al., 2007).

4.3 The regulatory effect of environmental stress on the accumulation of *Leonurus japonicus* alkaloids

The changes in natural conditions also profoundly affect the accumulation of alkaloids in motherwort. Whether it is extreme temperature, insufficient water, or excessive soil salinity, these stresses will change the hormone levels in plants, thereby triggering a series of stress-related transcription factors and further affecting metabolic pathways. For instance, the AP2/ERF family is considered to have a potential connection with alkaloid synthesis due to its significant role in adverse response (He et al., 2018).

What's more interesting is that environmental stress often does not act alone but exerts its influence through interaction with hormone signaling pathways. For instance, jasmonic acid-related transcription factors have been proven to regulate the synthesis of secondary metabolites under adverse conditions, and this mechanism may also exist in motherwort (Mertens et al., 2016). Therefore, this regulatory network can be understood as the way plants "self-regulate" in complex environments. It not only ensures the production of alkaloids but also enhances the defense and survival capabilities of the plants.

5 Molecular Research Methods of *Leonurus japonicus* Alkaloids

5.1 Application of transcriptomics and metabolomics in the research of *Leonurus japonicus* alkaloids

Transcriptomics and metabolomics are two indispensable tools when exploring the formation and regulation of alkaloids in *Leonurus japonicus*. Take the transcriptome as an example. It can help researchers identify key enzymes related to metabolic pathways in the vast amount of genetic information. The research on diterpene synthase is a typical case. This type of enzyme is closely related to the formation of complex diterpene structures. The functional analysis not only enables us to see the diversity of plant synthetic capabilities, but also provides important clues for understanding the synthetic pathways of alkaloids (Zhu, 2024). Through the analysis of gene expression profiles in the transcriptome, the regulatory network of alkaloid synthesis can be gradually outlined.

Meanwhile, metabolomics offers another perspective. It directly approaches from the metabolite level and uses methods such as LC-MS/MS and HPLC-DAD to conduct a comprehensive detection of the chemical components in *Leonurus japonicus* extract. In this way, not only can the presence of multiple alkaloids be confirmed, but also other secondary metabolites such as flavonoids and phenolic acids can be discovered simultaneously. When the data of the transcriptome and metabolome are combined, researchers can match gene expression with specific metabolites, thus forming a more complete picture. This comprehensive analysis is crucial for further understanding the metabolic mechanism of *Leonurus japonicus* and its potential pharmacological value (Shang et al., 2014; Li et al., 2019).

5.2 Application of CRISPR technology in the research of aloids from mothergrass

With the development of gene editing technology, CRISPR has become a powerful means for studying the molecular mechanism of motherwort. Although the related applications are still relatively limited at present, their potential cannot be ignored. Through this technology, researchers can precisely knock out or modify genes related to alkaloid synthesis, thereby regulating the yield of specific alkaloids. For example, the editing of certain key enzymes or regulatory genes may enable the optimization of the medicinal activity of *Leonurus japonicus*.

CRISPR also provides a direct way to verify gene functions. Candidate genes previously screened out through transcriptome studies, such as those encoding diterpene synthase, can be used to detect their specific roles in alkaloid synthesis through gene editing (Wang et al., 2022). This method can not only deepen our understanding of the genetic basis of alkaloid synthesis, but also open up a new direction for improving motherwort and breeding varieties with higher medicinal value (Rong et al., 2022).

5.3 Metabolic profiling analysis techniques were used to identify the alkali-related metabolites of *Leonurus japonicus*

Metabolic profiling analysis technology played a key role in the analysis of the chemical composition of motherwort. By means of LC-MS/MS and HPLC-DAD, researchers were able to isolate and identify multiple types of active components from complex plant extracts, including different types of alkaloids (Zhang et al., 2013). This information enables us to have a clearer understanding of which compounds are the "main characters" in the pharmacological effects of *Leonurus japonicus*.

More importantly, metabolic profiling analysis can not only present the final products but also reveal the intermediate products in the synthetic pathway. In this way, researchers can gradually piece together the complete process of alkaloid synthesis and then identify potential regulatory nodes. Especially when metabolic profiling is combined with transcriptomics, the correspondence between gene expression and metabolites becomes even clearer. This interdisciplinary integration enables us to have a more systematic understanding of the synthesis and regulation of *Leonurus japonicus* alkaloids, and also provides strong support for future functional research and application development (Kuchta et al., 2012).

6 Future Research Directions

6.1 The complexity of the Motherwort alkaloid regulatory network

Interestingly, although we already know that pathways such as PI3K-Akt-mTOR are related to melanin synthesis, how they specifically affect the synthesis of Leonurus alkaloids remains a mystery. The alkaloid content varies greatly in different parts-the content in leaves may be twice that in roots, suggesting that environmental factors may be more important than we think (Tan et al., 2020). However, it should be noted that merely identifying these differences is not enough. Techniques such as transcriptomics need to be used to map out the regulatory networks at different growth stages, especially those special metabolites that suddenly emerge, which may hold key clues.

6.2 Increasing production is no simple matter

Everyone says CRISPR gene editing is the master key, but in actual operation, just finding the targets such as diterpene synthase is quite a headache. An unexpected discovery is that adjusting the pH value can actually double the yield of a certain alkaloid (Zhang et al., 2022), which reminds us that instead of insisting on genetic modification, it is better to try the hydroponic system in combination with pH regulation first. Of course, combining these two methods might be more reliable, but the cost issue will be a hurdle.

6.3 The long journey from the laboratory to the pharmacy

Leonurine has anti-inflammatory and antioxidant properties, which sounds like a panacea. However, last year a team discovered that it would instead aggravate oxidative stress for certain cell types (Huang, 2024). Skin whitening applications do have a promising future. After all, extracts can indeed inhibit melanin. However, to turn this effect into a stable ingredient in skin care products, the long-standing problem of unstable active ingredients still needs to be addressed. Pharmacokinetic study? That's just the beginning. Even the most basic half-life data is still lacking now.

7 Conclusion

When it comes to motherwort, many people's first thought is that it is a good medicine for gynecology. But you may not know that behind this seemingly ordinary plant lies a complex "chemical factory". Scientists have discovered that the alkaloids with pharmacological activity in its body are not the result of a single step, but are extracted through a series of enzymatic reactions. Interestingly, although diterpene synthase (diTPSs) plays a key role in this process, environmental factors sometimes come to "cause trouble"-for instance, when the soil pH changes, the metabolic intermediates in plants will also change, and the final active ingredients obtained may be completely different.

Over the years, researchers have discovered many good things from different extracts of *Leonurus japonicus*. Besides the signature alkaloids, there are also "supporting roles" such as flavonoids and phenolic acids. However, what has drawn the most attention is still its star ingredient, Leonurine, which stands out in terms of antioxidation and anti-inflammation. But don't think it only treats gynecological diseases. Recently, there was an unexpected discovery: its extract can even inhibit melanin production, which caught the attention of cosmetic companies. Of course, the regulatory effect of components like 7-methylisoflavone on estrogen synthesis also suggests its potential in hormone therapy.

However, to be fair, our understanding of motherwort is still far from sufficient. Although advanced tools such as ultra-performance liquid chromatography are now available to compare the component differences of *Leonurus japonicus* from different origins and parts, how exactly are those active ingredients synthesized and regulated? What roles do genetic and environmental factors play respectively? None of these issues have been fully understood yet. What's more troublesome is that there might still be many active substances hidden in motherwort that we haven't discovered. If the methods of systems pharmacology can be applied in the future, perhaps more new ideas for treating diseases can be discovered. From this perspective, this ancient Chinese herbal medicine does indeed hold many treasures worth exploring in modern science.

Acknowledgments
I would like to thank Dr. Ding continuous support throughout the development of this study.

Conflict of Interest Disclosure
The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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