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Review Article **Open Access**

Research on the Extraction of Flavonoids from Hangbaiju (*Chrysanthemum morifolium*) and the Development of Functional Foods

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Abstract Hangbaiju is rich in various flavonoid components, and naturally possesses excellent antioxidant and anti-inflammatory activities. So, it is regarded as a high-quality resource for the development of functional foods. Its potential is not only confined to traditional drinking, but also reveals new possibilities in modern health products. This study focused on the flavonoids in Hangbaiju, sorted out its main chemical composition and functional characteristics, and compared the differences in efficiency and component retention among different techniques by combining traditional and modern extraction methods. The results show that, green extraction methods such as ultrasonic-assisted and enzymatic hydrolysis, not only increase the yield but also are more beneficial to the stability of the active substances. It further explored the application paths of Hangbaiju flavonoids in various food forms, like tea beverages, capsules, and nutritional supplements, and evaluated their functional effects and safety in both in vivo and in vitro. This study provides fundamental support for the high-value development of Hangbaiju resources, and also offers a reference for the extended application of functional products.

Keywords Hangbaiju; Flavonoids; Green extraction; Functional food; Antioxidant

1 Introduction

Hangbaiju (*Chrysanthemum morifolium*), an important cultivated variety of chrysanthemum, has a history of over three thousand years in China for medicinal and tea consumption. Traditionally, Hangbaiju has been used to treat colds, inflammation and cardiovascular diseases, and is widely consumed as a daily drink due to its health benefits (Hao et al., 2022; Liu et al., 2024). As a plant with both medicinal and edible properties, Hangbaiju has a profound root in Chinese culture. Different cultivated varieties, such as "Taiju" and "Duoju", are often used in flower tea and nutritional health products (Gong et al., 2019; Yang et al., 2022).

With the growing global interest in natural health products and functional foods, the market potential of Hangbaiju has also significantly increased. High safety, refreshing flavor, coupled with the background of "food and medicine sharing the same origin", makes it a valuable resource in the development of nutritional health products, functional beverages and food additives (Hao et al., 2022; Zhu et al., 2024). The increasing demand for natural antioxidants and anti-inflammatory components in the health industry has further enhanced the commercial value of Hangbaiju, especially as new applications of related active ingredients are constantly being discovered (Liu et al., 2024).

Flavonoids are one of the main secondary metabolites in Hangbaiju. They not only participate in the plant's own defense system, but also affect color and the ability to adapt to the environment (Wang et al., 2019; Lu et al., 2024). For humans, flavonoids are more like natural "protective umbrellas", which can resist oxidation and inflammation, and may also play a role in regulating immunity and preventing chronic diseases (Zhang et al., 2019; Chen et al., 2020; Hou et al., 2020).

In Hangbaiju, luteolin, apigenin, trifolin and their glycoside derivatives are abundant. Phenolic substances such as caffeylquinic acid are also often mentioned together (Gong et al., 2019; Lu et al., 2024). Recent metabolomics and

transcriptomic analyses, have further accelerated the identification of active components in Hangbaiju. Now, more than 60 kinds of flavonoids are known. Some are even regarded as "quality markers" or functional evaluation indicators, used to assist in product development and component control (Wang et al., 2019; Lu et al., 2024).

This study systematically analyzed the extraction techniques and composition characteristics of flavonoids in Hangbaiju, and combined with the evaluation of their functional activities, explored their practical application potential in the development of nutritional foods and health care products. We hope to provide feasible solutions for the high-value utilization of Hangbaiju resources, and at the same time offer references for the development and industrialization of natural functional components.

2 Chemical Composition and Bioactivity of Hangbaiju Flavonoids

2.1 Types of flavonoid compounds in Hangbaiju

Hangbaiju is rich in various flavonoids, primarily flavonols and flavonoid glycosides. Representative components, including luteolin-7-O-glucoside, apigenin-7-O-glucoside, and others like diosmetin-7-O-glucoside and rutin (Chen et al., 2020; Dong et al., 2023; Zhu et al., 2024).

In Hangbaiju, typical monomers that have been identified include luteolin, apigenin, trifoliin and their corresponding glycosides, which are considered to be the main contributors to its biological activity, and are also important quality markers for distinguishing different cultivars (Gong et al., 2019; Chen et al., 2020; Dong et al., 2023).

2.2 Main bioactivities of Hangbaiju flavonoids

The flavonoids in Hangbaiju, are particularly outstanding in terms of antioxidation. After the optimization of the extraction process, their ability to scavenge free radicals has been significantly enhanced, which has been confirmed by multiple studies (Gong et al., 2019; Zhu et al., 2024). But, antioxidation is only one of their many functions. In fact, such compounds can also exert anti-inflammatory effects and find their place in both traditional Chinese medicine and modern functional foods by regulating immune responses (Liu et al., 2024).

In addition to the above-mentioned functions, the Hangbaiju flavonoids also exhibit antibacterial activity that cannot be ignored. Some studies have pointed out that, they also have potential in protecting the liver and improving cardiovascular function. These functions combined enable it not only to assist in the prevention of various chronic diseases, but also to play an active role in daily health maintenance (Cai et al., 2024; Liu et al., 2024).

2.3 Factors influencing flavonoid content

Actually, the flavonoid in Hangbaiju is not fixed. The variety and environmental conditions play a key role. Take "Taiju" and "Duoju" for example. There is a difference in the concentration of the main flavonoids between them. Sometimes, even for the same variety, changing the soil, like with different mineral richness, can also cause changes in the accumulation of certain components, like rutin and apigenin-7-O-glucoside (Gong et al., 2019; Long et al., 2022).

Besides, the timing of picking and the post-harvest processing methods also have a significant impact. Flavonoids and caffeylquinic acid substances, have the highest content when the flower buds are just formed. After the flowers are fully open, they will gradually decrease instead (Lu et al., 2024). The duration of sunlight also has a positive effect on the accumulation of flavonoids. Stress conditions, like waterlogging, may interfere with the expression of its biosynthetic genes, thereby altering the final flavonoid composition (Wang et al., 2019; Lu et al., 2024) (Figure 1).

3 Extraction Techniques for Hangbaiju Flavonoids

3.1 Traditional extraction methods

Currently, water extraction and ethanol extraction remain the two most commonly used methods for extracting flavonoids from *Chrysanthemum morifolium*. The advantages of water extraction are obvious—it's safe and easy

to use, making it the most widely used method in traditional medicine and food processing. However, it also has limitations. Flavonoids are not very soluble in water, often resulting in suboptimal extraction concentrations. In contrast, extraction with ethanol, especially mixed water-alcohol solvents, is significantly more effective. Extraction efficiency is higher, and the flavonoid and polyphenol content is significantly higher than with water (Zhang et al., 2020). For example, when chrysanthemum leaves are extracted with water-alcohol, the polyphenol content is almost double that of water extraction, and the antimicrobial activity is also stronger.

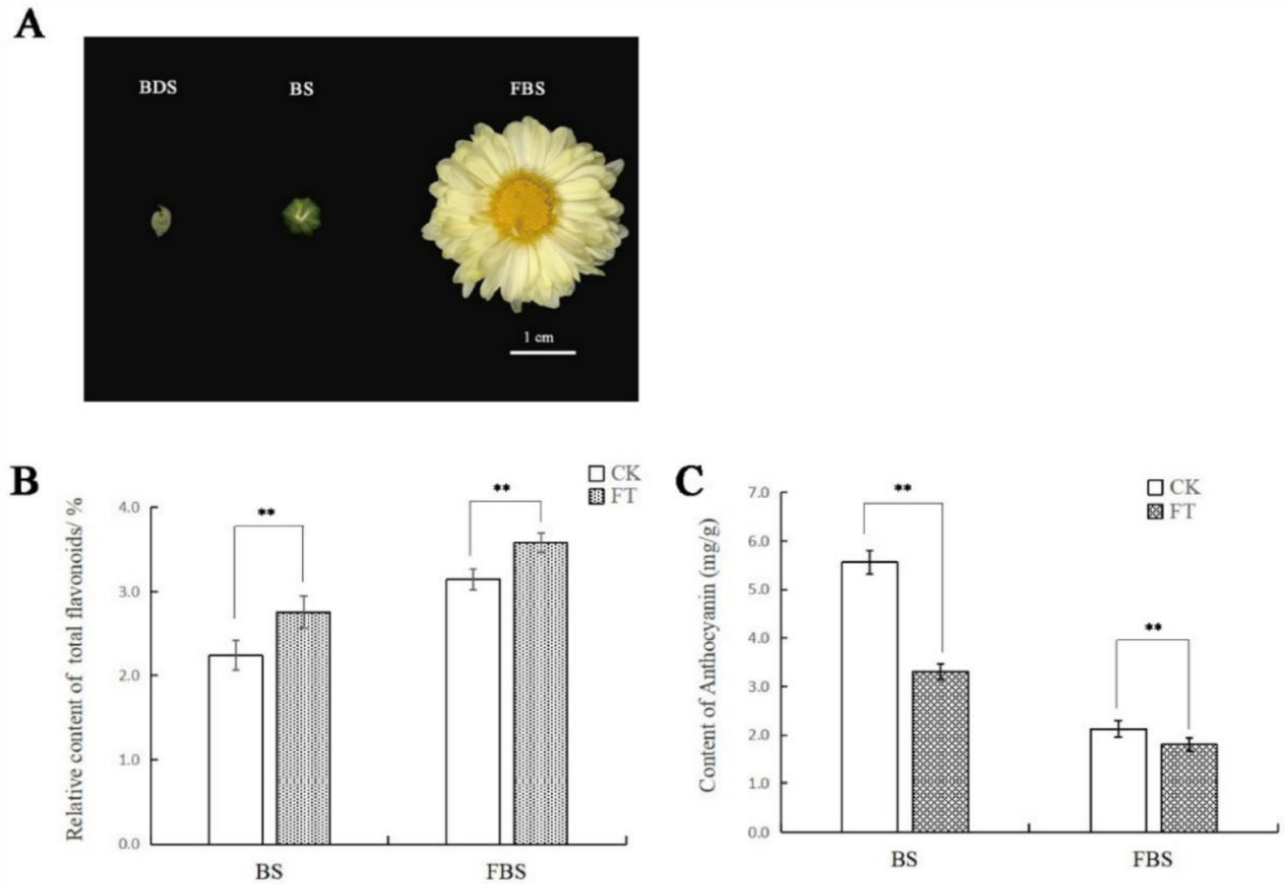


Figure 1 Content of total flavonoids and anthocyanins in different stages of "Hangju". (A) Morphological characteristics of "Hangju" capitula in different growth stages: flower bud differentiation stage (BDS), bud stage (BS) and flower bloom stage (FBS); (B) Content of total flavonoids and (C) anthocyanin in different stages after flooding stress. Data represent mean values ± SD of three independent measurements. ** indicates a significant difference at $p<0.01$ (Adopted from Wang et al., 2019)

Reflux extraction, is also an old method. It relies on continuous heating and condensation to keep the solvent temperature and volume constant, thereby improving the extraction efficiency. This method can indeed enhance the release of active ingredients, but it also has many "side effects" - it takes a long time, consumes a lot of energy, and uses a large amount of solvent, which is not very environmentally friendly. What is more troublesome is that high-temperature and long-term processing may cause the degradation of some heat-sensitive flavonoids, which instead affects the quality and activity of the extract (Zhang et al., 2020; Liu et al., 2022). So, although reflux extraction technology is mature, it is more suitable for small-scale laboratory operations and less suitable for the demands of industrial or green production.

3.2 Modern green extraction technologies

Although traditional extraction methods are classic, their efficiency and environmental burden have always been a difficult problem. To address these issues, many green extraction technologies have emerged in recent years. Ultrasound-assisted extraction (UAE) is one of them. It "shatters" the plant cell walls through ultrasonic waves, accelerating solvent penetration and component release, which not only increases the extraction rate but also saves a lot of time (Chaves et al., 2020; Liu et al., 2022).

Microwave-assisted extraction (MAE) relies on microwave heating to rapidly increase the temperature of the solvent and sample, thereby enhancing the extraction efficiency and selectivity. These two methods share a common feature: they use less solvent and consume less energy, and thus are regarded as more environmentally friendly options. At the same time, they are also milder to heat-sensitive flavonoids and preserve their activity better.

In addition to physical methods, biological means have also begun to be incorporated. Enzymatic hydrolysis method breaks down the cell wall structure through specific enzymes and releases flavonoids without destroying the activity of components (Wang et al., 2024). As for SFE, it uses supercritical CO_2, which has a low temperature, strong selectivity and almost no residue, and can retain the activity of flavonoids to the greatest extent (Huang et al., 2017; Chaves et al., 2020).

3.3 Optimization and comparison of extraction parameters

To extract more and better flavonoids, the regulation of extraction parameters is an unavoidable step. The most common approach is to conduct single-factor experiments, that is, to adjust one variable at a time, such as adjusting basic conditions (e.g., solvent concentration, temperature, and extraction time), to determine which combination is the most appropriate (Liu et al., 2022). However, this approach is safe, it is not very efficient. Later, statistical modeling methods, like the Response Surface Method (RSM), came in handy. It can analyze the interaction relationship among multiple variables at one time and predict the optimal extraction condition more accurately (Wang et al., 2024).

However, talking too much is not enough. When comparing different extraction methods, one should not only focus on the yield and purity, but also consider practical issues such as cost, environmental friendliness, and whether they can be widely applied. Judging from the current situation, green extraction technologies such as UAE, MAE, enzymatic hydrolysis, and SFE do have more advantages over traditional methods in terms of efficiency, selectivity, and environmental friendliness (Chaves et al., 2020; Wang et al., 2024). But, it's not without thresholds. For instance, SFE, although it has a good purification effect, has relatively high requirements for equipment and operation, which may be unaffordable for small laboratories or small and medium-sized enterprises (Huang et al., 2017).

4 Separation and Purification of Hangbaiju Flavonoids

4.1 Chromatographic separation techniques

Macroporous resin adsorption method, is one of the important techniques for the preliminary enrichment and separation of flavonoids in Hangbaiju. It takes advantage of the large specific surface area, and strong selective adsorption capacity of macroporous resins, and can efficiently capture flavonoids. Selective desorption and grading of flavonoids can be achieved, by using solvents with gradually increasing polarity for gradient elution, improving purity and facilitating subsequent analysis or product preparation (Zhu et al., 2024).

High performance liquid chromatography (HPLC), is the key technology for identifying, quantifying and preparing and separating the monomer flavonoids in Hangbaiju. HPLC can be used to detect key components, such as apigenin-7-O-glucoside, luteolin and trilobin, and is an important means for quality control and the development of functional food components (Gong et al., 2019; Yang et al., 2022). The method based on HPLC can also be used to identify different cultivated varieties of Hangbaiju, according to the flavonoid profile (Gong et al., 2019).

4.2 Membrane separation and novel purification methods

Membrane separation technologies (e.g., nanofiltration, ultrafiltration), are gentle and efficient means suitable for concentrating and purifying flavonoids from aqueous extracts. These technologies can selectively retain macromolecular compounds while allowing small-molecule impurities to pass through, thereby enhancing the purity of the flavonoid portion. This type of method has significant advantages for large-scale processing, and maintaining the biological activity of active ingredients (Zhu et al., 2024).

Nowdays, some new purification methods, such as electrodialysis, have also been gradually explored and applied to the separation of flavonoids in Hangbaiju. This method can achieve selective separation based on the molecular charge under mild conditions, effectively reducing the degradation of compounds. Although its specific application in Hangbaiju is still in the exploratory stage, it has a promising future in improving separation efficiency and selectivity.

4.3 Activity retention during separation and purification

During the isolation and purification process, the structural stability of flavonoids is easily affected by factors such as pH, temperature, light, and oxygen. For example, a shift in pH from acidic to alkaline during processing or digestion can alter the composition and stability of flavonoids (Song et al., 2022). Mechanical and thermal stress can also trigger the hydrolysis or degradation of glycosides and aglycones (Gong et al., 2021). Studies have found that, with the increase of steam pressure and processing time, the contents of some phenolic acids (like 3-O and 4-O-caffeoylquinic acids) and flavonoid glycosides (e.g., apigenin, luteolin, baicalein) in Hangbaiju increase. The main phenolic acid components, 5-O-caffeoylquinic acid and 3, 5-DI-O-caffeoylquinic acid, decreased (Figure 2).

To maximize the bioactivity of flavonoids, process conditions must be controlled to minimize exposure to heat, oxygen, and light, and rapid and gentle separation methods must be employed. For instance, steam explosion pretreatment, when properly optimized in terms of pressure and time, can not only improve flavonoid extraction efficiency, but also release the active ingredients without destroying or even enhancing their antioxidant activity (Gong et al., 2021; Zhu et al., 2024). Rational selection of purification strategies, and process parameters is key to enhancing the functional value of flavonoids from chrysanthemum.

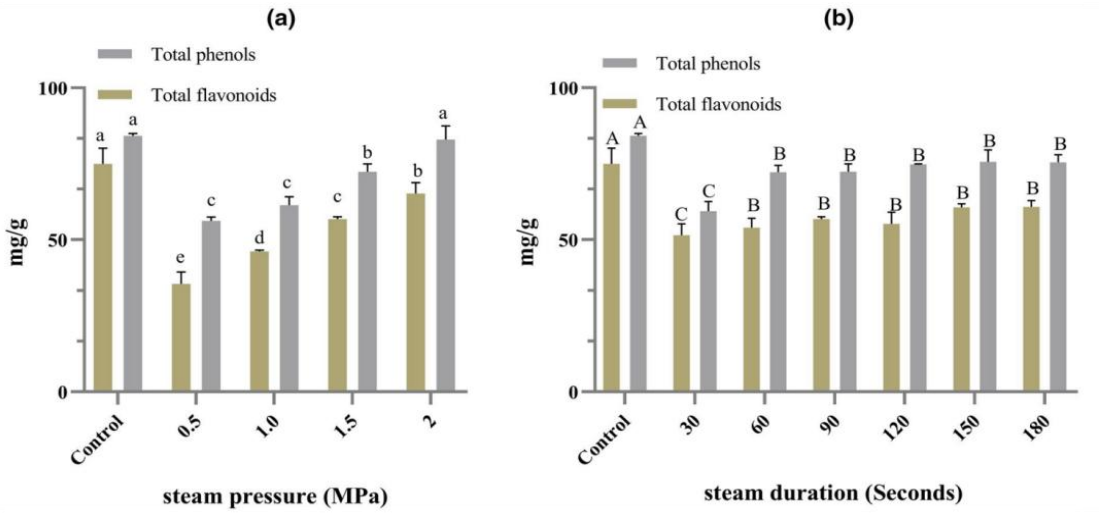


Figure 2 Effect of different steam pressure (a) and duration (b) on total phenols content and total flavonoids content in HBJ under steam explosion pretreatment. Control represented HBJ sample without steam explosion pretreatment. Different letters in the same category indicated significant difference at a significant level of 0.05 (Adopted from Gong et al., 2021)

Image caption: The figure shows that the total phenolic content and total flavonoid content of Hangbaiju slightly decreased at the initial stage of treatment but gradually increased with the rise in steam pressure or the extension of treatment duration, reaching relatively high levels under conditions of 2.0 MPa and 180 seconds (Adapted from Gong et al., 2021)

5 Functional Evaluation of Hangbaiju Flavonoids

5.1 In vitro activity studies

The antioxidant capacity of Hangbaiju flavonoids, has been widely evaluated by standard in vitro methods such as DPPH, ABTS and FRAP. A comparative study of different varieties of Hangbaiju found that, "Taiju" usually contains a higher level of caffeoylquinic acid, and its antioxidant activity is stronger than that of "Duoju", showing a high correlation between phenolic content and antioxidant effect (Gong et al., 2019). After steam blasting pretreatment of Hangbaiju stems and powder, the contents of total phenols and flavonoids increased, thereby enhancing their in vitro antioxidant capacity (Gong et al., 2021; Song et al., 2022; Zhu et al., 2024). Luteolin,

apigenin, tricloside and their glycosides, are the main contributors to antioxidant effects (Gong et al., 2019; 2021). The hyperspectral imaging technology developed can achieve rapid, and non-destructive detection of total flavonoids, providing an effective means for quality control in functional food production (He et al., 2018).

The anti-inflammatory effects of flavonoids in chrysanthemum are not merely theoretical speculation; studies have validated this through NF-κB reporter gene assays. Flavonoids, like apigenin-7-O-glucoside, luteolin-7-O-glucoside, and quercetin derivatives, have all been shown to significantly inhibit the activation of inflammatory signaling pathways (Han et al., 2015; Huang et al., 2023). Molecular docking and bioinformatics analyses suggest that, these flavonoids bind to various proteins involved in inflammatory responses, and liver protection, potentially exerting cytoprotective effects (Yang et al., 2022).

Spectrum-effect relationship studies also support this view. Studies have shown that luteolin, trifolioside-7-O-glucoside, and apigenin-7-O-glucoside play a key role in the anti-inflammatory effects of chrysanthemum, representing some of the most prominent active compounds (Huang et al., 2023).

5.2 *In vivo* functional studies

Previous studies have shown that the water extracts of other species in the genus *Chrysanthemum* have demonstrated certain liver-protecting effects in animal experiments. For example, in the model of acute alcoholic liver injury, they can improve liver function indicators and enhance antioxidant capacity, thereby exerting a protective effect (Chen et al., 2021). Some varieties also demonstrated a significant ability to regulate oxidative stress and inflammatory responses, reducing indicators such as malondialdehyde (MDA) and aspartate aminotransferase (AST), while increasing the levels of glutathione (GSH) and superoxide dismutase (SOD). This to some extent confirmed the relevant findings in in vitro experiments. It is worth noting that the results of bioinformatics analysis and molecular docking also gave similar hints, suggesting that Hangbaiju flavonoids may have anti-inflammatory and liver-protecting potential in the body (Yang et al., 2022).

However, at present, the animal experimental evidence regarding the role of Hangbaiju flavonoids in blood sugar regulation, lipid improvement or intestinal flora regulation is still relatively limited. Nevertheless, its performance in terms of antioxidation and anti-inflammation has provided a preliminary basis for the possibility of its application in the field of metabolic health and pointed out the direction for subsequent in-depth research (Gong et al., 2019; Yang et al., 2022).

5.3 Safety and toxicological analysis

Considering the traditional usage history of Hangbaiju in tea beverages and food, coupled with the relatively low toxicity of dietary flavonoids themselves, existing studies generally consider it safe at the conventional intake (Khan et al., 2021; Sarkar et al., 2022). Such plant-based ingredients have always been regarded as natural and mild, especially when consumed in low doses in the diet, with fewer side effects. However, some studies have cautioned that whether potential adverse reactions will occur if the intake dose is too high or taken for a long time cannot be completely ruled out at present and further systematic verification is still needed (Wang et al., 2022).

The problem lies in the fact that there is currently a lack of authoritative data support regarding the specific upper limit of safe intake and regulatory standards for flavonoids in Hangbaiju. Although the general view holds that a daily intake of no more than 100 milligrams of dietary flavonoids poses a lower risk and is beneficial to health, this is only a reference value. To apply them in functional foods or health products, more targeted research is needed to refine the dosage range and verify safety And lay the foundation for establishing standardized usage standards in the future (Khan et al., 2021)

6 Research on the Development of Functional Foods Based on Hangbaiju Flavonoids

6.1 Functional teas and instant products

Hangbaiju is traditionally consumed in the form of flower tea. Products such as "Taiju" and "Duoju", are widely used in tea beverages and dietary supplements. Studies have shown that advanced extraction techniques, like steam blasting, can increase the flavonoid content in the stems of Hangbaiju, thereby developing flavonoid

enriched flower tea and instant granule products with stronger antioxidant activity and health benefits (Zhu et al., 2024). Such products are convenient for daily intake and are an excellent source of bioactive ingredients.

The unique flavor characteristics of Hangbaiju, jointly determined by its volatile oil and flavonoid components, are important considerations in product development. Yang et al. (2022) systematically compared the metabolic differences and potential medicinal effects of Hangbaiju products "Taiju" and "Duoju" at different harvest periods. A total of 78 volatile oils and 63 flavonoids were identified, which can help achieve precise regulation and optimization of flavor and aroma, and improve the sensory quality of ready-to-drink tea. Further research has found that, Taiju has a relatively high content of most aromatic components, while Duoju is rich in odorless long-chain alkanes. Taiju has a higher content among the five flavonoid components except for hydroxyl glycosides, indicating that Taiju has more advantages in aroma expression and potential efficacy (Figure 3).

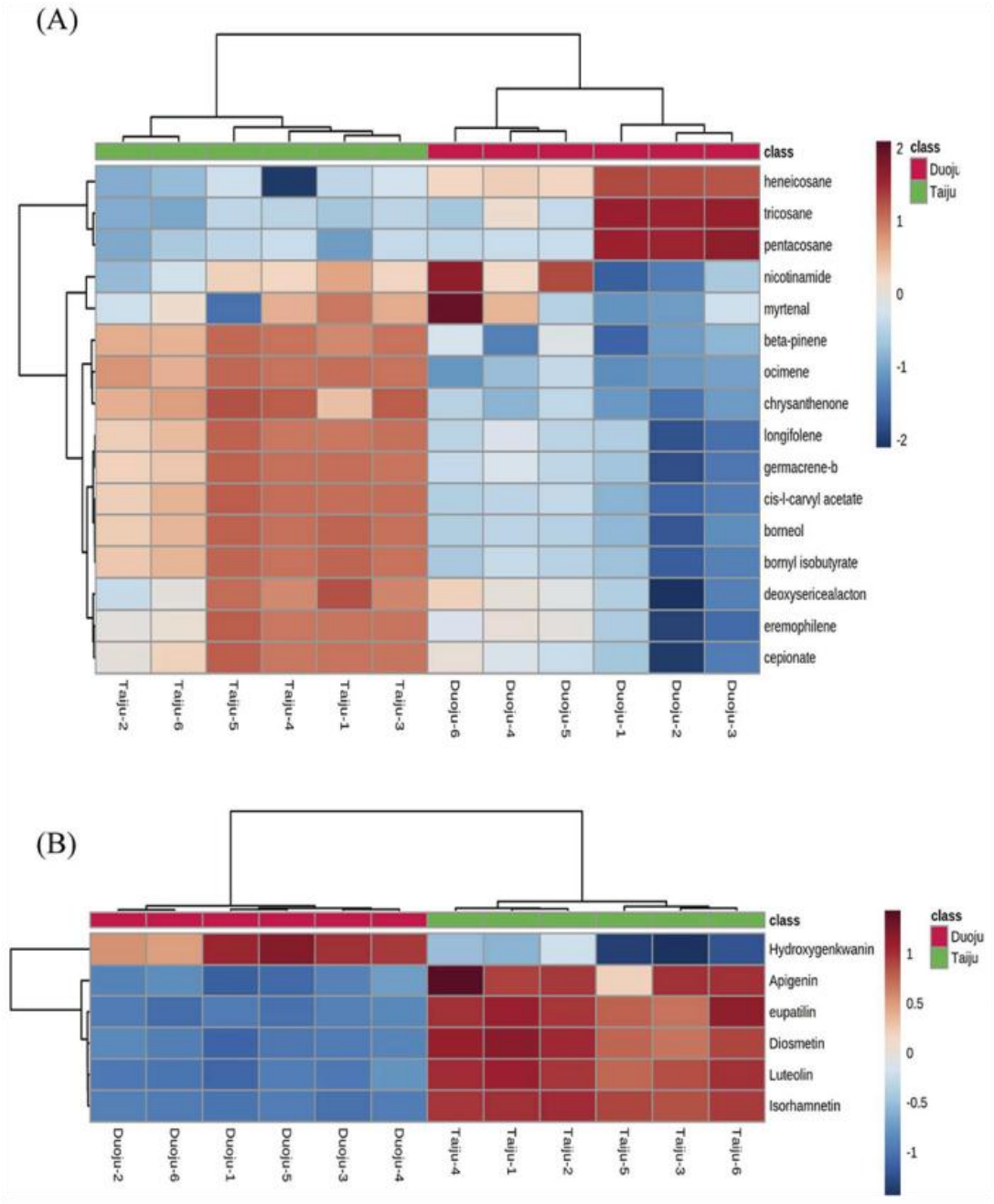


Figure 3 Heatmap of differential metabolites between Taiju and Duoju. (A) Volatile markers screened by GC-MS; (B) Flavonoid markers screened by LC-MS. Red indicates high content and blue indicates low content (Adopted from Yang et al., 2022)

6.2 Health foods and capsule formulations

Hangbaiju flavonoids not only have strong antioxidant capacity but also possess certain potential therapeutic value. Therefore, they are considered suitable for the development of health food products in the form of capsules, tablets, etc. This type of dosage form has a significant advantage - it is convenient for precise quantification and better meets consumers' demands for specific health benefits. The introduction of embedding technology has solved a common problem: the poor stability of hydrophobic flavonoids. Through encapsulation treatment, not only can the active substances be better protected during storage and digestion, but they can also be more easily integrated into various nutritional products (Premathilaka et al., 2022; Tang et al., 2024).

Of course, the effect of a single ingredient is sometimes limited. Combining Hangbaiju flavonoids with other plants or edible ingredients that are both medicinal and edible is an effective way to expand the functions of the product. Such combinations can not only bring about synergistic effects, but also enable personalized formula adjustments according to different populations and health goals (Tang et al., 2024). Among them, the structure-activity relationship of flavonoids provides theoretical support for this combination, making it more directional and targeted in physiological regulation.

6.3 Exploration of innovative food applications

Introducing Hangbaiju flavonoids into baked goods or snack foods is no longer just an idea but a direction that is increasingly attracting attention in the innovation of functional foods. The key lies in whether the structural characteristics and physicochemical behaviors of these flavonoids can be truly understood. Only in this way can it be considered clearly at the initial design stage: what kind of formula can both maintain activity and adapt to the processing requirements of different food matrices (Tang et al., 2024). Many practices have also shown that as long as the technology is appropriate, the flavor and function of flavonoids can actually be well integrated into a variety of daily foods.

Fortified beverages and nutritional supplements are also becoming the mainstream in the functional food market. However, the poor solubility and low stability of flavonoids themselves often pose challenges in the development process. Fortunately, the embedding technology can effectively solve these problems. It can not only improve its dispersibility in water, but also protect the activity from being damaged by high temperature or storage conditions, ensuring that the product still plays the expected health role throughout the processing chain (Premathilaka et al., 2022; Tang et al., 2024).

7 Concluding Remarks

People are paying increasing attention to natural active substances, especially in the fields of health promotion and functional food development. Medicinal and edible plants have once again been pushed to the forefront. Hangbaiju is a typical representative among them. The flavonoids it is rich in are active in terms of antioxidation and anti-inflammation, and are regarded as components with great development value. The research focused on the types and biological activities of flavonoids in Hangbaiju, sorted out their antioxidant and anti-inflammatory mechanisms, and compared traditional extraction methods with green extraction techniques such as ultrasonic, microwave, enzymatic hydrolysis, and supercritical fluid extraction. The key variables that affect the maintenance of extraction activity were also analyzed. At the product development level, various application forms ranging from flower tea, granular drinks, capsules to baked goods and nutritional beverages were demonstrated, laying a foundation for subsequent industrialization.

Although research is progressing, problems are not uncommon. For instance, there is still little in vivo experimental evidence, and the metabolic pathways, intestinal absorption processes, and long-term mechanisms of action of flavonoids, are not clear enough. The extraction and purification process, will also encounter practical obstacles when moving towards large-scale application, like high equipment investment, complex operation links, and difficulty in standardizing product quality.

In terms of safety, there is still a lack of information on the appropriate dosage, risk assessment, and regulatory support for flavonoids in chrysanthemums. Now, a systematic health efficacy evaluation system has not yet been formed. Some details cannot be ignored, such as the differences in ingredients caused by different cultivars, and different origins, and their mechanisms still need to be further studied.

In the future, research can make further progress from several directions. On the one hand, the integration of multi-omics technologies will help enhance the efficiency of identifying key active flavonoids and the depth of analysis of their functional mechanisms. On the other hand, the green extraction process still needs further optimization, such as achieving a balance between purity improvement and energy consumption control. At the same time, integrating modern nutrition and food science, developing functional foods that better meet individualized needs and have clear targeted effects will also be an important direction. Of course, the sensory experience of consumers cannot be ignored, and preclinical safety assessment also needs to be carried out simultaneously. Only in this way can Hangbaiju truly achieve a comprehensive leap from traditional drinking to modern precision nutrition.

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Conflict of Interest Disclosure

The authors affirm 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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