Research Progress on Delivery of Flavonoids by Nanocrystal Delivery Technology

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Abstract. Flavonoids are a kind of natural component widely used in plants. They have significant antioxidant, anti-inflammatory, anticancer and cardiovascular protective effects. Flavonoids can effectively remove free radicals, resist lipid peroxidation, improve antioxidant levels in the body, significantly reduce serum triglyceride content in animals and humans, and increase HDL cholesterol content. In addition, flavonoids also have the potential to prevent and cure cardiovascular and cerebrovascular diseases, which can effectively expand coronary blood vessels, increase coronary flow, improve myocardial ischemia, reduce platelet aggregation and inhibit coagulation and thrombosis. However, the clinical application of flavonoids is limited by their low bioavailability and poor pharmacokinetics. To address this issue, recent research has focused on using nanocarrier technology to improve the stability and bioavailability of flavonoids to achieve targeted delivery and reduce toxicity and adverse reactions. In this paper, the research status of antioxidant activity of the flavonoids and the progress of nano delivery system are reviewed, which provides a new idea for the further development of flavonoids.

Keywords: Flavonoids; Anti-oxidation; Bioavailability; Nanocarriers; Delivery system.

1. Introduction

Flavonoids are a class of natural compounds that exist widely in nature. Scientists know more than 4,000 kinds of flavonoids, which are mainly found in the roots, leaves, flowers and fruits of plants, usually in a free state or in the form of glycosides combined with sugars. Because flavonoids have a wide range of biological functions, including antioxidant, anti-inflammatory, anti-tumor, hypolipidemia, inhibition of platelet aggregation and regulation of immunity, they have great medicinal potential and have become the focus of research in the field of food science and phytochemistry. However, its practical medical applications are limited by low bioavailability and poor pharmacokinetic properties. Low water solubility and environmental sensitivity to heat, light and enzymes greatly limit their role as active ingredients in the body.

As a result, researchers have explored the use of advanced nano delivery systems to improve the bioavailability of flavonoids.

For example, studies have significantly improved quercetin's stability and bioavailability in vivo by encapsulating it in liposomes, enhancing its antioxidant and anti-inflammatory effects. Similarly, the researchers used nanocrystal technology to improve the water solubility and stability of resveratrol, increase its dissolution rate in the gastrointestinal tract by reducing the particle size, and extend the retention time in the body, thereby enhancing antioxidant and anticancer activities. In addition, the polymer-based nanoparticle carrier of curcumin significantly increased the bioavailability of curcumin, enhanced its anti-tumor activity, and reduced its toxicity to normal cells. In these instances, nanotechnology significantly improves the solubility, stability, and targeting of flavonoids, thereby enhancing biological effects and reducing potential toxic side effects. These studies show that the potential of flavonoids for practical medical applications can be effectively enhanced through nanotechnology.

Flavonoids have shown good application prospects in cardiovascular and cerebrovascular protection and antioxidants. Future research will focus on further developing and applying these compounds with a view to making a greater contribution to human health. With the in-depth study of

flavonoids, their importance in the future medical and health field will become increasingly prominent. This article will discuss the above mentioned.

1.1. Research background

Flavonoids are widely existing secondary metabolites in plants, mainly concentrated in the roots, leaves, skins and flowers of plants. Studies have shown that flavonoids have a variety of significant pharmacological activities, including antioxidant, anti-inflammatory, antiviral, anti-tumor, immune regulation, cardiovascular protection and neuroprotection. These effects have made flavonoids of great interest in the field of health food and drug development. Flavonoids have been extensively studied for scavenging free radicals in the body and have significant antioxidant capacity. Many studies have shown that flavonoids can effectively scavenge free radicals and reduce oxidative stress, thus fighting diseases related to inflammation, tumors and aging. For example, bamboo leaf flavonoids have been shown in vitro to scavenge free radicals and show protective effects at certain concentrations. In recent years, the protective effect of flavonoids on the cardiovascular system has also attracted widespread attention. A number of studies have shown that flavonoids such as hawthorn flavonoids and soybean isoflavones can significantly reduce blood lipids, regulate blood pressure, improve hemorrheology, and prevent the occurrence of cardiovascular diseases. In anti-cancer research, flavonoids have shown the potential to inhibit cancer cell proliferation and induce apoptosis, and researchers are exploring their development prospects as anti-cancer drugs. Despite their extensive pharmacological effects, their low bioavailability is a major obstacle. Due to the poor water solubility and instability of these compounds, conventional formulations such as tablets or capsules are difficult to effectively improve their solubility and bioavailability. Therefore, there is an urgent need to develop new agents to overcome this problem. The introduction of nanocrystal technology provides a new way to improve the bioavailability of flavonoids. By making flavonoids into nanocrystals, their solubility and bioavailability can be effectively improved, and the retention time of drugs in the body can be extended. The research and application of this technology is still in its infancy, and future research can focus on the development of nano-sized preparations of different flavonoids. The current study shows that some flavonoids can have a synergistic effect when used in combination with other antioxidants, such as vitamin C. In-depth study of its mechanism and the best collocation will help to improve its overall antioxidant capacity

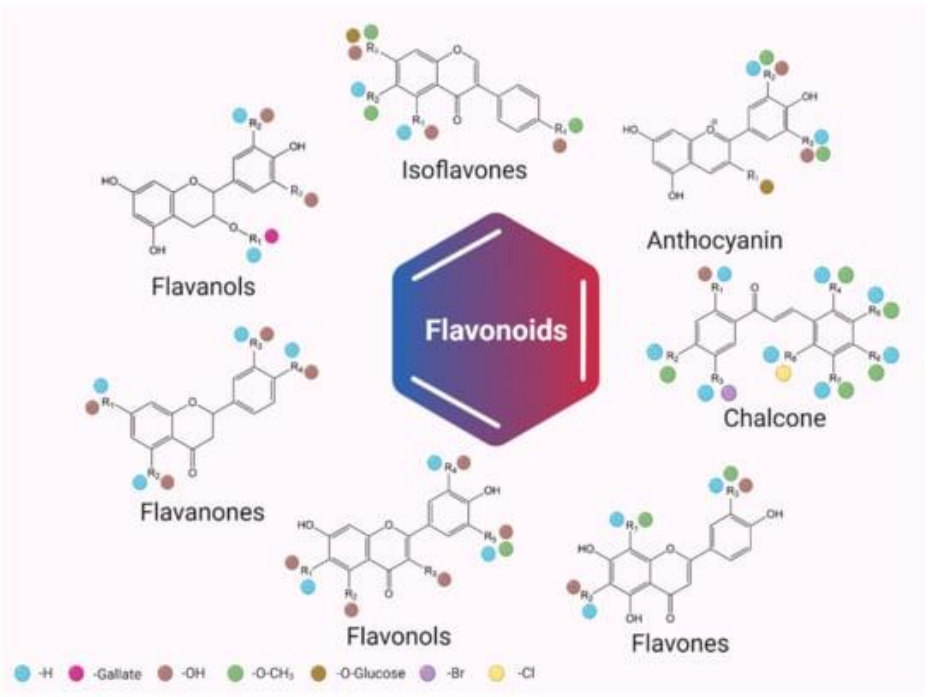

Figure 1 Flavonoids classification and their possible chemical structure(created with BioRender.com, accessed on 6 April 2022) [1].

2. Flavonoids that have Antioxidant and Scavenging Effects on Oxygen Free Radicals

Free radicals are closely related to diseases such as inflammation, autoimmunity, tumors and aging, and flavonoids have the ability to remove free radicals and antioxidants. Bamboo leaf flavonoids are made into a variety of dosage forms, such as health food Zhukangning capsule, recent studies have shown that it has significant effects on scavenging free radicals, antioxidant, protection of prostate, cardiovascular and cerebrovascular health, anti-cancer, diabetes prevention and skin care and whitening. Zhang Ronghua and Fu Jianyun et al. evaluated the antioxidant effect of bamboo leaf flavonoids by various experimental methods, and found that flavonoids had a significant effect at low doses, but could promote oxidation at high concentrations, showing a co-protective effect with other antioxidants [2].

In addition, Zheng Gongming et al. showed that both mature and immature lychee peel extracts had strong antioxidant activities, and the main components were flavonoids. The antioxidant effect of isoflavone FSMI extracted from fermented soybean meal was better than that of unfermented SMI, because the fermentation process transformed the isoflavone glycosides into aglycone with stronger activity. The extract of Golden lotus flower is rich in flavonoids, and has an obvious antioxidant effect on lard, and the addition amount is positively correlated with antioxidant activity. The study of Zhao Xuemei showed that flavonoids in pomelo peel had better scavenging ability on free radicals than monomer compounds, and showed that they were related to structure [3].

With the development of isolation and extraction technology, researchers have discovered many new flavonoids, and they are used in medicines and functional foods. For example, flavanone-based preparations are already on the market, such as Yufengningxin tablets and ginkgo biloba preparations, and are also widely used in natural sweeteners, antioxidants and pigments. Although there are many flavonoid products, the understanding of their absorption, metabolism and activity mechanism is still insufficient. Future research will focus on improving stability, clarifying the activity mechanism and exploring the relationship with metal ion catalysis. These studies provide a theoretical basis for the application of flavonoids in medicine and food, while promoting the effective development of plant resources [4].

3. Research Progress on antioxidant Active Components of Traditional Chinese Medicine Flavonoids

Flavonoids play an antioxidant role through the reduction of the hydroxyl group, and the phenolic hydroxyl group reacts with free radicals to form a stable structure, terminating the free radical chain reaction. The location and number of hydroxyl groups have a significant effect on the antioxidant capacity: in general, the more hydroxyl groups, the stronger the antioxidant effect. For example, the antioxidant effect of quercetin is better than that of glycyrrhiza and luteolin, while the antioxidant effect is weakened after hydroxyl glycosides are formed. C ring opening can enhance the antioxidant effect, such as isoliquiritin is better than liquiritin. In addition, flavonoids can also inhibit oxidation reactions by chelating metal ions, and the antioxidant effect of flavonols is generally superior to that of the corresponding flavonoid compounds [5,6].

In the past 60 years, advanced chromatographic separation and spectrum testing techniques have promoted the rapid development of flavonoids research. Flavonoids have attracted attention due to their cardiovascular and cerebrovascular protection, anti-tumor and anti-ultraviolet biological activities. However, its antioxidant effect is relatively weak, mainly due to the special structure resulting in low solubility, affecting the absorption in the body. Therefore, the solubility and antioxidant effect can be improved by structural modification. In the case of quercetin, the 5-OH site with the weakest antioxidant activity can be modified to enhance its effect [7].

As a natural antioxidant, flavonoid compounds have the characteristics of low toxicity and high efficiency, which can help prevent aging and related diseases and protect people's health. With the

development of traditional Chinese medicine, flavonoid compounds will have broad application prospects in the field of antioxidants, and it is expected that this paper will promote the development of new traditional Chinese medicine flavonoids [8].

4. Research Progress on Preparation and Application of Nanocrystals of Flavonoids

Nanocrystal technology plays an important role in drug delivery of flavonoids, which can significantly improve their bioavailability and solve the problems of low solubility and low bioavailability. Nanocrystals are suitable for a variety of administration routes, including oral, injectable and transdermal.

4.1. Oral Delivery

Oral administration is the most common route of administration of flavonoids, but due to its poor solubility, low permeability and poor stability, oral bioavailability is generally low. This is because most flavonoids tend to form planar structures in their molecular structure, making solvent molecules difficult to penetrate. This property results in extremely low solubility in water, for example, myricetin has a solubility in water of only 16.60 μg/mL, and oral bioavailability in rats is only 9.62% [9].

The researchers significantly improved this problem by preparing nanocrystals. Hong et al. made myricetin into nanocrystals and used different stabilizers (such as TPGS, soy lecithin, etc.), and its saturated solubility increased significantly, from 6.23 mg/mL to 399.63 mg/mL or higher of pure myricetin, and the maximum blood concentration also increased significantly. By reducing particle size and improving adhesion, nanocrystal technology extends the retention time of drugs in the gastrointestinal tract, thereby increasing absorption and improving the relative bioavailability of drugs.

Similarly, after naringenin was prepared into nanocrystals, its oral bioavailability was significantly improved in rats, and the maximum blood concentration and area under the drug curve were significantly increased compared with the suspension of the bulk drug. This applies not only to myricetin and naringin, but also to puerarin nanocrystals and hypericin nanocrystals [10].

In addition, nanocrystal technology can also be combined with preparation processing to further prepare these flavonoids nanocrystals into tablets, capsules, etc., to promote the commercialization of oral administration. Mauludin et al. prepared rutin nanocrystals by high pressure homogenization method and prepared them into tablets. The results showed that the dissolution rate of rutin nanocrystals was better than that of commercially available rutin microchips, demonstrating the broad prospect of nanocrystal technology in improving oral bioavailability of drugs [11].

4.2. Injectable Delivery

The application of nanocrystals in injection has significantly improved the bioavailability and safety of flavonoids. Compared with traditional flavonoid injection, nanocrystals, due to their smaller particle size, greatly reduce the risk of capillary obstruction and improve the safety of injection. In addition, the high drug load of nanocrystals can meet the injection needs of high doses of drugs.

The study showed that nanocrystals not only improved the bioavailability of flavonoids in the injection route, but also affected their tissue distribution behavior. For example, the study of Yu Shilong showed that after apigenin nanocrystals were administered through the tail vein, the area under the drug curve in rat plasma increased by 7.14 times, and the maximum blood concentration increased by 17.78 times, which significantly improved the absorption efficiency compared with the traditional suspension form [12].

Hydroxygenkwanin nanocrystals prepared by Ao et al. showed excellent anti-tumor effect in a mouse model of breast cancer, and high-dose intravenous injection (40 mg/kg) could significantly inhibit tumor volume growth, showing good dose-dependent and safety. Mice treated with a higher

dose of hydroxygenkwanin nanocrystals (360 mg/kg) had a 100% survival rate in acute toxicity tests, showing a higher safety compared to the bulk drug [13].

The study of Xu Hao further proved that quercetin nanocrystals had a high tumor inhibition rate (56.78%) when injected intravenously, while the effect of oral administration was limited by intestinal metabolism. This shows that the intravenous injection of nanocrystals can circumvent intestinal metabolism and improve the bioavailability of drugs, thus showing good development potential in clinical applications. To sum up, the advantages of nanocrystals in injection prescription make them have important application prospects in realizing rapid and effective drug delivery, improving therapeutic efficacy and safety [14].

5. Conclusion

As important plant secondary metabolites, flavonoids have attracted extensive attention in the field of health food and drug development due to their significant pharmacological activities, such as antioxidant, anti-inflammatory, antiviral and anti-tumor. However, its clinical application is limited by factors such as low bioavailability and poor water solubility. To overcome these obstacles, nano delivery systems, especially nanocrystal technology, have become an important means to improve the solubility and bioavailability of flavonoids. This technology has shown promising potential in many ways, including oral, injectable and transdermal delivery, to significantly improve efficacy and enhance disease treatment.

Nevertheless, the industrial production of nanocrystals still faces challenges, and most of the results are still in the laboratory stage, and there are few related products on the market. In addition, the accumulation of nanoparticles in the liver may pose a potential toxic risk that needs to be further explored at an early stage of research to ensure its safety and efficacy.

Future research needs to focus on combining flavonoid nanocrystals with new technologies, such as fluorescence tracking technology to monitor drug distribution and absorption mechanisms in the body, and bionic technology to improve drug targeting, thereby reducing side effects. At the same time of technology optimization, it is also necessary to explore the synergistic effect with other drugs to achieve better therapeutic effects. With the continuous progress and in-depth research of nanocrystal technology, the potential of flavonoids in medicine and daily applications will be further tapped to achieve a wider range of applications.

In general, the study of flavonoids is of great significance. By improving the delivery system to increase its bioavailability, it can better play its role in disease treatment while ensuring a safer treatment experience. In the future, through continuous innovation and cross-field application, flavonoids will not only make new breakthroughs in the field of medicine, but also may make new breakthroughs in emerging fields such as luminescence and diagnosis, which will have an important impact on the health industry and scientific and technological innovation

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