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Advances in the extraction and pharmacological effects of total flavonoids in Chinese herbal medicines

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Abstract: In recent years, the research in the field of flavonoids has been deepening, their extraction methods have been updated, and their pharmacological effects have been explored, and many new active effects have been discovered, providing new ideas for related fields. This paper provides a systematic review and elaboration on the basic properties, distribution, extraction methods and application cases of flavonoids, as well as some of the deeply researched pharmacological effects of total flavonoids, and discusses the challenges and prospects of total flavonoids in traditional Chinese medicines nowadays.

1. Introduction

In recent years, with the changing conditions of people's life rhythm, dietary habits and environmental changes, more and more people are concerned about their health, and flavonoids, as a kind of natural compounds with a variety of pharmacological activities, have entered the public's field of vision. Flavonoids, also known as flavonoids, are a series of polyphenolic compounds derived from the parent nucleus of 2-phenylchromenones, in which the two benzene rings in the parent nucleus are connected by a three-carbon chain to form the basic skeleton of C_6-C_3-C_6[1], which are widely distributed in nature, often according to the differences in the structure of the parent nucleus, including the degree of oxidation of the three-carbon chain, whether it is ring-forming, and the B-ring connection. , whether it is ring-forming or not, and the position of B-ring attachment, etc., flavonoids can be classified into: flavonoids, flavonols, dihydroflavonoids, dihydroflavonols, isoflavonoids, dihydroisoflavonoids, chalconoids, dihydrochalconoids, anthocyanins, flavanols, oranges (ohzololol), benzochromones, and bis-flavonoids, etc.[2]. Flavonoids, as a kind of plant secondary metabolites, have various active effects such as antioxidant, anti-inflammatory, antitumor, and antiviral[3]. It is now known that flavonoids are capable of scavenging free radicals to achieve antioxidant effects by hydrogen capture reaction with free radicals[4]; they are also capable of anti-inflammatory by directly inhibiting the NF-κB signaling pathway and selectively inhibiting the enzyme activities of COX-2 and 5-LOX[5]; the antiviral effect is achieved by interfering with the key links of viral infection and enhancing the host immune response [6]; in addition, the antitumor effect can also be achieved by inhibiting the proliferation of tumor cells and promoting apoptosis, interfering with cellular signaling pathways, affecting the cell cycle, and enhancing the body's immune function and other antitumor effects [7]. Flavonoids can be

used in the fields of medicine, food and nutraceuticals because of their diverse medicinal values. In this paper, we will systematically sort out the current research status of the extraction methods and pharmacological effects of total flavonoids in Chinese herbal medicines, which will help to comprehensively understand the progress of research in this field, discover the existing problems and deficiencies, provide ideas and directions for subsequent research, promote the in-depth research and development and utilization of the total flavonoids in Chinese herbal medicines, and accelerate the modernization of traditional Chinese medicines and the research and development of innovative medicines.

2. Extraction process of total flavonoids

2.1 Water extraction

Flavonoids often contain hydroxyl, carbonyl and other polar groups, water extraction is the use of water molecules and flavonoids to form hydrogen bonds and other interactions, through heating to make the active ingredient dissolved in the aqueous phase of the traditional extraction method. It is easy to operate, low cost, safe and environmentally friendly solvents, especially suitable for the extraction of water-soluble components such as flavonoids. The operation process usually includes pretreatment of raw materials, decoction, solid-liquid separation and concentration steps. The material-liquid ratio, extraction temperature, time and number of times will affect the extraction efficiency, for example, hawthorn leaf total flavonoids in the optimization of the aqueous extraction process, the material-liquid ratio of 1:20 (g/mL), extraction time of 120 minutes, extraction of two times, the extraction rate of up to 87.2%[8]. In addition, the pretreatment method (e.g., pulverization), water quality and pH value of the herbs may also affect the extraction effect. The limitation of this method is that the extract has more impurities and the high temperature will destroy some sensitive components, resulting in poor extraction results.

2.2 Alcoholic extraction

Alcohol extraction method is to use alcohol solvent and raw materials in the interaction of the components to achieve separation and purification. Its advantage lies in the strong solubility of ethanol and other substances to flavonoid components, the solvent is easy to recover, and has a certain antimicrobial effect, and the stability of the extract is high. The operation process includes herb crushing, ethanol immersion, heating reflux, filtration and solvent recovery. The solvent concentration, extraction temperature, time and material-liquid ratio will affect the extraction effect. Studies have shown that the optimal process for the alcoholic extraction of total flavonoids from Ghostwort is 80% ethanol concentration, 1:14 solid-liquid ratio, 0.5 h extraction time, and 90 ℃ extraction temperature[9]. In addition, the gradient adjustment of ethanol concentration can be targeted to remove impurities, such as 50%-60% ethanol can precipitate starch, and more than 75% can remove protein. However, this method is characterized by high solvent consumption, high cost, and safety issues during operation.

2.3 Ultrasonic extraction method

Ultrasonic extraction method is based on the synergistic effect of cavitation effect, mechanical effect and thermal effect, through high-frequency vibration to destroy the plant cell wall and accelerate the dissolution of the active ingredients of modern extraction technology. Its advantages are high extraction efficiency, short time, low temperature and wide adaptability. However, there are factors such as ultrasonic power, time, temperature, material-liquid ratio and solvent polarity

affecting this technology. Experiments showed that the optimal process conditions for the flavonoids of wild chrysanthemum stem and leaf roots were 65% ethanol concentration, material-liquid ratio of 1:40 (g/mL), ultrasound time of 45 min, and ultrasound power of 360 W, at which time the amount of flavonoids extracted was 3.68 g/100 g[10].

2.4 Supercritical fluid extraction method

Supercritical fluid extraction method utilizes the advantages of both gas-liquid characteristics of CO_2 in the critical state, and realizes the efficient extraction of flavonoids by adjusting the temperature and pressure. It is characterized by green environmental protection, high extraction efficiency and good product quality. Studies have shown that the extracted flavonoids content of Ginkgo biloba reaches more than 28%, and the recovery of flavonoids yield is high (>4% and >64%, respectively), and there is no harmful substance residue in the product[11].However, there are problems of high cost and difficult operation.

3. Mechanism of action of total flavonoids

3.1 Antioxidant effects

Phenolic hydroxyl groups in the molecular structure of flavonoids can directly scavenge free radicals (e.g., superoxide anion, hydroxyl radical), enhance the activity of antioxidant enzymes, such as SOD and GSH-Px, through activation of the Nrf2 pathway, and chelate metal ions in vitro to inhibit the Fenton reaction. In vivo experiments showed that the IC_{50} value of Garcinia cambogia flavonoids for DPPH scavenging was 22.524 μg/mL, and for hydroxyl radical scavenging, the IC_{50} value was 30.977 mg/mL[12]. In vitro experiments showed that Anji white tea flavonoids exhibited significant scavenging activities against O_2^- ; DPPH ; and H_2O_2[13]. In conclusion, the antioxidant effects of flavonoids can be used for anti-aging and prevention of cardiovascular diseases and other aspects of health.

3.2 Anti-inflammatory effects

Flavonoids can directly inhibit NF-κB and MAPK signaling pathways, downregulate the transcriptional expression of pro-inflammatory factors such as TNF-α, and reduce the release of inflammatory mediators such as IL-1β and TNF-α. For example, persimmon leaf flavonoids can significantly reduce the brain tissue of subacute aging mice with the expression of TNF-α, interleukin-1 beta (IL-1β) expression in the brain tissue of subacute aging mice[14]. It can also selectively inhibit the enzymatic activities of COX-2 and 5-LOX and reduce the synthesis of related inflammatory mediators, e.g., Ailanthus extract significantly down-regulated the expression of iNOS and COX-2 and inhibited NO production in LPS-induced RAW264.7 cells[15]. Flavonoids can also regulate the phosphorylation level of key inflammation-related signaling pathways, macrophage polarization and exert anti-inflammatory activities. In conclusion, the anti-inflammatory effects of flavonoids are promising in the field of anti-inflammatory drug development.

3.3 Anti-tumor effects

Flavonoids achieve anti-tumor effects by inducing cell cycle block (e.g., G1/S phase) and mitochondrial apoptotic pathway and regulating key signaling molecules. The main flavonoid (TTF1-NP) of Changbai Mountain Pearl Plum significantly inhibited the proliferation of

hepatocellular carcinoma cells Hep3B and Huh7 under hypoxic conditions, and was able to block hepatocellular carcinoma cells in the G0/G1 phases[16].Gao et al. [17] used Scutellariae baicalensis extracts in human lung cancer A549 and SK-MES-1 cells and found that it could increase the expression levels of pro-apoptotic key protein P53 and B-cell lymphoma/leukemia-2-related x protein (Bax) and induce apoptosis.

3.4 Antiviral effects

Flavonoids exert antiviral activity by interfering with viral adsorption, replication and release processes. Studies have shown that ZANDI et al.[18] demonstrated that baicalein was able to directly kill DENV activity in addition to its anti-DENV adsorption and blocking DENV-2 intracellular replication.KHANDELWAL et al.[19] found that apigenin pretreatment inhibited viral DNA, mRNA and protein synthesis.

4. Application prospects and challenges

Flavonoids, with their diverse biological activities, show a broad application prospect in the health industry and pharmaceutical field. In the field of health products, their functions such as antioxidant, immune regulation and metabolism improvement have been widely developed, such as goldenseal flavonoids can enhance the activities of TA0C, SOD and CAT[20]. In functional foods, flavonoids act as natural antioxidants and colorants to enhance food stability and confer health attributes, e.g., bamboo leaf flavonoids can reduce nitrite use and inhibit nitrosamine production when used in meat processing[21,22]. In the field of cosmetics, licorice and safflower flavonoids achieve whitening and blemish removal by inhibiting tyrosinase activity[23].

Flavonoids can be used as drug candidates or adjuvants. For example, soy isoflavones inhibit breast cancer proliferation by inhibiting tyrosine protein kinase, DNA topoisomerase I and cell cycle proteins[24]. In addition, flavonoids may delay diabetic nephropathy by regulating intestinal flora[25], providing new ideas for the treatment of chronic kidney disease.

However, current research still faces multiple challenges. In terms of extraction technology, the traditional aqueous and alcoholic extraction methods are characterized by low efficiency and high energy consumption, while emerging technologies such as supercritical fluid extraction and ionic liquid extraction have not yet been popularized due to cost constraints. Pharmacological mechanism studies are mostly confined to in vitro experiments, and the regulatory network of complex signaling pathways (e.g., Nrf2/Keap1, MAPK) and in vivo metabolism still need to be analyzed in depth. In terms of quality control, the difference in plant origin leads to the instability of flavonoid composition, and the existing detection methods (e.g., HPLC, spectrophotometry) are prone to result bias due to operational differences, so there is an urgent need to establish a standardized system covering the traceability of raw materials, fingerprinting, and multi-indicator quality control.

5. Conclusions and outlook

Flavonoids in Chinese herbal medicines have high research value as a kind of plant secondary metabolites with various pharmacological activities. With the development of science and technology nowadays, the traditional extraction methods have been improved, while modern extraction techniques and new methods have brought higher efficiency and significant innovations for the extraction of flavonoids. The activity studies of flavonoids are also more and more diverse, which helps us to better understand the activity and mechanism of flavonoids. However, there is still no low-cost and high-efficiency extraction method, and the targets, mechanisms and signaling processes of flavonoids have not been fully elucidated yet, and complex networks need to be

revealed with the help of multi-omics technologies. At the same time, the detection method is affected by many factors, and the lack of unified and effective quality evaluation standards and control system has seriously restricted the quality assurance and industrial development of total flavonoids-related products. In the future, the extraction method can combine the synergistic advantages of the present technology and the new extraction method to develop an efficient and environmentally friendly integrated process. Through metabolomics, molecular docking and other technologies to deeply analyze the action mechanism of flavonoids. In the field of medicine, the efficacy can be enhanced by combining flavonoids with other active ingredients. It is hoped that this article can provide some help for the research of flavonoids in Chinese herbal medicine.

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