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Research Progress of Bioflavonoids and Their Anticancer Activities

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Abstract

Flavonoids are the main components and active ingredients of many important Chinese herbal medicines. Flavonoids are important natural active compounds, which widely exist in the plant kingdom and have a wide variety, and most of the active flavonoids have broad-spectrum activity, low toxicity and high efficiency. Flavonoids are the internal signal molecules and metabolites of plants, belonging to polyphenols. They have the characteristics of various kinds, complex structures, broad-spectrum pharmacological activities and low toxicity, and have extensive significance for the treatment and prevention of cardiovascular and tumor diseases. Flavonoids are secondary metabolites of plants, which have many biological activities, such as anti-oxidation, anti-angiogenesis, anti-inflammation, anti-virus, hypoglycemic, hypolipidemic and anti-osteoporosis. They are widely distributed in vegetables, fruits and other plants. Studies have shown that dietary intake of rich flavonoids will reduce the risk of cancer such as colon cancer, prostate cancer and breast cancer. Therefore, in recent years, the antitumor activity and mechanism of flavonoids have become a research hotspot. Pharmacological studies have proved that these compounds have obvious inhibitory effects on a variety of human tumors.

Keywords

Bioflavonoids; Flavonoids; Cancer; Polyphenols.

1. Introduction

Natural flavonoids are the internal signal molecules and metabolites of plants, belonging to polyphenols [1]. They have the characteristics of various kinds, complex structures, broad-spectrum pharmacological activities and low toxicity, and have extensive significance for the treatment and prevention of cardiovascular and tumor diseases of human beings. The anticancer mechanism of flavonoids includes estrogen/estrogen inhibition mechanism, anti-proliferation mechanism, cell cycle blocking, antioxidation and so on[2]. Malignant tumor is one of the most important diseases that seriously affect human health and threaten human life. Drugs play an important role in the treatment of malignant tumors. Anti-tumor drugs are being developed from traditional cytotoxic drugs to new anti-tumor drugs with multi-link effects against mechanisms. Flavonoids are a kind of important natural products, which have many physiological functions and medicinal values. Flavonoids are a kind of natural products with rich physiological activities[3], which exist widely in nature. At present, a large number of studies focus on the antioxidant and antitumor activities of flavonoids, but the activities of flavonoids reported in different research systems are inconsistent or even contradictory.

Therefore, it is of great theoretical value and practical significance to establish a reasonable and effective activity measurement and evaluation system, and scientifically evaluate its activity from the mechanism and structure-activity relationship. Natural flavonoids and their derivatives have a variety of physiological activities, especially unique biological activities in anti-tumor growth [4]. They can not only interfere with tumor cell cycle, change mitochondrial membrane potential [5] of tumor cells

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and promote tumor cell apoptosis, but also improve human immunity, reduce immune escape of tumor cells and prevent tumor metastasis. In human body, they regulate biological signal transduction, leading to up-regulation of pro-apoptotic protein expression. By regulating the growth of vascular epithelial cells, they block the formation of blood vessels in tumor tissues, thus achieving the purpose of inhibiting the growth of solid tumors. The results show that flavonoids have significant preventive and therapeutic effects on many common cancers such as lung cancer, breast cancer, colon cancer, prostate cancer, liver cancer, leukemia, ovarian cancer and gastric cancer [6]. The anti-tumor mechanisms of flavonoids mainly include: anti-oxidation and anti-free radical, inducing tumor cell apoptosis, affecting cell cycle, regulating immunity, inhibiting tumor angiogenesis, inhibiting cyclooxygenase-2, and inhibiting telomerase activity.

2. Structure and Antitumor Activity of Flavonoids

2.1 Structure and Application of Flavonoids

Flavonoids are a large class of natural compounds[7], which have a wide variety and widely exist in the plant kingdom. They are one of the main components and active ingredients in many important Chinese herbal medicines such as honeysuckle, scutellaria baicalensis, hawthorn, mulberry bark, mulberry leaves, mistletoe, Sophora japonica, Prunella vulgaris, Polygonum aviculare, ginkgo biloba, epimedium, kudzu root, Anemarrhena asphodeloides, turnip flower, psoralea fruit and so on [8]. In recent years, the research on flavonoids has developed rapidly at home and abroad, and a large number of research reports and review articles have been published. There are many reports on the synthesis, structure confirmation and physiological activity of these compounds. By designing and synthesizing flavonoids with specific molecular structure, the correlation between its unique pharmacological effects and its structural characteristics was studied and analyzed. This is to explain the key structure-activity components, reveal the specific pharmacological and pharmacodynamic mechanism of flavonoids, and finally explore an effective method to obtain high-efficiency new flavonoids and realize artificial synthesis.

Flavonoids now generally refer to the basic skeleton structure of $C_6-C_3-C_6$. That is, a compound with two benzene rings (ring A and ring B) bridged by a C_3 part, in which C_3 part can be an aliphatic chain, or can be combined with ring A to form the C ring of six-membered or five-membered oxygen heterocyclic ring. It is classified according to the following five structural features: (1) C_3 bridge is open-loop or forms an oxygen heterocyclic ring with C_6; (2) If it is a ring, is it a five-membered ring or a six-membered ring; (3) the oxidation degree of C ring; (4) the connection position of ring B; (5) The compound is monomer, dimer or polymer. Riva, etc. were used to prepare 2,8- disubstituted flavone compounds, that is, propionyl salicylate and aroyl chloride were reacted in the presence of 2.1-3 times molar mass of L,8-diazabicyclo [5.4.0] undecane -7- ene (DBU), but ethyl 2- hydroxy - 3- propionyl benzoate was reacted with 2,2-hydroxybenzoate under similar conditions. For example, according to the degree of C_3 bridge ring opening, it can be divided into ring-opening chalcone, dihydrochalcone and ring-closing other flavonoids; The ring with C_6 can be divided into orange ketone and 2- phenylbenzofuran with five-membered ring C, flavone and isoflavone with six-membered ring C, etc. B ring connected to the 2- position is called flavone, and ring connected to the 3- position is called isoflavone; The oxidation degree of C_3 bridge ring can be divided into flavone, flavonol, dihydroflavone, dihydroflavonol, flavane, flavanone and anthocyanin. Common substituents on it are--OCH3,-oh and terpenoid side chains.

Flavonoids show different biological activities due to different structural characteristics, including cell signaling, biological activation, inflammatory reaction, angiogenesis, antioxidation, anti-inflammation, anti-tumor and so on[9]. Ketones can also act on tumor cells by inhibiting the activities of key enzymes in cell signal transduction, such as protein kinase, tyrosine protein kinase and phosphatidylinositol 3- kinase. Most free aglycones of flavonoids are insoluble in water, but soluble

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in organic solvents such as methanol, ethanol and DMSO. If the flavonoid is methyl, it will increase its solubility in organic solvents. However, after glycosylation, its water solubility will increase and its solubility in organic solvents will decrease. Flavonoids are mostly crystalline solids, and a few flavonoid glycosides are powder with no fixed shape. At present, there are many reports about the physiological activities of flavonoids, mainly focusing on antioxidation, anti-tumor, prevention and treatment of cardiovascular diseases, antivirus, antibacterial and immune regulation. Anti-tumor effect is a research hotspot of flavonoids natural products. Because of the wide variety of these compounds, their widespread existence in plants and low toxicity, the screening of their antitumor effects is still going on.

2.2 Antitumor Activity Research

Cancer is a kind of disease caused by abnormal mechanism of controlling cell growth and proliferation. It causes serious damage to the body through the endless and unlimited proliferation of cancer cells. The nutrients in patients are rapidly consumed, and cancer cells constantly release toxins, transfer and reproduce all over the body. The inhibitory effect of flavonoids on tumor cells is produced through many mechanisms, and cell cycle is one of its important mechanisms. The anti-cell proliferation activity of flavonoids suggests that it may prevent the occurrence and development of tumors by inhibiting cell cycle and inducing apoptosis. It has become a main way of cancer treatment to prevent the progress of cancer cell cycle by inhibiting the activity of cyclin and endogenous cyclin-dependent protein kinase in tumor cells. Flavonoids can also act on type ii DNA topoisomerase, which makes the DNA in tumor cells unable to replicate, thus affecting the progress of tumor cell cycle. The mixed components of flavonoids extracted from grapes, such as myricetin and resveratrol, can obviously inhibit the activity of type II DNA topoisomerase, and the inhibition of DNA unwinding is obviously dose-dependent.

These structural features may give it a variety of biological activities and great medicinal potential to a certain extent, so it is very suitable to be used as a lead compound for structural optimization and drug screening research, and to select antitumor compounds. Quercetin has the strongest antitumor activity, followed by baicalein, hesperetin, baicalin, hesperetin, isoquercetin and rutin. It can also be seen that the antitumor activity of flavonoid aglycones is greater than that of flavonoid glycosides, and the anticancer activity of flavonoid monosaccharides is greater than that of flavonoid disaccharides. Compared with antioxidant activity, glycosylation not only affects antioxidant activity, but also affects antitumor activity. However, there are some differences, not necessarily that the better the anti-oxidative damage ability, the better the anti-tumor activity. Flavonoids can also interfere with signal pathway by regulating the expression of related genes in cancer cells, so as to inhibit tumor growth. Abnormal signal transduction pathway is one of the reasons that slow down the growth rate of tumor cells. There are external and internal signal transduction pathways that mediate apoptosis. The external pathway includes death receptor-mediated pathway, and the internal pathway includes mitochondrial-mediated pathway. Saxifraga glauca is a perennial herb belonging to Saxifragaceae, which grows in forests, shrubs and alpine meadows at an altitude of (3 ~ 5) × 103m. It is rich in flavonoids such as quercetin and its derivatives. Studies have shown that Saxifraga glauca has antibacterial, antiviral, anti-inflammatory and anti-tumor effects. Products containing Hypericum have many medicinal values, such as antibacterial, anti-inflammatory, anti-viral, anti-tumor cell proliferation, analgesic and astringent activities, and can also be used to treat diseases such as depression, hepatitis and dysentery.

Flavonoids can induce tumor cell apoptosis, block cell division cycle, inhibit tumor angiogenesis, inhibit cyclooxygenase-2, regulate immune system, inhibit telomerase activity and sensitize the effect of chemotherapy drugs.

3. Progress in Anticancer Activity of Flavonoids

In the stage of cancer development, if the cells carrying damaged DNA can't repair themselves and escape the process of apoptosis, then the process of cell tumorigenesis caused by gene mutation will

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be initiated, and it will develop into tumor cells under the impetus of many tumor promoting factors (such as inflammatory factors, various hormones and growth factors). In the stage of cancer development and formation, rapidly proliferating malignant tumor cells can enter tissue blood vessels or lymphatic vessels through invasion, transfer to other organs, and gain more nutrition by promoting angiogenesis, and continue to proliferate to form malignant solid tumor tissues. In this process, flavonoids also showed a variety of anticancer activities, including inducing tumor cell differentiation, cell cycle arrest and apoptosis, inhibiting tumor cell invasion and metastasis, inhibiting angiogenesis, etc. Flavonoids are a huge family. Up to now, more than 6,000 natural flavonoid monomers have been identified. Among them, hesperidin adjuvant drugs are often used to improve patients' vascular diseases; Hesperidin has anti-inflammatory and analgesic effects, and when used in combination with digoxin, both in vivo and in vitro research results show obvious inflammatory protection. Combined with naringin, it has the effects of lowering cholesterol and resisting cancer; Clinical studies have also shown that it can alleviate menopausal symptoms of women. Recently, the research on flavonoids has been increasing. With the increasingly clear research on the anticancer mechanism of citrus flavonoids, its application as a new drug in clinical cancer treatment is just around the corner.

4. Summary

In the current society, the incidence of cardiovascular diseases and cancer is constantly increasing, so how to treat these diseases and the corresponding prevention has become a widespread concern of all sectors of society. At the same time, at present, the research on tea flavonoids is not deep enough, and it is necessary to invest more in the biological activities of tea flavonoids in related fields to ensure that they can effectively serve human health. By studying the relationship between antioxidant and antitumor activities of seven flavonoids and their structures, some effective data are provided for the subsequent application and chemical synthesis of flavonoids.

In the mechanism of antioxidation, firstly, the quantitative parameters of flavonoids were calculated by quantum chemistry, secondly, the free radical scavenging ability was measured by pure chemistry, and then the antioxidant damage ability of seven flavonoids was measured by HDHC model. From the above structure-activity analysis, the main structures that affect the antioxidant activity of flavonoids in cell model are C2-C3 double bonds, the number, position and glycosylation of phenolic hydroxyl groups, and the anti-tumor active sites are also distributed in the above structures, so the above structures are also the material basis for the correlation between antioxidant activity and anti-tumor activity of flavonoids. Whether in vitro cell experiments or in vivo animal experiments, the effects of monomeric flavonoids on the expression and signal pathways of multiple target proteins at the molecular level have been fully studied. Expand the sample size and enrich various structures of flavonoids. So as to describe the physiological activity of flavonoids more accurately. In vivo experiments prove that the antioxidant activity of flavonoids is consistent with anti-tumor, and improve the accuracy of the conclusion.

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