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**Review Article**

# Effect, main targets and molecular mechanisms of glycyrrhiza-derived flavonoids on malignant tumor in comprehensive cancer treatment

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## *Abstract*

*Glycyrrhiza flavonoids (GF) are essential antitumor components of Glycyrrhiza uralensis, Glycyrrhiza glabra, and Glycyrrhiza inflata roots and tubers, with antioxidant, anti-inflammatory, antibacterial, immune-enhancing amongst other properties. In recent years, significant progress has been made in understanding the mechanisms and targets of GF in various pharmacological settings. This review summarizes the clinical value, targets and research progress of the molecular mechanisms underlying GF in the treatment of malignant tumors. This will provide as a theoretical foundation for further studies into GF as a therapeutic option in the management of cancerous tumors.*

***Keywords:*** *Glycyrrhiza flavonoids, Anti-tumor, Molecular mechanism*



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## INTRODUCTION

Malignant tumors are among the most important diseases that cause human death worldwide and their clinical treatment is complex, occurring more frequently each year [1]. Tumor prevention and treatment have become a major focus in clinical medicine, drawing the attention of more researchers than ever before. Although Chinese plant therapy has become increasingly popular as important therapeutics in the West, little is known about its effectiveness, causes, or adverse effects.

*Glycyrrhiza uralensis* Fisch is a common Chinese medicinal material commonly used as a tonic in Chinese medicine in combination with other drugs. Modern pharmacological studies have shown that *Glycyrrhiza uralensis* Fisch has antioxidant, antitumor, anti-inflammatory, immunoregulatory and other activities closely related to its active ingredients. Research suggests that the main components of *Glycyrrhiza uralensis* Fisch include flavonoids, organic acids, and other constituents. Researchers have focused on flavonoids because of their promising

potential in various cancer treatments, including reducing tumor growth, metastasis, infiltration, angiogenesis, and medication tolerance [2].

### *Overview of Glycyrrhiza flavonoids*

In recent years, owing to advancements in both organic chemistry and biology, the molecular components of *Glycyrrhiza uralensis* Fisch have been isolated, characterized, and named. Many of these molecular components possess potent therapeutic effects against inflammation, germ cells, and cancer. As a result, *Glycyrrhiza uralensis* Fisch has attracted worldwide commitment to isolate, and characterize the active ingredients in *Glycyrrhiza uralensis* Fisch and study its mechanism of action. Glycyrrhiza flavonoids (GF) are one of the main components extracted from Glycyrrhiza root, which have shown great potential in various biological activities [3]. Glycyrrhiza flavonoids have been widely used in drugs, health products, and cosmetics in recent years.

## CHEMICAL CONSTITUENTS OF GLYCYRRHIZA FLAVONOIDS

Flavonoids are polyphenols that are widely present in nature and usually do not exist alone in a free state in plants but combine with sugar to form glycosides. Flavonoid compounds generally refer to 2-phenylchromone as their parent nucleus. They also refer to a series of compounds formed by connecting two benzene rings via three carbon atoms. These compounds are present in many quantities and types. Their structural types are also diverse and can be divided into several categories according to their parent nuclear structure, hydroxylation, substitution position, degree of polymerization and conjugation. For example, flavonoids can be divided into flavonoids, dihydro flavonoids, flavonols, isoflavones, chalcones and orange ketones according to their carbon chain composition.

*Glycyrrhiza uralensis* Fisch is rich in flavonoids. At present, more than 300 flavonoids have been identified from *Glycyrrhiza uralensis* Fisch [4], including dihydroflavones such as liquiritin, neoliquiritin, liquiritigenin, and apigenin liquiritin; chalcones such as isoliquiritin, isoliquiritigenin, and licochalcone A; flavonoid such as glycyrrhiza and apigenin; flavonols such as glycyrrhizin flavonol and isoliquiritin flavonol; isoflavones such as glycyrrhizone, licoisoflavanone A, and liquiritin A; other isoflavones such as glabridin and glabrene; dihydroisoflavones such as glycyrrhizin isoflavones and dihydroflavonols such as 3-hydroxyglabrol.

## PHARMACOLOGICAL EFFECTS OF GLYCYRRHIZA FLAVONOIDS

Due to the diversity of its structural types, glycyrrhiza flavonoids with different structures usually show various pharmacological activities, including oxidation resistance, antitumor, anti-inflammatory, anti-bacterial, hypoglycemia, anti-radiation and enhancing immunity, and are primarily employed for the treatment and avoidance of arterial, cerebral, and pulmonary disorders in medical settings.

### *Oxidation resistance*

The accumulation of free radicals is the primary cause of reactive degeneration of cells. Furthermore, an increase in free radicals in the body is closely associated with the onset and progression of many degenerative illnesses. Flavonoids in *Glycyrrhiza uralensis* Fisch, such as flavonoids, dihydro flavonoids, and chalcones, can eliminate different types of free radicals from the body. The antioxidant activity of flavonoids was evaluated by calculating their free radical scavenging rate. Zeng *et al* [5] studied the antioxidant activity of flavonoids in Glycyrrhiza extracts. Wang and others [6] reported that the antioxidant isoliquiritigenin ameliorated 2, 2', 4, 4'-tetrabromodiphenyl ether-induced embryonic defects in zebrafish.

### *Antitumor*

Many studies have shown that *Glycyrrhiza uralensis* Fisch has significant immunomodulatory and antitumor effects [7]. Glycyrrhiza flavone has been shown to substantially suppress the growth of a wide range of cancer cells. Anticancer properties have been studied and the extracts are effective against liver cancer [8], prostate cancer [9], gastric cancer [10] and other cancer cells *in vivo* with excellent antitumor effect.

### *Anti-inflammatory*

Inflammation is associated with the production of inflammatory cytokines and other mediators in the body. At the same time, flavonoids in *Glycyrrhiza uralensis* Fisch effectively inhibit the production and release of inflammatory cytokines. Some studies have shown that flavonoids, such as glabridin, glycyrrhizin, isoliquiritigenin, and Licochalcone A in

*Glycyrrhiza uralensis* Fisch have good anti-inflammatory effects. Recent studies have found that echinatin, a flavonoid of *Glycyrrhiza uralensis* Fisch, inhibits abnormal activation of the NLRP3 inflammasome when treating various inflammatory diseases [11].

In addition, Yu *et al* [12] used the formaldehyde-induced mouse inflammation model to study the multi-channel and multi-target synergistic regulation mechanism of Glycyrrhiza flavonoids, and Glycyrrhiza polyphenols were found to have a dose-dependent anti-inflammatory effect in rat model. The primary way to reduce inflammation is to control prostaglandin $E_2$ (PGE2) production. Yang *et al* [13] studied the anti-inflammatory active ingredients and mechanism of action of *Glycyrrhiza uralensis* Fisch and selected 13 flavonoids as active anti-inflammatory ingredients. The mechanism of action was mainly through the reduction in expression of tumor necrosis factor (TNF), matrix metalloproteinases (MMP), prostaglandin $E_2$ (PGE2), and other related inflammatory factors as well as inhibiting production of free radicals. Zhu *et al* [14] found that isoliquiritigenin in *Glycyrrhiza uralensis* Fisch prevents cognitive impairment and neuronal damage caused by lipopolysaccharide (LPS) (lipid sugar) through the promotion or maintenance of antioxidant capacity and inhibition of neuroinflammation. Yu *et al* [15] identified the active ingredients in Glycyrrhiza extract and evaluated the anti-inflammatory activity by studying the liver injury model induced by hydrogen peroxide.

### *Anti-bacteria*

According to several investigations, Glycyrrhiza compounds have also been shown to have potent antimicrobial action. Wu *et al* [16] studied the antibacterial activity, potential mechanism of action, and clinical application of Glycyrrhiza flavonoids. The results showed that glycol, licochalcone A, licochalcone CC, and licochalcone E showed high antibacterial activity, low cytotoxicity against methicillin-resistant *Staphylococcus aureus*, and no hemolytic activity. Fukai *et al* [17] showed that 19 flavonoids isolated from *Glycyrrhiza uralensis* Fisch were tested for their antibacterial efficacy against a panel of bacteria including methicillin-sensitive *S. aureus, S. aureu*s resistant to methicillin, *Micrococcus luteus, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. These findings demonstrated that *Glycyrrhiza uralensis* flavonoids exhibited potent antimicrobial activities.

### *Pathogenesis and modern treatment of malignant tumors*

Malignant tumor is a disease that is difficult to treat medically. At present, the mortality rate is second only to cardiovascular disease, which is seriously harmful to human health [1]. Traditional tumor treatment methods include surgical resection and chemotherapy. However, these methods do not effectively eradicate the disease and have serious side effects that cause significant harm to the human body during tumor treatment. Therefore, research and development of antitumor compounds have developed rapidly in recent years. The mainstream antitumor compounds include ultrasound-activated porphyrins for minimally invasive physical therapy and flavonoids extracted from plants [18].

## ETIOLOGY AND PATHOGENESIS

Tumors have been treated and prevented using traditional Chinese medicine for thousands of years [19-20]. In traditional Chinese medicine, "tumor" is called *"malignant flesh," "cancer," "rock," "stone gangrene," "symptomatic scrofula," "accumulation,*" and so on. According to tumor location, it is treated with syndrome differentiation, such as "*lung accumulation," "liver accumulation," "milk rock,*" and "*intestinal inflammation*" [20].

Traditional Chinese medicine believes that tumor syndrome is essentially empty, out solid, and its etiology mainly includes four aspects: The first is six exogenous pathogenic factors, toxins and evil enter from outside into the inside and making evil exist for a long time, resulting in the Yin-yang imbalance of Qi and blood in the viscera resulting in agglomeration of lesions. The second is that the seven emotions are not smooth, the moods are not triumphant, and Qi movement is delayed leading to Qi stagnation and blood stasis in the body for a long time gradually forming a block. The third is eating disorders which damage the spleen and stomach, causing spleen dyskinesia, phlegm and endogenous dampness slowly producing blood stasis. The fourth is that a patient has already had an old disease, with asthenia of healthy Qi and asthenia of pathogenic factors. The primary contributors to the development of this disease are an inadequate supply of

healthy Qi in the body, an accumulation of Qi obstruction, blood stasis, phlegm, heat toxicity over an extended period, and the development of bulk within the body.

Western medicine believes that tumors are formed by the abnormal proliferation of local tissues and cells under the action of various tumor-causing factors, which is consistent with the pathogenic theory of asthenia of healthy qi and asthenia of pathogenic factors in traditional Chinese medicine [20]. Tumors are susceptible to both interior and exterior environments. Acidity, oxygen, elevated pressure, immunological escape, and other features of the tumor milieu can facilitate tumor growth, angiogenesis, spread, and other dangerous behaviors. Although the views of traditional Chinese and Western medicine on tumor etiology and pathogenesis belong to different theoretical systems, there is a specific correlation between inflammatory cells, carcinogenic factors, inflammatory factors, vasoactive substances, and chemokines in the tumor microenvironment in the Western medicine theoretical system and phlegm toxin, heat toxin, blood stasis toxin, and other toxins in the traditional Chinese medicine system [12-15]. Tumor-associated fibroblasts, crucial for the emergence and progression of malignant tumors, have been found by contemporary research to be analogous to phlegm in traditional Chinese medicine, and secretion of various pathogenic factors has been compared to the "endotoxin" of phlegm dampness [20].

## CLINICAL TREATMENT

Traditional Chinese medicine (TCM) has a long history, a wealth of experience, and several other advantages in managing cancerous tumors [20]. This provides it with a distinct competitive edge. Traditional Chinese medical practice is underpinned by a theory of causation and pathophysiology. Clinical treatment of tumors in TCM focuses on strengthening health and eliminating pathogenic factors that complement each other and are indispensable. The treatment methods are adjusted according to disease development in different stages. In the early stages, an attack is performed. The middle stage involved diving and supplementing health simultaneously. In later stages, health and foundation are strengthened.

In clinical practice, TCM mainly begins with pathogenic toxin accumulation, qi stagnation, blood stasis, phlegm, dampness condensation, syndrome differentiation and treatment. Accordingly, it adopts the treatment methods of clearing heat and detoxification, activating blood circulation, removing blood stasis, resolving phlegm and dampness, softening hardness, dispersing stagnation, etc [20].

Modern medical treatment of malignant tumors mainly involves surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Radiotherapy effectively improves the local cure rate, prevents recurrence and kills subclinical lesions to prevent recurrence and metastasis. However, radiotherapy is a local treatment with limitations, and radiation pneumonia caused by radiotherapy endangers the lives of patients. Chemotherapy kills subclinical lesions to prevent recurrence and metastasis; however, it is a non-selective killing effect that damages normal cells and organs. Targeted drugs are highly selective antitumor drugs however, their antitumor effects are relatively weak and may need to be combined with chemotherapy [21-23].

In summary, modern medical treatments for malignant tumors also have disadvantages. In contrast, traditional Chinese medicine treatment of malignant tumors needs to run through the entire process of therapy, which has the advantages of exact curative effects, fewer adverse reactions, and prevention of recurrence and metastasis. As a result, antitumor traditional Chinese medicine research and development and establishment of active constituents are of utmost importance in contemporary therapeutic tumor treatment.

### *Evaluation of the antitumor activity of Glycyrrhiza flavonoids*

In recent years, many researchers have evaluated the antitumor activity of *Glycyrrhiza uralensis* Fisch and its flavonoids through cell and mouse experiments. The results showed that the Glycyrrhiza flavonoids possess antitumor and anticancer activities *in vivo* and *in vitro* [21-28].

## DERMATOMA

Shibata [18] revealed that licoricchalcone A has an antitumor, and anti-inflammatory in Xinjiang *Glycyrrhiza uralensis* Fisch. More than 40 chalcone compounds were tested and the study revealed that 3‘-and 4’-methyl-3-hydroxychalcone demonstrated most antitumor properties on the constructed animal model of mouse dermatoma.

## COLON CANCER

Isoglycyrrhizin prevents the occurrence of colon cancer induced by azomethane (AOM) in animal models. Zhao *et al* [19] studied the chemopreventive effects and its mechanism on colitis induced by isoliquiritigenin in the AOM/dextran sodium sulfate (DSS) in related tumor mouse model. The experimental results showed that isoliquiritigenin significantly reduced the incidence rate, diversity, and tumor size of mouse colon cancer. This mechanism may block the polarization of M2 macrophages mediated by the interaction between PGE2 and interleukin-6 (IL-6), achieved by downregulating the expression of PGE2 and IL-6 signals.

## PROSTATE CANCER

Kanazawa *et al* [9] examined the effects of isoliquiritigenin on cell proliferation, cell cycle regulation, and expression of cell cycle regulating genes using DU145 and LNCaP prostate cancer cell lines as targets. The study revealed that isoliquiritigenin successfully suppressed the proliferation of prostate cancer cell lines in a dose- and time-dependent manner. Analysis using fluorescence-activated cell sorting (FACS) demonstrated that isoliquiritigenin upregulated GADD153 mRNA and protein transcripts, both of which are associated with cell cycle standstill. In addition, isoliquiritigenin caused the S and G2 / M phases to become stationary.

## BREAST CANCER

Glabridin was able to inhibit the glucose uptake level of tumor cells and down-regulate expression of glucose transporter – 1 (GLUT1) protein, which suggests that glabridin can play an antitumor role by regulating the glycolysis process of tumor cells, which was found by researchers in studying triple-negative breast cancer MDA – MB-231 cells [21].

## GASTRIC CANCER

Shibata [18] found that 3 '- and 4' - methyl-3-hydroxychalcone significantly inhibited the proliferation of HGC-27 cells derived from human gastric cancer. Glucose regulatory protein 78 (GRP78) is a critical mediator of tumor biology. Lee *et al* [21] found that isoglycyrrhizin inhibits the expression of gastric cancer stem cell-like characteristics, dry-associated protein mediated by GRP78, cancer-related fibroblast activation, and gastric tumor growth in xenotransplantation research.

## ENDOMETRIAL CARCINOMA

Wu *et al* [22] experiments on living subjects were carried out to establish whether or not isoliquiritigenin has an inhibiting effect on the endometrial carcinoma cells of mice. According to the findings, isoliquiritigenin was able to suppress the activity of cancer cells in a dose and time-dependent manner. However, it had a minimal effect on the survival ability of normal cells, indicating that isoliquiritigenin targets tumor cells in patients and reduces side effects on normal cells.

## CERVICAL CANCER

Another study [23] used an animal tumor model established by inoculating mice with cervical cancer. They found that glycyrrhizin reduced tumor volume and activity in model mice. Mice exposed to glycyrrhizin had higher splenic and thymus indices, and the release of cytokines such as interleukin and tumor necrosis factor increased steadily, indicating that glycyrrhizin can play an antitumor role by improving immune function.

Some studies have found that the active ingredient of *Glycyrrhiza uralensis* Fisch, namely glabridin, effectively inhibited the activity of cervical cancer HeLa cells, while downregulating the cell ratio of G2 / M phase, G0 / G1 phase, and expression of cyclin D1 [29]. This showed that glabridin exerted antitumor effect by prolonging the cycle and inhibiting the activity of tumor cells.

## ORAL SQUAMOUS CELL CARCINOMA

Cancer stem cells (CSC) drive tumor formation and promote metastasis, cancer recurrence, and chemotherapy resistance in oral squamous cell carcinoma (OSCC). Hu *et al* [24] proved that isoliquiritigenin showed more significant toxicity in oral cancer stem cells (OSCC-CSC) by inhibiting the self-renewing ability of cancer cells, reducing expression of CSC markers, such as ALDH1 and CD44, and inhibiting the ability of OSCC-CSCs to invade, metastasize, and grow into colonies. Furthermore, isoliquiritigenin enhances the effects of chemotherapy and downregulates the expression of ABCG2, an ABC transporter associated with drug resistance.

### *Main antitumor targets and molecular mechanisms of Glycyrrhiza flavonoids*

In recent years, increasing evidence has shown that the antitumor mechanisms of glycyrrhiza flavonoids mainly include inhibiting

cell proliferation, inducing cell apoptosis, inducing autophagy, inducing necrosis, interfering with cell cycle, inducing aging, inhibiting cell migration, inhibiting glycolysis, regulating immunity, inhibiting tumor angiogenesis, reducing multidrug resistance of tumor cells, and intervening protein kinase in signal transduction pathway of tumor cells [25,26].

### INTERFERENCE WITH CELL CYCLE

Zhang *et al* [27] comprehensively summarized the antitumor activity of Glycyrrhiza flavonoids, investigated the potential molecular mechanisms, and evaluated therapeutic potential and side effects. Sixteen glycyrrhiza flavonoids were found to have anticancer activity, which inhibits the activity of tumor cells. Glycyrrhiza flavonoids have been shown to inhibit the cell cycle and regulate a wide variety of signaling pathways. Some of the most important pathways affected by these flavonoids are mitogen-activated protein kinase (MAPK), PI3K/AKT, NF-B, death receptor-dependent exogenous signaling, and mitochondrial apoptosis pathways. Chen *et al* [28] showed that neoisoliquiritigenin inhibited cell proliferation by inducing cell cycle stagnation in the G0 / G1 phase. Zhu *et al* [29] used C57BL/6 to investigate the antitumor activity of licorice in mice and evaluated the mechanism of action. The study revealed that licorice-induced growth cycle arrest of G0 / G1 of tumor cells by downregulating the CDK4-cyclin D1 complex, leading to an increase in the protein level of PD-L1. Wang *et al* [30] showed that licoricchalcone A suppressed HepG2 cell growth by causing death and halting cell cycle development in G2/M transition. Related mechanisms include upregulation of DR3, DR5, caspases-3, caspases-8, caspases-10, Fas, Bad, Bax, Bcl-2, Bak, PUMA and downregulation of PKCε, p70S6K, and Akt mRNA expression.

### ANTI-INFLAMMATORY AND OXIDATIVE STRESS

Li *et al* [31] revealed that glycyrrhiza flavonoids ameliorated inflammation and oxidative stress. Isoliquiritigenin was found to exert antitumor effects by suppressing tumor inflammatory response and reactive stress through modulation of NF-B and PI3K/AKT pathways.

### REGULATING IMMUNITY

Xu *et al* [32] investigated the mechanism of action of apigenin in immune regulation and revealed that the antitumor effect of apigenin mainly involves the PI3k/Akt, MAPK, NF-κ B, Wnt/β-catenin, and JAK/STAT signaling pathways. Programmed cell death ligand 1 (PD-L1) is a key regulator of immune response. Liu [33] further showed that glycyrrhizin chalcone A inhibited PD-L1 expression by blocking the interaction between p65 and Ras, thus enhancing the activity of cytotoxic T lymphocytes to kill tumor cells, inhibit tumor cell proliferation and promote tumor cell apoptosis.

### INDUCED AUTOPHAGY

Glycyrrhizin is a kind of natural polyphenol compound characterized by multiple targets that participate in multiple pathways and has been widely studied in different models of autophagy regulation. Shao *et al* [34] found that lupalbigenin (LPB) and 6,8-isoprene genistein (DPG) from licorice promoted autophagy and induced SW480 colorectal cancer cell death through the Akt/mTOR signal pathway. In addition, autophagy induced by flavonoids usually interacts with other mechanisms to comprehensively exert antitumor effects. Therefore, targeted autophagy may become the core mechanism of action of glycyrrhiza flavonoids in tumor treatment [27]. Currently, traditional Chinese medicine is used for the treatment of more than 70 % of cancer patients in China. These data show that traditional Chinese medicine (TCM) not only plays an antitumor role but also significantly improves sensitivity to chemotherapeutic drugs and reduces the harmful effects of pharmaceutical drugs [20].

## CONCLUSION

With the rising standards of medical care achieved in recent years, clinical problems faced by patients with malignant tumors have improved. Glycyrrhiza antioxidants have been a subject of promising cancer research. It is indisputable that contemporary medicine has not fully acknowledged the efficacy of traditional Chinese medicine in the prevention and treatment of cancer. Clinical treatment of tumors at this stage is still dominated by Western medicine. However, surgery, radiotherapy, chemotherapy, immunotherapy, and other treatment methods still cannot change the current situation of low cure rates and high mortality rates for malignant tumors. However, TCM may become the main treatment for malignant tumors at this stage. Therefore, there is a need to fully investigate existing theoretical and practical research to understand the potential mechanisms of malignant tumor occurrence and disease progression at the molecular and cellular

level. Furthermore, future studies should analyze and investigate the known mechanisms and important molecular signaling pathways of glycyrrhiza flavonoids in the treatment of tumors. Glycyrrhiza flavonoids are involved in a wide range of biological processes, such as inflammation, immunity, redox metabolism, cell growth, autophagy, apoptosis and cell cycle.

## DECLARATIONS

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### *Availability of data and materials*

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.



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