



Review

A review of compounds with anti-hepatoma properties in *Glycyrrhiza uralensis*

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Abstract

Hepatoma, one of the most common fatal malignant tumors, exhibits a rising global incidence, especially in developing countries. In recent years, traditional Chinese medicine has played an increasingly significant role in hepatoma treatment. *Glycyrrhiza uralensis* (*G. uralensis*), a perennial herb in the legume family, is also known as *G. uralensis*, sweet root, sweet grass, and ancient Chinese grass. Its roots and rhizomes are used medicinally for their properties to nourish Qi, detoxify, and harmonize the effects of various compounds. This study selected “Glycyrrhiza”, “hepatoma”, and “pharmacological effect” as key search terms. From PubMed, a total of 2,947 articles were retrieved containing these keywords in either the abstract or title, among which 12 were relevant to Glycyrrhiza and hepatoma. Additionally, from the Wanfang database, 19,632 papers were retrieved with “Glycyrrhiza” in the abstract or title, among which 197 were related to Glycyrrhiza and hepatoma. This review focuses on the anti-hepatoma properties of Glycyrrhiza, providing a comprehensive overview of its common extracts, such as flavonoids, triterpenoids, and polysaccharides, and elaborating on their chemical structures, anti-hepatoma cancer mechanisms, and other pharmacological effects.

keywords: *Glycyrrhiza uralensis*; anti-hepatoma cancer; pharmacological effects

1 Introduction

Glycyrrhiza uralensis (*G. uralensis*), commonly known as licorice, honey grass, or old man’s root, has several notable effects, including tonifying the Qi, expectorating cough, detoxifying, relieving pain, and easing drug side effects. Literature also attributes it with the ability to regulate overall bodily functions,

enhance muscle and bone strength, promote muscle growth, and alleviate traumatic infections and detoxification related to metal instruments.

As a traditional Chinese medicine, *G. uralensis* is widely used to harmonize the effects of other medicinal substances. Its therapeutic effects include soothing sore throats, alleviating coughs, resolving phlegm, and enhancing the functions of the spleen and stomach. Additionally, it can reduce the toxicity of certain drugs and harmonize complex herbal formulas. It is frequently employed to address ailments such as cough, asthma, physical fatigue, and adverse drug reactions.

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China is the first country in the world to study *G. uralensis*. Hepatocellular carcinoma (HCC) is the most prevalent and deadly malignant tumor globally. Among the five most lethal cancers, HCC is the only one exhibiting a steadily increasing annual incidence rate, particularly in developing countries [1]. According to statistics from the National Cancer Center, the incidence and mortality rates of HCC in China exceed

the global average [2]. Due to the often asymptomatic nature of early-stage HCC, timely detection is frequently challenging [3]. Consequently, most patients receive diagnoses in the middle to late stages of the disease, and the effectiveness of treatment remains a huge concern. Therefore, there is a pressing clinical need to investigate comprehensive treatment strategies for HCC. *G. uralensis*. example is shown in Fig. 1 [4].

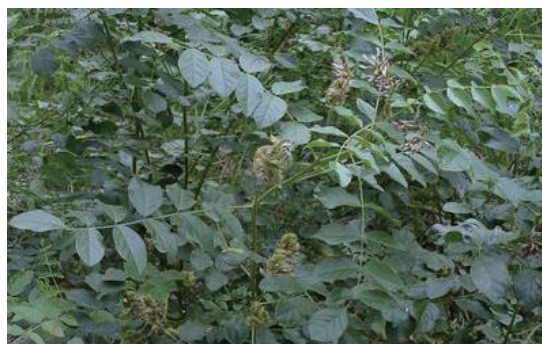


Fig. 1 Photo of *G. uralensis*

In recent years, in-depth study of cancer has brought increasing attention to the role of traditional Chinese medicine in cancer prevention and treatment. Traditional Chinese medicine is not only used as an auxiliary therapy, but also demonstrates enhanced efficacy when integrated with modern medicine. *G. uralensis*, one of the most commonly used herbs in traditional Chinese medicine prescriptions, was first recorded in the ancient pharmacological classic “*Shennong Bencao Jing*”. *Glycyrrhiza glabra* L. (*Glycyrrhiza* L.), a genus in the legume family Fabaceae, consists of perennial herbs or semi-shrubs that often possess spiky or scaly glandular structures. Among the genus, *G. uralensis* is a representative species.

Pharmacological studies have found that *G. uralensis* has a wide range of activities on inflammation, oxidative stress, immune regulation, virus infection, and cancer. Progress has been made in understanding the anti-hepatoma effect of *G. uralensis*. Based on this, we further studied the anti-hepatoma activity of *G. uralensis*, conducted in-depth pharmacological activity research,

and gained deeper understanding of the anti-hepatoma cancer mechanism [5].

2 Effective ingredients in *G. uralensis*

2.1 Flavonoids

Flavonoids are a series of structurally diverse compounds formed by connecting two benzene rings with phenolic hydroxyl groups through a central 3-carbon atom. They are active ingredients in many traditional Chinese medicines and have multiple pharmacological effects [6]. *Flavonoids* such as Licochalcone A, Licochalcone B, Isoliquiritigenin, Liquiritin, and Liquiritigenin have been reported to induce apoptosis in different types of hepatoma [7].

2.1.1 *G. uralensis* flavonoid monomers and their chemical structures

G. uralensis has effects such as clearing heat and detoxifying, tonifying the spleen and

replenishing qi, moistening the lungs, dispelling phlegm and relieving cough, and reconciling various medicines. It is the most widely used traditional Chinese herbal medicine in clinical practice. *G. uralensis* extract contains a variety of flavonoid

monomers, including *G. uralensis* chalcone A-F, *G. uralensis* chalcone, isoliquiritigenin, isoliquiritin, glabridin, liquiritigenin, and liquiritin (Fig. 2) [8]. The following table 1 shows Flavonoids isolated from *G. uralensis* in recent years [9].

Table 1 Flavonoids isolated from *G. uralensis* in recent years

No.	Compound name	Reference
1-6	Licochalcone A-F	10
7	Echinatin	10
8	Isoliquiritigenin	10
9	Isoliquiritin	10
10	Glabridin	10
11	Liquiritigenin	10
12	Liquiritin	10

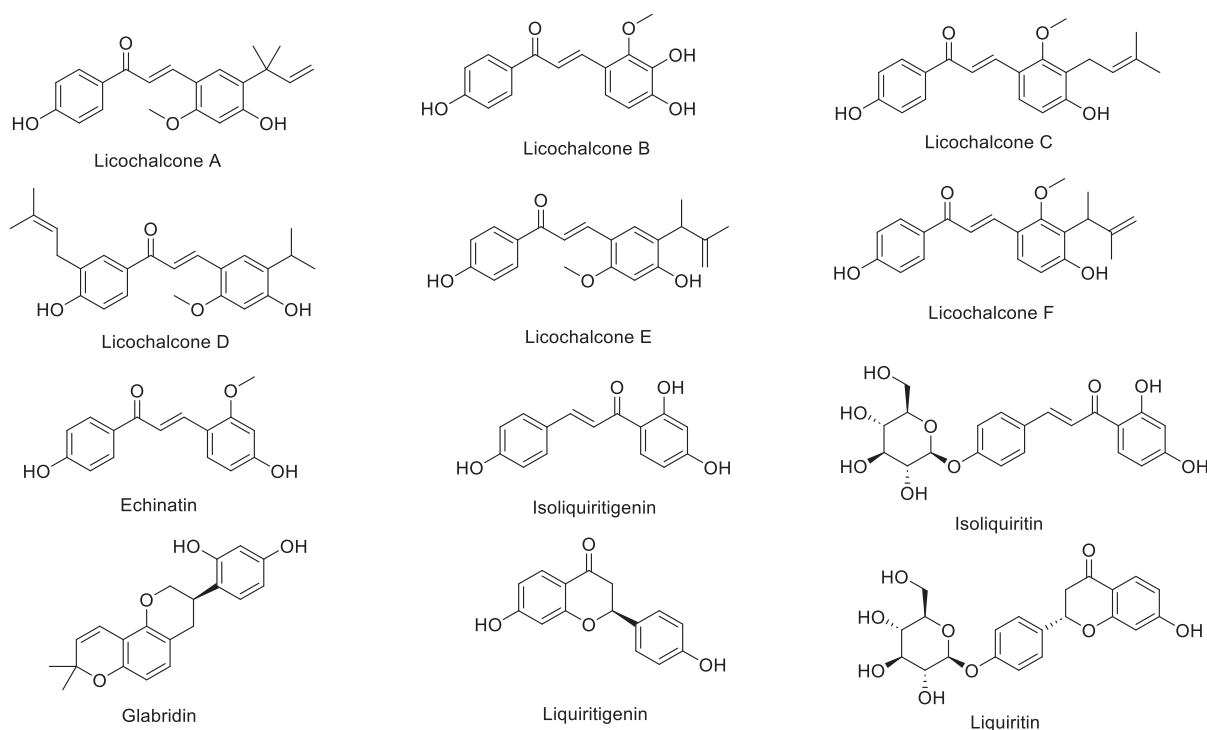


Fig. 2 Basic mother nucleus diagram of flavonoids in *G. uralensis*

2.1.2 Pharmacological effects of flavonoids

G. uralensis inhibits the hypoglycemic effect in chronic unpredictable mild stress (CUMS) rats

by increasing the content of BDNF, enhancing the activity of antioxidant enzymes, inhibiting lipid peroxidation, and reducing oxidative damage to the brain caused by chronic stress [11].



G. uralensis provides protection and nutrition for primary hippocampal neurons in three ways: inhibiting the $A\beta$ receptor of primary hippocampal neurons through the estrogen pathway, inhibiting acetylcholinesterase to promote the expression of M1 cholinergic receptor, and inducing the directional differentiation of the neural stem cells into cholinergic neurons *in vitro* [12].

Hu Qingyu et al. used 100 and 200 mg/kg isoliquiritigenin to treat neutrophilic asthma mice established by ovalbumin [13]. They found that isoliquiritigenin reduced airway resistance, serum white blood cell count, and IL-17 levels in mice by regulating the VSIG4/NLRP3 inflammatory complex pathway, increased the expression of VSIG4 protein in lung tissue, downregulated the expression of NLRP3 protein, and reduced airway inflammation caused by asthma.

Research shows that administration of 5-10 mg/kg licochalcone A promotes the expression of Nrf2 in the lungs of asthmatic mice and increases the secretion of HO-1 in the lungs, thereby increasing the level of glutathione in the lung tissue and reducing the levels of malondialdehyde and reactive oxygen species. It also confirms that licochalcone A exerts antioxidant activity by activating the Nrf2/HO-1 signaling pathway [14].

2.1.3 Anti-hepatoma cancer mechanism of flavonoids

G. uralensis flavonoids induce autophagy and apoptosis by inhibiting the activity of cellular proteasomes. These compounds inhibit the growth of human hepatoma cancer cells and transplanted tumors, indicating its anti-tumor effects both *in vitro* and *in vivo*.

In addition, *G. uralensis* flavonoids showed inhibitory activity against cell cycle-dependent protein kinase CDK1/cyclin B. In particular, the inhibitory activity of isoliquiritigenin on CDK1/cyclin B ($IC_{50} = 0.05 \pm 0.005 \mu\text{mol/L}$) was nearly 6

times higher than that of the positive drug Flazepine ($IC_{50} = 0.29 \pm 0.230 \mu\text{mol/L}$). *In vitro* antitumor activity studies showed that *G. uralensis* flavonoids had a strong inhibitory effect on liver cancer Bel-7402 cells. Among them, isoliquiritigenin showed the strongest inhibitory activity against Bel-7402 ($IC_{50} = 0.7 \pm 0.11 \text{ mol/L}$), which was 3 times higher than that of the positive control ($2.4 \pm 0.34 \text{ mol/L}$) [15].

G. uralensis flavonoids are likely to target CDK1 due to the structural features of certain bioactive constituents. Eight representative compounds, such as liquiritigenin A-F, liquiritigenin, and isoliquiritigenin, have an α,β -unsaturated ketone structure, which confers molecular flexibility, broad receptor-binding capacity, and anti-tumor pharmacophoric properties. The enzyme inhibitory activity of liquiritigenin A-F, liquiritigenin, and isoliquiritigenin is stronger than that of glabridin and liquiritigenin. The carbonyl group of the α,β -unsaturated ketone of isoliquiritigenin is linked to resorcinol, and the carbonyl group forms hydrogen bonds with the amino acid residues of the enzyme together with the hydroxyl group of resorcinol, so the enzyme inhibition activity of isoliquiritigenin is stronger than that of other types of *G. uralensis* flavonoids [16].

2.2 Triterpenoid saponins

Triterpenoids are monomeric compounds, generally composed of 30 carbon atoms, which can exist in free or bound forms. When combined with sugars, they are called triterpenoid saponins. The most important triterpenoid compound in *G. uralensis* is glycyrrhizic acid. Upon hydrolysis, glycyrrhizic acid loses its sugar acid chain to form glycyrrhetic acid, a compound 250 times sweeter than sucrose.

Glycyrrhetic acid is a single-chain glycoside triterpenoid saponin composed of hydrophobic triterpenoid glycosides and connected to hydrophilic glycosides. Glycyrrhizic acid is a

natural surfactant with amphiphilic properties [17]. In addition to glycyrrhizic acid and glycyrrhetic acid, there are also various triterpenoids such as glycyrrhetic terpenoids, glycyrrhetic lactone, deoxyglycyrrhetic lactone, isoglycyrrhetic lactone, glycyrrhizic benzofuran, β -sitosterol, and

mangiferin.

2.2.1 Chemical structures of common triterpenoids

The common parent nucleus structures of triterpenoids are as following Figs. 3-4 [18].

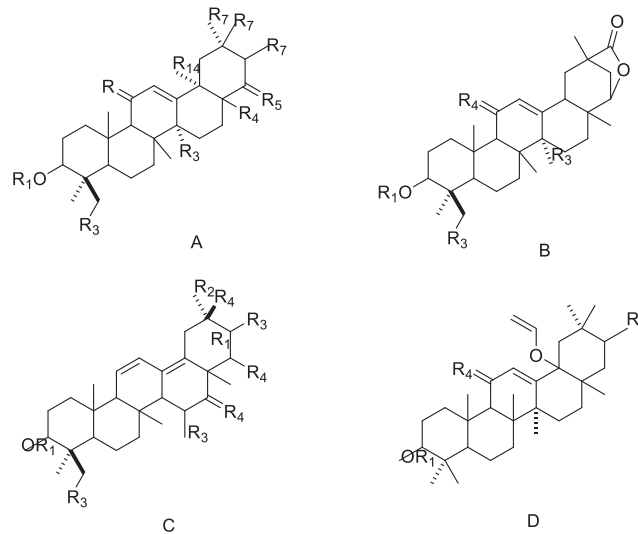


Fig. 3 Mother nucleus structures of common triterpenoids

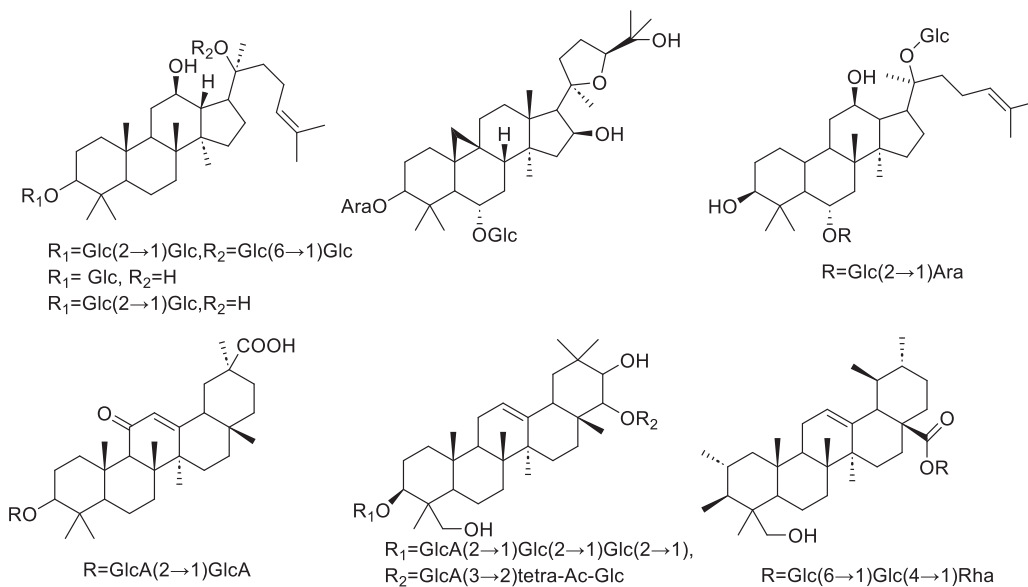


Fig. 4 Chemical structures of triterpenoid saponins

2.2.2 Pharmacological effects of saponins

Glycyrrhetic acid exhibits hepatoprotective

effect in various liver diseases, including nonalcoholic fatty liver disease (NAFLD), liver fibrosis, liver injury, and liver poisoning. Its mechanisms of action involve



inhibiting the excessive activation of macrophage signal transducer and activator of transcription (STAT3)/hypoxia-inducible factor-1 α (HIF-1 α) pathway and improving the excessive apoptosis of liver cells to inhibit the damage of macrophage autophagy flux and the excessive production of inflammatory factors caused by NAFLD, thus exerting the therapeutic effect of NAFLD [19].

Jie et al. used aluminum hydroxide gel and ovalbumin to establish bronchial asthma in mice [20]. They demonstrated that the administration of 10 mg/kg glycyrrhizic acid significantly inhibited alveolar destruction, mucosal epithelial hyperplasia, inflammatory cell infiltration, and other pathological changes, reduced the number of lymphocytes, macrophages, eosinophils, neutrophils, and lowered the levels of IL-1 β , IL-4, IL-5, and TNF- α in lavage fluid. The expression of NF- κ B, Toll-like receptor 4 (TLR4), and high mobility group protein B1 (HMGB1) in lung tissue was significantly decreased. The results confirmed that glycyrrhizic acid inhibited the activation of the NF- κ B signaling pathway by inhibiting the expression of TLR4 and HMGB1 to reduce airway inflammation.

In addition, glycyrrhizic acid has been shown to reduce airway inflammation by preventing the activation of the TGF- β 1/Smad signaling pathway. An experiment of glycyrrhizic acid in the treatment of asthmatic mice showed that the administration of 80 mg/kg glycyrrhizic acid significantly reduced the infiltration of inflammatory cells in the lung tissue of mice and significantly lowered the levels of IL-4, IL-5, IL-13, and IL-17 in the serum of mice. The effect was attributed to the reduction of the inflammatory response by inhibiting the activation of the TGF- β 1/Smad signaling pathway [21].

2.2.3 Anti-hepatoma mechanism of saponins

Glycyrrhizic acid/glycyrrhetic acid plays an active anti-cancer role in various cancers, especially HCC. The effect against HCC involves various mechanisms, including inducing cancer cell apoptosis, inhibiting cancer cell proliferation, invasion, and metastasis, and enhancing the immune microenvironment. The specific anti-hepatocellular carcinoma mechanism of glycyrrhizic acid/glycyrrhetic acid is shown in Table 2.

Table 2 The anti-hepatocellular carcinoma activity of glycyrrhizic acid/glycyrrhetic acid

Triterpenoid saponins	Anti-hepatoma activity	Mechanism of anti-hepatocellular carcinoma	Reference
Glycyrrhetic acid	Inducing apoptosis of hepatocellular carcinoma	Glycyrrhetic acid can reduce the anti-apoptotic proteins Bcl-2 and Bcl-xL by activating human caspase-8 (Caspase-8), triggering the activation of mitochondrial downstream pathways and Caspase-3, and eventually leading to apoptosis of HCC cells	22
	Inhibition of hepatocellular carcinoma metastasis	Glycyrrhetic acid can inhibit the migration and invasion of HCC cells induced by TGF- β through SHP 1 and SHP 2/STAT 3/Snail pathways	23
	Enhance the immune environment	Glycyrrhetic acid can enhance the immune microenvironment in the tumor by blocking the activation of HSCs, and enhance the lethality of T cells to tumor cells by reducing T cell apoptosis and regulating the expression of T cells, and ultimately inhibit the development of HCC cells	24
Glycyrrhizic acid	Inhibition of malignant differentiation of hepatocellular carcinoma	By targeting c-Jun N-terminal kinase 1 (JNK1), Glycyrrhizic acid can inhibit HCC cells' growth by inducing differentiation and inhibiting stemness	25



2.3 Polysaccharides

Glycyrrhiza polysaccharides represent another important bioactive substance in *G. uralensis*, in addition to flavonoids and triterpenoids. H L. Tookey and Quentin Jones [26] isolated a highly viscous seed gel from the seeds of *G. uralensis* Fisch, which was identified as a neutral polysaccharide.

Domestic and foreign scholars have conducted in-depth research on *G. uralensis* polysaccharides

and found that they have antiviral, immune regulatory, and anti-tumor activities. The biological activity of polysaccharides is not only related to their molecular weight but also to their composition and structure. In addition, studies have shown that *G. uralensis* polysaccharides can activate macrophages, lymphocytes, and natural killer (NK) cells, regulate cytokine release, mediate cell signaling pathways, and exert immunomodulatory effects. Fig. 5 below shows the Polysaccharides of *G. uralensis* [25].



Fig. 5 Polysaccharides extractions of *G. uralensis*

2.3.1 Common types of polysaccharides

G. uralensis polysaccharides were extracted using the boiling water method, followed by ethanal precipitation and purification. The resulting water-soluble *G. uralensis* polysaccharides were then obtained by vacuum freeze-drying and designated as GP-HW. GP-HW is mainly composed of polysaccharides, such as fucoidan, rhamnose, arabinose, galactose, glucose, and galacturonic acid

2.3.2 Biological activities of *G. uralensis* polysaccharides

Guo M [27] investigated the antioxidant capacity of polysaccharides extracted from *G. uralensis* residue by pectinase and cellulase, and found that these polysaccharides have scavenging

effects on DPPH, ABTS, and hydroxyl radicals.

Glycyrrhiza polysaccharides can significantly reduce the activities of GOT, GPT, LDH, AKP and TP, lower Alb levels in the serum of Jian carp with acute hepatoma injury, increase the activities of SOD, GPx, CAT, T-AOC in hepatoma tissue, and upregulate the mRNA expression of CYP1A, AHR2 and ARNT2, thereby exerting a hepatoprotective effect [28].

2.3.3 Anti-hepatoma cancer mechanism of polysaccharides

Glycyrrhiza polysaccharide is one of the main effective components of *G. uralensis*, which is mainly composed of rhamnose, glucan, arabinose, and galactose. Monosaccharides in *Glycyrrhiza* polysaccharides and their anti-hepatoma mechanism Table 3 [29].



Table 3 Monosaccharides in *Glycyrrhiza* polysaccharides and their anti-hepatoma mechanism

Name	Abbreviation	Anti-hepatoma mechanism	Reference
L-arabinose	Ara		29
D-glucose	Glc	They can arrest the growth cycle of hepatoma cells in S phase and induce apoptosis, thereby inhibiting the rapid proliferation of H22 hepatoma cells	
D-galactose	Gal		
D-mannose	Man	Man/ CpG-ODN-H22-Lipo was co-modified with mannose loaded with H22 cell lysates and CpG oligodeoxynucleotides. The nanoparticles can effectively target dendritic cells (DCs) <i>in vitro</i> and stimulate their maturation. It can produce efficient anti-tumor effects in liver cancer mice, delay tumor growth, and prolong the survival time of liver cancer mice. It can also reduce the number of MDSC and Treg, increase the frequency of IFN- γ positive cells, promote IgG secretion, inhibit tumor cell proliferation, reduce tumor local vascular density, and promote tumor cell apoptosis.	30

Although *Glycyrrhiza* polysaccharide do not directly act on tumor cells, it plays an anti-hepatoma role by activating the body's immune system, promoting the maturation, differentiation, and proliferation of lymphocytes, macrophages, and natural killer cells, activating the online endothelial system and complement, and promoting the production of various cytokines [31].

Yu has found that dendritic cell (DC) vaccines supplemented with *Glycyrrhiza* polysaccharides induce DC maturation and activation *in vitro* [32]. DC vaccines supplemented with *Glycyrrhiza* polysaccharides have a certain immune therapeutic effect on hepatoma cancer mice, and their anti-hepatoma mechanism involves promoting DC maturation, increasing IL-12 and IFN- γ secretion, mediating cellular immunity, and promoting tumor cell apoptosis. In addition, specific concentrations of *Glycyrrhiza* polysaccharides for tumor treatment have significant in tumor therapy. It can inhibit the occurrence of hepatoma cancer by blocking the PI3K/AKT pathway, inducing cell apoptosis, and suppressing the proliferation of human hepatocellular carcinoma tumor cells [33].

Immature DCs (imDCs) from H22 tumor-bearing mice cultured *in vitro* were divided into a control group, a tumor necrosis factor- α (TNF- α) group, a crude polysaccharide from *Glycyrrhiza inflata* Pall (GiP) group, and a purified polysaccharide (GiP-B1)

group. The cell viability of mature DCs (mDCs) from tumor-bearing mice, the positive expression rates of surface markers (CD11c, CD80, CD86, MHC-II), and the levels of interleukin-12p70 (IL-12p70) and IL-4 were detected. The GiP and GiP-B1 groups could promote the maturation of DC in tumor-bearing mice, effectively stimulate the proliferation of CD4⁺ T cells, and enhance the anti-tumor activity of CD4⁺ CTL. The mechanism is related to the activation of the IL-12/NF- κ B/STAT-4 signaling pathway [34].

3 Conclusion

Hepatoma is a common malignant tumor of the digestive tract. Despite recent therapeutic advances, it remains a leading cause of cancer-related mortality rate worldwide.

This article reviews the pharmacological effects of traditional Chinese medicine *G. uralensis* and analyzes the chemical structures, anti-hepatoma mechanisms, and other pharmacological activities of three key bioactive compounds in *G. uralensis*: flavonoids, triterpenoids, and polysaccharides, thereby highlighting its medicinal value.

Glycyrrhetic acid in flavonoids can alleviate allergic airway inflammation by inhibiting the NF- κ B signaling pathway. Glycyrrhizic acid exhibits anti-HIV activities, demonstrates direct inhibitory effects against hepatitis B virus, and may improve liver



function. Meanwhile, flavonoids from *G. uralensis* Fisch improve the antioxidant, anticoagulant, and anti-retention abilities of low-density lipoprotein in plasma.

In recent years, modern pharmacological studies have revealed that flavonoids in *G. uralensis* are also highly bioactive ingredients. They have a variety of pharmacological activities, such as antibacterial, anti-inflammatory, anti-ulcer, anti-oxidation, anti-diabetes, anti-tumor, and anti-depression effects. With low toxicity and minimal adverse effects, these flavonoids show promising clinical development potential.

Among saponins, fumarin has been shown to regulate blood lipids, inhibit HepG2 cell proliferation and promote its apoptosis, and inhibit renal fibrosis. Astragaloside reduces the invasive ability of MHCC97-H cells, while *Panax notoginseng* saponins effectively lower the blood lipid level of atherosclerotic mice and reduce the inflammatory reaction *in vivo*. Additionally, soyasaponin exerts an anti-colon cancer effect by inducing colon cancer cell apoptosis.

Other studies have shown that GL can inhibit oxidative stress and promote the release of inflammatory cytokines by targeting pkm2, thereby reducing the apoptosis of liver cancer cells and significantly reversing drug-induced liver cancer injury. Meanwhile, triterpenoids from *pennycress chinensis* inhibit the proliferation and growth of hepatoma cells by reducing the activity of hexokinase 2 (hK2).

Glycyrrhiza polysaccharide can significantly reduce acute liver injury and play a role in liver protection. It inhibits the growth of *Haemophilus parasuis* at high concentrations *in vitro*, and enhances the activity of the reticuloendothelial system. It also plays an anti-tumor role by activating the body's immune system, promoting the maturation, differentiation, and proliferation of lymphocytes, macrophages, and natural killer cells, activating the online endothelial system and complement, and promoting the production of various cytokines.

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