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Review

Antitumor Activities of Widely-used Chinese Herb—Licorice

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ABSTRACT

Licorice (the roots of *Glycyrrhiza uralensis*) is widely-used in Chinese herbal compound prescriptions for its functions of nourishing *qi*, alleviating pain, tonifying spleen and stomach, eliminating phlegm, relieving coughing, and harmonizing prescriptions. It contains more than 20 triterpenoids and approximately 300 flavonoids. In recent years, many studies have reported that it possesses various pharmacological activities, such as antitumor, antimicrobial, and antivirus effects. In this paper, the antitumor activity of licorice is deeply summarized. The antitumor active components and the possible antitumor mechanism are analyzed.

Key words

antitumor; flavonoid; glycyrrhetinic acid; *Glycyrrhiza uralensis*; glycyrrhizin; licorice

1. Introduction

Licorice (the roots of *Glycyrrhiza uralensis* Fisch., *G. inflata* Bat., and *G. glabra* L.), belonging to the Leguminosae family, is a dwarf shrub with oval leaflets, white or purplish flower clusters, flat pods, a main taproot, and numerous runners (Figure 1A). It is widespread in China, Spain, Persia, India, Afghanistan, Kazakhstan, Kyrghyzstan, Tajikistan, and Russia. North Inner Mongolia Autonomous Region, Gansu province, and Shanxi province are believed to be authentic regions of licorice in China. The Chinese name of licorice is *gancao*, which means "sweet grass". In *Chinese Pharmacopoeia 2010*, the roots of *G. uralensis*, *G. inflate*, and *G. glabra* are all identified as licorice.

The roots of licorice and its slices (Figure 1B) are widely used in traditional Chinese medicine (TCM) and are honored as the reconciler in Chinese herbal compound prescriptions. The earliest written literature to the use of licorice dated from 2100 BC in *Shennong's Classic of Materia Medica*, the first Chinese dispensary. In this book, licorice was recommended for its life-enhancing properties. Many modern studies have reported that licorice possesses various pharmacological activities, such as antitumor (Tao et al, 2013; Wang et al, 2013; Li et al, 2013), antiviral (Baltinar et al, 2012; Huang et al, 2012), anti-inflammatory (Zhang et al, 2011; Sun et al, 2010; Kim et al, 2010b), and immunity-stimulating activities (Kim et al, 2013b; Hong et al, 2009). Because of its medicinal and economic value, this Chinese herb has received considerable attention throughout the world.

In recent years, cancer has become one of the main reasons for human's death. The conventional therapy for cancer including surgery, chemotherapy, and radiotherapy has many side effects and deficiencies. Therefore it is very important and urgent to find novel effective therapeutic approaches for treatment of cancer. Using natural compounds without side effects on human has attracted the attention of many researchers and has proved to be the single most successful strategy. Lots of researches have proved that various natural components in licorice possess effective antitumor activity. At the same time, as one of the oldest and

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Figure 1 ***G. uralensis*** **(A) and licorice slices (B)**

most frequently-used traditional herbs, it is very significant to study its pharmacological activities for the development and modernization of TCM furtherly. Therefore, in this paper, a comprehensive review about the antitumor activity of licorice is summarized. And we just hope this work can provide a basis for the intensive studies concerned with safe and effective treatment of cancer using licorice.

2. Antitumor active components

Licorice contains a lot of natural active components, including more than 20 triterpenoids such as glycyrrhizin (**1**) and glycyrrhetinic acid (**2**), and approximately 300 flavonoids such as liquiritigenin, isoliquiritigenin (**8**), liquiritin, isoliquiritin, and glycyrrhiza polysaccharides. Up to date, many reports have shown that compounds **1** (Kim et al, 2013a), **2** (Li et al, 2012), prenylflavonoids (Kim et al, 2012), licochalcone A (**3**) (Kim et al, 2010a; Orlikova et al, 2011; Szliszka et al, 2012; Kim et al, 2013c), licochalcone B (**4**) (Wang et al, 2013), licochalcone D (**5**) (Wang et al, 2013), licochalcone E (**6**) (Kwon et al, 2013), glabridin (**7**), compound **8** (Cuendet et al, 2010), dehydroglyasperin C (**9**), dehydroglyasperin D (**10**), and isoangustone A (**11**) (Kim et al, 2012) possess the antitumor activity. The chemical structures of the above main components are listed in Figure 2.

2.1 Triterpenoids

More than 20 triterpenoids have been isolated from licorice, but only compounds **1**, **2**, and 11-deoxy glycyrrhetinic acid (11-DOGA) have been reported to possess the antitumor activity.

Compound **1** was believed to be the marker component in licorice for its antiviral, antitumor, and anti-inflammatory properties. Some researchers found that compound **1** had strong chemopreventive potential against DMH-induced colon carcinogenesis and it also inhibited the infiltration of mast cells (Khan et al, 2013). Zhao et al (2012) investigated the antitumor activity of compound **1** combined with quantum dots (QDs) in hepatocarcinoma cells. The results showed that this compound induced apoptotic response in a time- and dose-dependent manner, which suggested that it had therapeutic potential against cancer (Zhao et al, 2012). Compound **1** also has been reported to induce the apoptosis in leukemia cells through the caspase- and mitochondria-dependent pathways (Chueh et al, 2012).

Compound **2**, 18α- and 18β-glycyrrhetinic acid, is the ramification of compound **1** hydrolyzed by glucuronidase. Modern pharmacological studies suggested that compound 2 was a promising anti-angiogenic therapeutic agent to target the extracellular signal-regulated kinase (ERK) pathway (Li et al, 2012). Kim et al (2013b) showed that compound **2** possessed a better antitumor activity and unchanged pharmacokinetic behavior. Some researchers conjugated dehydrozingerone (DZ) analogs with compound **2**. In an *in vitro* anticancer assay using nine different human tumor cell lines, most of the conjugates showed significant potency, especially in LN-Cap, IA9, and KB cell lines. Results suggested that compound **2** was critical for antitumor activity (Tatsuzaki et al, 2007). Rudkin et al (2002) in his studies found that compound **2** significantly inhibited SCC-13 cell growth ($P < 0.05$) by altering gap junctional intercellular communication (GJIC) and the expression of connexins.

11-DOGA is produced by reduction of compound **2** 11-carbonyl to 11-hydroxyl to reduce the side effects. But the reports about the pharmacological activity of 11-DOGA are very infrequent. Lin et al (2014) found that 11-DOGA obviously inhibited the viabilities of gastric cancer cells in dose- and time-dependent manners. It induced gastric cancer cell apoptosis and cell cycle arrest in G_2 phase. The apoptosis in gastric cancer cells was associated with BID translocation from nucleus to mitochondria.

2.2 Flavonoids

About 300 flavonoids have been isolated from the dried licorice including phenolic acids, flavones, flavans, chalcones, isoflavonoids, etc. Up to date the main flavonoids with the

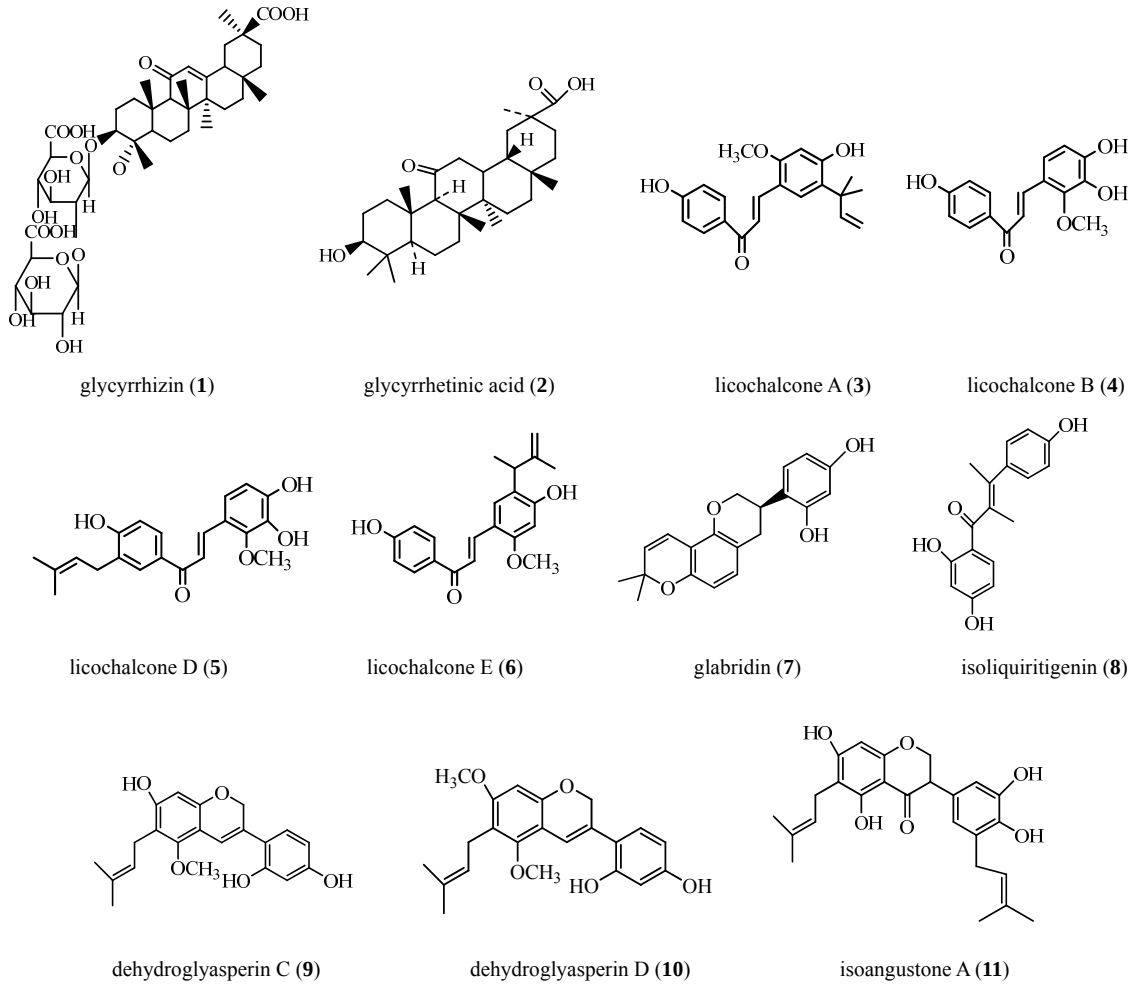

Figure 2 Chemical structures of antitumor components in licorice

antitumor function in licorice are chalcones, an important polyphenolic family, including a large number of naturally occurring molecules. Polyphenolic compounds such as compounds **3**−**6** and **8** have shown to interfere with initiation, promotion, and progression of carcinogenesis, suggesting that they can be used as potential anticancer drugs. (Cuendet et al, 2010; Kim et al, 2010a, Orlikova et al, 2011; Szliszka et al, 2012; Kim et al, 2013c; Wang et al, 2013; Kwon et al, 2013).

Kanazawa et al (2003) investigated the antitumor activity of compound **8** on DU145 and LNCaP prostate cancer cell lines *in vitro*. They found that compound **8** significantly inhibited the proliferation of DU145 and LNCaP cell lines in a dose-dependent and time-dependent manner. They also found that compound **8** enhanced the expression of GADD153 mRNA and protein associated with S and G_2/M cell cycle arrest. These results suggest that compound **8** is a candidate agent for the treatment of prostate cancer, and in which GADD153 may play an important role. Jung et al (2006) indicated that compound **8** induced apoptosis by depolarizing mitochondrial membranes in prostate cancer cells, and they cultured MAT-LyLu (MLL) rats and DU145 human prostate cancer cells with various concentration of compound **8** and found that compound **8** inhibited prostate cancer cell growth by the induction of apoptosis, which could be mediated through an evident disruption of the mitochondrial membrane potential, release of cytochrome c and Smac/Diablo, and activation of caspase-9. Park et al (2009) attempted to investigate the underlying mechanism by which compound **8** induced cell cycle arrest and cytotoxicity in HeLa human cervical cancer cells. Results showed that compound **8** functioned as a topoisomerase II poison and arrest in mitotic metaphase-like stage contributed to its antiproliferative effects. All above suggest that compound **8** is one of the antitumor components in licorice.

Kim et al (2010a) investigated the inhibition of compound **3** on carcinogenesis and metastasis in mouse models. The results showed that compound **3** significantly increased the survival of mouse and inhibited liver metastasis, which suggested that compound **3** had potent antitumor and antimetastatic activity. Szliszka et al (2012) indicated that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced the apoptosis in cancer cells without toxicity to normal cells, which played a very important role in immune surveillance and defense against cancer cells. Chalcones can sensitize cancer cells to TRAIL-induced apoptosis, they augmented the antitumor activity of TRAIL and confirmed their cancer chemopreventive properties. Wang et al (2013) also reported the antitumor activity of compounds

4 and **5**. Yuan et al (2014) reported that exposure of human malignant bladder cancer cell lines T24 or EJ to compound **4** obviously inhibited the cell proliferation and resulted in S phase arrest in T24 or EJ cell lines. Kwon et al (2013) investigated the inhibition of compound **6** on mammary tumor growth and metastasis using animal and cell models. They found that compound **6** inhibited tumor growth and lung metastasis in the mouse model, and it also inhibited cell migration, invasion, and tube formation *in vitro*.

In addition to chalcones, prenylflavonoids including compounds **9**−**11** also showed the strong ferric reducing activities and high free radical scavenging capacity in human hepatoma HepG2 cells, which suggests that it has the potential as antitumor drugs (Kim et al, 2012). Compound **7** showed the effect to inhibit the migration, invasion, and angiogenesis of human non-small cell lung cancer A549 cells and MDA-MB-231 human breast adenocarcinoma cells by suppressing the focal adhesion kinase (FAK)/Rho signaling pathway (Tsai et al, 2011; Hsu et al, 2011).

2.3 Extract from licorice

Some researchers investigated the antitumor activity of licorice extract. Sheela et al (2006) identified an aqueous extract from licorice and found that it inhibited the proliferation of Ehrlich ascites tumor cells *in vivo* and *in vitro*. The extract decreased cytokine VEGF production and neovascularization. It is known that bold vessel plays an important role in solid tumor development and blocking of angiogenesis, and the action of cytokine VEGF is possible in cancer therapy. Therefore the above findings suggest that the extract from licorice may be a potential supplemental source for cancer therapy.

Rafi et al (2002) assessed licorice extract for the effects on anti-apoptotic protein Bcl-2 to identify novel cytotoxic derivatives. The results showed that Bcl-2 phosphorylation and G_2/M cell cycle arrest were induced by licorice extract, which was similarly to clinically used antimicrotubule agents such as paclitaxel. Six compounds were identified in the following HPLC separation experiment, and one of them was responsible for Bcl-2 phosphorylation. The compound was identified as 1-(2,4-dihydroxyphenyl)-3-hydroxyl-3-(4′-hydroxyphenyl)-1-propanone (β-hydroxy-DHP). They believed that the effect on Bcl-2 was structure specific, and Bcl-2 phosphorylation, G_2/M cell cycle arrest, apoptosis, and altered microtubule structure in breast and prostate tumor cells were induced by pure β-hydroxy-DHP.

Lee et al (2013) and Seon et al (2012) also reported that the ethanol extract and the hexane/ethanol extract of roasted licorice had the anti-breast cancer activity by inhibiting cell-cycle progression in DU145 human prostate and 4T1 mouse breast cancer cells.

3. Antitumor activity and possible mechanism for cancer prevention

Up to date, the licorice extract including all above components has shown the significant inhibitory effects on colorectal cancer (Leonetti et al, 2006; Huang et al, 2014), breast cancer (Tatsuzaki et al, 2007; Rossi et al, 2003; Li et al, 2013; Lorusso and Marech, 2013; Lee et al, 2013; Kwon et al, 2013; Wang et al, 2013a; 2013b; Seon et al, 2012; Patel et al, 2011), prostate cancer (Rafi et al, 2002; Kanazawa et al, 2003; Jung et al, 2006; Shetty et al, 2011; Lee et al, 2013; Szliszka et al, 2010), glioblastoma (Li et al, 2014), etc. Among ascites tumor (Sheela et al, 2006), liver cancer (Kim et al, 2008; Zhang et al, 2012; Zhao et al, 2012; Wei et al, 2011; Tsai et al, 2014), gastric cancer (Xiao et al, 2011; Lin et al, 2014; Lee et al, 2011), uterus tumor (Park et al, 2009), melanoma (Song et al, 2013), leukemia (Chueh et al, 2012), bladder cancer (Jiang et al, 2014; Yuan et al, 2014), lung cancer (Tsai et al, 2011; Seo, 2013; Choi et al, 2013), oral cancer (Kim et al, 2014; Lee et al, 2012), and a variety of solid tumors (Yoon et al, 2007; Lee et al, 2008; Jung et al, 2006). When combined with chemotherapy drugs cisplatin, it has also shown an activity to reduce the oxidative stress and decrease its side effects.

3.1 Colorectal cancer

Khan et al (2013) indicated that compound **1** obviously attenuated the level of TNF-α and it also declined the depletion of the mucous layer and the shifting of sialomucin to sulphomucin. Their findings suggested that compound **1** had strong chemopreventive potential against DMH-induced colon carcinogenesis (Khan et al, 2013). Huang et al (2014) tested the antitumor effect of a group of representative licorice-derived compounds and found that compound **11** promptly inhibited the survival of SW480 human colorectal cancer cells by inducing mitochondrial outer membrane in a time- and concentration-dependent pattern. It activated capase-dependent pro-apoptotic signaling and induced significant apoptosis. It strongly inhibited Akt phosphorylation in 5 min. It deserves further investigations as a novel anti-colorectal cancer agent (Huang et al, 2014).

3.2 Breast cancer

In all of the reports about antitumor activity of licorice, the reports about anti-breast cancer are the most. In the past three years, many researchers contributed to this field. Lorusso and Marech (2013) found that low concentration of compound **8** had therapeutic potential in the treatment of aggressive breast cancer. Lee et al (2013) reported that the ethanol extract of fried licorice inhibited breast cancer-mediated bone destruction. Kwon et al (2013) suggested that compound **6** directly inhibited the migration and invasion of both MDA-MB-231 human breast cancer cells and 4T1 cells. Wang et al (2013) suggested that compound **8** also suppressed the migration of MDA-MB-231 cells by inhibiting the upstream signaling pathways, this conclusion was according to Wang et al (2013). Seon et al (2012) found the anti-breast cancer activity of hexane/ethanol extract from *G. uralensis* by inhibiting cell-cycle progression in DU145 human prostate and 4T1 mouse breast cancer cells.

Hsu et al (2011) indicated that compound **7** inhibited migration, invasion, and angiogenesis of MDA-MB-231 human breast adenocarcinoma cells by inhibiting focal adhesion kinase/Rho signaling pathway.

3.3 Prostate cancer

Shetty et al (2011) investigated the anticancer effects and mechanism of compound **2** on the androgen-independent metastatic prostate cancer cell line DU-145 and found that compound **2** inhibited the proliferation and growth of DU-145 cells by inducing apoptosis and prevented the invasion of DU-145 cells on matrigel coated transwells by down-regulation of NF-κB, VEGF, and NMP-9 expression. This study suggests that compound **2** may be a promising anticancer agent for the chemoprevention and treatment of prostate cancer. Lee et al (2013) analyzed the inhibitory effects of compound **11** on the growth of *PTEN*-deleted human prostate cancer cells *in vitro* and *in vivo*. They found that compound **11** was a potent molecular inhibitor of CDK2 and mammalian target of rapamycin (mTOR) for the treatment of prostate cancer. Szliszka et al (2010) examined the cytotoxic and apoptotic effects of chalcones and dihydrochalcones on TRAIL-mediated apoptosis in LNCaP prostate cancer cells and confirmed the important role of chalcones in chemoprevention of prostate cancer.

3.4 Liver cancer

The inhibiting effect of compound **1** on the proliferation of liver cancer cell SMMC-7721 was investigated *in vitro* (Zhang et al, 2012). The results showed that compound **1** inhibited the growth of SMMC-7221 obviously, and the mechanism was related to the up-regulation of p53 expression. Tsai et al (2014) reported that compound **3** inhibited the migratory and invasive abilities of human hepatocellular carcinoma cell SK-Hep-1 and HA22T/VGH in a dose-dependent manner. It was found that compound **3** induced a dose-dependent inhibition of uPA activity and expression, as well as reduced mRNA levels in SK-Hep-1 and HA22T/VGH cells. It was also found to inhibit the expression of phosphor-JNK and phosphor-MKK4 in SK-Hep-1 cells.

3.5 Gastric cancer

Xiao et al (2011) investigated the anticancer effects of seven licorice compounds in MKN-28, MKN-45, and AGS gastric cancer cells and human gastric epithelium immortalized cells. The results showed that compound **3** was the most cytotoxic licorice compound of the seven compounds, and it inhibited gastric cancer cells growth in a dose-dependent manner by blocking cell cycle progression at the G_2/M transition and inducing apoptosis. Lin et al (2014) reported that compound **2** and 11-DOGA effectively inhibited tumor formation of gastric cancer cells in nude mice, they induced gastric cancer cells apoptosis and cell cycle arrest in G_2 phase.

3.6 Bladder cancer

The reports about anti-bladder cancer effects of licorice are relatively infrequent. In the past three years, only compounds **3** and **4** have been reported to inhibit the proliferation of bladder cancer. Researches of Jiang et al (2014) indicated that compound **3** inhibited human bladder cancer T24 proliferation by increasing the levels of intracellular ROS, and resulted in an oxidative stress status in T24 cells, with the IC_{50} value of approximately 55 μmol/L. Yuan et al (2014) investigated the mechanisms by which compound **4** inhibited the proliferation of human bladder cancer cell lines (T24 and EJ) *in vitro* and antitumor activity *in vivo* in MB49 tumor model. Results showed that compound **4** significantly inhibited T24 or EJ cell lines proliferation in a concentration- and time-dependent manner. Consistently, compound **4** also significantly limited the tumorigenicity of MB49 cells. These reports provided support for the use of compound **4** in chemoprevention and bladder cancer therapy.

3.7 Lung cancer

Tsai et al (2011) reported that compound **7** inhibited the migration and invasion of human non-small cell lung cancer A549 cells, and it also decreased A549-mediated angiogenesis by suppressing the FAK/Rho signaling pathway. Compound **7** decreased the active forms of FAK and Src, and enhanced the levels of inactivated phosphorylated Src. The interaction of FAK and Src was decreased, which also blocked Akt activation, resulting in reduced activation of RhoA and myosin light chain phosphorylation. Therefore compound **7** may be a novel anticancer agent for the therapy of lung cancer in three different ways such as inhibition of migration, invasion, and angiogenesis. Choi et al (2013) reported that compound **3** induced the apoptosis in HepG2 human hepatocellular carcinoma cells by endoplasmic reticulum stress via a phospholipase Cγ1-, Ca^{2+}-, and reactive oxygen species (ROS)-dependent pathway.

3.8 Other cancers

The reports about antitumor effects of licorice on the oral cancer, human melanoma, and leukemia are relatively infrequent. The findings of Kim et al (2014) demonstrated that compound **3** induced the apoptosis in KB oral cancer cells by a caspase-dependent FasL-mediated death receptor pathway. Song et al (2013) found that compound **11** inhibited the proliferation of human melanoma cells. It obviously suppressed the cell-cycle progression at G_1 phase and blocked the expression of G_1 phase regulatory proteins, including cyclins D1 and E in SK-MEL-28 human melanoma cell line. Chueh et al (2012) reported that compound **1** induced the apoptosis in leukemia cells. And the possible mechanism of this effect is through the caspase- and mitochondria-dependent pathways.

Based on the above, the licorice extract and many single components including triterpenes such as compounds **1**, **2**,

and 11-DOGA, and flavonoids such as compounds **3**, **4**, and **8**, have shown a significant inhibitory effect on dozens of cancers. Among them, flavonoids, especially chalcones as an important polyphenolic family, play a very important role. The antitumor active components exert their cytotoxic activity multitudinously by increasing the intracellular ROS levels, enhancing the mRNA expression of p53 and GADD153, and inducing the apoptosis and mitochondrial outer membrane. They also inhibit the upstream and focal adhesion kinase/Rho signaling pathway, the activity of topoisomerase II, Ca^{2+}, protein kinase C (PKC), c-Jun N-terminal Kinase 1, the expression of NF-κB, VEGF, NMP-9, uPA, G1 phase regulatory proteins, and the mitochondrial membrane potential. They reduce the depletion of the mucous layer, the shifting of sialomucin to sulphomucin, and the cancer cell proliferation.

4. Discussion

The licorice is widely used in TCM. The demand for this herb is very huge in China. Recent irresponsible excessive exploitation of wild licorice has caused the decrease and extinction of wild licorice resources. The Chinese government has imposed restrictions on the collection of wild licorice plants. A systematic study of pharmacological activities is helpful for the effective use and conservation of licorice. In this paper, one of the pharmacological activities of licorice, the antitumor activity, is summarized in detail.

A large and growing body of evidence has shown that licorice may be an effective herbal medicine for chemoprevention. Many single components including triterpenes and flavonoids have shown a significant inhibitory effect on dozens of cancers. It is time to develop a human clinical trial under carefully controlled conditions with a high-risk population. Many researches also showed that the biological activities of licorice are due to the effects of several licorice components combination, and the licorice extract seemed more effective than a specific active ingredient on some diseases. And we suggest this is an interesting direction of research.

In some previous reports, the clinical safety of compounds **1** and **2** has been evaluated (Shibata et al, 2000; Olukoga and Donaldson, 2000; Vogel et al, 1992). It is true that some people are sensitive to compounds **1** or **2**, but when patients with previous breast cancer received 0.02−0.04 mmol/kg (body weight) without evidence of significant toxicity, there was apparently a great individual variation in the susceptibility to compound **2**. It is necessary to develop a special strategy to evaluate the possible adverse effects of licorice triterpenes. The evaluations about other components of licorice are very infrequent. The antitumor activity of flavonoid, especially chalcone is deserved to confirm. Looking for new triterpenes with a skeleton similar to compound **1** without side-effects is another very interesting future direction of research.

The combination or prescription of several drugs on the basis of their synergistic activity is a new strategy for modern cancer prevention. In TCM, using a single herb is very rare for disease treatment. So the combination of licorice and other herbs possibly has a significant effect on cancer treatment.

This paper indicates that licorice represents interesting and important hits for antitumor drug discovery and development. And we just hope this work can provide a basis for further studies concerned with fully revealing the antitumor mechanism of licorice and safe use of licorice.

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