

A Systematic Review of the Anticancer Properties of Compounds Isolated from Licorice (Gancao)

Authors

Zheng-Hai Tang¹, Ting Li¹, Yun-Guang Tong², Xiao-Jia Chen¹, Xiu-Ping Chen¹, Yi-Tao Wang¹, Jin-Jian Lu¹

Affiliations

¹ State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macao, China

² Department of Medicine, Cedars-Sinai Medical Center, University of California at Los Angeles School of Medicine, Los Angeles, CA, USA

Key words

- *Glycyrrhiza glabra*
- Leguminosae
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- flavonoids

Abstract

▼
Licorice (Gancao in Chinese) has been used worldwide as a botanical source in medicine and as a sweetening agent in food products for thousands of years. Triterpene saponins and flavonoids are its main ingredients that exhibit a variety of biological activities, including hepatoprotective, antiulcer, anti-inflammatory, antiviral and anticancer effects among others. This review attempts to summarize the current knowledge on the anticancer properties and mechanisms of the compounds isolated from licorice and obtain new insights for further research and development of licorice. A broad spectrum of *in vitro* and *in vivo* studies have recently demonstrated that the mixed extracts and purified compounds from licorice exhibit evident anticancer properties by inhibition of proliferation, induction of cell cycle arrest, apoptosis, autophagy, differentiation, suppression of metastasis, angiogenesis, and sensitization of chemotherapy or radiotherapy. A combined treatment of licorice compounds and clinical chemotherapy drugs remarkably enhances anticancer effects and reduces the side effects of chemotherapeutics. Furthermore, glycyrrhizic acid and glycyrrhetic acid in licorice have been indicated to present obvious liver-targeting effects in targeted drug delivery systems for hepatocellular carcinoma treatment.

Abbreviations

▼
20-HETE: 20-hydroxyeicosatetraenoic acid
70% EEL: 70% ethanol (volume, CH₃CH₂OH: H₂O = 70:30) extracts of licorice
70% MEL: 70% methanol (volume, CH₃OH: H₂O = 70:30) extracts of licorice
80% EEL: 80% ethanol (volume, CH₃CH₂OH: H₂O = 80:20) extracts of licorice
AOM: azoxymethane

AP-1: activator protein 1
β-hydroxy-DHP: 1-(2,4-dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl) 1-propanone
CDK: cyclin-dependent kinase
COX-2: cyclooxygenases-2
CP: cyclophosphamide
CYP19: cytochrome P450 19
DMBA: dimethylbenz[a]anthracene
DR4: death receptor 4
DSS: dextran sulfate sodium
EAT: Ehrlich ascites tumor
ER: endoplasmic reticulum
ERK: extracellular regulated protein kinases
FasL: Fas ligand
GA: glycyrrhetic acid
GBD: glabridin
GL: glycyrrhizic acid
GLY: glycyrol
GSH: glutathione hormone
HCC: hepatocellular carcinoma
HEEL: hexane/ethanol extraction of licorice
HMGB1: high-mobility group box 1
HUVECs: human umbilical vein endothelial cells
i. g.: intragastric administration
i. m.: intramuscular injection
i. p.: intraperitoneal injection
i. t.: intratumor injection
i. v.: intravenous injection
IAA: isoangustone A
ICAM: intercellular adhesion molecule
IL: interleukin
ISLG: isoliquiritigenin
ISLT: isoliquiritin
JNK: c-Jun N-terminal kinase
LCA: licochalcone A
LCB: licochalcone B
LCE: licochalcone E
LCM: licocoumarone
LG: liquiritigenin
LRD: licoricidin
LT: liquiritin

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Correspondence

Dr. Jin-jian Lu
State Key Laboratory of Quality Research in Chinese Medicine
Institute of Chinese Medical Sciences
University of Macau
Avenida da Universidade
Taipa, Macao 999078
China
Phone: + 853 88224674
Fax: + 853 28841358
jinjianlu@umac.mo

MMP:	mitochondrial membrane potential	PKC:	protein kinase C
MMP-2:	matrix metalloproteinase-2	ROS:	reactive oxygen species
MMP-9:	matrix metalloproteinase-9	s.c.:	subcutaneous injection
mTOR:	mammalian target of rapamycin	STAT3:	signal transducer and activator of transcription 3
MVD:	microvessel density	TCM:	traditional Chinese medicine
NAT:	N-acetyltransferase	TDDS:	target drug delivery systems
NF- κ B:	nuclear factor- κ B	TNF- α :	tumor necrosis factor- α
NSCLC:	non small cell lung carcinoma	Top I:	topoisomerase I
ODC:	ornithine decarboxylase	TPA:	12-O-tetradecanoylphorbol 13-acetate
p.o.:	<i>per os</i>	uPA:	urokinase-type plasminogen activator
PARP:	poly(ADP-ribose)-polymerase	UVB:	ultraviolet radiation b
PCNA:	proliferative cell nuclear antigen	VCAM:	vascular cell adhesion molecule
PGE ₂ :	prostaglandin E ₂	VEGF:	vascular endothelial growth factor
PI3 K:	phosphoinositide-3 kinase	VEGFR-2:	vascular endothelial growth factor kinase receptor-2

Introduction

Licorice (*Glycyrrhiza* in botany, Gancao in Chinese), a perennial herb that extensively grows wild in China, Japan, Russia, Spain, and India, is one of the best-known and most frequently used herbal medicines worldwide [1]. In China, licorice was first recorded in Sheng Nong's herbal classic (Sheng Nong Ben Cao Jing in Chinese), the earliest TCM code, and belongs to "top-grade" herbs (herbs with the lowest side effects or nontoxic usefulness for health care) [2]. Licorice has been subsequently recorded in numerous classic TCM writings and famous prescriptions, such as in one of the earliest TCM books, Treatise on Exogenous Febrile Disease (Shang Han Lun in Chinese), and 70% of prescriptions have included licorice [3]. In Japan, GL (one of the main compounds from licorice) preparation (Stronger Neo-Minophagen C) has been clinically used as an antihepatitis and antiallergic agent for more than 60 years [4]. Licorice is traditionally used to improve health, lengthen life span, and cure coughs or stomachaches [5].

At present, more than 400 compounds have been isolated from licorice and demonstrated a variety of pharmacological activities, such as anticancer, anti-inflammatory, antiviral, hepatoprotective, expectorant, and memory enhancing activity [6–9]. The triterpene saponins of licorice, especially GL (about 1.84% to 9.82% of licorice, depending on the sources and methods of extraction), are the major constituents and bioactive ingredients of licorice, and more than 18 saponins have been isolated from licorice [9–12]. Flavonoids (about 1.78% to 4.82% of licorice, depending on the sources and methods of extraction) are the other main bioactive compounds from licorice, and more than 300 flavonoid compounds have been identified, including LT, ISLT, LG, ISLG, LCA, and GBD [9, 11, 13, 14]. In the 2010 edition of the Chinese Pharmacopoeia, GL and LT are selected as the biomarkers for licorice, and GL and LT content should exceed 2% and 0.5%, respectively [15]. In addition, a series of polyphenols and polysaccharides obtained from licorice have indicated remarkable bioactivity, such as anticancer and immunopotentiating effects [16–18]. The pharmacological effects of licorice, including anti-inflammatory, antiviral, and hepatoprotective effects, were documented in 2008 [6]. However, in recent years, more compounds, especially flavonoids, have been isolated and identified from licorice and have been demonstrated to possess evident anticancer properties both *in vitro* and *in vivo*. Therefore, reviewing and summarizing the anticancer effects and mechanisms of mixtures and purified compounds from licorice is necessary to better understand the

anticancer properties of licorice and to provide data that may be useful for future anticancer research on this herb.

Mixtures from Licorice

The mixed extracts of licorice can generally be acquired using aqueous or organic solutions. Aqueous solutions are mainly used to isolate crude extracts, whereas organic solvents, including methanol, ethanol, trichloromethane, and hexane, are utilized to obtain purified compounds. At present, several mixtures from licorice have been demonstrated to possess anticancer properties both *in vitro* and *in vivo* by inhibition of proliferation and induction of cell cycle arrest, apoptosis, and autophagy.

Inhibition of proliferation

Trichloromethane, hexane, ethyl acetate, and 70% MEL inhibit the proliferation of human breast cancer cell MCF7 in concentration- and time-dependent manners [19]. The 70% MEL also inhibits the cell proliferation of the hepatocellular carcinoma cell HepG2 [20] and human monoblastic leukemia cell U-937 [21] in a concentration-dependent manner. The 70% EEL shows concentration- and time-dependent cytotoxicity to human breast cancer cell MDA-MB-231 [22] and human prostate cancer cell LNCaP [23]. In human prostate cancer cell DU 145 and human colon cancer cell HT-29, the ethanol extracts of roasted licorice exhibit considerably higher cytotoxicity than that of the ethanol extract of unroasted licorice, and the active compound of the ethanol extracts of roasted licorice is LCA [24]. Besides, the purified fraction (diethyl ether, chloroform, and water fraction from the EEL) exhibits higher proliferative inhibition on MCF7, human stomach adenocarcinoma cell AGS, and human hepatocellular carcinoma cell Hep3B and less cytotoxicity to human normal hepatic cell WRL-68 compared with the EEL [25].

Induction of cell cycle arrest

The 80% EEL induces G1 cell cycle arrest in MCF7 by increasing the expression of p53 and p21 proteins and decreasing cyclin E and CDK2 protein expressions [26]. The HEEL also induces G1 phase arrest by the reduction of the protein expression of cyclin A, cyclin D1, CDK2, and CDK4 in DU 145 and murine mammary cancer cell 4T1. A further study also indicates that the active compound in HEEL may be IAA [27]. In addition, G2/M cell cycle arrest in LNCaP and human breast cancer T47D cells is observed with 70% EEL and EEL treatment, respectively [23, 28].

Induction of apoptosis

The EEL induces apoptosis in MCF7 cells with the activation of Bax, PARP, and caspase-7 proteins as well as the inhibition of the expression or induction of the phosphorylation of the Bcl-2 protein [26,28]. In LNCaP cells, the 70% EEL (228 µg/mL) stimulates apoptotic effects by activation of the caspase-dependent pathway and dissipation of the MMP, while pretreatment with Z-VAD-FMK completely abolishes licorice-induced apoptotic cell death [23]. HEEL also excites apoptosis in DU 145 and 4T1 cells by activating caspase-9, caspase-8, caspase-7, caspase-3, and PARP, upregulating Fas and DR4, and inducing the dissipation of the MMP and the release of cytochrome c [27,29]. In addition, the 70% MEL induces apoptosis in U-937 cells [21].

Induction of autophagy

The treatment of 228 µg/mL 70% EEL for 24 h in LNCaP cells induces autophagy-related cell death by the downregulation of the Bcl-2 protein and inhibition of the mTOR pathway [23].

Inhibition of angiogenesis

The 50% ethanol (volume, CH₃CH₂OH:H₂O = 50:50) extracts of licorice inhibits angiogenesis by reducing the VEGF level and microvessel density count in the peritoneum of Ehrlich ascites tumor cells in EAT-bearing mice [30].

In vivo anticancer effects

In 4 T1-injected female BALB/c mice, the addition of HEEL (5 mg/kg) to drinking water inhibits the tumor volumes by reducing the expression of CDK2, CDK4, and PCNA proteins, without affecting the body weight of the mice [27]. I.p. of MEL (500 µg) or aqueous extracts of licorice (600 µg) for 7 d inhibits the growth of EAT cells and the formation of ascitic fluid in EAT-bearing mice by angiogenesis inhibition [30]. In MDA-MB-231 xenograft Balb/c mice, p.o. of 70% EEL (2 mg/kg, once per day for 5 consecutive days, followed by a weekly administration for 44 d) blocks tumor progression [22]. In addition, in mouse colon carcinoma cell CT26 xenograft BALB/c mice, treatment of 0.5, 1, and 2 mg/kg of the 95% ethanol (volume, CH₃CH₂OH:H₂O = 95:5) extracts of licorice (95% EEL) inhibits tumor volume by 38%, 57%, and 71%, respectively. The combined treatment of 2 mg/kg 95% EEL and cisplatin evidently decreases cisplatin-induced nephrotoxicity and hepatotoxicity by inhibiting of cisplatin-induced oxidative stress [31].

Purified Compounds from Licorice

A panel of purified anticancer compounds has been isolated and identified from licorice (● Fig. 1), including triterpenoids GL and GA, flavonoids ISLG, LCA, LCB, LCE, LG, IAA, GBD, ISLT, and LRD, phenolic LCM, GLY, and β-hydroxy-DHP. Among these substances, GA, ISLG, and LCA have been extensively studied and present evident anticancer effects by inhibiting cancer cell proliferation, inducing cell cycle arrest, apoptosis, and autophagy, and inhibiting metastasis and angiogenesis.

Triterpenoids

Triterpenoids are the main ingredients and characteristic compounds in licorice. More than 18 triterpenoid saponins, such as GL, GA, licorice-saponin A3, and licorice-saponin L3, have been isolated [9]. At present, GL and its aglycone GA have been widely demonstrated to present evident anticancer effects both *in vitro* and *in vivo*. In addition, GL and GA have been utilized as hepatic

targeting ligands in targeted drug delivery systems for HCC treatment because of highly expressed target binding sites in liver cells [32,33].

Glycyrrhizic acid

Inhibition of proliferation: GL (100 µM) exhibits no or slight cytotoxicity on several types of cancer cells, such as melanoma cells SK-MEL-2, SK-MEL-28, and B16 as well as human cervix tumor cell SiHa [34–36]. Meanwhile, the inhibitory effect of GL on cancer cells emerges at relatively higher concentrations. GL inhibits mouse leukemia cell WEHI-3 and human leukemia cell TF-1 in a dose-dependent manner [37,38]. The treatment of HepG2 with GL for 24 h exhibits an IC₅₀ of more than 1.2 mM [39]. In addition, the proliferation and growth of human lung cancer cell A549 [40], glioblastoma cell U251 [41], and human prostate cancer cells LNCaP [42] and DU 145 [42] are inhibited by GL with IC₅₀s at the millimole level.

Induction of cell cycle arrest: The 200 µM to 400 µM GL concentration range induces dose- and time-dependent G0/G1 phase arrest in WEHI-3 cells [37].

Induction of apoptosis: GL triggers apoptotic cell death in various cancer cells, such as WEHI-3 [37], LNCaP and DU 145 [42], MCF7 [43], U251 [41], and A549 [40]. This activation may be mediated by the promotion of ROS production [37], reduction of MMP [37], deactivation of the NF-κB pathway [41], and induction of DNA damage [37,42].

Inhibition of metastasis: In a melanoma cell B16F10-implanted mouse model, GL inhibited pulmonary metastasis by regulating tumor-associated T helper type 2 cells [44]. GL also inhibited human leukemia cell TF-1 migration via inhibition of the Akt/mTOR/STAT3 cascade [38].

Inhibition of angiogenesis: A previous study indicated that 82 µg/mL GL increases tube formation, which is critical for angiogenesis [45]. However, recent studies suggest that the “no cytotoxicity concentration” of GL (100 µM) decreases the angiogenic activity of bladder cancer cell ECV304 by decreasing motility, invasion, and tube-forming properties by blocking ROS generation and extracellular ERK activation [46].

Chemosensitization or radiosensitization: GL reverses cisplatin resistance in the hepatocellular carcinoma cell Huh7 by inhibiting cisplatin efflux from the cells [47]. Pretreatment of 30 µM of GL enhances UVB-induced apoptosis in SK-MEL-28 cells [35]. Furthermore, GL is identified as an inhibitor of Ku86, one of the key proteins in reducing radiotherapy efficacy by repairing DNA breaks on cancer cells [48]. In SKH-1 mice, UVB-induced cancer formation and apoptotic sunburn cells can be blocked by pretreatment with GL [49].

Others: The overexpression of the HMGB1 protein often results in cancer cell proliferation and motility as well as angiogenesis [50–53]. GL can directly inhibit the DNA binding activity of HMGB1 to decrease tumor proliferation [52,54,55]. GL inhibits proliferation and induces apoptosis in A549 cells (TxAS protein overexpression) by inhibiting TxAS expression and activity. However, the antiproliferative effect of GL disappears with TxAS protein knock-down. Interestingly, GL cannot inhibit lung cancer cell NCI-H23 proliferation (TxAS protein low expression). When NCI-H23 cells are transfected with TxAS cDNA, GL completely suppresses the growth of NCI-H23 cells [40]. In addition, GL inhibits the activity of NAT and DNA-2-aminouorene adduct formation in colon cancer cell COLO 205 [56]. This combination of NAT and DNA-2-aminouorene is associated with the increased risk of several types of cancer [57–59]. Several hepatic TDDS utilizing GL as a hepatic lig-

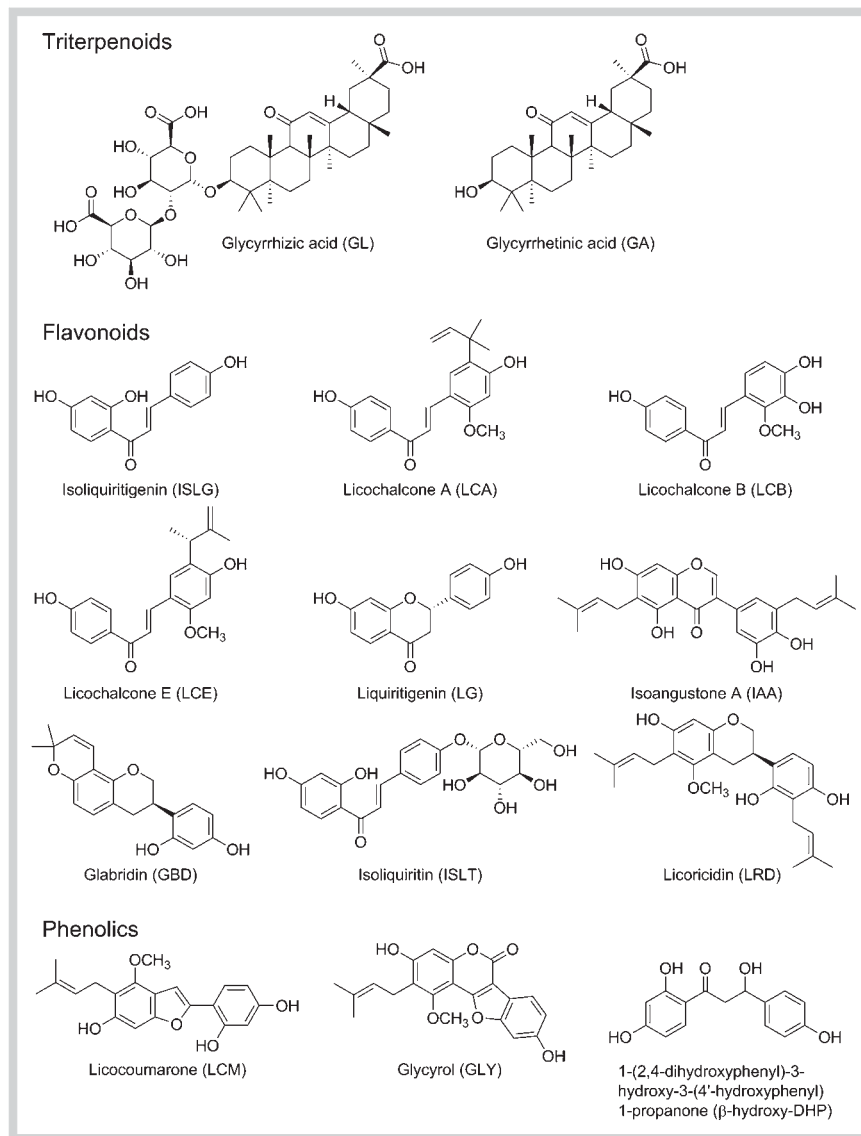


Fig. 1 Chemical structures of the anticancer compounds isolated from licorice.

and have been developed, such as GL modified O-carboxymethyl chitosan nanoparticle loaded paclitaxel [60], GL modified N-caproyl chitosan nanoparticles [61], and GL modified chitosan nanoparticles [62]. These nanoparticles preferentially accumulate in HCC cells to enhance anti-HCC effects and to reduce the side effects of chemotherapeutics.

In vivo anticancer effects: Several *in vivo* anticancer research studies on GL have been conducted. In an ovariectomized mouse model, GL (p.o.) suppressed M-methyl-N-nitrosourea solution-induced endometrial cancer progress by inhibiting the expression of COX-2, TNF- α , and IL-1 [63]. In Renca cell-implanted BALB/c mice, GL (p.o., 50 mg/kg, once a day for a week) suppressed about 35% of tumor weight and 60% of tumor volume by reducing angiogenesis [46]. In acetate-induced hyperproliferative activity in Wistar rats, GL (p.o., 300 mg/kg, 5 d), before acetate i.p., significantly inhibited tumor promotion by decreasing ODC activity and DNA synthesis [64]. In A549 tumor xenograft nude mice, GL (i.p., 50 mg/kg) also inhibited tumor growth by inhibition of TxA2 expression [40]. In addition, p.o. of GL in drinking water to SENCAR mice inhibited TPA- and DMBA-induced skin tumorigenesis by decreasing ODC activity and DNA synthesis [65,66]. I.m. of BALB/c mice with GL (2 mg) also decreased

the diethylnitrosamine-induced incidence rate of hepatocellular carcinoma from 64% to 21% [67].

Glycyrrhetic acid

Inhibition of proliferation: GA inhibits cell proliferation in a series of cancer cells, including human cervix cancer cell SiHa [34], melanoma cells 518A2 [68], SK-MEL-2, and SK-MEL-28 [35], HCC cell HepG2 [39], human epithelial ovarian cancer cells OVCAR-3 and SK-OV-3 [69,70], gastric cancer cells BGC823 and SGC7901 [71], human breast cancer cell MCF7 [68,72], lung cancer cells NCI-H460 and A549 [68,73], human pharynx cancer cell FaDu, human submandibular cancer cell A-253, human skin cancer cell A-431, anaplastic thyroid cancer cells 8505 C and SW1736 [68], human prostate cancer cells LNCaP and DU-145 [74], colon cancer cells DLD-1, HCT 116, HCT-8, HT-29, and SW480 [68,75], human bladder cancer cell NTUB1 [76], and human promyelocytic leukemia cell HL-60 [77]. In addition, GA exhibits the most tumor-selective toxicity among other clinical drugs (adriamycin, cisplatin, cytarabine, etoposide, fluorouracil, and manumycin A) through GSH downregulation [78–80]. The same GA concentration also inhibits the proliferation of MCF7 cells without affecting immortalized normal mammary epithelial cells [81].

Induction of cell cycle arrest: GA obviously induces G1 phase arrest in HepG2, A549, and NCI-H460 cells in a concentration-dependent manner [39,82]. In BGC823 and SGC7901 cells, GA triggers G2 phase arrest in concentration- and time-dependent manners by upregulation of p21 and downregulation of cdc2 and cyclin B1 expression [71].

Induction of apoptosis: GA induces apoptosis in a panel of cancer cells, including HepG2 [39,83], SK-MEL-2 [35], DU 145 [74], SiHa [34], stomach cancer cell KATO III [71,84], HL-60 [77,84], NCI-H460 and A549 [68,73], BGC823 and SGC7901 [71], and MCF7 [72,81] with the activation of caspase-8 [39], caspase-9 [39,73,81], caspase-3 [34,73], PARP [41,73], Bax [81], and Bim [81] as well as the inhibition of the protein expression of Bcl-xL [39,73], Bcl-2 [39,73,81], Bid [71], and connexin 32 [39]. The induction of MMP dysfunction [34,81] and DNA damage [39,81], increase of the intracellular Ca²⁺ concentration [72] and cytochrome c release [34,71,81], upregulation of ROS generation, depletion of glutathione [34], and reduction of Akt kinase activity [81] all participate in GA-induced apoptosis. GA also induces apoptosis by suppressing the pro-survival mediator phosphorylation of PKC α/β and activating the JNK kinase. Pretreatment of the PKC promoter or JNK inhibitor reverses GA-induced apoptosis [73]. Furthermore, GA potentiates the Hsp90 inhibitor- and trichostatin A-induced apoptotic effect by activation of the caspase-8- and Bid-dependent pathways [69,70].

Induction of autophagy: GA obviously induces autophagy in a concentration-dependent manner by activation of the ERK pathway in HepG2 and Hep3B cells, and inhibition of autophagy by chloroquine or bafilomycin A1 increases the GA-induced apoptosis, suggesting that the GA-stimulated autophagy might decrease its anticancer effects [83].

Inhibition of metastasis: GA concentration dependently inhibits the metastasis of LNCaP cells by downregulating MMP-9 and VEGF via inhibition of PI3K/Akt-mediated NF- κ B activity [85]. GA also inhibits tube formation of HUVECs and invasion of DU-145 cells by decreasing the expression of NF- κ B, VEGF, and MMP-9 [74]. In breast cancer cells, GA inhibits MMP-2 and MMP-9 expression via breaking p38-AP1 signaling [86].

Chemosensitization or radiosensitization: Combined treatment of 50 μ M GA evidently enhances the antiproliferative and proapoptotic effects of mitomycin c, doxorubicin, and camptothecin in SiHa cells [34]. The proliferative inhibition of vinblastine in P-glycoprotein-overexpressing human carcinoma KB-C2 and doxorubicin in KB/MDR cells are also enhanced with the combined treatment of GA [87].

Others: GA induces anoikis-like cell death and disturbs cytoskeletal protein expression in central nervous system tumorigenic cells [88]. In NSCLC cells, GA inhibits cell proliferation by inhibiting the activity of the thromboxane synthase protein, which is overexpressed in NSCLC and carries a poor prognosis [89]. GA also reverses hepatic stellate cell-mediated immunosuppression by enhancing the ability of T cells to attack tumor cells in the tumor microenvironment [90]. In addition, GA inhibits the aldo-keto reductase 1B10, which has been recently identified as a tumor marker in several types of cancers [91]. Furthermore, GA has been widely utilized as a liver ligand in HCC TDDS to enhance the anticancer effects and to reduce the side effects of chemotherapeutic drug-loaded nanoparticles [92–94].

In vivo anticancer effects: In an SGC7901 xenograft nude mice model, subcutaneous injection of GA (30 mg/kg) inhibited the average weight of the subcutaneous tumor from 2.8 g to 0.7 g and induced apoptosis by decreasing the expression of Bid [71].

In DMBA- and TPA-induced skin tumors in SENCAR mice, GA pretreatment resulted in the protection against tumor initiation and promotion [95]. In hepatoma cell H22-bearing mice, an i.v. of GA-modified alginate nanoparticle-loaded doxorubicin (7 mg/kg doxorubicin, once every 4 d for 16 d) evidently inhibited tumor growth as evidenced by the tumor weight inhibitory rate and the mean tumor volume of about 76.6% and 2.9 mm³ in the GA-modified alginate nanoparticle loaded doxorubicin group, respectively, compared with 52.6% and 9.2 mm³ in the doxorubicin group. In addition, the side effects of doxorubicin are obviously decreased after being loaded with GA-modified alginate nanoparticles [96].

Flavonoids

The flavonoids of licorice include various types, such as flavanones or flavanones (LG, LT, and licoflavanone), chalcones (ISLG, ISLT, LCA, LCB, and LCE), isoflavans (IAA, GBD, and LRD), and isoflavones (glabrone, licoisoflavone A, and gancaonin H) [9]. These flavonoids present significant anticancer, antioxidative, antimicrobial, and antiviral effects among others. [6,97,98]. According to this study, chalcones, ISLG, LCA, and IAA, in particular, are licorice anticancer compounds that act mainly by the induction of cell cycle arrest, apoptosis, and autophagy as well as the inhibition of metastasis and angiogenesis.

Isoliquiritigenin

Inhibition of proliferation: ISLG inhibits cell proliferation in human cervical cancer cells C-33 A, Ca Ski, HeLa, SiHa, and U14 [99–102], gastric cancer cells AGS, MKN-28, MKN-45, and SGC7901 [103], colon cancer cells COLO 320DM, Colon 26, CT26, HCT 116, HT-29, and RCN-9 [104–106], prostate cancer cells C4-2, DU 145, and LNCaP [107–109], myeloma cells ARH-77, CZ-1, MPC-11, RPMI 8226, SP2/0, and U266 [110], breast cancer cells MCF7 and MDA-MB-231 [111,112], human promyelocytic leukemia cell HL-60 [113], lung cancer cells A549, HCC827, NCI-H1650, and NCI-H1975 [114–116], human epithelial ovarian cancer cell SK-OV-3 [117], human glioma cell U-87 [118]; mouse renal cancer cell Renca [119], HCC cell HepG2 [120–122], and mouse melanoma cell B16-F0 [123] in time- and dose-dependent manners. Furthermore, ISLG presents lower toxicity to normal cells (gingival fibroblast cell HGF, periodontal ligament fibroblast cell HPLF, normal myometrium cells, and normal intestinal epithelial tissue cell IEC-6) [108,109,124,125] than to cancer cells (oral cancer cells HSC-2 and HSC-3, submandibular gland cancer cells HSG and HL-60, and uterine leiomyoma cells), indicating that ISLG may be a promising lead compound for cancer therapy.

Induction of cell cycle arrest: The phase of cell cycle arrest induced by ISLG varies among the cancer cells and treatment time. ISLG induces cell cycle arrest in U266 [110], C-33 A, Ca Ski, HeLa, SiHa, U14 [99,101,126], HCT 116 [104], A549 [114], HepG2 [122], uterine leiomyoma cells [125], and oral squamous cell carcinoma [127]. ISLG induces G2/M phase arrest by decreasing the protein expression of CDK2, cyclin B, cyclin A, cdc2, cdc25 C, and human papillomavirus type 16 E6 [99,101,104,125], activating the Rb, p53, p21, and ataxia telangiectasia mutated proteins [99,101,114,115,122,125,126], inducing DNA damage [126], and inhibiting the activity of topoisomerase II [99]. In U-87 cells, ISLG induces both S and G2 phase arrest by inducing the expression of p21 and p27 [118]. In MPC-11 cells, ISLG hinders the G1 phase [110]. Interestingly, the cell phase arrest by ISLG in DU 145 is time-dependent. Within 2 h of treatment, ISLG induces G1 arrest by decreasing the protein expression of cyclin D1, cyclin E, and

CDK 4 and increasing p27 expression [128], whereas ISLG induces S and G2/M arrest within 4 h to 24 h treatment by increasing the expression of cyclin B and phosphorylation of cdc2 [107, 128]. The ISLG-induced cell cycle arrest in A549 is controversial. Li et al. reported that ISLG induces G2/M arrest in A549 in concentration- (15, 30, and 40 μM after 24 h treatment) and time-dependent (40 μM after 4, 8, 16, and 24 h treatment) manners by upregulating p21 mRNA [114]. However, Hsu et al. indicated that ISLG treatment (20 and 40 μM) for 24 h induces G1 phase arrest with the increasing protein expression of p53 and p21 [115].

Induction of apoptosis: ISLG induces apoptosis in various cancer cells, such as HT-29, HCT 116, COLO 320DM, and Colon 26 [104, 106, 129, 130], MCF7 and MDA-MB-231 [111, 131], HepG2 [120–122], HeLa [99–101], Ca Ski, SiHa, C-33 A [101], U266 [110], DU 145 [109], SK-OV-3 [117], HL-60 [124], A549, HCC827, NCI-H1650, and NCI-H1975 [115, 116], U-87 [118], adenoid cystic cancer cells ACC-2 and ACC-M [132], gastric cancer cell MGC-803 [133], and uterine leiomyoma cells [125] by activating caspase-9 [99, 101, 109, 111, 124, 130], caspase-8 [101, 109, 122, 124], caspase-7 [109], caspase-3 [101, 104, 106, 109, 111, 124, 125, 132], PARP [100, 101, 104, 109, 111, 125, 132], Bax [99, 101, 109, 120, 122, 132, 134], Bak [99], Fas [109, 115, 122, 125], FasL [109], and Bid [109] as well as inhibiting Bad [111], Bcl-xL [99, 104, 110, 111, 121, 134], and Bcl-2 [99, 101, 104, 110, 120, 121, 125, 132] activities.

Potential mechanisms may involve downregulating the arachidonic acid metabolic network by inhibiting the mRNA expression of multiple key enzymes, such as phospholipase A2, COX-2, and cytochrome P450 4A [111], deactivating the PI3 K/Akt and NF- κ B pathways [111, 121], increasing the protein expression of p53 and p21 [101, 122], increasing intracellular ROS production [100, 117, 120], triggering ER stress by the upregulation of ER stress-related molecules α -subunit of eukaryotic initiation factor 2, 78 kDa glucose-regulated protein, X-box binding protein 1 expression, and cleavage of activating transcription factor 6 α [117], thus enhancing the concentration of intracellular Ca^{2+} [133], inducing MMP dysfunction [99, 101, 109, 133], and increasing the release of mitochondrial cytochrome c [101, 109, 111]. In addition, the decreased protein expression of human papillomavirus type 16 E6 and cellular inhibitors of apoptosis protein expression [101, 121] and the enhanced release of smac/diablo from the mitochondria into the cytoplasm [109] as well as inhibited glucose transmembrane transport [134] are also observed in ISLG-induced apoptosis.

Induction of autophagy: Both *in vitro* and *in vivo* studies have demonstrated that ISLG activates autophagy by suppressing the mTOR pathway in adenoid cystic carcinoma cells, and the inhibition of autophagy obviously decreases the ISLG-induced cell death [132].

Induction of differentiation: In HL-60 cells, 10 $\mu\text{g}/\text{mL}$ ISLG changes the cell morphology from round to star shape by enhancing the protein expression of terminal differentiation markers CD11b and CD14 and increasing the nitroblue tetrazolium chloride reductive activity [113]. ISLG also induces B16-F0 cell differentiation with morphological changes, ROS generation, and melanogenesis. However, pretreatment with an ROS inducer or scavenger either increases or depletes ISLG-induced cell differentiation and melanin secretion [86, 123]. Furthermore, NADPH oxidase-derived ROS generation presents a positive regulation in ISLG-induced HL-60 cell differentiation [135].

Inhibition of metastasis: The epidermal growth factor induced the expression of uPA, MMP-9, VEGF, ICAM, VCAM, and integrin- α 2,

which are essential for cell adhesion, migration, and invasion and are blocked by ISLG by decreasing the DNA binding activity of AP-1 and the phosphorylation of JNK [136]. ISLG also inhibits NF- κ B degradation and ROS generation, subsequently blocking VCAM and E-selectin expression to inhibit the adhesion of human endothelial cells [137, 138]. In addition, in highly metastatic MDA-MB-231 cells, the nontoxic concentration of ISLG (10 μM) inhibits the secretion and protein expression of VEGF, MMP-2, and MMP-9 by inhibiting hypoxia-inducible factor 1- α protein expression, decreasing p38 and PI3 K/Akt activity, and inhibiting the DNA binding activity of NF- κ B [112]. ISLG also decreases COX-2 and CYP 4A signaling to inhibit MDA-MB-231 and BT-549 metastasis by preventing anoikis resistance, migration, and invasion [131]. Furthermore, in Renca xenograft BALB/c male mice, 0.1, 0.5, 2, and 10 mg of ISLG (*i.p.*, once a day for 10 d) decreases 40.59%, 45.59%, 60.00%, and 68.23% of metastatic nodules in the lung, respectively, by decreasing the amount of VEGF and activating the immune system. These ISLG doses are approximately 1/6 to 1/600 of the lethal dose 50 [119].

Inhibition of angiogenesis: Previous *in vitro* and *in vivo* studies have demonstrated that the antiangiogenesis effect of the water extractions of licorice root mainly depend on ISLG, which exhibits the most antitube formation ability among other licorice-derived flavonoids [45, 139]. In addition, the phorbol myristate acetate-induced motility, tube formation, and activation of MMP-2 can be inhibited by ISLG treatment by blocking the JNK and p38 pathways in HUVECs [140]. Furthermore, after treating MDA-MB-231 implanted Balb/c mice, ISLG (*p.o.*, 10 mg/kg, 5 times a week for 5 weeks) remarkably decreased the number of lung surface metastases by decreasing the intratumoral levels of MMP-2 and MMP-9 [131].

Chemosensitization or radiosensitization: Pretreatment of 10 $\mu\text{g}/\text{mL}$ ISLG for 6 h evidently enhances the radiosensitivity of HepG2 through the disturbance of the redox status and inhibition of nuclear factor erythroid-2-related factor 2 expression [120]. In cervical cancer cells, the combined treatment of ISLG upregulates the inhibitory effects of CP both *in vitro* and *in vivo*, and the CP-induced genotoxic activity is decreased by the inhibition of DNA strand breaks in white blood cells and micronucleus formation in polychromatic erythrocytes [102]. Furthermore, in CT26 colon carcinoma cell inoculated BALB/c mice, ISLG (*p.o.*, 1 mg/kg) inhibits tumor growth by 52%. By combining with cisplatin, the tumor growth inhibition of the combination is enhanced to 79%, and cisplatin-induced nephrotoxicity and hepatotoxicity are alleviated [105].

Others: ISLG also regulates the expression and activity of certain cancer-related enzymes. The polymorphisms of the CYP19 enzyme have been implicated in the etiology of breast cancer [141, 142]. In wild-type MCF7 cells, ISLG inhibits the protein expression and transcriptional activity of CYP19 by inhibiting the MEK/ERK pathway and the activity of promoters I.3 and II [142]. ISLG decreases polycyclic aromatic hydrocarbon-induced expression, which is associated with the initiation of cancer, by antagonizing aryl hydrocarbon receptor translocation [143]. ISLG also inhibits mammary carcinogenesis by decreasing breast cancer stem cells [144]. Furthermore, ISLG inhibits the ErbB3 protein, which is frequently observed in human cancer cells and currently constitutes the primary target of anticancer strategies [145].

***In vivo* anticancer effects:** The *in vivo* anticancer effects of ISLG in several animal models have also been documented. In MDA-MB-231 xenograft nude mouse models, treatment of ISLG (*i.p.*, 100 mg/kg) for 5 weeks evidently decreases tumor weight

by 62.3% by decreasing the intratumoral PGE₂, 220-HETE, and phosphorylation of Akt levels and by inducing the expression of intratumoral cleaved caspase-3 and cleaved PARP productions [111]. In U266 xenograft SCID mice, ISLG (i.p.) decreases tumor volume by decreasing the expression of IL-6 and MVD as well as the phosphorylation of ERK and STAT3 [110]. In ACC-M cell-implanted BALB/c nude mice, ISLG (p.o., 0.5 g/kg, 30 d) inhibits tumor growth by the induction of mTOR-dependent autophagic and apoptotic cell death [132]. In ddY mice, ISLG (p.o., 15 ppm in drinking water) suppresses the AOM-induced colonic aberrant crypt focus and cancer formation, with an inhibitory ratio of 37.3% [146].

Licochalcone A

Inhibition of proliferation: LCA dose- and time-dependently inhibits cell proliferation of several kinds of cancer cells, such as MKN-28, SGC7901, AGS, and MKN-45 [103], HepG2, Hep3B, and SNU878 [147], LNCaP [23, 148], prostate cancer cell PC-3 [149], colon cancer cells CT26 and HCT-15 [150, 151], OVCAR-3 and SK-OV-3 [151, 152], HeLa [153], bladder cancer cell T24 [154, 155], A549 [151], oral squamous cancer cells HN22 and HSC4 [156], and malignant pleural mesothelioma cells MSTO-211 H and H28 [127], gastric cancer cell BGC-823 [157]. LCA presents the highest cytotoxicity against multiple gastric cancer cells and the lowest cytotoxicity to the normal human gastric epithelial cell GES-1 compared to the cell cytotoxicity of licorice compounds (ISLG, LCA, GA, GBD, GL, etc.) [103]. Furthermore, the obvious antiproliferative concentrations of LCA on cancer cells exhibit no or only slight cytotoxicity to human normal liver cells [147], human normal gastric epithelial cells [103], and human primary normal oral keratinocytes [158].

Induction of cell cycle arrest: The phase of cell cycle arrest induced by LCA varies according to the kind of cancer cells. In rat vascular smooth muscle cells, pretreatment with LCA evidently suppresses platelet-derived growth factor-induced cell proliferation by inducing G1 phase arrest through decreasing the protein expression of cyclin A, cyclin D, CDK2, and CDK4, inhibiting the phosphorylation of Rb and ERK, and increasing the protein expression of p27 [159]. Induction of G1 phase arrest by LCA is also observed in LNCaP cells [23]. However, in MKN-28 and PC-3 cells, LCA induces G2 phase arrest by reducing the protein expression of cyclin A, cyclin B, cyclin D, cyclin E, cdc2, CDK4, and CDK6 as well as the phosphorylation of Rb [103, 149].

Induction of apoptosis: LCA presents proapoptotic effects in bladder cancer cell T24 [155], cervical cancer cell HeLa [153], HepG2 [34, 147], OVCAR-3 and SK-OV-3 [152], MKN-28, AGS, and MKN-45 [103], LNCaP and PC-3 [23, 148, 149], KB, HSC4, and HN22 [156, 158], MCF7 [160], and BGC-823 [157] as well as HL-60 [160] by activating caspase-9 [147, 152, 155], caspase-8 [152, 158], caspase-4 [147], caspase-3 [147, 152, 155, 156, 158], PARP [103, 147, 152, 155, 158, 160], Bax [103, 152, 155], FasL [158], and p53 [152] proteins as well as inhibiting Bcl-2 [103, 152, 155, 160], Bid [152], Bcl-xL [152], and survivin [152] activity. Triggering ER stress [155], elevating ROS generation [155, 157], and inducing MMP dysfunction [152, 155] may be the potential mechanisms for LCA-induced apoptosis.

Induction of autophagy: 12.5 μM of LCA induces autophagic cell death by the inhibition of Bcl-2 and mTOR in LNCaP cells, as evidenced by the conversion of the cytosolic form of microtubule-associated protein light-chain 3 to a lipidized form as well as abundant autophagic vacuole formation [23].

Inhibition of metastasis: In oral squamous cancer cell SCC-25, 50 μg/mL of LCA evidently inhibits the motility, adhesion, migration, and invasion of cancer cells with decreased MMP-2 and NF-κB activities [161].

Inhibition of angiogenesis: The antiangiogenesis effects of LCA were also studied. The proliferation, migration, and tubule formation of HUVECs are inhibited by 20 μM of LCA treatment with decreasing levels of IL-6 and IL-8. To further study the mechanisms, the VEGF-stimulated phosphorylation of VEGFR-2 is blocked by LCA. Upon VEGFR-2 protein knockdown, the LCA-stimulated inhibitory effect on proliferation, migration, and tube formation of HUVECs is depleted [162]. LCA also inhibits platelet-derived growth factor-induced rVSMC proliferation by decreasing the phosphorylation of ERK [159]. In a CT26 transplant BALB/c mice model, LCA (p.o., 30 mg/kg, daily for 2 weeks) inhibits tumor growth with an average tumor size from 899 ± 59 mm³ to 333.9 ± 53.8 mm³ by the inhibition of tumor angiogenesis and the promotion of apoptosis [162].

Chemosensitization: Treatment with 7.5 μM of LCA increases 10 μM of geldanamycin-induced cell death from 36% to approximately 74% in OVCAR-3 cells by enhanced geldanamycin-induced apoptosis-related protein activation and ROS formation, whereas the combined effect is decreased by the addition of oxidant scavengers [163]. In addition, the antiproliferative effects of paclitaxel and vinblastine can be enhanced by the combined treatment with LCA [160].

Others: LCA inhibits the proliferation of A549, SK-OV-3, SK-MEL-2, and HCT-15 by inhibiting the activation of Top I in a concentration-dependent manner [151]. LCA also inhibits cell proliferation and survival by inhibiting the phosphorylation and nuclear localization of STAT3 [164].

In vivo anticancer effects: In the AOM/dextran sulfate sodium-induced colon carcinogenesis in C57BL/6 mice, 5, 15, and 30 mg/kg of LCA (p.o.) present approximately 41%, 75%, and 98% inhibitory rates in cancer growth, respectively. In addition, tumor metastasis is inhibited by decreasing MMP-9 activity [165]. DMBA-initiated and TPA-promoted mouse skin papilloma are also inhibited by LCA [166]. In addition, in CT26 cell injected Balb/c mice, LCA (p.o.) obviously reduces cisplatin-induced nephrotoxicity and hepatotoxicity by blocking cisplatin-induced oxidative stress without affecting the chemotherapeutic efficacy of cisplatin [150].

Licochalcone B

LCB inhibits the proliferation of bladder cancer cells T24, EJ, and MB49 by inducing S phase cell cycle arrest and apoptosis through the reduction of cyclin A, CDK1, CDK2, cdc25 A, cdc25B, Bcl-2, and survivin expression as well as the enhancement of Bax expression. In MB49 xenograft C57BL/6 mice models, LCB has been shown to inhibit cancer cell growth without evident toxicity to mice by assessing mice weight, serum glutamate oxaloacetate aminotransferase, and glutamate pyruvate aminotransferase [167].

Licochalcone E

LCE inhibits the proliferation of A549, SK-OV-3, SK-MEL-2, and HCT-15 by reducing Top I activity, DNA binding activity of NF-κB, and Bcl-2 expression [151, 168]. LCE dose-dependently inhibits the migration and invasion of MDA-MB-231 and 4T1 cells by decreasing the secretion of uPA, VEGF, and MMP-9. Furthermore, in 4T1 xenograft BALB/c mice models, LCE (p.o., 14 mg/kg) suppresses tumor growth and metastasis by reducing the expression

of Ki67, CDK4, CDK2, cyclin A, cyclin D, VEGF, lymphatic vessel endothelial receptor-1, COX-2, and hypoxia inducible factor-1 as the protein expressions of Bax and cleaved caspase-3 are increased [169].

Liquiritigenin

The antiproliferative effects of LG in hepatic cancer cell SMMC-7721 and HeLa cells are mainly achieved by the induction of apoptosis with the upregulation of Bax and caspase-3 proteins as well as through the inhibition of the expression of Bcl-2 and survivin by increasing the generation of ROS, activating p53, inducing MMP dysfunction, and decreasing GSH and the activities of superoxide dismutase. Meanwhile, in pretreatment with an ROS scavenger, LG-induced apoptosis is obviously decreased [170, 171]. The noncytotoxic concentration of LG inhibits the adhesion and migration of A549 cells by decreasing MMP-2 activity, hindering phosphorylation of Akt, and activating ERK [172]. Moreover, LG inhibits the expression of VEGF in HeLa cells in a dose-dependent manner. In HeLa-implanted nude mice, i.g. of LG (40 mg/kg, once a day for 28 d) also exhibits a more than 50% inhibitory rate on tumor growth by decreasing VEGF and MVD expression [173]. Furthermore, in the H22 bearing mice model, treatment of LG (i.g., 20 mg/kg) inhibits the tumor growth by decreasing MDA content and inducing apoptosis [174].

Isoangustone A

The antiproliferation of IAA in SW480 [175], pancreatic cancer cells PC3, LNCaP, and DU 145 [29, 176], 4 T1 [29], and melanoma cells SK-MEL-2, SK-MEL-5, SK-MEL-28, and WM-266-4 [177] are achieved by the induction of cell cycle arrest and apoptosis. IAA induces PC3, LNCaP, SK-MEL-28, DU 145, and 4 T1 cells in G1 phase cell cycle arrest through the reduction of the protein expression of cyclin A, cyclin D, cyclin E, CDK2, and CDK4. This inhibitory effect may be achieved by the downregulation of mTOR, PI3 K, Akt, and JNK activities [27, 176, 177]. IAA also induces apoptosis in SW480 and DU 145 cells by activating caspase-3, caspase-9, PARP, and DR4, suppressing Bcl-2 protein expression, disrupting MMP and ATP synthesis, and inducing cytochrome c release [27, 29, 175]. In addition, the pretreatment of Z-VAD-FMK or knockdown of the DR4 obviously attenuates IAA-induced apoptosis [29, 175]. Furthermore, in PC3 xenograft BALB/c nude mice, IAA (i.p., 5 mg/kg) reduces about 70.0% and 53.6% of tumor volume and tumor weight, respectively, through the inhibition of PCNA expression and the induction of G1 phase arrest [176]. In an SK-MEL-28-injected male BALB/c mice model, 2 or 10 mg/kg IAA (i.p., daily for 5 weeks) inhibits tumor volume and weight without affecting the body weight [177].

Glabridin

The migration, invasion, and epithelial-mesenchymal transition of A549, MDA-MB-231, and HUVECs can be inhibited by GBD treatment by decreasing the FAK, Src, Akt, myosin, and myosin light chain phosphorylation, the FAK and Src interaction, and the RhoA activity [178, 179]. GBD also inhibits the migration and invasion of Huh7 and Sk-Hep-1 cells by decreasing the expression, activities, and protein levels of MMP9, phosphorylation of ERK1/2 and JNK1/2, upregulation of the tissue inhibitor of metalloproteinase-1, and downregulation of the NF- κ B and AP-1 signaling pathways [180]. GBD inhibits angiogenesis in nude mice models [179]. The accumulation of daunorubicin in KB-C2 cells can be enhanced by GBD treatment [87]. Furthermore, the nontoxic concentration of GBD (15 μ M) prevents UVB-irradiated normal

human keratinocyte damage by inhibiting ROS production and cleaved PARP expression [181]. In SK-Hep-1 xenograft BALB/c nude mice, GBD (i.p., 10 mg/kg, three times a week) dramatically suppressed tumor growth without statistically significant changes in body weight [180].

Isoliquiritin

ISLT exhibits a 50-fold greater inhibitory effect on the angiogenesis of granuloma tissue than that of licorice extractions. This inhibitory effect is achieved by inhibiting tube formation [45].

Licoricidin

The noncytotoxic concentration of LRD inhibits the migration and adhesion of DU 145 cells in a concentration-dependent manner through the reduction of MMP-9, uPA, VEGF, integrin- α 2, ICAM, and VCAM secretion [182].

Phenolics

Several licorice phenolics, such as LCM, GLY, and β -hydroxy-DHP, also demonstrated anticancer effects by the induction of cell cycle arrest and apoptosis.

Licocoumarone

LCM inhibits the proliferation of U-937 cells in a concentration-dependent manner through the induction of apoptosis [21].

Glycyrol

In human Jurkat cells, GLY induces S phase cell cycle arrest and apoptosis in time- and dose-dependent manners through the activation of Fas, caspase-8, and caspase-9 proteins [16]. It also induced cell cycle arrest, apoptosis, and defective autophagy in AGS and HCT 116 cells with the activation of the JNK pathway [38]. *1-(2,4-Dihydroxyphenyl)-3-hydroxy-3-(4'-hydroxyphenyl) 1-propanone*: β -Hydroxy-DHP decreases the viability of MCF7 cells in a dose-dependent manner, and this proliferative inhibition is mainly due to induced apoptosis. The 50 μ M concentration of β -hydroxy DHP also induces apoptosis in HL-60 cells and G2/M cell cycle arrest in T47D cells [28].

Discussion and Conclusion



We have summarized the *in vitro* and *in vivo* anticancer properties (● Tables 1 and 2) and potential mechanisms of mixed extracts and purified compounds from licorice (● Fig. 2). A series of licorice compounds have been indicated as possessing anticancer effects by inhibiting cancer cell proliferation and metastasis. Present studies focusing on extracts are rather limited, and the active compounds of extracts are not clear. The anticancer effects of purified compounds, such as GA, ISLG, and LCA, attracted considerably more studies than these extracts. However, most studies focus on the phenomena without detailed mechanism analysis, and *in vivo* anticancer effects are also restrained. In addition, the pharmacokinetic assay and maximum tolerated dose are also important for the development of licorice. Several pharmacokinetic studies of licorice compounds, such as GL, GA, ISLG, and LG, etc., have been carried out in some animal models [183–185]. In an Sprague-Dawley rat model (468 mg/kg of licorice, p.o.), the peak plasma concentrations of LG and ISLG were 2.83 μ g/mL and 0.28 μ g/mL, respectively [186]. However, in a Sprague-Dawley rat model, the peak plasma concentrations of LG (1920 mg/kg, p.o.), ISLG (180 mg/kg, p.o.), GL (170 mg/kg,

Table 1 The antiproliferative properties of licorice compounds *in vitro*.

Compounds	Cancer tissue/disease	Cancer cell	Concentration	Inhibition rate	Method	Ref.
Ethanol extract of roasted licorice	Prostate	DU 145	6 µg/mL	50% (72 h)	MTT	[24]
		MLL	4.3 µg/mL	50% (72 h)	MTT	[24]
	Colon	HT-29	12 µg/mL	50% (72 h)	MTT	[24]
	Breast	MCF-7	30 µg/mL	88% (48 h)	MTT	[24]
		MDA-MB-231	30 µg/mL	82% (48 h)	MTT	[24]
	Melanoma	B16-F10	30 µg/mL	80% (48 h)	MTT	[24]
	Skin	A375	30 µg/mL	94% (48 h)	MTT	[24]
A2058		30 µg/mL	93% (48 h)	MTT	[24]	
Ethanol extract of un-roasted licorice	Prostate	DU 145	12.3 µg/mL	50% (72 h)	MTT	[24]
		MLL	12.2 µg/mL	50% (72 h)	MTT	[24]
	Colon	HT-29	31 µg/mL	50% (72 h)	MTT	[24]
Ethanol extracts of licorice 80% ethanol (volume, CH ₃ CH ₃ OH:H ₂ O = 70:30) extracts of licorice	Breast	MCF7	100 µg/mL	about 25% (72 h)	MTT	[26]
	Breast	MCF7	100 µg/mL	about 50% (72 h)	MTT	[26]
70% methanol (volume, CH ₃ OH:H ₂ O = 70:30) extracts of licorice	Leukemia	U973	50 µg/mL	about 70% (16 h)	ABS	[21]
	Liver	HepG2	530 µg/mL	50% (72 h)	MTT	[20]
Glycyrrhizic acid	Prostate	LNCaP	8.5 mM	50% (48 h)	CCK-8	[42]
		DU 145	12.5 mM	50% (48 h)	CCK-8	[42]
	Lung	A549	1 mM	50% (72 h)	MTS	[40]
	Glioblastoma	U251	2 mM	28% (24 h), 75% (48 h), and 90% (72 h)	CCK-8	[41]
Glycyrrhetic acid	Stomach	AGS	125.2 µM	50% (48 h)	MTT	[103]
		BGC823	30 µM	65% (24 h)	MTT	[71]
		MKN-28	146.7 µM	50% (48 h)	MTT	[103]
		MKN-45	157 µM	50% (48 h)	MTT	[103]
		SGC7901	30 µM	46% (24 h)	MTT	[71]
		SGC7901	135.7 µM	50% (48 h)	MTT	[103]
	Colon	DLD-1	81.21 µM	50% (96 h)	SRB	[68]
		HCT 116	78.33 µM	50% (96 h)	SRB	[68]
		HCT-8	78.85 µM	50% (96 h)	SRB	[68]
		HT-29	80.09 µM	50% (96 h)	SRB	[68]
		SW480	86.80 µM	50% (96 h)	SRB	[75]
	Lung	A549	82.76 µM	50% (96 h)	SRB	[68]
		A549	165.7 µM	50% (24 h)	XTT	[73]
		NCI-H460	131.7 µM	50% (24 h)	XTT	[73]
	Prostrate	LNCaP	200 µM	35% (48 h)	MTT	[74]
		DU 145	200 µM	52% (48 h)	MTT	[74]
	Ovary	OVCAR-3	25 µM	24% (24 h), 42% (48 h), and 52% (72 h)	MTT	[69]
		SK-OV-3	25 µM	23% (24 h), 42% (48 h), and 51% (72 h)	MTT	[69]
	Melanoma	SK-MEL-28	30 µM	55% (48 h)	MTT	[35]
		SK-MEL-2	30 µM	50% (48 h)	MTT	[35]
		518A2	83.92 µM	50% (96 h)	SRB	[68]
	Thyroid	8505 C	86.50 µM	50% (96 h)	SRB	[75]
		SW1736	76.93 µM	50% (96 h)	SRB	[68]
	Cervix	SiHa	50 µM	58% (24 h)	MTT	[34]
	Liver	HepG2	80 µM	50% (72 h)	TBD	[39]
		HepG2	40 µM	50% (48 h)	MTT	[34]
	Submaxillary salivary gland	A-253	80.78 µM	50% (96 h)	SRB	[68]
	Skin	A-431	79.58 µM	50% (96 h)	SRB	[68]
	Pharynx	FaDu	84.55 µM	50% (96 h)	SRB	[75]
Breast	MCF7	84.70 µM	50% (96 h)	SRB	[68]	
Leukemia	HL-60	63.2 µM	50% (96 h)	SRB	[77]	

cont.

p.o.), and GA (580 mg/kg, p.o.) were 37 µg/mL, 42 µg/mL, 55 µg/mL, and 90 µg/mL, respectively [183]. More pharmacokinetic studies on licorice using different models should be carried out, and the maximum tolerated dose of licorice or pure compounds is also critical for licorice's clinical use. Also, whether the concentration of the compounds in a tumor microenvironment can

reach the doses used *in vitro* (due to the *in vitro* concentrations of some compounds used being too high, such as GL) needs to be considered further. Therefore, the evaluation of the *in vivo* anticancer effects of licorice might be much more significant. Although numerous proteins or genes can be affected by licorice compounds, the actual targets and mechanisms still remain un-

Table 1 Continued

Compounds	Cancer tissue/disease	Cancer cell	Concentration	Inhibition rate	Method	Ref.
Isoliquiritigenin	Cervix	C-33 A	40 μ M	62% (24 h), 64% (48 h), and 72% (72 h)	MTT	[101]
		Ca Ski	40 μ M	23% (24 h), 56% (48 h), and 56% (72 h)	MTT	[101]
		HeLa	9.8 μ M	50% (48 h)	XTT	[99]
		HeLa	40 μ M	42% (24 h), 36% (48 h), and 55% (72 h)	MTT	[101]
		SiHa	40 μ M	32% (24 h), 38% (48 h), and 61% (72 h)	MTT	[101]
	Breast	U14	97.56 μ M	about 61.57% (48 h)	MTT	[102]
		MCF7	10 μ M	50% (48 h)	MTS	[111]
		MCF7	50 μ M	about 50% (72 h)	MTT	[112]
		MCF7aro	5 μ M	about 65% (48 h)	MTT	[142]
		MDA-MB-231	5 μ M	50% (48 h)	MTS	[111]
		MDA-MB-231	25 μ M	about 50% (72 h)	MTT	[112]
	Colon	CT26	60 μ M	about 40% (24 h) and 70% (72 h)	MTT	[105]
		Colon 26	14.6 μ M	50% (48 h)	MTT	[106]
		COLO 320DM	17.9 μ M	50% (72 h)	MTT	[106]
		HCT 116	40 μ M	25% (48 h), 40% (72 h), and 50% (96 h)	MTT	[104]
		HT-29	40 μ M	30% (24 h), 38% (48 h), and 42% (72 h)	MTT	[104]
		RCN-9	19.5 μ M	50% (48 h)	MTT	[106]
		Prostate	C4-2	87 μ M	50% (24 h)	MTT
	DU 145		11 μ M	50% (48 h)	TBD	[107]
	DU 145		20 μ M	25% (24 h), 39% (48 h), and 56% (72 h)	MTT	[109]
	LNCaP		13 μ M	50% (48 h)	TBD	[107]
	LNCaP		100 μ M	62% (24 h)	MTT	[108]
	MLL		5 μ M	11% (24 h), 41% (48 h), and 50% (72 h)	MTT	[109]
	Myeloma	ARH-77	14.6 μ M	about 50% (48 h)	CCK-8	[110]
		CZ-1	13.9 μ M	about 50% (48 h)	CCK-8	[110]
		MPC-11	4.4 μ M	about 50% (48 h)	CCK-8	[110]
		RPMI 8226	9.1 μ M	about 50% (48 h)	CCK-8	[110]
		SP2/0	22.9 μ M	about 50% (48 h)	CCK-8	[110]
		U266	8.6 μ M	about 50% (48 h)	CCK-8	[110]
	Stomach	AGS	147.3 μ M	50% (48 h)	MTT	[103]
		MKN-28	167.8 μ M	50% (48 h)	MTT	[103]
		MKN-45	128.4 μ M	50% (48 h)	MTT	[103]
		SGC7901	157.9 μ M	50% (48 h)	MTT	[103]
	Oral cavity	HSC-2	79 μ M	50% (24 h)	MTT	[124]
		HSC-3	97 μ M	50% (24 h)	MTT	[124]
	Liver	HepG2	156.1 μ M	about 50% (48 h)	MTT	[120]
		HepG2	41 μ M	about 50% (48 h)	XTT	[121]
	Lung	A549	18.5 μ M	50% (72 h)	TBD	[114]
		A549	27.14 μ M	50% (24 h)	XTT	[115]
	Leukemia	HL-60	58.5 μ M	about 86.7% (72 h)	MTT	[113]
		HL-60	22 μ M	50% (24 h)	MTT	[124]
	Kindeg	Renca	39 μ M	about 30% (72 h)	ABS	[119]
	Submandibular gland	HSG	125 μ M	50% (24 h)	MTT	[124]
Brain	U-87	40 μ M	20% (24 h), 53% (48 h), and 75% (72 h)	MTT	[118]	
Ovary	SK-OV-3	156.1 μ M	about 83.1% (24 h)	MTT	[117]	
Licochalcone A	Stomach	AGS	41.1 μ M	50% (48 h)	MTT	[103]
		MKN-28	42 μ M	50% (48 h)	MTT	[103]
		MKN-45	40.7 μ M	50% (48 h)	MTT	[103]
		SGC7901	40.8 μ M	50% (48 h)	MTT	[103]
	Liver	HepG2	10 μ M	54% (24 h)	MTT	[147]
		Hep3B	10 μ M	40% (24 h)	MTT	[147]
		SNU878	10 μ M	38% (24 h)	MTT	[147]
	Ovary	OVCAR-3	15 μ M	68% (24 h)	MTT	[152]
		SK-OV-3	15 μ M	61% (24 h)	MTT	[152]
		SK-OV-3	13.5 μ M	about 50% (48 h)	SRB	[151]
	Prostate	PC-3	25 μ M	80% (48 h) and 83% (72 h)	TBD	[149]
		LNCaP	50 μ M	5.5% (48 h)	MTT	[148]
	Colon	CT26	20 μ M	56.3% (24 h) and 74.3% (72 h)	MTT	[150]
		HCT-15	10.1 μ M	about 50% (48 h)	SRB	[151]
	Cervix	HeLa	50 μ M	17.4% (24 h)	MTT	[153]
	Bladder	T24	100 μ M	54% (12 h), 64% (24 h), and 79% (48 h)	MTT	[167]
	Lung	A549	14.3 μ M	about 50% (48 h)	SRB	[151]
	Skin	SK-MEL-2	7.9 μ M	about 50% (48 h)	SRB	[151]

cont.

Table 1 Continued

Compounds	Cancer tissue/disease	Cancer cell	Concentration	Inhibition rate	Method	Ref.
Licochalcone B	Bladder	T24	60 μ M	25% (24 h), 55% (48 h), and 67% (72 h)	MTT	[167]
		EJ	60 μ M	50% (24 h), 65% (48 h), and 75% (72 h)	MTT	[167]
Licochalcone E	Colon	HCT-15	10.1 μ M	about 50% (48 h)	SRB	[151]
	Skin	SK-MEL-2	8.5 μ M	about 50% (48 h)	SRB	[151]
	Lung	A549	17.3 μ M	about 50% (48 h)	SRB	[151]
	Ovary	SK-OV-3	15.5 μ M	about 50% (48 h)	SRB	[151]
Liquiritigenin	Stomach	AGS	339.3 μ M	50% (48 h)	MTT	[103]
		MKN-28	314.7 μ M	50% (48 h)	MTT	[103]
		MKN-45	376.7 μ M	50% (48 h)	MTT	[103]
		SGC7901	358 μ M	50% (48 h)	MTT	[103]
	Cervix	HeLa	200 μ M	24% (24 h), 48% (48 h), and 65% (72 h)	MTT	[171]
Isoangustone A	Prostrate	PC3	10 μ M	52% (24 h)	MTT	[176]
	Colon	SW480	6 μ M	40% (24 h)	MTT	[175]
Glabridin	Stomach	AGS	69.6 μ M	50% (48 h)	MTT	[103]
		MKN-28	61 μ M	50% (48 h)	MTT	[103]
		MKN-45	83.7 μ M	50% (48 h)	MTT	[103]
		SGC7901	84.2 μ M	50% (48 h)	MTT	[103]
Licoumarone	Lymphocyte	U-937	147 μ M	about 75% (16 h)	ABS	[21]
β -Hydroxy-DHP	Breast	MCF7	13 μ M	50% (72 h)	MTT	[28]

ABS: Alamar Blue assay; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; MTS: 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfo-phenyl)-2 H-tetrazolium, inner salt assay; MCF7aro: stably transfected with human CYP19 cells; XTT: 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-5[(phenylamino)carbonyl]-2 H-tetrazolium hydroxide assay; TBD: trypan blue dye assay; SRB: Sulforhodamine B assay

Table 2 The anticancer properties of licorice compounds *in vivo*.

Compounds	Models	Treatments	Outcomes	Ref.
Methanol extracts of licorice	EAT-bearing mice	i. p., 500 μ g, 7 days	inhibition of growth of EAT cells and formation of ascites fluid by inhibition of angiogenesis	[30]
Aqueous extracts of licorice	EAT-bearing mice	i. p., 600 μ g, 7 days	inhibition of growth of EAT cells and formation of ascites fluid by inhibition of angiogenesis	[30]
Hexane/ethanol extracts of licorice	4 T1-injected female BALB/c mice	In drinking water, 5 mg/kg/day,	inhibiting the tumor volumes by reducing the expression of CDK2, CDK4, and PCNA	[27]
70% ethanol (volume, CH ₃ CH ₃ OH: H ₂ O = 70:30) extracts of licorice	MDA-MB-231 xenografted Balb/c mice	i. g., 2 mg/kg, once a day for 5 days, followed by further administration once a week for 44 days	blocking the tumor growth and tumor volume	[22]
95% ethanol (volume, CH ₃ CH ₃ OH: H ₂ O = 95:5) extracts of licorice	CT26 xenografted BALB/c mice	i. g., 0.5, 1, and 2 mg/kg, once a day for 15 days	inhibiting tumor growth by 38%, 57%, and 71%, respectively	[31]
Glycyrrhizic acid	Renca cells inject s. c. into BALB/c mice.	i. p., 50 mg/kg, once a day for a week	suppressing 35% of tumor weight and 60% of tumor volume by reducing angiogenesis	[46]
	ovariectomized mice models	p. o., diet containing 0.0625% wt of GA, two weeks	GA suppressed the endometrial cancer progress by inhibiting the expression of COX-2, TNF- α , and IL-1	[63]
	acetate-induced hyperproliferative activity in Wistar rats	p. o, 300 mg/kg, once a day for 5 days before i. p. of acetate	inhibition of ODC activity and DNA synthesis	[64]
	A549-bearing mice models	i. p., 50 mg/kg, once every other day for 8 weeks	inhibiting the tumor growth by reduction of TxA2 expression	[40]
	diethylnitrosamine-induced hepato tumor of BALB/c mice models	i. m., 2 mg/mouse, three times a week for 32 weeks	suppression of the mean number of liver tumors from 1.64 to 0.71 and reduction of the incidence rate of hepatic tumors from 64% to 21%	[67]
Glycyrrhetic acid	SGC7901 xenografted nude mice	s. c., 30 mg/kg, once every other day for 4 weeks	inhibition of tumor tissues growth and induced apoptosis by decreasing the expression of Bid	[71] cont.

clear. Thus, we suggest that more high throughput technologies, such as genomics, proteomics, biochip, and high-content screening, may be utilized to promote the explorative speed of the anticancer mechanisms of licorice [187, 188]. For example, by utilizing the oligonucleotide microarray analysis to screen 3360 genes

after treatment with 0.25 μ g/mL tanshinone IIA for 72 h in MCF7 cells, 41 genes were increased and 24 genes were decreased. Among these genes, the ADP-ribosyltransferase gene exhibited the maximum induction, thus indicating that the gene may be the main target [189]. Besides, through the use of frontal affinity

Table 2 Continued

Compounds	Models	Treatments	Outcomes	Ref.
Isoliquiritigenin	MDA-MB-231 xenografted nude mice	i. p., 50 and 100 mg/kg, three times a week for 5 weeks	decreasing the tumor weight about 43.1% and 62.3%, respectively, with the downregulation of the intratumoral PGE ₂ , 20-HETE, and p-Akt levels, while induction of intratumoral cleaved caspase-3 and cleaved PARP levels	[111]
	MDA-MB-231 implanted Balb/c mice	p. o., 10 mg/kg, 5 times a week for 5 weeks	remarkably inhibition of the number of lung surface metastases with decreasing the intratumoral levels of MMP-2 and MMP-9	[131]
	U14-implanted Kunming female mice model	p. o., 20 mg/kg, once a day for 10 days	inhibiting the tumor weight about 43.55% and enhancing the antitumor growth of CP from 35.57% to 65.66%	[102]
	B16-F0 cells (treated or untreated with 15 µg/mL ISL for 48 h) were inoculated s.c into C57BL/6 mice	10 days	inhibiting the tumor weight about 29.6%	[123]
	U266 xenografted SCID mice	i. p., 100 and 200 µg/kg, 20 days	suppressing the tumor volume about 47.56% and 64.55%, respectively	[110]
	MPC-11 xenografted BABL/C mice	i. p., 100 and 200 µg/kg, 15 days	inhibiting the tumor volume about 82.30% and 90.64%, respectively	[110]
	ACC-M xenografted BALB/c nude mice models	p. o., 0.5 g/kg or 1 g/kg, daily for 30 consecutive days	inhibiting the tumor growth by induction of the mTOR-dependent autophagic and apoptosis	[132]
	Renca xenografted BALB/c male mice models	i. p., 0.1, 0.5, 2, 10 mg/day, once a day for 10 days	decreasing 40.59%, 45.59%, 60.00%, and 68.23% of metastatic nodules in lungs, respectively, by suppressing the amount of VEGF and activating the immune system	[119]
	CT26 inoculated into BALB/c mice models,	p. o., 1 mg/kg, once a day for 15 days	suppressing the 52% of tumors growth, enhancing the antitumor growth effects of cisplatin, and alleviating the cisplatin-induced nephrotoxicity and hepatotoxicity by blocking the oxidative stress and intracellular ROS generation	[105]
	in the AOM-induced colonic aberrant crypt focus and cancer formation of ddY mice model	p. o., 15 ppm in drinking water, 4 weeks	exhibition of 37.3% inhibitory rate of the colonic aberrant crypt focus and cancer formation	[146]
Licochalcone A	CT26 cells inoculated into Balb/c mice	p. o., 1 mg/kg, once a day for 15 days	inhibited the growth of tumors by 49%	[150]
	AOM/DSS-induced colon carcinogenesis C57BL/6 mice	p. o., 5, 15, and 30 mg/kg, three times a week for 46 days	exhibition of 41%, 75%, and 98% inhibitory rate in cancer growth, respectively, and inhibition of the tumor metastasis with decreasing β-catenin expression and MMP-9 activity in cancer tissue	[165]
Licochalcone B	MB49 xenografted C57BL/6 mice model	i. t., 100 µL of LCB (160 µM) once every other day for 23 days	obviously inhibiting the tumor growth by inducing apoptosis	[167]
Liquiritigenin	H22-bearing mice models	i. g., 20 mg/kg, once a day for 15 days	exhibition of 49.3% of tumor growth inhibitory rate, reduction of the MDA content, and induction of apoptosis	[174]
	HeLa implanted nude mice	i. g., 40 mg/kg, once every other day for 28 days	exhibition of more than 50% inhibitory rate on the tumor growth, and inhibition of VEGF and MVD expressions	[173]
Isoangustone A	PC3 xenografted in BALB/c nude mice	i. p. 5 mg/kg, once a day for 8 weeks	reducing tumor volume and tumor weight about 70.0% and 53.6%, respectively, inhibiting about 58% of PCNA expression, and inducing G1/S phase arrest by decreasing p27 ^{kip1} expression	[176]
	SK-MEL-28-injected male BALB/c mice,	i. p., 2 or 10 mg/kg, once a day for 5 weeks	inhibiting the tumor volume and weight by decreasing the expression of PCNA, and inhibiting PI3 K, MKK4, and MKK7 activities without losing body weight	[177]
Glabridin	in SK-Hep-1 xenograft BALB/c nude mice	i. p., 10 mg/kg, three times a week	suppressing the tumor growth without statistically significant changes in body weight	[180]

chromatography with mass spectrometry detection, the erythropoietin-producing hepatocellular B2 inhibitor has been successfully identified [190]. Therefore, those research methods can also be performed in the future to study the targets and mechanisms of licorice compounds.

Licorice has been traditionally recognized as a "guide drug" (drugs that enhance the effectiveness and reduce the toxicity of other ingredients) and is added to most traditional and modern prescriptions [15, 191]. Basic *in vitro* and *in vivo* pharmacological studies indicate that the combined treatment of licorice compounds,

Compounds	Mechanisms						
	Cell cycle arrest	Apoptosis	Autophagy	Anti-metastasis	Anti-angiogenesis	Differentiation	Sensitization
Mixed extracts							Inhibition of mTOR signaling, induction of p53 and Bax, etc.
Glycyrrhizic acid							Inhibition of NF- κ B, E-selectin, TNF- α , and HMGB1, etc.
Glycyrrhetic acid							Inhibition of NF- κ B, PKC, and GSH, etc.
Isoliquiritigenin							Inhibition of NF- κ B, and JNK, etc.
Licochalcone A							Blockage of ERK, NF- κ B, and STAT3 signals, etc.
Licochalcone B							Inhibition of Bcl-2 and survivin, induction of Bax, etc.
Licochalcone E							Inhibition of DNA topoisomerase I, NF- κ B, and Ki67, etc.
Liquiritigenin							Retardation of Akt, activation of p53, production of ROS, etc.
Isoangustone A							Blockage of mTOR and JNK signaling, activation of DR4, etc.
Glabridin							Down-regulation of RhoA, FAK, Akt, and Src, etc.
Isoliquiritin							Down-regulation of tube formation, etc.
Licoricidin							Inhibition of uPA, MMP-9, and ICAM, etc.
Licocoumarone							Up-regulation of DNA fragmentation, etc.
Glycyrol							Induction of caspase-8, caspase-9, and Fas, etc.
β -hydroxy-DHP							Induction of Bcl-2 phosphorylation, etc.

Fig. 2 The anticancer properties and molecular mechanisms of the mixed extracts and purified compounds isolated from licorice. The left panel indicates the anticancer compounds from licorice, the middle panel indicates the impacts of each compound on anticancer studies (the highlighted boxes color means the relevant anticancer effects in the heading have been studied), and the right panel indicates the potential targets or mechanisms contributing to anticancer activities. (Color figure available online only.)

such as GA, ISLG, and LCA, with clinical chemotherapy drugs presents both synergistic antineoplastic effects and a reduction of the side effects of chemotherapeutics [34, 102, 105, 148]. GL also reverses cisplatin resistance in hepatocellular carcinoma cells [47]. Furthermore, GL pretreatment enhances UVB-induced apoptosis in melanoma cells, blocks UVB-induced skin tumor formation, and hinders ionizing radiation-induced tumor cell extravasation and lung metastasis [35, 49]. All of these findings indicate that a combined therapy may provide an optimal venue for licorice compounds in clinical application.

Among the purified compounds from licorice, the exploitation of the anticancer effects of GA may be much more compelling. First, GA is of high content and can easily be accessed from licorice with a spectrum of bioactivities [6, 97, 192]. Second, GA has been widely and successfully structure-modified to enhance its anticancer effects and other bioactivities [193–195]. For example, aminoalkyl-modified GA methyl esters successfully yield novel GA derivatives, which exhibit IC_{50} values between 0.6 and $3.0 \mu\text{M}$ in 14 kinds of cancer cells, while maintaining an IC_{50} of GA of $80 \mu\text{M}$ in those cancer cells [75]. Furthermore, GA has been widely utilized as a hepatic-targeting ligand in TDDS because of the abundant receptors for GA on the hepatocyte membrane [32, 96]. Numerous hepatic TDDSs have been developed, such as doxorubicin-loaded GA-modified alginate nanoparticles [96], doxorubicin-loaded GA-modified sulfated chitosan [94], and 5-fluorouracil-loaded GA-modified chitosan nanoparticles [93] among others. Those nanoparticles not only enhance the hepatic accumulation of chemotherapeutics to enhance the anticancer effects, but also decrease the side effects.

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Conflict of Interest

The authors declare that they have no competing interests.

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