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Review

Preventive and Therapeutic Effects of Chinese Herbal Compounds against Hepatocellular Carcinoma

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Academic Editor: Derek J. McPhee

Received: 16 November 2015 ; Accepted: 20 January 2016 ; Published: 27 January 2016

Abstract: Traditional Chinese Medicines, unique biomedical and pharmaceutical resources, have been widely used for hepatocellular carcinoma (HCC) prevention and treatment. Accumulated Chinese herb-derived compounds with significant anti-cancer effects against HCC have been identified. Chinese herbal compounds are effective in preventing carcinogenesis, inhibiting cell proliferation, arresting cell cycle, inducing apoptosis, autophagy, cell senescence and anoikis, inhibiting epithelial-mesenchymal transition, metastasis and angiogenesis, regulating immune function, reversing drug resistance and enhancing the effects of chemotherapy in HCC. This paper comprehensively reviews these compounds and their effects on HCC. Finally, the perspectives and rational application of herbal compounds for HCC management are discussed.

Keywords: hepatocellular carcinoma; Chinese herbal compound; phytopharmacology; prevention; treatment

1. Introduction

Despite advances in diagnosis and treatment, hepatocarcinoma remains the sixth most common malignancy and the third principal cause of cancer deaths worldwide [1], underscoring the need to develop novel approaches for liver cancer control. Traditional Chinese Medicines (TCMs) play a positive role in the management of hepatocarcinoma [2,3]. TCMs are effective in alleviating clinical symptoms, improving quality of life and immune function, preventing recurrence and metastasis, delaying tumor progression, and prolonging survival of hepatocarcinoma patients [4]. Accumulated Chinese herbal compounds have been identified and demonstrated anti-cancer effects against hepatocellular carcinoma (HCC). Chinese herbal compounds represent an important medical and pharmaceutical resource for the development of new treatments for hepatocarcinoma. These compounds and their effects on HCC are comprehensively reviewed in present work.

2. Prevention of Hepatocarcinogenesis

TCMs have long been used for disease prevention, including liver cancer. Increasing numbers of Chinese herbal compounds have been isolated and demonstrated preventive effects against hepatocarcinogenesis. Ursolic acid is a natural triterpenoid widely found in Chinese herbs, such as *Gardenia jasminoides* Ellis (Zhi-Zi), *Prunella vulgaris* (Xia-Ku-Cao) and *Hedyotis diffusa* Willd.

(Bai-Hua-She-She-Cao). Ursolic acid is effective in preventing diethylnitrosamine (DEN)-induced oxidative stress and hepatocarcinogenesis [5,6] (Figure 1, Table 1).

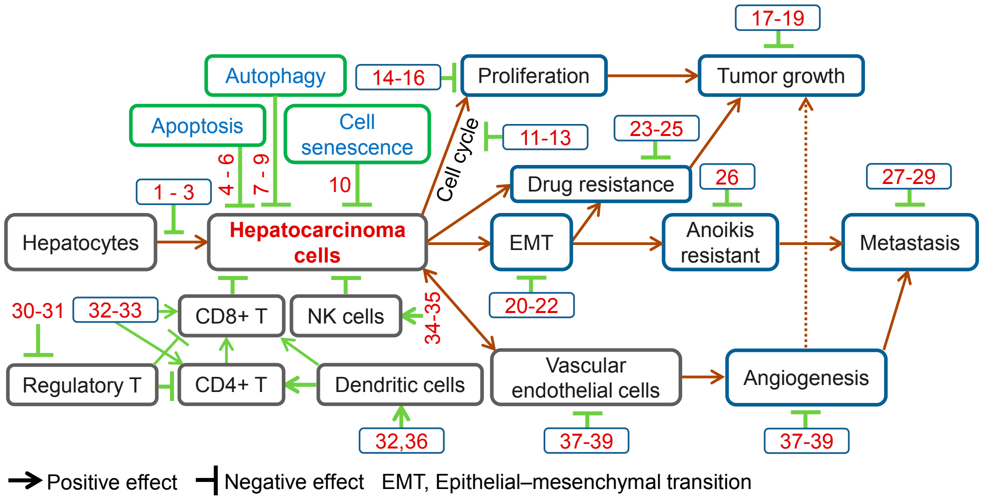

Figure 1. Anti-cancer effects of herbal compounds against hepatocarcinoma. 1, Ursolic acid; 2, Penta-acetyl geniposide; 3, Curcumin; 4, Matrine; 5, Solamargine; 6, Ponicidin; 7, Tetrandrine; 8, Baicalein; 9, Bufalin; 10, Ganoderiol F; 11, Rhein; 12, Oridonin; 13, Curcumol; 14, Salvianolic acid B; 15, Steroidal saponins; 16, Davidiin; 17, β-Elemene; 18, Ardipusilloside-I; 19, Raddeanin A; 20, Tanshinone IIA; 21, Cordycepin; 22, Huaier polysaccharides; 23, Astragaloside II; 24, Oroxylin A; 25, Tetramethylpyrazine; 26, Arecoline; 27, Artemisinin; 28, Resveratrol; 29, Isofraxidin; 30, Astragalus polysaccharides; 31, *Radix Glycyrrhizae* polysaccharides; 32, *Lycium barbarum* polysaccharide; 33, Polysaccharides from *Artemisia annua* L.; 34, Gastrodin; 35, Shikonin; 36, Gekko sulfated polysaccharide-protein complex; 37, Gekko-sulfated glycopeptide; 38, Pedicularioside G; 39, Vitexin compound **1**.

Table 1. Herbal compounds that inhibit hepatocarcinogenesis.

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Ursolic acid	*Gardenia jasminoides* Ellis (Zhi-Zi), *Prunella vulgaris* (Xia-Ku-Cao), *Hedyotis diffusa* Willd. (Bai-Hua-She-She-Cao), *etc.*	↓ DEN induced hepatocarcinogenesis	↓ Oxidative stress	[5,6]
Penta-acetyl geniposide	*Gardenia jasminoides* Ellis (Zhi-Zi)	↓ AFB1 induced hepatocarcinogenesis	↓ GGT foci	[7]
Curcumin	*Curcuma kwangsiensis* (Yu-Jin or Er-Zhu), *C. phaeocaulis* (Yu-Jin or Er-Zhu), *C. wenyujin* (Yu-Jin or Er-Zhu), *C. longa* (Yu-Jin or Jiang-Huang), *etc.*	↓ DEN induced hepatocarcinogenesis	↓ p21(ras), PCNA and CDC2	[8]
Berberine	*Coptis chinensis* Franch. (Huang-Lian), *Phellodendron chinense* Schneid. (Huang-Bai)	↓ DEN-plus-PB induced hepatocyte proliferation	↓ iNOS, cytochrome P450, CYP2E1 and CYP1A2	[9]
Saikosaponin-d	*Bupleurum chinense* (Chai-Hu)	↓ DEN induced hepatocarcinogenesis	↓ COX-2 and C/EBPβ	[10]
Gomisin A	the fruits of *Schisandra chinensis* or *Schisandra sphenanthera* (Wu-Wei-Zi)	↓ 3′-MeDAB induced hepatocarcinogenesis	Unknown	[11]
Tea polyphenols and tea pigments	Tea	↓ DEN induced hepatocarcinogenesis	↑ p21WAF1 and Bax, ↓ Bcl-2	[12]
Astragalosides, Astragalus polysaccharide and salvianolic acids	*Astragalus membranaceous* (Huang-Qi), *Salvia miltiorrhiza Bunge* (Dan-shen)	↓ DEN induced hepatocarcinogenesis	↓ GST-P and α-SMA	[13]

↓ Inhibit or down-regulate, ↑ up-regulate; DEN, diethylnitrosamine; AFB1, aflatoxin B1; PB, phenobarbital; 3′-MeDAB, 3′-methyl-4-dimethylaminoazobenzene.

Pentaacetyl geniposide, a component of *G. jasminoides* Ellis (Zhi-Zi), protects rats from aflatoxin B1 (AFB1)-induced hepatocarcinogenesis [7] (Figure 1). Curcumin, a common component present in *Curcuma kwangsiensis* (Yu-Jin or Er-Zhu), *C. phaeocaulis* (Yu-Jin or Er-Zhu), *C. wenyujin* (Yu-Jin or Er-Zhu) or *C. longa* (Yu-Jin or Jiang-Huang), is effective in preventing DEN-induced hepatocarcinogenesis accompanied by down-regulation of p21(ras), PCNA and CDC2 [8] (Figure 1). Berberine, a component of *Coptis chinensis* Franch. (Huang-Lian) or *Phellodendron chinense* Schnied. (Huang-Bai), inhibits hepatocyte proliferation induced by DEN and phenobarbital (PB) [9] (Table 1).

Saikosaponin-d, a compound isolated from *Bupleurum chinense* (Chai-Hu) inhibits DEN-induced hepatocarcinogenesis via down-regulation of COX-2 and CCAAT/enhancer binding protein β (C/EBPβ) [10]. The fruits of *Schisandra chinensis* or *S. sphenanthera* (Wu-Wei-Zi) inhibit mutagenicity and hepatocarcinogenesis induced by AFB1 [14,15]. Gomisin A, a component of these fruits, inhibits 3′-methyl-4-dimethylaminoazobenzene-induced hepatocarcinogenesis [11]. Tea polyphenols and tea pigments up-regulate p21WAF1 and Bax, and down-regulate Bcl-2 to inhibit DEN-induced hepatocarcinogenesis [12] (Table 1).

The compound *Astragalus* and *Salvia miltiorrhiza* extract, a herbal component formula composed of astragalosides, *Astragalus* polysaccharide and salvianolic acids, has demonstrated efficacy in preventing DEN-induced hepatocarcinoma in a dose-dependent manner, accompanied by down-regulation of glutathione S-transferase placental type (GST-P) and α-SMA [13] (Table 1).

3. Inhibition of Cell Proliferation

Cancer is characterized by uncontrolled cell proliferation and tumor growth. Inhibition of cell proliferation and tumor growth is one of the primary goals of cancer therapy. Some herbal compounds are effective in inhibiting HCC cell/tumor growth.

Salvianolic acid B, isolated from *S. miltiorrhiza* Bunge (Dan-Shen), inhibits proliferation in hepatoma cells [16]. Steroidal saponins, derived from the rhizomes of *Dioscorea bulbifera* (Huang-Du or Huang-Yao-Zi), inhibit cell proliferation in HCC cells [17]. Davidiin, extracted from *Polygonum capitatum* (Tou-Hua-Liao), inhibits cell proliferation and tumor growth in HCC by targeting EZH2 [18] (Figure 1, Table 2).

β-Elemene, derived from *C. Wenyujin* (Er-Zhu or Yu-Jin) inhibits H22 tumor growth and enhances expression of histone H1 [19]. Ardipusilloside-I, a compound in *Ardisia pusilla* (Jiu-Jie-Long), inhibits tumor growth in H22 HCC [20]. Raddeanin A, a compound isolated from *Anemone raddeana* Regel (Liang-Tou-Jian), inhibits tumor growth in H22 HCC [21] (Figure 1, Table 2).

Indole-3-acetonitrile-4-methoxy-2-C-β-D-glucopyranoside, isolated from *Isatis indigotica* (Song-Lan) inhibits cell proliferation in HepG2 hepatoma cells [22]. Pinocembrin-7-*O*-[3-*O*-galloyl-4″,6″-hexahydroxydiphenoyl]-β-glucose (PGHG) and thonningianins A (Th A) from *Penthorum chinense* Pursh (Che-Gen-Cai) have been shown to have anti-HCC activities [23]. Annonaceous acetogenin-containing *Annona squamosa* (Li-Zhi-He) extract showed antiproliferative effects in liver cancer cells [24] (Table 2).

4. Induction of Apoptosis

Apoptosis is one of the most frequently studied cell processes for elucidating the effective mechanisms of herbal compounds against HCC. A triterpenoid and 20(*R*)-ginsenoside Rg3, isolated from *Panax ginseng*, induces apoptosis in liver cancer cells [25,26]. Gypenoside, a component of *Gynostemma pentaphyllum* (Jiao-Gu-Lan), induces apoptosis in hepatoma cells [27]. Isorhamnetin isolated from *Hippophae rhamnoides* (Sha-Ji) and liquiritigenin from *Glycyrrhiza uralensis* (Gan-Cao) induce apoptosis in HCC cells [28,29] (Table 2).

Table 2. Direct anticancer effects of herbal compounds against hepatocarcinoma.

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Salvianolic acid B	*Salvia miltiorrhiza* Bunge (Dan-Shen)	↓ HepG2 cell proliferation	↓ CYP3A4 and CYP1A2, ↑ GST	[16]
Steroidal saponins	*Dioscorea bulbifera* (Huang-Du or Huang-Yao-Zi)	↓ SMMC7721 and Bel-7402 cell proliferation	Unknown	[17]
Davidiin	*Polygonum capitatum* (Tou-Hua-Liao)	↓ Hepatocellular tumor growth	↓ EZH2	[18]
β-Elemene	*Curcuma kwangsiensis* or *C. phaeocaulis* or *C. wenyujin* (E-Zhu)	↓ H22 tumor growth	↑ Histone H1	[19]
Ardipusilloside-I	*Ardisia pusilla* (Jiu-Jie-Long)	↓ SMMC-7721 tumor growth; ↓ invasion and metastasis in HCC	Unknown; ↓ MMP-9 and -2, ↑ Rac1 and E-cadherin	[20,30]
Raddeanin A	*Anemone raddeana* Regel (Liang-Tou-Jian)	↓ H22 tumor growth	Unknown	[21]
Indole-3-acetonitrile-4-methoxy-2-C-β-D-glucopyranoside	*Isatis indigotica* (Song-Lan)	↓ HepG2 cell proliferation	Unknown	[22]
Pinocembrin-7-*O*-[3-*O*-galloyl-4′′,6′′-hexahydroxydiphenoyl]-β-glucose and thonningianins A	*Penthorum chinense* Pursh (Che-Gen-Cai)	↓ Hepatocarcinoma cell growth	Unknown	[23]
20(*R*),22(xi),24(*S*)-dammar-25(26)-ene-3beta,6 alpha,12 beta,20,22,24-hexanol	*Panax ginseng* (Ren-Shen)	↓ proliferation, ↑ apoptosis, arrest cell cycle at the G1 phase	↑ p53 phosphorylation, activate caspase-3	[25]
20(*R*)-ginsenoside Rg3	*Panax ginseng* (Ren-Shen)	↑ apoptosis, ↓ liver cancer growth	↓ PCNA, ↑ TNF	[26]
Gypenoside	*Gynostemma pentaphyllum* (Jiao-Gu-Lan)	↓ proliferation, ↑ apoptosis in Hep3B and HA22T cells	Unknown	[27]
Isorhamnetin	*Hippophae rhamnoides* (Sha-Ji)	↓ proliferation, ↑ apoptosis in Bel-7402 cells	Unknown	[28]
Liquiritigenin	*Glycyrrhiza uralensis* (Gan-Cao)	↑ apoptosis, ↓ H22 tumor growth	Unknown	[29]
N-butylidenephthalide	*Angelica sinensis* (Dang-Gui)	↑ apoptosis in HepG2 and J5 cells, ↓ cell and tumor growth	↑ Nurr1, NOR-1, Nur77, CREB, caspase-9 and caspase-3, ↓ phosphor-AKT	[31]
Lycium barbarum polysaccharide	*Lycium barbarum* (Gou-Qi)	↓ proliferation, ↑ apoptosis, arrest cell cycle at S phase in QGY7703 cells	↑ Intracellular Ca2+	[32]
Apigenin	*Eclipta prostrate* (Mo-Han-Lian), *etc.*	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in Huh7 cells	↑ 1336 genes, ↓ 428 genes	[33]
Icariin	*Epimedium brevicornum* Maxim. (Yin-Yang-Huo)	↑ apoptosis in SMMC-7721 cells	↑ ROS, JNK, Bax/Bcl-2 and caspase	[34]
Icaritin	*Epimedium brevicornum* Maxim. (Yin-Yang-Huo)	↑ apoptosis in HepG2 cells	↑ JNK1, Bax/Bcl-2 and caspase-3	[35]
Oxymatrine	*Sophora flavescens* (Ku-Shen)	↓ proliferation, ↑ apoptosis, arrest cell cycle at S and G2/M phase in SMMC-7721 cells	↓ Bcl-2, ↑ p53	[36]
Scutellarin	*Scutellaria baicalensis* Georgi (Huang-Qin)	↓ proliferation, ↑ apoptosis in HepG2 cells	↓ ROS, STAT3, Bcl-XL and Mcl-1	[37]

Table 2. *Cont.*

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Sarsasapogenin	*Anemarrhena asphodeloides* (Zhi-Mu)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in HepG2 cells	Unknown	[38]
Pheophorbide a	*Scutellaria barbata* (Ban-Zhi-Lian)	↑ apoptosis in HepG2 and Hep3B cells	↓ Bcl-2, ↑ pro-caspase 3 and pro-caspase 9	[39]
Solamargine	*Solanum nigrum* (Long-Kui)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in SMMC-7721 and HepG2 cells	↑ caspase-3	[40]
Ponicidin	*Rabdosia rubescens* (Dong-Ling-Cao)	↓ proliferation, ↑ apoptosis in QGY-7701 and HepG-2 cells	↓ Survivin and Bcl-2, ↑ Bax	[41]
Paeonol	*Paeonia suffruticosa* (Mu-Dan-Pi)	↓ tumor growth, ↑ apoptosis in HepA-hepatoma bearing mice	↓ Bcl-2, ↑ Bax, IL-2 and TNF-alpha	[42]
Cryptotanshinone, dihydrotanshinone, tanshinone I, tanshinone IIA	*Salvia miltiorrhiza* Bunge (Dan-shen)	↑ apoptosis in HepG2 cells	↑ ROS	[43]
Resveratrol-4-*O*-D-(2′-galloyl)-glucopyranoside	*Polygonum cuspidatum* (Hu-Zhang)	↓ proliferation, ↑ apoptosis in SMMC-7721 cells	↑ caspase-3 and -9, p-JNK, ↓ p-ERK	[44]
Tubeimoside I	*Bolbostemma paniculatum* (Tu-Bei-Mu)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in HepG2 cells	↑ caspase-3 and -9, Bax/Bcl-2	[45]
Norcantharidin	Mylabris (Ban-Mao)	↓ proliferation, ↑ apoptosis in HepG2 cells	↑ ROS, caspase-3 and -9, and Bax, ↓ Bcl-2	[46]
Resveratrol-4-*O*-D-(2′-galloyl)-glucopyranoside	*Polygonum cuspidatum* (Hu-Zhang)	↓ proliferation, ↑ apoptosis in SMMC-7721 cells	↑ caspase-3 and -9, p-JNK, ↓ p-ERK	[44]
Toosendanin	*Melia toosendan* (Chuan-Lian-Zi)	↓ proliferation, ↑ apoptosis in SMMC-7721 and Hep3B cells	↑ Bax, ↓ Bcl-2	[47]
Honokiol	*Magnolia officinalis* (Hou-Po)	↑ apoptosis in liver cancer cells	↓ Bcl-X(L), Bcl-2, procaspase-3 and -9, ↑ MAPK and active caspase-3	[48]
Magnolol	*Magnolia officinalis* (Hou-Po)	↑ apoptosis in HepG2 cells	↑ caspase-3, -8, and -9, ↓ Bcl-2	[49]
Oleanolic acid and ursolic acid	The fruit of *Ligustrum lucidum* Ait. (Nü-zhen-zi), *Salvia chinensis* (Shi-Jian-Chuan), *Hedyotis diffusa* Willd. (Bai-Hua-She-She-Cao), *etc.*	↓ proliferation and adhesion, ↑ apoptosis in liver cancer cells	↑ caspase-3 and -8, ↓ Na(+)-K(+)-ATPase activity, VEGF and ICAM-1	[50]
Chrysophanol	*Rheum palmatum* L. or *R.tanguticum* Maxim.ex Balf. or *R.officinale* Baill. (Da-Huang)	↓ proliferation, ↑ necrosis in J5 cells	↓ ATP level, ↑ ROS and lactate dehydrogenase activity	[51]
Rhein	*Rheum palmatum* L. or *R.tanguticum* Maxim.ex Balf. or *R.officinale* Baill. (Da-Huang)	↑ apoptosis in HepG2 cells; ↓ proliferation, ↑ apoptosis, arrest cell cycle at S phase in Bel-7402 cells	↑ caspase-3; ↑ caspase-3, ↓ c-Myc	[52,53]
Vitexin compound 1	*Vitex negundo*(Huang-Jing)	↓ proliferation, ↑ apoptosis in liver cancer cells	↑ caspase-3, -8 and -9, FOXO3a, Bim, TRAIL, DR4 and DR5, ↓ phosphorylation of AKT and ERK1/2	[54]
Quercetin	*Bupleurum chinense* (Chai-Hu), *Euphorbia lunulata* Bunge (Mao-Yan-Cao) and *Taxillus chinensis* (Sang-Ji-Sheng), *etc.*	↓ proliferation, ↑ apoptosis in HA22T/VGH cells	↑ ROS	[55]

Table 2. *Cont.*

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Gambogic acid	*Garcinia hanburyi* (Teng-Huang)	↓ proliferation, ↑ apoptosis in SMMC-7721 cells	↑ Bax, ↓ Bcl-2	[56]
Flavonoids	*Polygoni Orientalis* Fructus (Shui-Hong-Hua-Zi)	↓ proliferation, ↑ apoptosis, arrest cell cycle at S phase in SMMC-7721 cells	Unknown	[57]
TSP02	*Ardisia japonica* (Zi-Jin-Niu)	↓ proliferation, migration and invasiveness, ↑ apoptosis in HepG2 cells	↓ CDK1, 2, 4, and TGF-beta1, ↑ Caspase-8 and E-cadherin	[58]
Bufothionine	*Bufonis Venenum* (Chan-Su)	↓ proliferation, ↑ arrest cell cycle at G2/M phase in hepatocarcinoma cells	Unknown	[59]
Oridonin	*Rabdosia rubescens* (Dong-Ling-Cao)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in HepG2 cells	↑ p-JNK, p-p38, p-p53, p21, cyclin B1/p-Cdc2 (Tyr15), caspase-9 and -3, ↓ p-ERK	[60]
Curcumol	*Curcuma kwangsiensis* or *C. phaeocaulis* or *C. wenyujin* (E-Zhu)	↓ proliferation, arrest cell cycle at G1 phase in HepG2 cells	↑ pRB1, cyclin D1, CDK2, CDK8, p27KIP1, p53 and p21WAF1, ↓ cyclin A1	[61]
Saikosaponin d	*Bupleurum chinense* (Chai-Hu)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G1 phase in HepG2 and Hep 3B cells	↑ p53, p21/WAF1, Fas/APO-1, mFasL, sFasL, Bax and IkappaBalpha, ↓ NF-kappaB and Bcl-XL	[62]
Waltonitone	*Gentiana waltonii* (Chang-Geng-Qin-Jiao)	↓ proliferation, arrest cell cycle at S phase in Bel-7402 cells	↑ Akt and ERK1/2 phosporylation	[63]
Nobiletin	*Citrus aurantium* (Zhi-Shi)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2 phase in SMMC-7721 cells	↑ Bax and caspase-3, ↓ Bcl-2 and COX-2	[64]
Matrine	*Sophora flavescens* (Ku-Shen)	↓ proliferation, ↑ apoptosis and autophagy, arrest cell cycle at G1 phase in HCC cells; ↓ invasion in SMMC-7721 cells	↑ Bax/Bcl-2 and Beclin 1; ↓ MMP-9 and NF-κB	[65–67]
Berberine	*Coptis chinensis* Franch. (Huang-Lian) or *Phellodendron chinense* Schnied. (Huang-Bai)	↑ apoptosis, arrest cell cycle at G1 phase in HuH7 cells; ↑ apoptosis and autophagy in HepG2 cells	↓ PCNA, Bid and Bcl-2, ↑ caspase-3 and -7; ↑ AMPK, ↓ mTORC1	[68,69]
Baicalein	*Scutellaria baicalensis* Georgi (Huang-Qin)	↑ apoptosis, arrest cell cycle at G2/M phase in J5 cells; ↓ proliferation, ↑ apoptosis and autophagy in SMMC7721 cells	↑ caspase-9 and -3, and Bax/Bcl-2 ratio; ↑ Beclin 1, ↓ CD147	[70,71]
Oroxylin-A	*Scutellaria baicalensis* Georgi (Huang-Qin)	↓ proliferation, ↑ apoptosis and autophagy in HepG2 cells; reverse drug resistance and enhance apoptosis inducing effect of Paclitaxel in drug resistant HepG2 cells	Induction of Bax translocation, activation and oligomerization, ↑ Beclin 1, ↓ PI3K-PTEN-Akt-mTOR signaling pathway; ↓ Integrin β1	[72–74]
Shikonin	*Lithospermum erythrorhizon* (Zi-Cao)	↑ apoptosis in Huh7 and BEL7402 cells; ↑ autophagy in HCC cells; ↓ proliferation and migratory ability on HepJ5 and Mahlavu cells	↑ ROS, ↓ Akt and RIP1/NF-κB; ↑ ROS and ERK, ↓ RIP pathway; ↓ MMP-2 and -9, vimnetin, AKT and IκB phosphorylation, NF-κB	[75–77]
Curcumin	*Curcuma kwangsiensis* (Yu-Jin or Er-Zhu), *C. phaeocaulis* (Yu-Jin or Er-Zhu), *C. wenyujin* (Yu-Jin or Er-Zhu), *C. longa* (Yu-Jin or Jiang-Huang), *etc.*	↑ apoptosis in Huh7 cells; ↑ apoptosis and autophagy in HepG2 cells; ↓ proliferation, EMT and migration in hypoxic HepG2 cells	↑ p38, FasL and caspase-3; ↑ caspase-3, ↓ Bcl-2/Bax; ↓ HIF-1alpha	[78–80]

Table 2. *Cont.*

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Resveratrol	*Polygonum cuspidatum* (Hu-Zhang), *etc.*	↓ proliferation, ↑ apoptosis in Hepa 1-6 cells; ↓ proliferation, ↑ apoptosis and autophagy, arrest cell cycle at S phase in HuH7 cells; ↓ invasion in HCC cells	↑ROS and caspase-3; ↑ p21/WAF1, Atg5, Atg7, Atg9, and Atg12, ↓ cyclin E, cyclin A, CDK2, phospho-ERK and phospho-p38; ↓ MMP-9	[81–84]
Bufalin and cinobufagin	Toad skin and venom	↑ apoptosis in HepG2 cells (Bufalin and cinobufagin); ↑ apoptosis and autophagy in HepG2 cells (Bufalin)	↑ Fas, Bax and Bid, caspase-3, -8, -9 and -10, ↓ Bcl-2 (Bufalin and cinobufagin; ↑ Beclin 1 and AMPK phosphorylation, ↓ p62 and mTOR signaling (Bufalin)	[85,86]
Tetrandrine	*Stephania tetrandra* (Han-Fang-Ji)	↓ proliferation, ↑ apoptosis and autophagy, arrest cell cycle at G2/m phase in liver cancer cells	↑ ROS, ERK MAP kinase and ATG7, ↓ Akt	[87–89]
Arenobufagin	Toad venom	↑ apoptosis and autophagy in HepG2 cells	↑ Bax/Bcl-2, ↓ PI3K/Akt/mTOR pathway	[90]
Allicin	Garlic	↓ proliferation, ↑ autophagy in HepG2 cells	↑ AMPK/TSC2 and Beclin-1 signaling, ↓ p53, the PI3K/mTOR signaling and Bcl-2	[91]
Galangin	*Alpinia officinarum* Hance (Gao-Liang-Jiang)	↓ proliferation, ↑ apoptosis and autophagy in HepG2 cells	↑ p53	[92]
Kaempferol	*Euphorbia lunulata* Bunge. (Mao-Yan-Cao)	↓ proliferation, ↑ autophagy, arrest cell cycle at G2/M phase in SK-HEP-1 cells	↑ p-AMPK, LC3-II, Atg 5, Atg 7, Atg 12 and beclin 1, ↓CDK1, cyclin B, p-AKT and p-mTOR	[93]
EGCG	Tea	Inhibit autophagy to enhance anti-cancer effects of doxorubicin in Hep3B cells	↓ Beclin 1 and Atg5	[94]
Elemene injection	*Curcuma kwangsiensis* or *C. phaeocaulis* or *C. wenyujin* (E-Zhu)	Induce autophagy and prevent HepG2 cells from undergoing apoptosis	↓ Bcl-2/Bax and LC3 I/LC3 II ratio	[95]
Ganoderiol F	*Ganoderma amboinense* (Lu-Jiao-Ling-Zhi)	↓ proliferation, ↑ cell senescence in HepG2 cells	↑ EKR and p16	[96]
Arecoline	*Areca catechu* L. (Bing-Lang)	↑ anoikis in HA22T/VGH cells	↑ Bax, caspase-3 and Rho/Rock activation, ↓ beta1-integrin, IL-6, STAT3 and p190RhoGAP phosphorylation, SHP2, Bcl-XL and Bcl-2	[97]
Tanshinone II-A	*Salvia miltiorrhiza* Bunge (Dan-shen)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G0/G1 phase in SMMC-7721 cells; ↓ EMT and metastasis in HCC; ↓ migration and invasion in HCC cells	↓ Bcl-2 and c-myc, ↑ Fas, Bax and p53; ↑ VEGFR1/PDGFR; ↓ MMP-2 and -9, NF-κB	[98–100]
Dihydroartemisinin	*Artemisia annua* L. (Qing-Hao)	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M phase in HCC cells; ↓ invasion and metastasis in HCC cells	↑ p21, caspase-9 and -3 , Noxa and active Bak, ↓ cyclin B, CDC25C and Mcl-1; ↓ MMP2, ↑ TIMP2, Cdc42 and E-cadherin	[101,102]
Cordycepin	*Cordyceps sinensis* (Dong-Chong-Xia-Cao)	↓ proliferation, EMT and migration/invasion	↓ integrin α3, integrin α6, integrin β1 and phosphorylated FAK	[103]
Polysaccharides	Huaier	↓ proliferation, EMT, adhesion, migration and invasion in MHCC97-H cells	↓ AEG-1	[104]
Platycodin D	*Platycodon grandiflorum* (Jie-Geng)	↓ proliferation, adhesion, migration and invasion in HCC cells	↑ Bax, ↓ survivin	[105]
Isofraxidin	*Acanthopanax senticosus* (Ci-Wu-Jia)	↓ invasion in HCC cells	↓ MMP-7 and ERK1/2	[106]

Table 2. *Cont.*

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
β-Ionone	*Aucklandia lappa* Decne or *Vladimiria souliei* (Franch.) Ling (Mu-Xiang)	↓ invasion, migration and adhesion in SK-Hep-1 cells	↓ MMP-2 and -9, urokinase-type plasminogen activator activities, FAK, Rho, Rac1 and Cdc42, ↑ TIMP-1 and -2, plasminogen activator inhibitor-1 and nm23-H1	[107]
Hesperidin	*Citrus reticulata* Blanco (Chen-Pi)	↓ acetaldehyde-induced cell invasion in HepG2 cells	↓ MMP-9, NF-kappaB, AP-1, JNK, and p38 signaling pathways	[108]
Astragalosides, *astragalus* polysaccharide and salvianolic acids	*Astragalus membranaceous* (Huang-Qi), *Salvia miltiorrhiza* Bunge (Dan-shen)	↓ TGF-beta(1)-induced cell invasion in HepG2 cells	Modulating TGF-beta/Smad signaling	[109]
Astragalus polysaccharides	*Astragalus membranaceous* (Huang-Qi)	↑anti-tumor effect of Adriamycin in H22 hepatocarcinoma	↑ IL-1α, IL-2, IL-6 and TNF-α, ↓ IL-10 and MDR1	[110]
Tetramethylpyrazine	*Ligusticum chuanxiong* Hort (Chuan-Xiong)	Reverse multidrug resistance in BEL-7402/ADM cells	↓ MDR1, MRP2, MRP3 and MRP5	[111]
Epicatechin gallate and epigallocatechin gallate	Tea	Increase intracellular DOX accumulation and enhance DOX-induced cell killing activities against BEL-7404/DOX cells	↓ MDR1	[112]
Hedyotiscone A	*Hedyotis corymbosa* (San-Fang-Hua-Er-Cao)	↑ apoptosis in multidrug-resistant hepatocellular carcinoma cells	↑ caspases-3, -7 and -9	[113]
Polyphyllin D	*Paris polyphylla* Sm. (Chong-Lou)	↑ apoptosis in multi-drug resistant HepG2 cells	Mitochondrial dysfunction	[114]
Ursolic acid	*Gardenia jasminoides* Ellis (Zhi-Zi), *Prunella vulgaris* (Xia-Ku-Cao), *Hedyotis diffusa* Willd. (Bai-Hua-She-She-Cao), *etc.*	↑ apoptosis in doxorubicin-resistant human hepatoma cells	↑ Bak and apoptosis-inducing factor	[115]
Pseudolaric acid B	*Pseudolarix kaempferi* (Tu-Jin-Pi)	↑ apoptosis and arrest cell cycle at G2/M phase in conventional and P-gp-overexpressing hepatocarcinoma cells	Disrupts cellular microtubule networks and inhibits the formation of mitotic spindles	[116]
Imperatorin	*Angelica dahurica* (Bai-Zhi)	↑ apoptosis in multidrug-resistant liver cancer cells	↑ proteosome-dependent Mcl-1 degradation to release Bak and Bax	[117]

↓ Inhibit or down-regulate, ↑ promote or up-regulate.

N-Butylidenephthalide, derived from *Angelica sinensis* (Dang-Gui), is effective in inducing apoptosis in HCC cells [31]. Polysaccharide from *Lycium barbarum* (Gou-Qi) induces apoptosis in liver cancer cells [32]. Apigenin, a common compound abundantly present in *Eclipta prostrate* (Mo-Han-Lian) and other herbs, fruits or vegetables, induces apoptosis and arrests cell cycle at G2/M phase in HCC cells [33]. Icariin and icaritin, isolated from *Epimedium brevicornum* Maxim. (Yin-Yang-Huo), up-regulate JNK and Bax/Bcl-2 to induce apoptosis in liver cancer cells [34,35] (Table 2).

Matrine and oxymatrine from *Sophora flavescens* (Ku-Shen) induce apoptosis in HCC cells [36,65] (Figure 1). Berberine, a compound from *C. chinensis* Franch. (Huang-Lian), induces apoptosis in liver cancer cells via the mitochondrial pathway [68]. Scutellarin, baicalein, and oroxylin-A, derived from *Scutellaria baicalensis* Georgi (Huang-Qin), induce apoptosis in HCC cells [37,70,72]. Sarsasapogenin from *Anemarrhena asphodeloides* (Zhi-Mu) induces apoptosis and G2/M cell cycle arrest in liver cancer cells [38] (Table 2).

Pheophorbide A, a component purified from *S. barbata* (Ban-Zhi-Lian), inhibits Bcl-2 expression and induces apoptosis via a mitochondria-mediated intrinsic pathway in HCC cells [39]. Solamargine purified from *Solanum nigrum* (Long-Kui) induces apoptosis and G2/M cell cycle arrest in SMMC-7721 cells [40] (Figure 1). Ponicidin, a compound from *Rabdosia rubescens* (Dong-Ling-Cao), induces apoptosis accompanied by down-regulation of Survivin and Bcl-2 and up-regulation of Bax in HCC cells [41] (Figure 1). Shikonin from *Lithospermum erythrorhizon* (Zi-Cao) induces apoptosis in HCC cells through generation of reactive oxygen species (ROS) and down-regulation of Akt and RIP1/NF-κB pathways [75]. Paeonol from *Paeonia suffruticosa* (Mu-Dan-Pi) induces apoptosis in HCC [42] (Table 2).

Curcumin, a component in *Curcuma kwangsiensis* (Yu-Jin or Er-Zhu) or *C. phaeocaulis* (Yu-Jin or Er-Zhu), *C. wenyujin* (Yu-Jin or Er-Zhu), *C. longa* (Yu-Jin or Jiang-Huang), induces apoptosis via p38 activation [78]. Cryptotanshinone, dihydrotanshinone, tanshinone I and tanshinone IIA derived from *S. miltiorrhiza* Bunge (Dan-Shen), and resveratrol and resveratrol-4-*O*-D-(2′-galloyl)-glucopyranoside from Hu-Zhang (*Polygunum cuspidatum*), induce apoptosis in HCC cells [43,44,81,98]. Tubeimoside I, an ingredient derived from *Bolbostemma paniculatum* (Tu-Bei-Mu), up-regulates Bax/Bcl-2 and induces intrinsic apoptosis in hepatoma cells [45] (Table 2).

Norcantharidin potently increases ROS production, down-regulates Bcl-2, up-regulates Bax, and activates caspase-3 and -9 to induce apoptosis in liver cancer cells [46]. Bufalin and cinobufagin, isolated from toad skin and venom, induce apoptosis via Fas- and mitochondria-mediated pathways in HCC cells [85]. Tetrandrine, a compound isolated from *Stephania tetrandra* (Han-Fang-Ji), induces apoptosis in HCC cells by activating ROS production and repressing Akt activity [87]. Toosendanin, isolated from *Melia toosendan* (Chuan-Lian-Zi), induces mitochondria-dependent apoptosis in HCC cells [47]. Honokiol and magnolol, isolated from *Magnolia officinalis* (Hou-Po) induce apoptosis in liver cancer cells [48,49] (Table 2).

Oleanolic acid and ursolic acid, compounds widely present in the fruit of *Ligustrum lucidum* Ait. (Nü-zhen-zi), *Salvia chinensis* (Shi-Jian-Chuan), *H. diffusa* Willd. (Bai-Hua-She-She-Cao) and other herbs, have demonstrated apoptosis-inducing effects in HCC cells [50]. Chrysophanol and rhein, compounds isolated from *Rheum palmatum* L. or *R. tanguticum* Maxim.ex Balf. or *R. officinale* Baill. (Da-Huang), induce necrosis or apoptosis in HCC cells [51,52]. Vitexin compound 1 from the seed of *Vitex negundo* (Huang-Jing) induces apoptosis in HCC cells via activation of FOXO3a and down-regulation of AKT and ERK1/2 phosphorylation [54] (Table 2).

Quercetin, a common compound in many herbs such as *B. chinense* (Chai-Hu), *Euphorbia lunulata* Bunge (Mao-Yan-Cao) and *Taxillus chinensis* (Sang-Ji-Sheng), induces apoptosis in HCC cells and is related to ROS generation [55]. Gambogic acid, a compound in *Garcinia hanburyi* (Teng-Huang), induces apoptosis in HCC with relatively less adverse effects on normal hepatocytes [56]. Flavonoids isolated from *Polygoni Orientalis* Fructus (Shui-Hong-Hua-Zi) induce apoptosis and G2/M phase cell cycle arrest in HCC cells [57]. TSP02, a triterpenoid saponin from *Ardisia japonica* (Zi-Jin-Niu) has demonstrated apoptosis-inducing effects in hepatoma cells [58] (Table 2).

5. Cell Cycle Arrest

Cancer is characterized by uncontrolled proliferation cycle and stopping the cell cycle is an ideal approach for cancer treatment. Some herbs are effective at arresting the cell cycle. Bufothionine inhibits cell proliferation and arrests cell cycle at G2/M phase in liver cancer cells [59]. Rhein, a component of *R. palmatum* L, *R. tanguticum* Maxim.ex Balf. or *R. officinale* Baill. (Da-Huang), is effective in inhibiting cell growth, inducing apoptosis and arresting cell cycle at S phase in HCC cells [53]. Oridonin, a compound from *R. rubescens* (Dong-Ling-Cao), induces G2/M cell cycle arrest and apoptosis in HepG2 cells through activation of the MAPK and p53 pathways [60] (Figure 1, Table 2).

Curcumol, a compound present in *C. phaeocaulis*, *C. wenyujin* or *C. kwangsiensis* (Er-Zhu), inhibits cell proliferation and induces G0 phase cell cycle arrest by activating the p53/RB pathway that involves cyclin A1, CDK2, CDK8, p21WAF1 and p27KIP1 in HCC cells [61] (Figure 1). Tanshinone IIA, isolated from *S. miltiorrhiza* Bunge (Dan-Shen), inhibits proliferation and induces G2/M cell cycle arrest accompanied by up-regulation of calreticulin, caspase-12 and GADD15, and down-regulation of Bcl-2, Cdc25c and Cdc2 in HCC cells [118]. Resveratrol, a compound can be found in *P. cuspidatum* (Hu-Zhang), induces cell cycle arrest, apoptotic and autophagic cell death in liver cancer cells [82] (Table 2).

Tetrandrine, a compound isolated from *S. tetrandra* (Han-Fang-Ji), inhibits proliferation and arrests cell cycle at G2/M phase in HCC cells [88]. Dihydroartemisinin, a semi-synthetic derivative of artemisinin isolated from *Artemisia annua* L. (Qing-Hao), induces apoptosis, and G2/M cell cycle arrest through induction of p21 and inhibition of cyclin B and CDC25C in liver cancer cells [101]. Saikosaponin d, a compound isolated from *B. chinense* (Chai-Hu), has demonstrated potency in inducing apoptosis and G0 cell cycle arrest by up-regulating p53 and p21/WAF1 in HCC cells [62] (Table 2).

Waltonitone, a compound isolated from *Gentiana waltonii* (Chang-Geng-Qin-Jiao), is effective in inhibiting cell proliferation and inducing S phase cell cycle arrest through activation of Akt and ERK1/2 phosporylation in liver cancer cells [63]. Nobiletin, a compound from *Citrus aurantium* (Zhi-Shi) or other herbs, induces apoptosis and G2 phase cell cycle arrest in HCC cells [64]. *S. nigrum* L. (Long-Kui) polyphenolic extract induces apoptosis and G2/M cell cycle arrest by down-regulating CDC25A, CDC25B and CDC25C in hepatoma cells [119]. Triterpene-enriched extracts from *Ganoderma lucidum* (Ling-Zhi) could suppress PKC, activate JNK and p38 MAPK to prolong G2 phase and inhibit cell growth in Huh-7 cells [120] (Table 2).

6. Induction of Autophagy

Autophagy, type II programmed cell death, is a process in which organelles and proteins are sequestered and subsequently degraded through fusion with lysosomes, and has been recognized as a target for HCC treatment [121,122]. Tetrandrine, isolated from *S. tetrandra* (Han-Fang-Ji), promotes ROS generation and activates ERK MAP kinase to induce autophagy in HCC cells [89] (Figure 1). Shikonin, a naphthoquinone from *L. erythrorhizon* (Zi-Cao), induces autophagy in HCC cells via ROS production and ERK activation [76]. Matrine, a compound from *S. flavescens* Ait. (Ku-Shen), induces apoptosis and autophagy in HepG2 cells [66] (Table 2).

Baicalein, a compound from *S. baicalensis* Georgi (Huang-Qin), down-regulates CD147 and induces autophagy in liver cancer cells [71] (Figure 1). Oroxylin A, another compound from *S. baicalensis* Georgi (Huang-Qin), induces autophagy by suppressing PI3K-PTEN-Akt-mTOR signaling in HepG2 cells [73]. Berberine, a compound isolated from *C. chinensis* Franch. (Huang-Lian) and other herbs, is effective at inducing apoptosis and autophagy associated with AMPK activation and mTORC1 inhibition [69] (Table 2).

Bufalin, a component from toad skin, has demonstrated efficacy in the induction of AMPK-dependent autophagy accompanied by enhanced Beclin-1 expression, and decreased p62 expression and mTOR signaling in HepG2 cells [86] (Figure 1). Arenobufagin, a natural bufadienolide from toad venom, is a potent inducer of apoptosis and autophagy by down-regulating PI3K/Akt/mTOR pathway in HepG2/ADM hepatoma cells [90]. Curcumin, a common compound in herbs belonging to the plant genus *Curcuma*, when combined with Adriamycin, induces apoptosis and autophagy in Hep G2 cells by down-regulating Bcl-2/Bax [79] (Table 2).

Allicin, a major phytochemical found in garlic, is effective at inducing autophagy in HepG2 cells by decreasing the level of cytoplasmic p53, PI3K/mTOR signaling and Bcl-2, and up-regulating the expression of AMPK/TSC2 and Beclin-1 [91]. Galangin, a component of *Alpinia officinarum* Hance (Gao-Liang-Jiang), has demonstrated potency in up-regulating p53 and inducing apoptosis and autophagy in HepG2 cells [92]. Kaempferol, a common compound in *E. lunulata* Bunge. (Mao-Yan-Cao) and other herbs, induces G2/M cell cycle arrest, apoptosis, and autophagy, and related to CDK1/cyclin B expression and AMPK and AKT signaling pathways [93] (Table 2).

However, in a different context, autophagy may promote cell death and contribute to anticancer therapeutic response, or inhibit cell death and thus contribute to drug resistance [123]. Inhibition of autophagy may enhance chemotherapy or target therapy-induced cell death in HCC cells [124,125]. As an autophagy inhibitor, epigallocatechin-3-*O*-gallate (EGCG) strengthens doxorubicin (DOX)-mediated anticancer effects in hepatoma cells [94]. As an autophagy inducer, elemene injection (a herbal injection) protects hepatoma cells from apoptosis induced by apatinib or serum-free starvation [95]. These observations suggest that autophagy-inducing herbal compounds need to be more thoroughly investigated in combination with other treatments such as chemotherapy and targeted therapy Table 2.

7. Induction of Cell Senescence

Cell senescence is a stable, irreversible cell cycle arrest triggered by a variety of stimuli. Induction of senescence has been suggested as novel approach for HCC treatment [126]. Ganoderiol F, a tetracyclic triterpene from *Ganoderma amboinense*, activates ERK and up-regulates p16 to induce cell senescence in hepatoma HepG2 cells [96] (Figure 1, Table 2).

L. lucidum Ait. Fruit (Nü-zhen-zi) up-regulates p21, activates caspases-8, -9 and -3 to induce apoptosis, and down-regulates RB phosphorylation to induce cell senescence in heaptocarcinoma cells [127]. The known compounds in *L. lucidum* Ait. fruit include oleanolic acid, ursolic acid and tartaric acid. The compound(s) responsible for inducing cell senescence need further study.

Liver Yin tonifying formula (LYTF) activates caspases-8, -9 and -3 to induce apoptosis, and up-regulates p16 and p21 and down-regulates RB phosphorylation to induce cell senescence in Bel-7402 cells [128]. The known compounds in LYTF include oleanolic acid, ursolic acid and emodin. The compound(s) responsible for inducing cell senescence need further investigation.

8. Induction of Anoikis

Anoikis, an apoptotic process occurring when a cell detaches from extracellular matrix, is associated with cell survival in suspension and metastasis of HCC [129]. Arecoline, an alkaloid from *Areca catechu* L. (Bing-Lang), induces anoikis in HA22T/VGH cells by inhibiting STAT3 and increasing RhoA/Rock activation [97] (Figure 1, Table 2).

P. cuspidatum (Hu-Zhang), a common herb used for HCC treatment, activates caspase-3 and -9 and induces anoikis in human HCC cells accompanied by ROS generation and FAK down-regulation [130]. The known compounds in Hu-Zhang include resveratrol, emodin, polydatin and physcion. However, the compound(s) contributing to Hu-Zhang-induced anoikis need further study.

Modified Yi Guan Jian (MYGJ) may activate caspase-3, -8 and -9, inhibit the expression and phosphorylation of p38 MAPK, and induce anoikis in human HCC cells [131]. The known compounds in MYGJ include coumarin, glucosides, betane and toosendanin. Further study is needed to identify the compound(s) responsible for MYGJ-induced anoikis.

9. Inhibition of Epithelial-Mesenchymal Transition (EMT)

EMT is a biological process in which polarized epithelial cells (including epithelial cancer cells) switch to a fibroblastoid or mesenchymal cellular phenotype [132]. During EMT, the epithelial marker E-cadherin (E-cad) is down-regulated and mesenchymal markers, such as N-cadherin (N-Cad) and vimentin, are up-regulated. EMT contributes to cancer metastasis by enhancing cell migration and invasiveness. EMT also contributes to drug resistance [133].

Tanshinone IIA, a compound isolated from *S. miltiorrhiza* Bunge (Dan-Shen), has demonstrated effects in inhibiting EMT and metastasis in HCC after palliative resection [99] (Figure 1). Curcumin, a common herbal compound in herbs of the plant genus *Curcuma*, inhibits hypoxia-induced EMT in hepatoma HepG2 cells [80]. Cordycepin, a compound isolated from *Cordyceps sinensis* (Dong-Chong-Xia-Cao), may up-regulate E-cad and down-regulate integrins and phosphorylation of FAK to inhibit proliferation, migration and invasion in HCC cells [103] (Figure 1 Table 2).

Huaier polysaccharides are effective in inhibiting proliferation, adhesion, migration and invasion in HCC cells accompanied by EMT inactivation as indicated by marker gene expression [104] (Figure 1, Table 2). Songyou Yin, a formula composed of five herbs, has reported efficacy in attenuating EMT and inhibiting metastatic potential in residual HCC resulted from oxaliplatin treatment [134]. The known compounds in Songyou Yin include tanshinone IIA and astragaloside IV.

10. Inhibition of Metastasis

Chinese herbal compounds have demonstrated potency in inhibiting metastatic potential in HCC cells, such as adhesion, migration, invasion, and metastasis. Matrine, a component of Ku-Shen (*S. flavescens* Ait.), down-regulates MMP-9 and NF-κB and inhibits invasion in liver cancer cells [67]. Shikonin, an ingredient of *L. erythrorhizon* (Zi-Cao), inhibits migration in HCC cells via down-regulation of vimentin, MMP-2 and MMP-9 [77]. Artemisinin, from *A. annua* L. (Qing-Hao), inhibits HCC metastasis by down-regulation of MMP2 and phosphorylation of p38 and ERK1/2, and up-regulation of TIMP2, Cdc42 and E-cadherin [102] (Figure 1, Table 2).

Gekko sulfated polysaccharide-protein complex inhibits HCC cell migration through calcium-mediated regulation of actin cytoskeleton reorganization [135]. Tanshinone IIA, a component isolated from *S. miltiorrhiza* (Dan-Shen), inhibits invasion and metastasis of HCC cells by inhibiting MMP-2 and MMP-9 activities and blocking NF-κB activation [100]. Resveratrol inhibits adhesion, migration, invasion and MMP-9 expression in liver cancer cells [83,84] (Figure 1). Platycodin D, a compound isolated from *Platycodon grandiflorum* (Jie-Geng), inhibits cell adhesion, migration and invasion of HCC cells [105]. Ardipusilloside I, a compound isolated from *A. pusilla* (Jiu-Jie-Long), inhibits liver cancer survival, invasion and metastasis by down-regulating MMP-9 and MMP-2 and activating Rac 1 to enhance E-cadherin activity [30] (Table 2).

Isofraxidin, isolated from *Acanthopanax senticosus* (Ci-Wu-Jia), inhibits MMP-7 expression and cell invasion in human hepatoma cells [106] (Figure 1). β-Ionone, a compound found in *Aucklandia lappa* Decne, *Vladimiria souliei* (Franch.) Ling (Mu-Xiang) and other herbs, inhibits cell invasion, migration and adhesion in HCC cells [107]. Hesperidin, a compound can be found in *Citrus reticulata* Blanco (Chen-Pi) and other herbs, has reported efficacy in inhibiting acetaldehyde-induced MMP-9 expression and cell invasion in HCC cells [108] (Table 2).

In addition to single compound, multiple herbal ingredients can be combined and used as a formula. Compound *Astragalus* and *Salvia miltiorrhiza* extract (CASE), a herbal component formula comprising astragalosides, astragalus polysaccharide and salvianolic acids, inhibits TGF-β1 mediated invasion in hepatoma HepG2 cells by modulating TGF-β/Smad signaling [109] (Table 2).

11. Targeting Drug Resistance

Drug resistance contributes to chemotherapy-refractory HCC [136]. The search for effective herbal components to reverse drug resistance has become a research focus area in liver cancer studies. *Astragalus membranaceus* (Huang-Qi) polysaccharides enhance the anti-tumor effects of adriamycin in H22 hepatocarcinoma by up-regulating IL-1α, IL-2, IL-6 and TNF-α, as well as down-regulating IL-10 and MDR1 [110]. Astragaloside II, another component from *A. membranaceus* (Huang-Qi), is effective in enhancing cytotoxicity of 5-fluorouracil (5-Fu) in 5-Fu-resistant HCC cells accompanied by down-regulation of P-gp, phosphorylation of ERK1/2, p38 and JNK [137] (Figure 1, Table 2).

Oroxylin A, a compound isolated from *S. baicalensis* Georgi (Huang-Qin) potently inhibits integrin β1, reverses drug resistance and enhances apoptosis-inducing effect of paclitaxel in drug-resistant HepG2 cells [74] (Figure 1). Tetramethylpyrazine, a bioactive constituent isolated from *Ligusticum chuanxiong* Hort (Chuan-Xiong), down-regulates MDR1, MRP2, MRP3 and MRP5 in adriamycin-resistant HepG2 cells [111] (Figure 1). Epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) inhibits MDR1 expression, increases intracellular DOX accumulation and enhance DOX-induced cytotoxicity in BEL-7404/DOX cells [112] (Table 2).

In addition to reversing drug resistance, some herbal compounds have direct effects against drug-resistant liver cancer cells. Hedyotiscone A, a compound isolated from *H. corymbosa* (San-Fang-Hua-Er-Cao), activates caspases-3, -7 and -9 to induce apoptosis in multidrug resistant HCC cells [113]. Polyphyllin D, derived from *Paris polyphylla* Sm. (Chong-Lou), induces apoptosis in multidrug resistant HepG2 cells via mitochondrial dysfunction [114]. Ursolic acid, a common component in multiple herbs, activates Bak and promotes release of apoptosis-inducing factor to induce apoptosis in doxorubicin-resistant human hepatoma cells [115] (Table 2).

Pseudolaric acid B, a compound present in *Pseudolarix kaempferi* (Tu-Jin-Pi), may disrupt cellular microtubule networks and inhibit mitotic spindle formation to induce apoptosis and G2/M cell cycle arrest in conventional and P-gp-overexpressing HCC cells [116]. Imperatorin, a compound isolated from *Angelica dahurica* (Bai-Zhi), induces proteosome-dependent Mcl-1 degradation to release Bak and Bax and triggers apoptosis in multidrug-resistant liver cancer cells [117] (Table 2).

12. Regulation of Immune Function

The major cell populations for cellular immunity against cancer include CD4+ T helper (Th) and CD8+ T lymphocytes. CD4+ Th1 cells produce cytokines, such as IL-2 and IFN-γ, to evoke cell-mediated immunity or phagocyte-dependent inflammation. CD4+ Th2 cells secrete cytokines, such as IL-4 and IL-6, and are correlated with humoral immunity. Antigen-presenting cells, such as dendritic cells (DCs) and macrophages, processed antigens are necessary to prime CD4+ and CD8+ T cells to elicit antigen-specific immune response.

L. barbarum (Gou-Qi) polysaccharides increase CD4+ and CD8+ T cells in H22 hepatoma bearing mice [138]. Polysaccharides isolated from *A. annua* L. (Huang-Hua-Hao) increase CD4+ and CD8+ T cells and IFN-γ and IL-4 secretion in HCC bearing mice, and induce cancer cell apoptosis in HCC [139] (Figure 1, Table 3).

Gastrodin, isolated from *Gastrodia elata* Blume (Tian-Ma), up-regulates NF-κB, IL-2 and Bcl-2 in CD4+ T cells, and enhances cytotoxic activities of natural killer (NK) and CD8+ T cells against H22 hepatic cancer cells [140]. Shikonin, a major component of *L. erythrorhizon* (Zi-Cao) and *Arnebia euchroma* (Ruan-Zi-Cao), is effective in increasing CD3+ and CD19+ lymphocytes, and improving NK activities, lymphocyte transformation and IL-2 production in hepatoma HepA22 bearing mice [141] (Figure 1, Table 3).

The proteins extracted from Lei-Wan (*Omphalia lapidesces*) are effective in increasing spleen mass and IFN-γ production in H22 HCC bearing mice [142] (Table 3). *Eupolyphaga sinensis* Walker (Tu-Bie-Chong) ethanol extract enhances Th1 type cytokines (TNF-α and IFN-γ) production, and induces cell apoptosis in H22 HCC bearing mice [143].

DCs are important antigen-presenting cells for anticancer immunity. *L. barbarum* (Gou-Qi) polysaccharides promote DCs to stimulate allogeneic lymphocyte proliferation, produce IL-12p70 and IFN-γ and may relate to NF-κB expression [144]. Chen *et al.* have found that HCC SMMC-7721 cells may impair the biorheological properties of DCs, such as cell deformability, migration, and electrophoresis mobility, and altered organizations of cytoskeletal proteins. *Gekko Chinensis* (Tian-Long) sulfated polysaccharide-protein complex partially restores the defective biorheological features of DCs mediated by SMMC-7721 cells [145] (Figure 1, Table 3).

CD4+ CD25+ regulatory T cells (Tregs) originate from CD4+ Th0 cells upon stimulation of TGF-β and Foxp3 expression. Tregs may produce IL-10 and function as a negative immune regulator. Astragalus (Huang-Qi) polysaccharides (APS) inhibits Foxp3 expression and proliferation of CD4+ CD25+ Treg cells. APS also inhibits Treg cell migration by blocking SDF-1 or its receptor via CXCR4/CXCL12 pathway [146]. *Radix Glycyrrhizae* (Gan-Cao) polysaccharide down-regulates Tregs, related cytokines IL-10 and TGF-β, and Foxp3 expression, and increases IL-2 and IL-12p70 level in serum in H22 HCC-bearing mice [147] (Figure 1, Table 3).

Table 3. Effects of herbal compounds on immune function and angiogenesis in hepatocarcinoma.

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Lycium barbarum polysaccharide	*Lycium barbarum* (Gou-Qi)	↑ CD4+ and CD8+ T cells in H22 hepatoma; promote dendritic cells to stimulate allogeneic lymphocyte proliferation, produce IL-12p70 and IFN-γ	Unknown; NF-κB	[138,144]
Polysaccharides	*Artemisia annua* L. (Huang-Hua-Hao)	↑ CD4+ and CD8+ T cells, IFN-γ and IL-4 secretion, and induce cancer cell apoptosis in human hepatoma 7402 bearing mice	Unknown	[139]
Gastrodin	*Gastrodia elata* Blume (Tian-Ma)	↑ cytotoxic activities of NK and CD8+ T cells against H22 cells	↑ NF-κB, IL-2 and Bcl-2 in CD4+ T cells	[140]
Shikonin	*Lithospermum erythrorhizon* (Zi-Cao)	↑ CD3+ and CD19+ lymphocytes, NK activities and IL-2 in HepA22 bearing mice	Unknown	[141]
Proteins extract	*Omphalia lapidesces* (Lei-Wan)	↑ spleen mass and IFN-γ production in H22 hepatocarcinoma bearing mice	Unknown	[142]
Gekko sulfated polysaccharide-protein complex	*Gekko swinhonis Guenther* (Tian-Long)	Restore the defective biorheological characteristics of dendritic cells mediated by SMMC-7721 cells	Unknown	[145]
Astragalus polysaccharides	*Astragalus membranaceous* (Huang-Qi)	↓ proliferation and migration in CD4+ CD25+ Treg cells	↓ Foxp3, SDF-1 or its receptor through the CXCR4/CXCL12 pathway	[146]
Polysaccharide	*Radix Glycyrrhizae* (Gan-Cao)	↓ Tregs cells	↓ Foxp3	[147]
Gekko-sulfated glycopeptide	*Gekko swinhonis Guenther* (Tian-Long)	↓ bFGF stimulated proliferation and migration of endothelial cells, angiogenesis and tumor growth in liver cancer	↓ bFGF secretion and binding to heparin/heparan sulfate	[148]
Pedicularioside G	*Pedicularis striata* (Ma-Xian-Hao)	↓ proliferation and migration in HUVEC cells, and angiogenesis in chicken embryo chorioallantoic membrane and hepatoma	↓ reactive oxygen species	[149]
Vitexin compound 1	*Vitex negundo* (Huang-Jing)	↓ proliferation and cell cycle arrest at G1/G0 in hepatocellular carcinoma cells, and HUVEC tube formation	↓ VEGF	[150]
Resveratrol	*Polygonum cuspidatum* (Hu-Zhang), *etc.*	↓ proliferation in liver cancer cells	↓ hypoxia-induced activation of ERK1/2 and Akt, HIF-1α and VEGF expression	[151,152]
Cinobufotalin, Panax notoginseng saponins, Ginsenosides Rg3 and Lentinan	*Bufonis Venenum* (Chan-Su), *Panax notoginseng* (San-Qi), *P. ginseng* (Ren-Shen), *Lentinula edodes* (Xiang-Gu)	↓ angiogenesis and tumor growth in H22 hepatocellular carcinoma	↓ VEGF, EGFR and MMP-2 expression	[153]

↓ Inhibit or down-regulate, ↑ promote or up-regulate.

13. Inhibition of Angiogenesis

Angiogenesis, the process of new blood vessels generating from existing vessels, plays a crucial role in tumor growth and metastasis and has been recognized as a potential target for HCC treatment [154,155]. Some Chinese herbal components have demonstrated anti-angiogenic effects.

G. chinensis (Tian-Long) inhibits tumor growth, induces apoptosis, and inhibits angiogenesis accompanied by down-regulation of VEGF and bFGF in H22 HCC [156]. Gekko-sulfated glycopeptide decreases bFGF secretion and binding to its low affinity receptor heparin/heparan sulfate, inhibits bFGF stimulated proliferation and migration of endothelial cells, and thus inhibits angiogenesis and tumor growth in liver cancer [148] (Figure 1, Table 3).

Pedicularioside G, a phenylpropanoid glycoside isolated from *Pedicularis striata* (Ma-Xian-Hao), inhibits proliferation and migration in human umbilical vein endothelial cells (HUVEC), and angiogenesis in chicken embryo chorioallantoic membrane and human hepatoma. Pedicularioside G also inhibited cell proliferation and migration and tumor growth in human hepatoma. The effects of pedicularioside G are partially related to down-regulation of ROS [149] (Figure 1, Table 3).

Vitexin compound 1, a compound isolated from *V. negundo* (Huang-Jing), inhibits cell proliferation and arrests cell cycle at G1/G0 in HCC cells. Vitexin compound 1 also inhibited VEGF secretion and HUVEC tube formation [150] (Figure 1). Resveratrol, a compound that can be isolated from *P. cuspidatum* (Hu-Zhang), may inhibit proliferation and VEGF expression in HepG2 hepatoma cells [151]. Resveratrol also reduces hypoxia induced accumulation of hypoxia inducible factor-1α and VEGF expression in hepatoma HepG2 cells [152] (Table 3).

QHF, a herbal component formula composed of cinobufotalin, *Panax notoginseng* saponins, ginsenosides Rg3 and lentinan, inhibits VEGF, EGFR and MMP-2 expression, as well as angiogenesis and tumor growth in H22 HCC [153] (Table 3).

14. Herbal Compound-Based Combinational Treatment

Chinese herbs are usually prescribed as formulas guided by TCM theories, *i.e.*, combining multiple herbs in a prescription [157]. It is rational to use herbal components in the same principle.

C. kwangsiensis or *C. phaeocaulis* or *C. wenyujin* or *C. longa* (Yu-Jin) and *P. cuspidatum* (Hu-Zhang) are frequently used simultaneously as herbal-pairs in liver cancer treatment based on complementary traditional efficacy. Curcumin is a component of Yu-Jin and resveratrol is a compound can be isolated from Hu-Zhang. We have found that curcumin combined with resveratrol may synergistically inhibit XIAP (X-linked inhibitor of apoptosis protein) and survivin expression, up-regulate ROS production, and activate caspase-3, -8 and -9 to induce apoptosis in HCC cells [158] (Table 4).

Based on TCM principles, Chen *et al.* have established a herbal components formula composed of cinobufotalin, cantharidin, *Panax notoginseng* saponins (PNS), tanshinone, ginsenosides Rg3 and lentinan. These compounds are derived from toad skin (Gan-Chan-Pi), *Mylabris phalerata* Pallas or *M. cichorii* Linnaeus (Ban-Mao), *Panax notoginseng* (San-Qi), *S. miltiorrhiza* Bunge (Dan-Shen), *P. ginseng* (Ren-Shen) and *Lentinula edodes* (Xiang-Gu), respectively. The formula has demonstrated efficacy in inhibiting tumor growth, prolonging survival time, enhancing anticancer effects and reducing toxicity of cisplatin in HCC bearing mice [159] (Table 4).

In addition to components from different herbs, different components from the same herb can also be used synchronously for liver cancer treatment. Acetylshikonin and β,β-dimethylacrylshikonin, components of *L. erythrorhizon* (Zi-Cao), exhibit anticancer activity against HCC [160,161]. Aikete injection, a mixture composed of acetylshikonin and β,β-dimethyl-acrylshikonin, inhibits proliferation, induces apoptosis, and arrests cell cycle at the G2/M phase accompanied by down-regulation of Bcl-2 and Bcl-2/Bax ratio in HCC cells [162] (Table 4).

Table 4. Herbal compound-based combinational treatment.

Compounds	Herbs	Effects	Targets/Molecular Events	Ref.
Astragalosides, Astragalus polysaccharide and salvianolic acids	*Astragalus membranaceous* (Huang-Qi), *Salvia miltiorrhiza* Bunge (Dan-shen)	↓ DEN induced hepatocarcinogenesis; ↓ TGF-β1-induced cell invasion in HepG2 cells	↓ GST-P and α-SMA; modulating TGF-β/Smad signaling	[13,109]
Cinobufotalin, Panax notoginseng saponins, Ginsenosides Rg3 and Lentinan	*Bufonis Venenum* (Chan-Su), *Panax notoginseng* (San-Qi), *Panax ginseng* (Ren-Shen), *Lentinula edodes* (Xiang-Gu)	↓ angiogenesis and tumor growth in H22 hepatocellular carcinoma	↓ VEGF, EGFR and MMP-2 expression	[153]
Curcumin and resveratrol	*Curcuma kwangsiensis* (Yu-Jin or Er-Zhu) or *C. phaeocaulis* (Yu-Jin or Er-Zhu) or *C. wenyujin* (Yu-Jin or Er-Zhu) or *C. longa* (Yu-Jin or Jiang-Huang), and *Polygonum cuspidatum* (Hu-Zhang), *etc.*	↓ proliferation, ↑ apoptosis in Hepa1-6 cells	↓ XIAP and Survivin, ↑ ROS production, caspase-3, -8 and -9	[158]
Cinobufotalin, Cantharidin, Panax notoginseng saponins, Tanshinone, Ginsenosides Rg3 and Lentinan	*Bufonis Venenum* (Chan-Su), *Mylabris phalerata* Pallas or *M. cichorii* Linnaeus (Ban-Mao), *Panax notoginseng* (San-Qi), *Salvia miltiorrhiza* Bunge (Dan-Shen), *Panax ginseng* (Ren-Shen), *Lentinula edodes* (Xiang-Gu)	Inhibit tumor growth, prolong survival time, enhance anticancer effects and reduce toxicity of cisplatin in hepatocellular carcinoma bearing mice	Unknown	[159]
Acetylshikonin and β,β-dimethylacrylshikonin	*Lithospermum erythrorhizon* (Zi-Cao)	↓ proliferation, ↑ apoptosis, arrest cell cycle in G2/M phase in SMMC-7721 cells	↓ Bcl-2 and Bcl-2/Bax ratio	[162]

↓ Inhibit or down-regulate, ↑ promote or up-regulate.

15. Conclusions and Future Directions

In summary, Chinese herbal compounds have demonstrated multiple effects against HCC, including prevention of hepatocarcinogenesis, inhibition of cell proliferation, induction of apoptosis, autophagy, cell senescence and anoikis, cell cycle arrest, inhibition of EMT, metastasis and angiogenesis, regulation of immune function, reversal of drug resistance and enhancement of chemotherapeutic effects (Figure 1). These observations provide the basis for further development of new drugs for HCC management.

Chinese herbs are natural products and most herbs are safe for human consumption. One herb may contain multiple anticancer compounds, e.g., *C. wenyujin* (Er-Zhu or Yu-Jin) contains curcumin, curcumol and β-elemene. One herbal compound may have multiple effects on HCC, such as curcumin, which has demonstrated effects in inhibiting hepatocarcinogenesis and cell proliferation, inducing apoptosis and autophagy, and inhibiting EMT in HCC cells via multiple targets [8,78–80].

Chinese herbs have a long history of clinical use. Thousands years of clinical experiences provide clues for pharmacological studies. Compounds in some clinically-used anticancer herbs have not yet been fully identified, such as *S. lyratum* Thunberg (Bai-Ying) and *Patrinia scabra* Bunge (Mu-Tou-Hui). Whether compounds from these herbs possess more potent anticancer effects on HCC are worthy of further study.

Some anticancer compounds containing herbs are neither commonly clinically used nor recognized as anticancer herbs so far, for example, *A. pusilla* (Jiu-Jie-Long) [21] and *P. capitatum* (Tou-Hua-Liao) [22]. Whether these herbs possess anticancer effects on HCC warrants more investigation.

Some herbal compounds shown significant anticancer effects in HCC, but the corresponding herbs are not clinically used as anticancer herbs or their anticancer effects have not been observed so far, such as *A. dahurica* (Bai-Zhi) [117], *M. officinalis* (Hou-Po) [48,49] and *A. officinarum* Hance (Gao-Liang-Jiang) [92]. The different effects between herb and herbal components may result from relatively insufficient quantities of anticancer compounds in those herbs.

Combinational treatment with multiple herbal compounds is a promising strategy for application of herbal compounds. The combinational principles or compatibility of Chinese herbs provide a theoretical basis for combinational treatment with multiple herbal compounds for HCC. In addition, Chinese herbal formulas or known active herbal-pairs provide clues for the extraction of compounds from multiple herbs and combinational treatment with these compounds.

Current treatments for HCC are less than satisfactory. Anticancer herbal compounds are importent resources for the development of new drugs for liver cancer treatment. These compounds can be developed as single herbal compound drugs with or without chemical modifications, or in combination with other herbal compounds, herbs and even modern drugs guided by the principles of TCM and/or pharmacological interaction.

Acknowledgments: This work was partially supported by National Natural Science Foundation of China (81273726 and 81473625), Three-year Action Program of Shanghai Municipality for Traditional Chinese Medicine (ZY3-CCCX-3-3025), and Opening Research Fund of Shanghai Key Laboratory of Tissue Engineering (TE1401).

Author Contributions: B.H. conceived, wrote and revised the manuscript. H.-M.A., S.-S.W, J.-J.C. and L.X. wrote parts of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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