Biological effects of corosolic acid as an anti-inflammatory, anti-metabolic syndrome and anti-neoplasic natural compound (Review)

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Abstract. Accumulating evidence has indicated that corosolic acid exerts anti-diabetic, anti-obesity, anti-inflammatory, anti-hyperlipidemic and anti-viral effects. More importantly, corosolic acid has recently attracted much attention due to its anticancer properties and innocuous effects on normal cells. Furthermore, the increasing proportion of obese and/or diabetic populations has led to an epidemic of non-alcoholic fatty liver disease (NAFLD), which frequently progresses to hepatocellular carcinoma (HCC). Evidence has indicated that NAFLD is closely associated with the development of HCC and comprises a high risk factor. The present review summarizes the anticancer effects of corosolic acid *in vitro* and *in vivo,* and its related molecular mechanisms. It also describes the inhibitory effects of corosolic acid on the progression of NAFLD and its associated molecular mechanisms, providing guidance for future research on corosolic acid in NAFLD-related HCC prevention and treatment. To the best of our knowledge, a review of corosolic acid as an anticancer agent has not yet been reported. Due to its multitargeted activity in cancer cells, corosolic acid exerts anticancer effects when administered alone, and acts synergistically when administered with chemotherapeutic drugs, even in drug-resistant cells. In addition, as a novel tool to treat metabolic syndromes, corosolic acid uses the same mechanism in its action against cancer as that used in the progression of NAFLD-related HCC. Therefore, corosolic acid has been suggested as an agent for the prevention and treatment of NAFLD-related HCC.

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1. Introduction

Cancer is one of the most common causes of mortality worldwide. However, it is not only a serious threat to public health, but also a global socioeconomic burden (1). An estimated 2,814,000 cases of cancer-related death and 4,292,000 new cancer cases occurred in China in 2015 (2). Based on GLOBOCAN (a global cancer statistics database), in 2018 the number of cases of cancer-related death was 9.6 million, and the number of new cancer cases was 18.1 million worldwide (3). However, data also indicate a decline in the number of new cases, which may be associated with lifestyle changes or reduced exposure to high-risk environmental factors in developed countries (4). Accumulating evidence also suggests that the proteins encoded by a variety of aberrantly-expressed regulatory genes promote tumorigenesis; these include anti-apoptotic proteins, transcription factors, growth factors and their respective receptors (5-7). Tumorigenesis is a multistep process characterized by numerous abnormalities, rather than a single mutation, during cancer initiation, promotion and progression; therefore, a single target agent is unlikely to inhibit cancer growth (8,9). Currently, the primary treatment strategies against tumors include the following: Surgery, chemoradiotherapy, immunotherapy, molecular targeted therapy and Traditional Chinese Medicine. Although chemotherapy has been proven to improve survival in patients with cancer, drug resistance and severe adverse side effects, such as damage to liver function, bone marrow suppression

and neurotoxicity, are major obstacles that cause treatment failure (10,11). There is therefore an urgent need to develop novel and more effective drugs with fewer side effects for various types of cancer.

Due to their selective molecular targets, novel bioactive components from plant sources have emerged as new and reliable therapeutic elements for treating various types of human cancer (12,13). Indeed, over the past half century, numerous plant derivatives and secondary metabolites have been used in clinical practice for the treatment of cancer (14,15). For example, pentacyclic triterpenes constitute a group of promising anticancer drugs that comprise the lupane, oleanane and ursane groups (16,17). Since Pisha *et al* (18) first reported in 1995 that betulinic acid (19), a plant secondary metabolite, is a highly promising anticancer drug, experimental studies have largely focused on the cytotoxic effects of betulinic acid and other types of triterpenes, particularly their apoptosis-inducing mechanisms, initially in melanoma cell lines *in vitro* and *in vivo* (20-22). The cytotoxic effects of betulinic acid were subsequently confirmed in other cell lines, such as those derived from breast (23), colon and lung cancer (24), as well as neuroblastoma (25). In the last decade, triterpenes were also found to have additional effects on cancer through several modes of action, such as induction of apoptosis and enhancement of endoplasmic reticulum (ER) stress (23-25).

Corosolic acid, also known as 2α-hydroxyursolic acid, has a molecular formula of $C_{30}H_{48}O_4$, and a molecular weight of 472.70 g/mol (Fig. 1). As a prevalent pentacyclic triterpenoid and the principal component of Banaba leaves, corosolic acid has received a great deal of attention due to its anti-diabetic properties (26). Corosolic acid is known as a 'phyto-insulin' or 'botanical insulin' (27). It is the principal component of *Lagerstroemia speciosa* leaves (also called Banaba), a tropical plant found in the Philippines, Vietnam, Malaysia and Southern China (28,29). Table I lists the plant species able to biosynthesize corosolic acid (28-50). Corosolic acid has also been isolated from European and South American plants.

Experimental studies have indicated that corosolic acid plays a pivotal anticancer role in several tumorigenic processes *in vitro* and *in vivo*, including cellular proliferation, apoptosis, angiogenesis, lymphangiogenesis, metastasis and tumor immunity, and it exerts a synergistic effect when administered with other anticancer agents (Fig. 2) (51-53). In addition, corosolic acid has the ability to modulate multiple cancer-related signaling pathways and processes, such as the nuclear factor kappa-B (NF-κB), phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) and Wnt/β-catenin pathways, apoptosis, nuclear factor erythroid 2-related factor 2 (Nrf2) and several other components associated with cellular proliferation or mortality (Table II) (49,51,54,55). However, more research is required to determine its potential in human clinical trials. The most recent registry data from Surveillance, Epidemiology and End Results shows that the morbidity of liver and intrahepatic bile duct cancers have risen on average 3.0% each year between 2004 and 2013 in the United States (56). In particular, hepatocellular carcinoma (HCC) is an aggressive cancer with a poor prognosis. Chronic liver diseases, such as hepatitis B and C virus infections, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD) and cirrhosis are the most common underlying causes of HCC (41). NAFLD in particular, has been

recognized as one of the leading etiologies for the development of HCC (57,58). NAFLD encompasses a spectrum of chronic liver diseases, ranging from simple steatosis to liver injury, which are closely associated with metabolic syndrome (MS) and are characterized by conditions such as obesity, diabetes and dyslipidemia (59-61). The understanding of the pathogenesis of NAFLD-related HCC is limited, and several possible mechanisms of NAFLD-related HCC have been described, including obesity-induced inflammation (62-64), insulin resistance (IR) (65-68), oxidative stress (69,70) and adaptive immune responses (71,72).

Accumulating experimental evidence has suggested that corosolic acid possesses a variety of biological properties, exerting anti-diabetic, anti-obesity, anti-hyperlipidemic, anti-viral, anti-inflammatory and anticancer effects (26,73,74). Therefore, the present review describes the anticancer effects and related molecular mechanisms of corosolic acid, highlighting its ability to inhibit NAFLD progression, and providing guidelines for future research on its use as an agent in NAFLD-related HCC prevention and treatment.

2. Corosolic acid exerts anticancer effects *in vitro*

Effects and mechanisms of corosolic acid in neoplasic cell lines from the digestive system. Cancer cell migration is a critical process in tumor development and metastasis (75,76), and is closely associated with vascular growth factor receptor (VEGFR) signaling (57,58); thus, the inhibition of VEGFR, and VEGFR2 in particular, is considered an important treatment approach for HCC and prevent HCC metastasis (77-79). Ku *et al* (48) showed that the half-maximal inhibitory concentration (IC_{50}) for corosolic acid was 2.5 μM for migratory ability, and 50 μM for cytotoxicity on the HCC Huh7 cell line. In addition, corosolic acid treatment resulted in a decrease in Huh7 cell migration in a dose-dependent manner, and corosolic acid at a dose of 2.5 μM induced low cytotoxicity for 24 h (IC_{50} cytotoxicity/IC_{50} migration=20), compared to the untreated control (48). The authors further demonstrated that the cytotoxic effects observed with corosolic acid might be associated with the markedly suppression of the VEGFR2/steroid receptor coactivator/focal adhesion kinase (FAK)/cell division cycle42 (cdc42) signaling pathway and the inhibition of the kinase activity of VEGFR2. On the other hand, Xu *et al* (80) reported that corosolic acid had reduced efficacy in treating liver cancer, since it accelerated the degradation of the transcription factors of Yes-associated protein (YAP) by enhancing large tumor suppressor gene 1-induced phosphorylation and β-transductin repeat containing protein (βTrCP)-dependent ubiquitination. However, Xu *et al* (80) also demonstrated that corosolic acid-induced apoptosis of liver cancer cells was enhanced by combined treatment with actinomycin D, which resulted in elevated YAP protein levels and decreased βTrCP protein activity. This study suggests that the effectiveness of liver cancer treatment with corosolic acid (at a final concentration of 10 μM) might be improved by its combined administration with 5 μg/ml actinomycin D for 24 h (80).

In gastric cancer cells, corosolic acid has been shown to effectively inhibit the progression of carcinogenesis through multiple mechanisms, including targeting of the adenosine
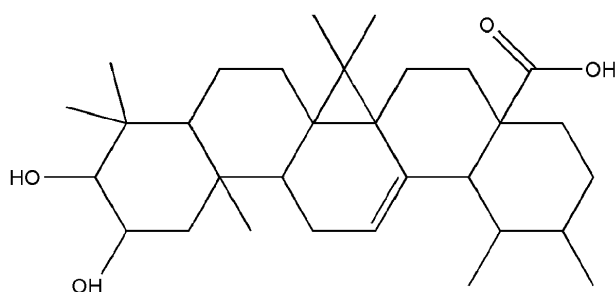
Figure 1. Molecular structure of corosolic acid.

Table I. Corosolic acid biosynthesizing/accumulating plant species.

First author/s, year	Plant species	(Refs.)
Ulbricht *et al*, 2007	*Banaba*	(28)
Park and Lee, 2011	*Banaba*	(29)
Kim *et al*, 2011	*Vaccinium macrocarpon (cranberry)*	(30)
Aguirre *et al*, 2006	*Ugni molinae*	(31)
Hou *et al*, 2009	*Eriobotrya japonica*	(32)
Hu *et al*, 2006	*Eriobotrya japonica*	(33)
LV *et al*, 2008	*Eriobotrya japonica*	(34)
Lu *et al*, 2009	*Eriobotrya japonica*	(35)
Rollinger *et al*, 2010	*Eriobotrya japonica*	(36)
Banno *et al*, 2004	*Perilla frutescens*	(37)
Kim *et al*, 2005	*Campsis grandiflora*	(38)
Na *et al*, 2006	*Symplocos paniculata*	(39)
Thuong *et al*, 2006	*Weigela subsessilis*	(40)
Lee and Thuong, 2010	*Weigela subsessilis*	(41)
Yang *et al*, 2006	*Glechoma longituba*	(42)
Shen *et al*, 2006	*Potentilla chinensis*	(43)
Kang *et al*, 2008	*Rubus bioflorus*	(44)
Liu *et al*, 2007	*Phlomis umbrosa*	(45)
Li *et al*, 2017	*Rosa laevigata Michx*	(46)
Huang *et al*, 2014	*Rubus stans*	(47)
Huang *et al*, 2016	*Rosa cymosa Tratt*	(47)
Ku *et al*, 2015	*Actinidia chinensis*	(48)
Cheng *et al*, 2017	*Actinidia valvata Dunn.Radix*[a]	(49)
Manayi *et al*, 2013	*L. Salicaria*	(50)

[a]Dunn.Radix means root.

monophosphate-activated protein kinase (AMPK)-mammalian target of rapamycin (mTOR) signaling pathway, the inhibition of the NF-κB pathway, the downregulation of EGFR2/neu oncogene, the promotion of the anticancer activities of 5-fluorouracil (5-FU) via mTOR inhibition, and the reduction of 5-FU chemoresistance through the activation of the AMPK pathway (49,81,82). In human gastric cancer NCI-N87 cells, corosolic acid has been shown to inhibit the expression of human epidermal growth factor receptor 2 (HER2) and AMPK-mTOR signal phosphorylated proteins, such as Akt and extracellular signal-regulated protein kinase (ERK), which are involved in signaling pathways downstream of HER2, with the inhibitory effect of corosolic acid being both dose- and time-dependent (25 μM for 12, 24 and 48 h, and 50 μM for 24 h) (81). Furthermore, corosolic acid has been found to induce G_0/G_1 arrest, which was associated with the induction of cyclin-dependent kinase inhibitor 1B and the downregulation of cyclin D1 (81). In addition, Lee *et al* (81) found that corosolic acid could effectively inhibit cell proliferation in both a dose- and time-dependent manner (1, 5, 10 and 50 μM for 24 h, and 25 μM for 3, 6, 12, 24 and 48 h). Furthermore, corosolic acid has been shown to induce cell cycle arrest and apoptosis through the downregulation of the HER2/neu oncogene, suggesting that it may play a role in patients with HER2-amplified gastric cancers (81). Moreover, at an IC_{50} value of 16.9±2.9 μM, corosolic acid has been shown to inhibit the proliferation of human gastric cancer SNU-601 cells via AMPK-mTOR signaling (82). Another study has reported that corosolic acid treatment at a concentration of 10, 20, 40 and 80 mg/ml for 72 h induces apoptosis in human gastric cancer BGC823 cells in a dose-dependent manner (49). This effect is achieved by inhibiting the NF-κB (p65 subunit) pathway, by decreasing the mRNA and protein expression of p65, apoptosis antigen 1 (Fas), second mitochondria derived activator of caspase, and B-cell lymphoma-2 (Bcl-2), whilst increasing that of Bcl-2 associated X (Bax), inhibitor of NF-κB (IκB) α and survivin (49). In addition, the experimental data of Sung *et al* (83) provides insights into the molecular mechanisms through which corosolic acid induces the apoptosis of colorectal cancer cells. Corosolic acid, at an IC_{50} value of 24 μM for 24 h, inhibits the viability of colorectal cancer HCT116 cells by inducing apoptotic cell death in a dose-dependent manner, through a molecular mechanism associated with the upregulation of the proapoptotic proteins Bax, Fas and Fas ligand (FasL), and the downregulation of the anti-apoptotic proteins Bcl-2 and survivin. Of note, corosolic acid was proven to be an ideal antagonist of the Wnt/β-catenin pathway (51). Corosolic acid decreased the level of intracellular β-catenin and suppressed the proliferation of colon cancer HCT-15 and DLD-1 cells with an APC mutation in a dose-dependent manner (20, 40 and 60 μM for 8 h), which was achieved by promoting N-terminal phosphorylation and degrading the proteasomes of β-catenin (Table II) (51).

Effects and mechanisms of corosolic acid on tumor cells from the urogenital system. Accumulating evidence has suggested that activated Nrf2 plays a critical role in the proliferation and survival of tumor cells, making its inhibition a promising therapeutic strategy for cancer treatment (84-87). A previous report on several Nrf2 inhibitors showed that these are promising therapeutic agents (88). Of note, corosolic acid at a concentration of 0.25-32 μM for 3 or 5 days inhibited the proliferation of TRAMP-C1 cells, a type of anchorage-independent human prostate cancer (PCa) cell line with increased levels of mRNA and
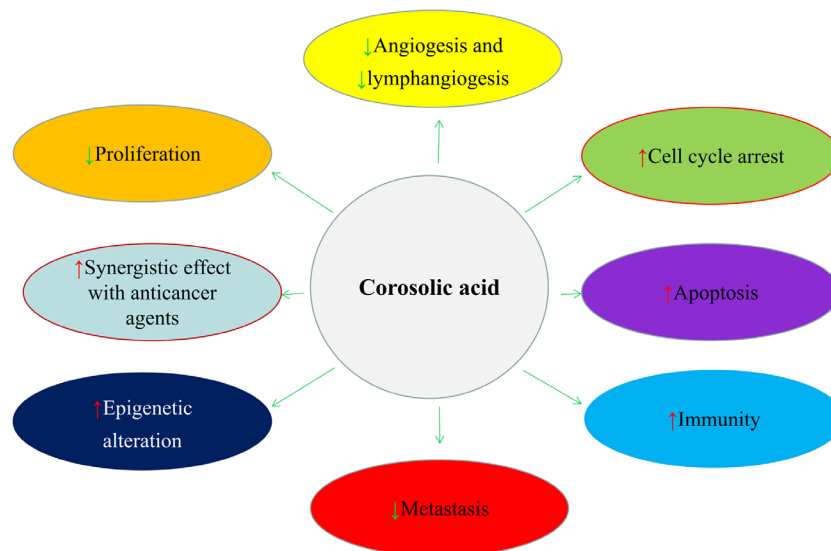
Figure 2. Effects of corosolic acid on malignant cells. Anticancer roles of corosolic acid include the inhibition of tumor cell proliferation, angiogenesis and lymphangiogenesis, metastasis, induced apoptosis, tumor immunity and synergistic effects with anticancer drugs.

protein expression of Nrf2, heme oxygenase-1 (HO-1) and nicotinamide adenine dinucleotide phosphate quinone oxido-reductase 1; however, corosolic acid did not exert the same inhibitory effect in Nrf2-knockout TRAMP-C1 cells (54). These findings indicate that the significant cytotoxic effect of corosolic acid might be associated with its ability to restore the expression of Nrf2 via epigenetic modification (54). In addition, in the PCa, PC-3 and DU145 cell lines, (ER) stress was activated by 0, 5, 10 and 15 μM corosolic acid after 24 and 48 h, through two proapoptotic signaling pathways: The inositol-requiring ER-to-nucleus signal kinase 1/apoptosis signal regulating kinase 1/Jun N-terminal kinase (JNK) pathway and the protein kinase RNA-like ER kinase/eukary-otic initiation factor 2 α/activating transcription factor 4/C/EBP-homologous protein signaling pathway, which induced apoptosis and suppressed cell proliferation (89). However, Woo *et al* (90) found that the corosolic acid-induced death of human renal carcinoma Caki cells (at 10 μM for 24 h) was inhibited by the use of α-tocopherol (a hydrophobic anti-oxidant that prevents free radical damage), but was not inhibited by benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone (an apoptosis inhibitor), necrostatin-1 (a necroptosis inhibitor), ferrostatin-1 or deferoxamine (ferroptosis inhibi-tors) (90). Futhermore, corosolic acid induces lipid oxidation, and α-tocopherol markedly prevents corosolic acid-induced lipid peroxidation and cell death. Anti-chemotherapeutic effects of α-tocopherol are dependent on inhibition of lipid oxidation rather than inhibition of ROS production (90). It was therefore speculated that corosolic acid induced the non-apoptotic cell death associated with lipid peroxidation in cancer cells (90). Furthermore, in renal carcinoma ACHN and A498 cells, treatment with 10 μM corosolic acid for 24 h induced non-apoptotic cell death (90). Xu *et al* (91) reported that treating human cervix adenocarcinoma HeLa cells with 40 μM corosolic acid for 24 h could induce cell cycle arrest at the S phase, and promote apoptosis by activating caspases-8, -9 and -3 and disrupting mitochondrial membrane poten-tial (91). In another report on CaSki human cervical cancer

cells, the results indicated that 10, 50 and 100 μM corosolic acid treatment for 12, 24 and 48 h effectively inhibited proliferation in a dose- and time-dependent manner (55). In addition, the results revealed that the cytotoxic effects of corosolic acid inhibited tumor cell proliferation by inducing apoptosis and cell cycle arrest, and suppressing the PI3K/Akt signaling pathway (55). It has also been demonstrated that in epithelial ovarian cancer (92), glioma and lymphoma (93,94) cells, the activation of signal transducer and activator of transcription 3 (STAT3) was induced by co-culturing the cells with M2, but not M1 macrophages. However, Fujiwara *et al* (95) demonstrated that corosolic acid, at a minimum of 30 μM for 48 h, suppressed STAT3 activation in co-culture experiments with epithelial ovarian cancer ES-2 cells treated with bromodeoxyuridine (used to abrogate macrophage differentiation into the M2 phenotype), and that STAT3 inhibition was associated with the prevention of M2 macrophage polarization. In addition, the epithelial ovarian cancer cell line SKOV3 treated with 20 μM corosolic acid for 24 h, showed no effect on the viability of these cells, suggesting that corosolic acid have no anticancer proper-ties at this concentration. By contrast, 20 μM corosolic acid enhanced the inhibitory effect of paclitaxel (PTX; 10 μM) on the proliferation of the epithelial ovarian cancer cell lines SKOV3, RMG-1 and ES-2. These results demonstrated that corosolic acid enhances the anticancer activity of anticancer drugs such as PTX in epithelial ovarian carcinoma cells (95). Notably, the combination of 20 μM corosolic acid and 10 μM paclitaxel for 24 h also inhibited STAT3 activity in the epithelial ovarian cancer cells, but corosolic acid alone or PTX alone had lesser effects on the STAT3 activity (95). These data suggested that corosolic acid enhanced cancer cell chemosensitivity and effectively inhibited cancer cell proliferation, which was also found to be associated with the prevention of M2 polarization via the suppression of STAT3 activation (95). These findings were similar to those showing that corosolic acid (30 μM for 1 h) suppressed the M2 macrophage polarization and proliferation of U373 and

Table II. Summary of the effects of corosolic acid in different types of cancers *in vitro*.

First author/s, year	Cancer type	Cell types	Molecular mechanism	Effects	Drug synergism	(Refs.)
Xu et al, 2017 and Ku et al, 2015	Liver cancer	Huh7	βTrCP-dependent Ubiquitination of YAP (↑YAP, ↓βTrCP) VEGFR2/Src/FAK pathway (↓VEGFR2, Src, FAK)	↑Apoptosis ↓Migration activity, cell motility	Actino-mycin DNA	(48,80)
Woo et al, 2018		SK-Hep1, Huh7	↑Lipid peroxidation	↑Non-apoptotic cell death	NA	(90)
Lee et al, 2010	Gastric cancer	NCI-N87	HER2/neu oncogene	↑Cell cycle arrest and apoptosis pathway (↓HER2, Akt, Erk; ↑P27^{kip1}, cyclin D1)	Adria-mycin, 5-FU	(81)
Cheng et al, 2017		BGC823	NF-κB pathway (↓P65, Fas, FasL, Bcl-2, Smac; ↑IκBα, Bax, survivin)	↑Cell cycle arrest and apoptosis	NA	(49)
Lee et al, 2010		SNU-601	AMPK-mTOR pathway (↑AMPK; ↓mTOR)	↑Cell cycle arrest and apoptosis	NA	(82)
Lee et al, 2015		SNU-620	mTOR signaling pathway (↓mTOR); caspase-dependent pathway (↑caspase-8,-9 and -3)	↑Cell cycle arrest and apoptosis	5-FU	(106)
Yamaguchi et al, 2006		SNU-620/5-FU^R	AMPK-mTOR pathway (↓Bcl-2, TS, mTOR/4EBP1, PARP; ↑AMPK, Bim, caspase-3, poly-ADP-ribose)		5-FU	(109)
Sung et al, 2014	Colon cancer	HCT116	caspase-dependent pathway (↑caspase-8,-9 and -3, Bax, Fas, FasL; ↓Bcl-2, survivin)	↑Apoptotic cell death	NA	(83)
Yoo et al, 2015		CT-26	FAK pathway (↓angiopoetin-1, FAK, ERK1/2); caspase-dependent pathway (↑caspase-8,-9 and -3)	↓Tumor proliferation; ↑cell cycle arrest and apoptosis	NA	(53)
Kim et al, 2014		APC-mutated HCT15	Wnt/β-catenin pathway (↓β-catenin)	↓Tumor proliferation	NA	(51)

Table II. Continued.

First author/s, year	Cancer type	Cell types	Molecular mechanism	Effects	Drug synergism	(Refs.)
Nho et al, 2013	Lung cancer	A549	Mitochondrial/caspase-dependent pathway (↑ caspase -7,-8,-9 and -3, ROS; ↓ Bcl-2, survivin, Bid)	↑ Apoptotic cell death	NA	(99)
Woo et al, 2018	Kidney cancer	Caki, ACHN, A498	↑ Lipid peroxidation	↑ Non-apoptotic cell death	NA	(90)
Woo et al, 2018	Breast cancer	MDA-M, B231	↑ Lipid peroxidation	↑ Non-apoptotic cell death	NA	(90)
Ma et al, 2018	Prostate cancer	PC-3, DU145	ER stress; IRE-1/ASK1/JNK signaling pathway and PERK/eIF2α/ATF4/CHOP signaling pathway (↑ IRE-1, PERK, CHOP, TRIB3; ↓ AKT)	↑ ER stress-dependent apoptosis	NA	(89)
Yang et al, 2017		TRAMP-C1	Nrf2/HO-1 pathway (↑ H3KK27ac; ↓ DNMTs, HDACs, H3k27me3)	↑ Epigenetic alterations	NA	(54)
Xu et al, 2009	Cervical cancer	HeLa	mitochondrial pathway and caspases activation (↑ Bax/Bcl-2 ratio, caspase-8,-9 and -3)	↑ Cell cycle arrest and apoptosis	NA	(91)
Yong et al, 2016		CaSki	PI3K/Akt signaling pathway (↓ PI3K/Akt)	↑ Cell cycle arrest and apoptosis	NA	(55)
Fujiwara et al, 2013	Ovarian Cancer	SKOV3, RMG-1 and ES-2 SKOV3	STAT3 pathway (↓ STAT3) and ↓ M2 macrophage polarization	↓ Chemoresistance; ↓ Tumorigenic macrophages	PTX, CDDP and DOX	(95)
Fujiwara et al, 2011	Glioblastoma	U373, T98G	JAK-STAT3, NF-κB pathway (↑ T lymphocytes infiltration; ↓ MDSC, COX2 mRNA, CCL-2 mRNA, M2 polarization)	↑ Antitumor immunity	NA	(96)
Cai et al, 2011	Osteosarcoma	MG-63	Mitochondria-mediated apoptosis pathway (↑ caspase-3/9)	↑ Mitochondria-mediated apoptosis	Adriamycin, cisplatin	(97)
Wang et al, 2018	Retinoblastoma	Y-79	MELK-FoxM1 signaling (↓ MELK, FoxM1)	↑ Cell cycle arrest and apoptosis; ↑ cytotoxicity	NA	(101)

NA, not applicable; HER2, human epidermal growth factor receptor 2; AMPK, adenosine monophosphate; mTOR, activated protein kinase-mammalian target of rapamycin; CCL-2, chemokine (C-C motif) ligand 2; Fas, apoptosis antigen 1; VEGFR, vascular growth factor receptor; Src, steroid receptor coactivator; FAK, focal adhesion kinase; cdc42, cell division cycle42; Smac, second mitochondria derived activator of caspase; Bax, B-cell lymphoma-2 associated X; NF-κB, nuclear factor kappa-B; IκBα, inhibitor of NF-κBα; ER, endoplasmic reticulum; IRE-1, inositol-requiring ER-to-nucleus signal kinase 1; ASK1, apoptosis signal regulating kinase 1; JNK, Jun N-terminal kinase; PERK, protein kinase RNA-like ER kinase; eIF2α, eukaryotic initiation factor 2α; ATF4, activating transcription factor 4; CHOP, C/EBP-homologous protein; p27^{Kip1}, cyclin-dependent kinase inhibitor 1B; MELK, maternal embryonic leucine-zipper kinase; FoxM1, forkhead box M1; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; STAT3, signal transducer and activator of transcription 3; MDSCs, myeloid-derived suppressor cells; COX-2, cyclooxygenase-2; Akt, protein kinase B; ERK, extracellular signal-regulated protein kinase; YAP, Yes-associated protein; Bid, BH3 interacting domain death agonist; FasL, TNF ligand superfamily member 6; P65, NF-κB subunit; 5-Fu, 5-Fluorouracil; TS, thymidine synthase; Bim, Bcl-2 interacting mediator of cell death; PARP, poly ADP-ribose polymerase; ROS, reactive oxygen species; H3KK27ac, lysine H3K27 acetylation; DNMTs, DNA methyltransferases; HDACs, histone deacetylases; H3K27me3, trimethylation of lysine 27 on histone 3; PTX, paclitaxel; CDDP, Cisplatin; DOX, doxorubicin; ↑, indicates upregulation; ↓, indicates downregulation.

T98G glioblastoma cells in parallel with inhibiting both STAT3 and NF-κB activation (Table II) (96).

Effects and mechanisms of corosolic acid in neoplasic cell lines from osteosarcoma and lung metastasis. The response of osteosarcoma MG-63 cells to corosolic acid treatment has been previously reported (97,98). The results shared by both studies indicate that the viability of osteosarcoma MG-63 cells was significantly inhibited by corosolic acid (35 μM for 12 h, and 20, 30 and 40 μM for 24 h), and that corosolic acid induced apoptosis through the activation of caspases-3 and -9 to cause mitochondrial dysfunction (97,98). Moreover, using human osteosarcoma Saos2 and HSOS-1 cell lines and the murine osteosarcoma LM8 cell line, Horlad *et al* (52) reported that treatment with 30 μM corosolic acid for 24 h inhibited lung metastasis by inhibiting STAT3 activation, increasing the number of infiltrating lymphocytes in the tumor tissues and abrogating the immunosuppressive effect of myeloid-derived suppressor cells (MDSCs) through the decreased expression of cyclooxygenase-2 (COX-2) and chemokine (C-C motif) ligand 2 (CCL2) mRNA in these MDSCs (52) (Table II).

Effects and mechanisms of corosolic acid in the lung cancer A549 cell line. Corosolic acid (10-40 μM for 6-48 h) had a significant inhibitory effect on A549 cells, a human lung adenocarcinoma cell line, in a concentration- and time-dependent manner (99). Exposure to corosolic acid induced cell cycle arrest at the sub-G_1 stage and caused apoptotic death in A549 cells (99). In addition, corosolic acid also activated caspases-3/-7, -8 and -9 and poly (ADP-ribose) polymerase, and increased the levels of reactive oxygen species (ROS). Corosolic acid-induced apoptosis was inhibited by exposure to the ROS scavenger N-acetylcysteine (99). These results indicate that corosolic acid induced apoptosis through mitochondria-mediated and caspase-dependent processes in a ROS-dependent manner (99). In addition, under $CoCl_2$-stimulated hypoxic conditions, corosolic acid (IC_{50} of 12.5 μg/ml for 48 h) induced marked cytotoxicity in cancerous cells, and its action was associated with the suppressed expression of hypoxia-inducible factor-1 α and β and its downstream target genes (Table II) (100).

Effects and mechanisms of corosolic acid in the retinoblastoma Y79 cell line. The response of human retinoblastoma Y-79 cells to corosolic acid was investigated (101). The results showed that corosolic acid (10 μM for 24 h) could induce cell cycle arrest and apoptosis through its cytotoxic activity (IC_{50} of 4.15 μM for 24 h or 3.37 μM for 48 h) in a dose-dependent manner (101). The results also showed that the transcriptional activity of forkhead box M1 (FoxM1) was self-induced or driven by maternal embryonic leucine-zipper kinase (MELK), and that corosolic acid inhibited the expression levels of MELK and FoxM1 (101). The report established a promising therapeutic target of human retinoblastoma via MELK-FoxM1 signaling (Table II) (101).

3. Corosolic acid exerts anticancer effects *in vivo*

Banno *et al* (37) published the first study on the cancer-preventing and anti-inflammatory activities of corosolic acid *in vivo*. Corosolic acid exhibited a marked anti-inflammatory effect, with an IC_{50} of 0.09-0.3 mg per ear on 12-*O*-tetradecanoylphorbol-13-acetate-induced inflammation (1 μg/ear) in mice; however, corosolic acid with an IC_{50} of 0.09-0.3 mg per ear did not exhibit an anticancer activity in a mouse tumor model. *In vivo* experiments in a murine sarcoma model showed that subcutaneous tumor development and lung metastasis was significantly suppressed by orally administered corosolic acid (17.5 mg/kg, 2 times/week for 21 days) (102). Corosolic acid was indicated as a potential new anticancer agent, as it targets macrophage polarization (102). In a murine osteosarcoma model, it was shown that orally administered corosolic acid (17.5 mg/kg/day for 7 days) significantly suppressed subcutaneous tumor development and pulmonary metastasis (52). It was also indicated that corosolic acid has a potential anticancer effect through targeting macrophage polarization and the immunosuppressive activity of MDSCs (52) Corosolic acid (20 μM) also displayed synergistic effects with anticancer agents, such as adriamycin (10 μM) and cisplatin (10 μM) after 24 h (52). In a mouse model of colon carcinoma, 5 and 25 mg/kg/day corosolic acid, administered via a peritumoral injection for 12 days inhibited allograft colon tumor growth. The results found that corosolic acid reduced the final tumor volume and the blood and lymphatic vessel densities of tumors, indicating that it suppresses *in vivo* angiogenesis and lymphangiogenesis (53). This was the first report of the anti-angiogenic and anti-lymphangiogenic effects of corosolic acid (53). Ma *et al* (89) established a xenograft tumor model of castration-resistant prostate cancer, and 10 and 20 mg/kg corosolic acid every 2 days for 14 days, administered via an intraperitoneal injection, was found to reduce tumor growth. Ku *et al* (48) reported that 5 mg/kg/day corosolic acid for 21 days effectively inhibited HCC Huh7 tumor growth in a male NOD/SCID mice model, and combined treatment of corosolic acid with sorafenib showed a synergistic inhibitory effect on tumor growth (corosolic acid 2.5 mg/kg/day with sorafenib 10 or 20 mg/kg/day) compared with corosolic acid alone, for 21 days in a mouse model (Table III).

4. Corosolic acid exerts synergistic anticancer activity with chemotherapeutic drugs

Accumulating experimental evidence has highlighted the pivotal role of STAT3 activation in the resistance to chemotherapy and radiotherapy in the thyroid cancer-derived CD133+ cells (103) and human epithelial ovarian cancer cells (104). It is thought that inhibiting STAT3 might be effective for treating patients with malignant tumors (103-105). A report by Fujiwara *et al* (95) suggested that 20 μM corosolic acid, as a selective STAT3 inhibitor, is able to increase sensitivity to chemotherapeutic agents, including paclitaxel (10 μM), cisplatin (10 μM) and doxorubicin (10 μM), in epithelial ovarian cancer SKOV3, RMG-1 and ES-2 cell lines for 24 h. In addition, the results of a study by Lee *et al* (81) showed that 25 μM corosolic acid enhances the inhibitory effect on human gastric cancer NCI-N87 cell proliferation when combined with adriamycin (0.01 to 2 mg/ml) and 5-FU (0.1 to 50 mg/ml), but not with docetaxel (0.01 to 2 mg/ml) or paclitaxel (0.01 to 6 mg/ml). Lee *et al* (106) indicated that corosolic acid

Table III. Summary of the effects and mechanisms of corosolic acid in different types of cancer *in vivo*.

First author, year	Cancer model type	Corosolic acid mechanism of action	Corosolic acid dose; administration	Effects	(Refs.)
Horlad *et al*, 2013	Murine sarcoma xenograft model	↓ STAT3 activation, ↑ CD4$^+$ and CD8$^+$ lymphocytes, ↓ the suppressive effect of MDSC	17.5 mg/kg/day; oral	Impaired subcutaneous tumor development and lung metastasis	(52)
Ku *et al*, 2015	Mouse HCC Huh7 xenograft model	VEGFR2/Src/FAK pathway (↓ VEGFR2, Src, FAK, ↓ phosphorylation of VEGFR2 and FAK)	5 mg/kg/day; intraperitoneal injection	85% reduction in tumor mass compared to the control group	(48)
Yoo *et al*, 2015	Mouse xenograft colon CT-26 model	Anti-angiogenic and anti-lymphangiogenic effects	5 or 25 mg/kg/day; peritumor rejection	Reduced the final tumor volume and blood and lymphatic vessel density of tumors	(53)
Ma *et al*, 2018	Mouse xenograft PC-3 model	ER stress, IRE-1/ASK1/JNK signaling pathway, and PERK/eIF2α/ATF4/CHOP signaling pathway (↑ IRE-1, PERK, CHOP, TRIB3; ↓ AKT)	10 or 20 mg/kg/2 days; intraperitoneal injection	Reduced the final tumor volume in a dose-dependent manner	(89)
Fujiwara *et al*, 2014	Mouse LM8 sarcoma model	Inhibits macrophage polarization to M2 phenotype by suppressing STAT3 activation	17.5 mg/kg, 2 times/week; oral	Reduced the final tumor volume	(102)

HCC, hepatocellular carcinoma; MDSCs, myeloid-derived suppressor cells; Src, steroid receptor coactivator; FAK, focal adhesion kinase; cdc42, cell division cycle42; ER, endoplasmic reticulum; STAT3, signal transducer and activator of transcription 3; VEGFR2, VEGFR, vascular growth factor receptor 2; IRE-1, inositol-requiring ER-to-nucleus signal kinase 1; ASK1, apoptosis signal regulating kinase 1; JNK, Jun N-terminal kinase; PERK, protein kinase RNA-like ER kinase; eIF2α, eukaryotic initiation factor 2α; ATF4, activating transcription factor 4; CHOP, C/EBP-homologous protein; TRIB3, tribbles pseudo-kinase 3; ↑, indicates upregulation; ↓, indicates downregulation.

(50 μM) enhances the anticancer activity of 5-FU (20 μg) after 24 h in human gastric carcinoma SNU-620 cells in an mTOR inhibition-dependent manner. In addition, a report by Fujiwara *et al* (102) showed that corosolic acid (20 μM) also displayed synergistic effects with anticancer agents, such as adriamycin (10 μM) and cisplatin (10 μM) 24 h. Furthermore, in a study by Park *et al* (107), a 5-FU-resistant gastric cancer cell line (SNU-620/5-FUR) was established, which had a marked reduced AMPK phosphorylation when compared with the parental cell line, SNU-620. Cell treatment with 25 μM corosolic acid for 24 h was found to enhance the chemosensitivity of 5-FU-resistant gastric cancer cells, and the reduction of AMPK phosphorylation by compound c (AMPK inhibitor) was revealed to be associated with increased 5-FU-resistant cell viability (107). Corosolic acid treatment significantly reduced cell viability while compound c reversed corosolic acid-induced cell growth

inhibition (107). The corosolic acid-induced AMPK activation was markedly increased by additional 5-FU treatment, while compound c reversed AMPK phosphorylation (107). These results imply that corosolic acid can activate AMPK and sensitize gastric cancer to 5-FU (150 μM; Table II).

5. Corosolic acid exerts anti-inflammatory and anti-MS effects

Nelson *et al* (108) first reported that corosolic acid (2 μmol twice-weekly over a 2-week period) may be an effective anti-inflammatory agent. Yamaguchi *et al* (109) further explored corosolic acid isolated from Banaba leaves and found that it prevented oxidative stress and reduced the inflammation caused by MS. In SHR-cp rats with characteristics that included obesity, hyperglycemia, hyperlipidemia, hypertension, hyperinsulinemia, oxidative stress and inflammation, a
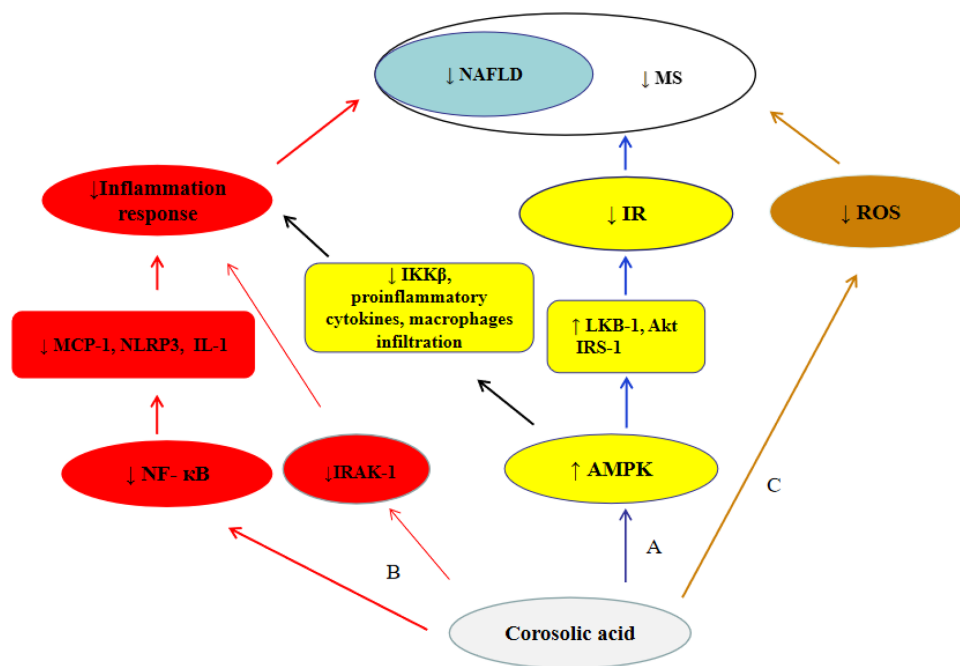
Figure 3. Effects and mechanisms of corosolic acid-induced anti-inflammatory and anti-MS activities. The characteristics of MS include ROS, IR and inflammation. (A) Corosolic acid downregulates IKKβ and proinflammatory cytokines, inhibits macrophage infiltration and inflammation, and upregulates LKB-1, IRS-1 and Akt, which ameliorates IR via enhancing. AMPK activation in a LKB1-dependent manner. (B) Corosolic acid downregulates the expression of MCP-1, NLRP3 and IL-1 via the NF-κB pathway, downregulates the expression of IRAK-1, and inhibits inflammation. (C) Corosolic acid prevents ROS in MS. IKKβ, inhibitor of nuclear factor kappa-B kinase; LKB-1, liver kinase B1; IRS, insulin receptor substrate-1; Akt, protein kinase B; IR, insulin resistance; MCP-1, monocyte chemoattractant protein-1; NLRP3, NLR family pyrin domain containing 3; IL-1, interleukin-1; NF-κB, nuclear factor kappa-B; IRAK-1, inhibitor of IL-1 receptor-associated kinase; ROS, reactive oxygen species; AMPK, adenosine monophosphate-activated protein kinase; MS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; ↑, indicates upregulation; ↓, indicates downregulation.

diet rich in 0.072% corosolic acid for 14 weeks ameliorated hypertension, regulated hyperlipidemia, prevented oxidative stress and ameliorated inflammation (109). A report by Chen *et al* (110) suggested that 6 μM corosolic acid treatment for 30 min was able to inhibit monocyte chemoattractant protein-1 expression, and that 2 μg/kg/day corosolic acid for 10 days ameliorated atherosclerosis by regulating the nuclear factor-κB signaling pathway in apolipoprotein E-deficient mice. Furthermore, Kim *et al* (111) reported that exposure of lipopolysaccharide (LPS)-pretreated bone marrow-derived monocytes to corosolic acid downregulated the NF-κB target genes pyrin domain-containing protein 3 (NLRP3) and interleukin-1 (IL-1), which was similar to the effects observed for LPS-pretreated bone marrow-derived monocytes with an inhibitor of IL-1 receptor-associated kinase (IRAK; a signaling molecule upstream of LPS-induced activated toll-like receptor 4) or with LPS and Bay11-7082 (an IκB) (111). Treatment with Bay11-7082 (an inhibitor of IκB-α), had no effect on corosolic acid-mediated inhibition of IRAK-1 activation, indicating that corosolic acid-mediated attenuation of IRAK-1 phosphorylation was independent of NF-κB signaling (111). These data indicate that corosolic acid plays a vital inhibitory role in acute inflammation by regulating IRAK-1 phosphorylation in an NF-κB-independent manner (111). In addition, a report by Yang *et al* (27) revealed that 10 mg/kg/day corosolic acid for 8 weeks improved insulin sensitivity and glucose intolerance, and attenuated hyperlipidemia in C57BL/6 mice. In addition, corosolic acid suppressed the phosphorylation of inhibitor of nuclear factor kappa-B kinase (IKKβ) and downregulated the

expression of proinflammatory cytokine genes, which in turn alleviated adipose tissue inflammation (27). Corosolic acid also enhanced the phosphorylation of serine (Ser)/threonine on insulin receptor substrate-1 (IRS-1) and its downstream effector Akt, and enhanced insulin signal transduction (27). Finally, in AMPKα-knockdown adipocytes, the inhibitory effects of corosolic acid on IRS-1 and IKKβ Ser phosphorylation were abolished, indicating that corosolic acid ameliorated IR and inhibited inflammation through the activation of AMPK in a liver kinase B1-dependent manner (27) (Fig. 3).

6. Proposed mechanisms underlying the inhibition of NAFLD-related HCC progression by corosolic acid

The characteristics of NAFLD include obesity, IR, hypertension and dyslipidemia, which are also the most common characteristics observed in livers affected by MS (112). Furthermore, the development of NAFLD-related HCC is increasingly recognized, since patients with NAFLD are at high risk of developing HCC (112). NAFLD-associated HCC has been estimated to account for 10-12% of HCC cases in Western populations and 1-6% of HCC cases in Asian populations from 42 sites in 14 countries from 2005 to 2012 (58). Based on multiple studies, accumulated evidence has suggested that type 2 diabetes mellitus (T2DM) and obesity are independent risk factors for the development of HCC in patients with NAFLD.

Animal and human studies and *in vitro* systems have indicated that corosolic acid has multiple properties, including anti-diabetic, anti-obesity, anti-inflammatory, anti-hyperlipidemic and anti-viral
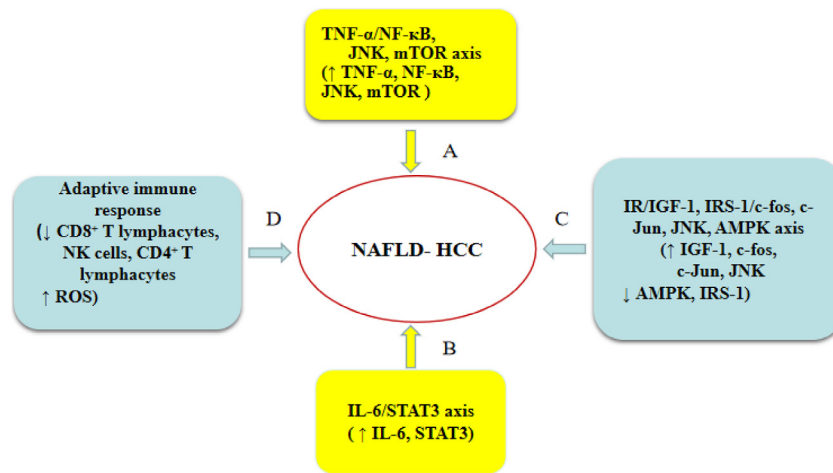
Figure 4. Molecular mechanisms of NAFLD-HCC. (A) TNF-α/NF-κB, JNK, mTOR axis. Pro-oncogenic pathways, such as NF-κB, JNK, mTOR are stimulated by TNF-α; (B) Chronic activation of the IL-6/STAT3 axis; Hepatocytes with previously acquired oncogenic mutations will continue malignant transformation that is induced by the chronic activation of the IL-6/STAT3 axis. (C) IR/IGF-1, IRS-1/c-fos, c- Jun, JNK, AMPK axis; IGF-1 is increased by IR, IGF-1 contributes to the upregulated expression of the proto-oncogenes c-fos and c-Jun, and the downregulation of AMPK, which is associated with the development of HCC. JNK-induced phosphorylation and downregulation of IRS-1 are responsible for obesity-induced IR, and JNK signaling plays a pivotal role in hepatocarcinogenesis. (D) ROS and adaptive immune response. Mitochondria-derived ROS promotes selective depletion of CD4+ T lymphocytes; carcinogenesis is induced by the metabolic activation of CD8+ T lymphocytes and NK cells in the liver. NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; IR, insulin resistance; IRS-1, insulin receptor substrate-1; IL-6, interleukin-6; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; JNK, Jun N-terminal kinase; mTOR, adenosine monophosphate-activated protein kinase; STAT3, signal transducer and activator of transcription 3; IGF-1, insulin-like growth factor-1; AMPK, adenosine monophosphate-activated protein kinase; ROS, reactive oxygen species; NK, natural killer; ↑, indicates upregulation; ↓, indicates downregulation.
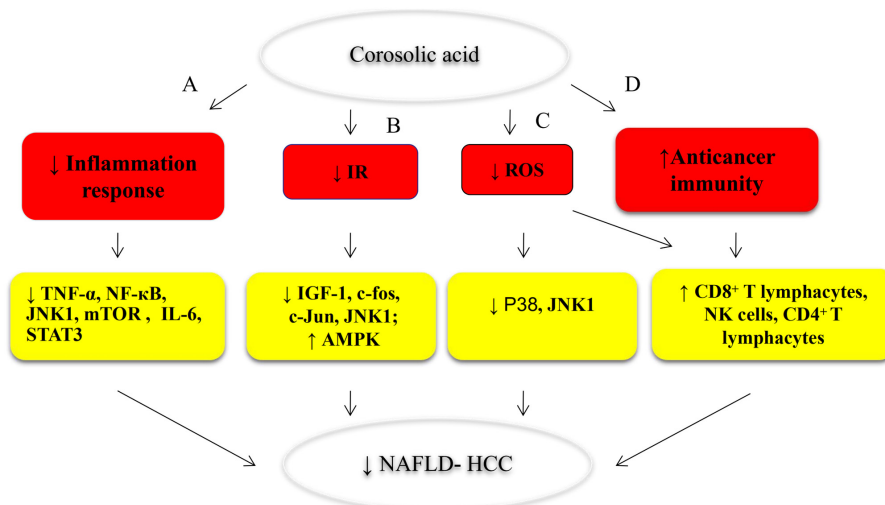

Figure 5. Proposed mechanisms through which corosolic acid inhibits NAFLD-related HCC progression. Corosolic acid suppresses NAFLD-HCC by inhibiting inflammation, IR, ROS and enhancing anticancer immunity. (A) Corosolic acid downregulates the proinflammatory cytokines, such as TNF-α and IL-6, NF-κB, JNK1, STAT3 and mTOR. (B) Corosolic acid ameliorates IR through the activation of AMPK, and downregulates IGF-1, c-fos, c-Jun and JNK1. (C) Corosolic acid downregulates the activation of P38 and JNK1, and increases the number of infiltrating CD4+ T lymphocytes via the inhibition of ROS. (D) Corosolic acid increases the number of infiltrating CD4+ T lymphocytes, CD8+ T lymphocytes and NK cells. NAFLD, non-alcoholic fatty liver disease; HCC, hepatocellular carcinoma; IR, insulin resistance; AMPK, adenosine monophosphate-activated protein kinase; IL-6, interleukin-6; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; JNK1, Jun N-terminal kinase 1; mTOR, adenosine monophosphate-activated protein kinase; STAT3, signal transducer and activator of transcription 3; IGF-1, insulin-like growth factor-1; IR, insulin resistance; ROS, reactive oxygen species; NK, natural killer; ↑, indicates upregulation; ↓, indicates downregulation.

activity (26,73,74). On the other hand, as aforementioned, corosolic acid has shown an ability to modulate multiple cancer-related signaling pathways, including the adenosine mitogen-activated protein kinase (AMPK), NF-κB, PI3K/Akt/mTOR, Wnt/β-catenin, FAK, ERK1/2, STAT3 in MDSCs, Nrf2/HO-1 and numerous other signaling pathways associated with cell proliferation and cell death, among other cellular processes in multiple types of

malignant tumors (as observed in preclinical *in vitro* and *in vivo* experiments) (48,49,51,52,54,55,81-83,91-96,107). Due to its anticancer and anti-immunity activities, corosolic acid has attracted growing attention. A schematic plot of the proposed mechanisms of the corosolic acid-induced inhibition of NAFLD-related HCC progression is presented in Fig. 5. The release of an increased number of proinflammatory cytokines, such as tumor necrosis

factor-α (TNF-α) and interleukin-6 (IL-6), is promoted by obesity and adipose tissue expansion (62). NF-κB, JNK, mTOR and extracellular signal-related kinases, such as those associated with pro-oncogenic pathways, are stimulated by TNF-α (63). It is highly likely that hepatocytes with previously acquired oncogenic mutations will continue the malignant transformation that is induced by the chronic activation of the IL-6/STAT3 axis (64). As aforementioned, as an agent with anticancer and anti-inflammatory activity, corosolic acid plays vital roles in the inhibition of proinflammatory cytokine and mTOR expression, and the downregulation of ERK, while as a STAT3 and NF-κB inhibitor, it can enhance anticancer activity (53,95,111). NAFLD promotes systemic and hepatic IR with the resultant hyperinsulinemia-activated proinflammatory cytokines and lipotoxic activity in obesity and T2DM (112). A previous report showed that the production of IRS-1 and insulin-like growth factor-1 (IGF-1) was increased by IR and hyperinsulinemia (65). IGF-1 promotes cell proliferation, inhibits apoptosis and stimulates cell growth (65). Furthermore, IGF-1 contributes to the upregulated expression of the proto-oncogenes c-fos and c-Jun *in vitro*, and the downregulation of AMPK, which is associated with the development of HCC (66). JNK, another important intracellular marker, is closely linked to obesity, IR, NAFLD and HCC (67). It has also been indicated that JNK-induced phosphorylation and activation of IRS-1 are responsible for obesity-induced IR (67). A report by Chang *et al* (68) showed that JNK signaling might play a pivotal role in hepatocarcinogenesis, where an increased JNK1 activation was detected by immunostaining in 17/31 HCC samples relative to their paired adjacent normal tissues. In addition, recent studies have revealed the potential role of the adaptive immune system in the development of NAFLD-related HCC (71,72). A report by Ma *et al* (71) revealed that hepatocytes exhibit increased linoleic acid secretion and mitochondria-derived ROS, both of which led to enhanced carcinogenesis. The same report also found that CD4+ T lymphocytes have greater mitochondrial mass than CD8+ T lymphocytes and generate higher levels of mitochondrially derived ROS. The disruption of mitochondrial function by free fatty acids such as palmitic acid accumulated in NAFLD, caused more oxidative damage and in turn promoted selective depletion of CD4+ T lymphocytes. In addition, blockade of ROS reversed NAFLD-induced hepatic CD4+ T lymphocyte decrease and delayed NAFLD-promoted HCC in mouse models of NAFLD-associated HCC. Wolf *et al* (72) developed a mouse model recapitulating key features of human metabolic syndrome, non-alcoholic steatohepatitis, and HCC by feeding mice a choline-deficient high-fat diet, and found that carcinogenesis was induced by the metabolic activation of CD8+ T lymphocytes and natural killer cells in the liver. Corosolic acid exerted anticancer immunity by inhibiting STAT3 and NF-κB activation; this immunity was associated with MDSC depletion, decreased levels of COX-2 and CCL2 expression, and an increased number of infiltrating CD8+ T lymphocytes. Furthermore, corosolic acid can also downregulate the activation of P38 and JNK via the inhibition of ROS (Fig. 4) (99,109).

7. Conclusions and future perspectives

The present review summarizes current advancements in our understanding of the anticancer activity and mechanisms of corosolic acid *in vitro* and *in vivo*. Due to the ability of corosolic

acid to target multiple components of cancer cells, it acts not only as an anticancer agent but also as a synergistic adjuvant when administered alongside chemotherapeutic drugs, even in drug-resistant cells. In addition, parts of the same corosolic acid mechanism that ameliorates MS also induces anticancer activity and suppresses the progression of NAFLD-related HCC. Therefore, corosolic acid, a potential tool in MS treatment, is being considered as a possible agent in NAFLD-related HCC prevention and treatment (Figs. 3 and 5).

Availability of data and materials

Not applicable.

Authors' contributions

JZ, HZ, YA, KS and LY participated in the design and interpretation of the studies, the revision of the manuscript. JZ, HZ, YA and KS wrote the review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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