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Recent Updates on Herbs for Hepatocellular Carcinoma

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ABSTRACT:
Hepatocellular carcinoma (HCC) is a devastating malignancy with a rising global incidence, presenting substantial challenges in terms of diagnosis and treatment. Understanding the pathogenesis of HCC is crucial for developing effective therapeutic strategies. This review article provides a comprehensive overview of recent updates on herbs used in the management of HCC and explores their potential mechanisms of action. HCC arises predominantly in the setting of chronic liver diseases, such as hepatitis B and C infection, cirrhosis, and non-alcoholic fatty liver disease (NAFLD). The pathogenesis of HCC involves a complex interplay of genetic, epigenetic, and environmental factors. Key pathways implicated in HCC development include Wnt/β-catenin signaling, PI3K/AKT/mTOR signaling, and oxidative stress, among others. In recent years, natural compounds derived from herbs have garnered significant attention for their potential in preventing and treating HCC. This review highlights several promising herbs and their active components, including curcumin, resveratrol, green tea polyphenols, gingerol from ginger, sulforaphane from broccoli sprouts, silymarin from milk thistle (*Silybum marianum*), thymoquinone from *Nigella sativa* (black seed), glycyrrhizin from *Glycyrrhiza glabra* (licorice), *Lycium barbarum* (Goji berry), and xanthorrhizol from *Curcuma xanthorrhiza*. These herbs exhibit diverse pharmacological properties, such as anti-inflammatory, antioxidant, anti-proliferative, and pro-apoptotic effects, which target various stages of HCC pathogenesis. Additionally, they have shown the ability to modulate key signaling pathways involved in HCC progression, providing a multi-faceted approach to HCC management. In conclusion, this review provides valuable insights into the recent advances in herbal therapies for HCC, shedding light on their potential roles in preventing, slowing, or even reversing HCC progression. The exploration of the intricate mechanisms by which these herbs exert their effects offers new avenues for therapeutic interventions in HCC. However, further clinical studies and rigorous evaluation are necessary to establish their efficacy and safety as adjunctive treatments in the management of HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is ranked as the sixth most prevalent cancer globally and is the third most deadly type of tumor, causing approximately 700,500 deaths each year worldwide. The mortality rate linked to HCC has been on a rapid rise over the past decade, and estimates indicate that by 2025, more than a million people will be diagnosed with liver cancer annually (1). The natural processes that normally suppress tumor growth in healthy cells often distinguish between cancer cells that are developing abnormally and normal cells. However, certain environmental factors like radiation, pollutants, diseases, as well as human behaviors such as a poor diet, smoking, and alcohol consumption, can hinder the function of these tumour-suppressing genes. Regardless of advancements in human development, cancer has emerged as a leading global cause of death. Several risk factors contribute to cancer, including hepatitis B and C viruses, fatty liver disease, various infections, obesity, alcoholic cirrhosis, iron deficiency, smoking, malnutrition, improper dietary habits, and exposure to aflatoxin B1 (AFB1) (2). Chronic hepatitis B virus (HBV) infection accounts for approximately 50% of HCC cases, while non-alcoholic steatohepatitis (NASH) is rapidly gaining recognition as an emerging cause. Due to the limited treatment options available for HCC, primarily surgical interventions, and the poor prognosis associated with the disease, there is a critical need for additional therapies that can improve survival rates and quality of life. Therefore, there is a pressing need for

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modern drug combinations that target multiple signaling pathways to reduce the likelihood of drug resistance in cancer cells. Throughout history, natural products derived from medicinal plants have been used for treating various diseases. Many natural phytoconstituents have become crucial for drug discovery and research, especially in the context of managing different diseases, including cancer. These phytochemicals have demonstrated their effectiveness in reversing the initiation, growth, and progression of cancer by influencing various pathways such as cell proliferation, cell division, apoptosis, angiogenesis, and metastasis (1–3).

2. Pathogenesis of HCC

Under certain conditions, such as metabolic disorders, hepatitis B or hepatitis C virus (HBV or HCV), and toxin exposure, normal hepatocytes can transform into malignant tumour cells (Fig. 1). Globally, persistent HBV or HCV infection is linked to more than 80% of HCC incidence. It is estimated that HBV infection accounts for half of all HCC cases, with HCV infection accounting for the remaining 25% (4). HBV may be pathogenic for HCC via at least three mechanisms: integration of HBV DNA into the DNA of host cells, chronic infection and the development of cirrhosis, and the activity of one of the HBV proteins, the X protein. HBV DNA fragments can be found integrated into the cellular DNA of carriers in patients with chronic HBV infection. This integration appears to occur during hepatocyte regeneration following HBV-related necroinflammatory activity. HBV DNA integration appears to happen without a specific pattern within the genome. When viral DNA integrates, it can interfere with the normal function of regulatory genes, potentially leading to chromosomal instability, a characteristic seen in various types of cancer (5). In contrast to HBV; HCV does not possess reverse transcriptase activity, which means it does not integrate into the host's genetic material. As HCV is a virus that replicates entirely in the cytoplasm, the leading theory regarding its role in causing hepatocellular carcinoma suggests that it indirectly contributes to cancer development through chronic inflammation and continuous damage to liver cells. Several HCV proteins have been identified as contributors to the development of HCC in experimental research involving cell cultures and animal models. Among these proteins, the HCV core protein plays a crucial role in viral particle assembly and the formation of complete virions. However, it also participates in various cellular processes, such as cell signalling, activation of transcription, apoptosis, lipid metabolism, and cell transformation. The HBV-encoded X antigen (HBxAg) and core protein of the Hepatitis C Virus can attach themselves to two important tumour suppressor proteins, namely p53 and pRb. This interaction leads to the alteration of Cyclin-dependent kinase inhibitor 1A (p21)/ Wound-Associated Factor (Waf) expression, a protein that plays a crucial role in regulating the cell cycle. Additionally, the HCV core protein can also engage with signal transduction molecules in the cell's cytoplasm to control transcription processes (5–7). Conditions like diabetes, NAFLD and galactosemia also contribute to the development of HCC. Diabetes mellitus (DM) is associated with an increased risk of different types of cancer, including HCC (8). Diabetes appears to be a risk factor for HCC, according to several studies (5,9). Non-alcoholic fatty liver disease, a prevalent condition in developed nations, encompasses a spectrum from simple steatosis (accumulation of fat) to NASH (Fig. 1). It stands as the most widespread liver disorder in developed regions. The activation of Mitogen-activated protein kinase (MAPK), in particular, facilitates the transcription of proto-oncogenes c- fos and c-jun, which subsequently impact cell growth (10,11). Moreover, the byproducts resulting from the breakdown of lipids (lipid peroxidation) and the higher levels of reactive oxygen species (ROS) trigger the release of various pro-inflammatory and inflammatory substances, including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α). Additionally, these processes affect the secretion of adipokines, specifically leptin and adiponectin. The increased expression of IL-6 activates the oncogenic pathway known as signal transducer and activator of transcription 3 (STAT-3), which promotes cell proliferation, inhibits apoptosis, and contributes to the development of HCC. Furthermore, elevated levels of TNF-α lead to the activation of pro-oncogenic pathways, notably nuclear factor κB (NF-κB), through the c-Jun N- terminal kinase (JNK) pathway and the phosphorylation of the inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta (IKKβ) (12). One significant contributing factor that encourages the development of liver cancer is exposure to harmful substances, such as aflatoxins, cigarette smoke, androgenic steroids, and alcohol (Fig. 1). Aflatoxins are substances produced by fungi found in food, and they have harmful effects on the liver, causing toxicity, carcinogenicity, and mutagenicity (13). Aflatoxin B1 (AFB1) is the most potent liver cancer-causing substance. After ingestion, AFB1 is metabolized by the cytochrome P-450 system, leading to the creation of an unstable reactive compound called AFB1-8,9-epoxide at the 8,9-vinyl bond (14). This reactive intermediate can chemically bind to DNA, forming AFB1-guanine adducts, and also bind to proteins, forming AFB1-albumin and other protein adducts (15–17). The formation of AFB1-guanine adducts in the liver's DNA is crucial for the carcinogenic effects of AFB1 in animals, causing mutations in key genes (18)

Journal of Chemical Health Risks

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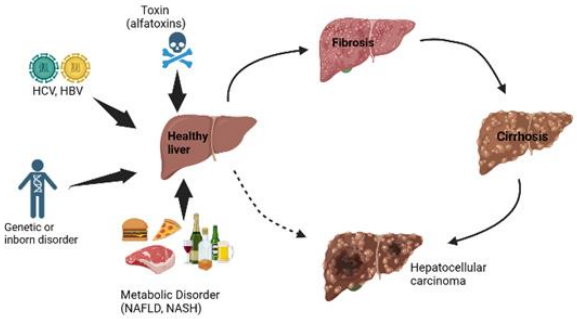

Fig. 1. Figure depicts risk factors such as hepatitis B or hepatitis C virus (HBV or HCV), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), aflatoxins and genetic or inborn disorders associated with HCC. The healthy liver as a result of exposure to these risk factors progressively undergoes fibrosis followed by cirrhosis and development of HCC.

Potential herbal drugs for hepatocellular carcinoma

Curcuma longa

Curcumin is a polyphenol molecule derived from the rhizomes of Curcuma longa that have been researched for three significant qualities concerning HCC: anti-angiogenesis of HCC, anti-HCC, and anti-metastatic activity of HCC (Fig. 2). Chuang *et al.* assessed the effect of curcumin on an N-diethylnitrosamine (DEN)-induced HCC animal model. Curcumin was reported to effectively prevent DEN-induced hepatocarcinogenesis in C3H/HeN mice. The levels of p21 (ras), proliferating cell nuclear antigen (PCNA), and cell division cycle 2 (CDC2) proteins in the hepatic tissue of DEN-treated mice were significantly higher, while curcumin reversed the levels of all these biological markers. In another investigation carried out by the identical research team, it was found that curcumin exhibits substantial inhibition of hepatic inflammation and hyperplasia induced by DEN in a rat model of HCC (19). Ohashi *et al*. used an orthotopic implantation HCC model with CBO140C12 cells to investigate the anti-metastatic mechanism. They discovered that daily oral curcumin administration inhibited intrahepatic metastasis of orthotopic implanted HCC cells. Curcumin was also tested for its ability to suppress tumour cell adhesion and hepatotactic migration to fibronectin and laminin *in vitro* (20). Curcumin's antiangiogenic properties in HCC were also demonstrated, with H22HCC cells being treated *in vitro* with various doses of curcumin (Fig. 2). In addition, a mouse xenograft model was employed to examine the expression levels of vascular endothelial growth factor (VEGF) protein and proteins from the phosphoinositide 3 kinase (PI3K)/AKT serine/threonine kinase 1 (AKT) signalling pathway. Curcumin decreased H22 cell growth and accelerated H22 cell death *in vitro* in a dose-dependent manner. Curcumin therapy also reduced tumour growth *in vivo* at dosages of 50 and 100 mg/kg, p.o. Curcumin therapy also reduced VEGF expression and PI3K/AKT signalling substantially (21).

Even though various *in vitro* and animal studies have indicated that curcumin has considerable chemopreventive effects and consequently has an anti-HCC impact, the specific mechanism is still unknown because of its poor systemic absorption and complexity.

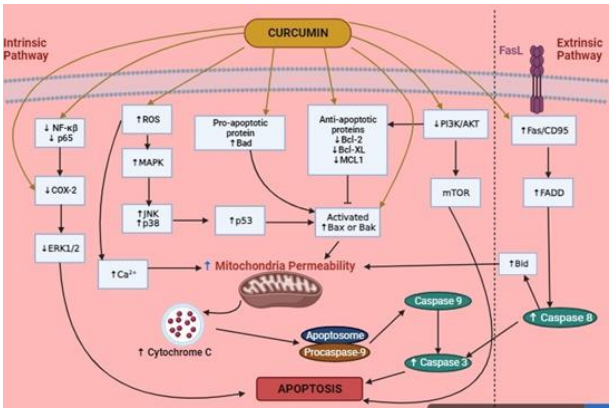

Fig. 2. Pictorial representation of various molecular targets of curcumin in the treatment of HCC. There are two main pathways leading to apoptosis. Intrinsic pathways including NF-kB, MAPK-JNK, PI3K/AKT mediated through mTOR signalling mechanisms, decrease in anti-apoptotic proteins, and activation of apoptotic proteins. The extrinsic pathway is mediated through FasL-associated caspase 8 followed by caspase 3 activation.

Resveratrol

Resveratrol (RSV) is present in grape skins, peanuts, berries, and red wine, and has been proven to suppress the growth of different human cancer cells, including HCC. It is readily absorbed and accumulates in the liver. Seda *et al.* studied the effects of various concentrations of RSV against DEN-induced hepatocellular carcinoma in rats. They found that an RSV dose of 100 mg/kg resulted in a considerable increase in apoptotic cancer cells. (22). Notas *et al.* used Human liver cancer cell line (HepG2 cells) to investigate the effect of resveratrol on cell proliferation and to investigate some potential pathways. Their findings show that the stilbene resveratrol suppresses cell growth, lowers ROS generation, and promotes apoptosis via cell-cycle arrest in the G1 and G2/M phases. They also discovered that resveratrol affects the NO/NOS system by boosting the expression of inducible nitric oxide synthase (iNOS) and endothelial nitric oxide synthase (eNOS), as well as nitric

Journal of Chemical Health Risks

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oxide synthase (NOS) activity and nitric oxide (NO) generation (23). Resveratrol, like curcumin, has been studied for its anti-metastatic activity. Chao-Bin et al. performed certain assays and concluded that Resveratrol is a potent natural substance that can be used in cancer prevention and therapy medicines. They revealed that resveratrol can effectively suppress phosphorylation of JNK 1/2 and SP-1 DNA binding activities, resulting in a decrease in urokinase-type plasminogen activator (u-PA) production and thereby inhibiting metastasis (24). RSV appears to protect the liver from NAFLD. The mechanism involves the activation of adenosine 5'-monophosphate-activated protein kinase (AMPK), which reduces triglycerides (TG) buildup and improves insulin resistance (IR) (25). In HCC rats, the expression of myosin light chain kinase (MLCK) was found to be elevated compared to both normal rats and rats treated with resveratrol (Table I). This heightened expression of MLCK played a crucial role in promoting cell proliferation and exerting anti-apoptotic effects within the liver. However, resveratrol was also found to reduce MLCK expression, which decreased liver tumorigenesis and enhanced cell death (26).

Camellia sinensis

Green tea (*Camellia sinensis*) leaves have been linked to the prevention of liver disease. Green tea originated in China and was then exported to Asian countries such as Korea, Vietnam, and Japan. At doses of 50-100 g/ml, epigallocatechin-3-gallate (EGCG), a key polyphenol found in green tea, reduced the development of HCC cell lines like HLE, HepG2, HuH-7, and PLC/PRF/5. In both in vitro and in vivo studies, EGCG promoted apoptosis in human lens epithelial (HLE) cells and appears to have down-regulated B-cell lymphoma 2α (Bcl-2α) and B-cell lymphoma-extra-large (Bcl-xL) through inactivating NF-κB (27). In experimental alcohol-induced liver injury, co-administration of whole green tea extract with alcohol reduced hepatic oxidative stress and decreased the form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase systems. Green tea extract in alcohol effectively lowered the quantities of O2, H2O2, and HOCl, owing to the catechin content rather than caffeine (28). Jujube leaf green tea extracts (JLGTE) exerted cytotoxic, anti-proliferative, and pro-apoptotic activities against HepG2 and primary HCC cells. JLGTE-induced AMPK activation and HepG2 cell death were decreased by silencing AMPKα1 by targeted short hairpin RNAs or CRISPR-Cas9 genome editing. Therefore, JLGTE-mediated anti-HCC cell action needed AMPK activation (29). The formation of foci related to glutathione S-transferase placental form (GST-P+) was inhibited through the administration of EGCG in the drinking water due to a reduction in hepatic fibrosis, triglyceride content, inflammation, oxidative stress, and suppression of excessive hepatocyte proliferation (30). The objective of meta-analysis is to assess the relationship between the intake of green tea and the likelihood of developing liver cancer. The findings indicate that individuals who consume the highest amount of green tea (approximately 5 cups per day) have a 38% lower risk of liver cancer compared to those who do not drink green tea. The results were statistically significant, with a confidence interval of 95% ranging from 0.49 to 0.79. Green tea consumption was found to have a significant dose-response relationship with the risk of liver cancer (31).

Zingiber officinale

The extract derived from the ginger root (*Zingiber officinale*), along with its spicy elements like gingerol, paradol, and shogaol, display promising abilities in terms of reducing inflammation, acting as antioxidants, and potentially combating cancer. The cytotoxic effects on HepG2 cell line are more potent when using ginger extracted through the soxhlet technique compared to extractions obtained through Maceration and Sonication. The soxhlet-extracted ginger can trigger apoptosis in HepG2 cell lines, regardless of whether they are cultured in 2D or 3D culture conditions. Unlike the sonication and maceration methods, which lacked the necessary strength to disrupt the ginger plant cell wall and release specific active compounds, the soxhlet method exhibited the capability to achieve this breakdown (32). Ginger polysaccharide (GP) prompts the apoptosis of HepG2 cells by reducing the mRNA expression of Bcl-2 and enhancing the expression of various proteins and genes like Bcl-2- associated X protein (Bax), Fas cell surface death receptor (also known as CD95), Fas ligand (FasL), cyclin-dependent kinase inhibitor 1A (p21), tumour protein p53, cysteine-aspartic acid protease 3 (caspase-3). Bax and Bcl-2 proteins, crucial components of the Bcl-2 family, control the apoptosis process by forming Bax/Bax homodimers and Bax/Bcl-2 heterodimers. Elevated Bax protein levels lead to an increase in Bax/Bcl-2 homodimers, triggering apoptosis through the activation of the death signal. Conversely, increased Bcl-2 protein levels cause an upsurge in Bax/Bcl-2 heterodimers, diminishing the apoptosis tendency and prolonging cell survival. Cyl-t (caspase-3 antibody) substantially enhances caspase-3 protein activation, and Bax and Bcl- 2 mediate cyl-t release via the mitochondrial pathway. Elevated Bax protein expression promotes the release of cyl-t through its homodimers, which subsequently activate caspase-3 protein and induce apoptosis. On the other hand, heightened Bcl-2 expression impedes Cyl-t release via heterodimers, thereby inhibiting caspase-3 protein and inducing apoptosis (33). Ginger exhibits significant efficacy in managing experimental cancer within a rat model. Administering a daily dose of approximately 50 mg/kg

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of ginger extract led to a reduction in the levels of growth factors and α-fetoprotein (a marker for liver tumors) in the rats (34). Ginger comprises various elements such as clavatol, pinostrobin, and geraniol. These active compounds were identified using gas chromatography and mass spectrometry techniques. The research revealed that ginger has the ability to hinder cell growth in the HepG-2 cell line, with an IC50 of 900 μg/ml (35). Plant polyphenols, specifically [6]-gingerol, is the primary spicy element within fresh ginger. [6]-gingerol, a key constituent, exhibits anti-tumor properties. It produces antioxidant benefits, shields human leukemia HL-60 cells from oxidative stress, triggers DNA fragmentation, and suppresses the activity of the anti-apoptotic gene B-cell leukemia/lymphoma-2 within HL-60 cells (36). 6-shogaol and 6-gingerol appear to have the potential to reduce the invasiveness of hepatoma cells (HepG2 and Hep3B cells) by controlling matrix metalloproteinase (MMP)-9 and tissue inhibitor metalloproteinase protein (TIMP)-1 levels. Additionally, 6-shogaol might also have a role in regulating urokinase-type plasminogen activity (37) (Table I).

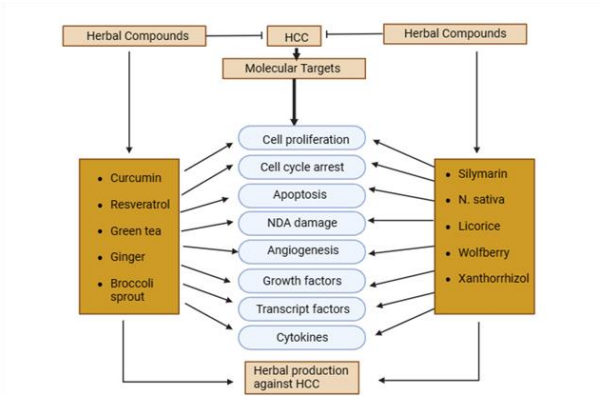

Fig. 3. The figure summarises molecular targets of herbal compounds in HCC.

Broccoli sprouts

Broccoli, a widely cultivated plant, stands out for its rich antioxidant content. Key antioxidant elements in this plant are vitamins, flavonoids, and carotenoids. A notable antioxidant compound derived from glucosinolate, called isothiocyanates, plays a significant role in safeguarding DNA from harm due to its antioxidative properties (38). Sulforaphane is a diverse constituent of broccoli, which has major cell-protective effects that involves boosting the Kelch-like ECH-associated protein 1 (Keap1)-NF-E2-related factor 2 (Nrf2) and other anti-inflammatory actions, like inhibiting NF-κB (39,40). Nrf2 is crucial for safeguarding liver health, shielding it not only from toxic substances but also from lifestyle-related factors like excessive calorie intake (Fig. 3) (41,42). In animal studies, dietary sulforaphane has proven effective in safeguarding the liver against various diseases caused by toxic chemicals, alcohol, and high-calorie diets (43,44). In clinical trials, induction of glucosinolates (GLSs) is linked to a decrease in the excretion of aflatoxin-N7-guanine and the prevention of HCC through chemoprevention mechanisms (45,46). In multiple research studies, broccoli sprouts demonstrated substantial cytotoxic activity against a range of cancer cell lines. These included MCF7 (breast adenocarcinoma), SW480 (colorectal adenocarcinoma), Caco-2 (colorectal adenocarcinoma), HepG2 (hepatocellular carcinoma cells), PC-3 (prostate carcinoma) and AGS (gastric adenocarcinoma) etc (47,48). Some study's findings also indicated significant inhibitory effects on the growth of various cancer cell lines by GLSs (49,50). The addition of sulforaphane-rich broccoli sprout (BS) to the diet is expected to have a significant positive impact on liver health by effectively decreasing oxidative stress which prevents DNA damage and enhancing liver function (51).

Silymarin

Silymarin, derived from the milk thistle plant *Silybum marianum* within the *Asteraceae* family, is a complex blend of seven primary flavonolignans (including silybin A, silybin B, also known as silibinin, isosilybin A, isosilybin B, silychristin, isosilychristin, and silydianine), along with one flavonoid. The therapeutic and liver-protective benefits of these components in silymarin are attributed to their potent antioxidant and anti-inflammatory characteristics (52). Rats exposed to N-nitrosodiethylamine (NDEA) exhibited significant hyperlipidemia, and their cyclooxygenase- 2 (COX-2) expression levels were heightened. However, when silymarin was added to their diet, it mitigated this hyperlipidemia and reduced COX-2 expression. This leads us to the conclusion that substances such as silymarin, which demonstrate robust hypolipidemic properties, hold great potential as preventive agents for liver cancer treatment (53). Treatment using *Silybum marianum* total extract (STE), silymarin (Sm), and silibinin (Sb) effectively hindered the growth of cancerous lesions in rats subjected to diethyl nitrosamine/2- acetylaminofluorene (AAF)/carbon tetrachloride (CCl4) (Fig. 3). This inhibitory effect was linked to a reduction in Ki-67 expression (Kiel-67-protein marker) and the suppression of signalling pathways such as Hepatocyte Growth Factor/ Cellular Met Proto-Oncogene Tyrosine Kinase, Wingless-Type MMTV Integration Site Family Member/ Beta-Catenin (HFG/cMet, Wnt/β- catenin), and phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR). Moreover, STE, Sm, and Sb demonstrated a positive impact on liver function

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 3567-3580 | ISSN: 2251-6719

indicators and tumor markers like Alpha-fetoprotein, carcinoembryonic antigen and carbohydrate antigen sialyl Lewis a (AFP, CEA, and CA19.9). Additionally, they increased the levels of total protein and albumin in the serum. Notably, these treatments also reduced the production of lipid peroxides in the liver, enhanced hepatic glutathione content, and stimulated the activity of hepatic antioxidant enzymes in AAF/CCl4/DEN-treated rat (54). Improved silymarin nanoemulsion formulations demonstrated a decrease in cell viability and an increase in ROS intensity and chromatin condensation in human liver carcinoma cells while sparing normal cells from harm. The small particle size of silymarin, combined with its larger surface area, allows for a faster drug release rate and improved absorption, ultimately leading to enhanced bioactivity with lower drug doses (55). Silymarin and its constituents exhibit antiviral properties against HCV infection in cell cultures. Additionally, they demonstrate antioxidant, anti-inflammatory, and immune-modulating effects, all of which contribute to their ability to protect the liver. In the present study, the hepatoprotective effects of the seven primary flavonolignans and one flavonoid found in Silymarin were observed to involve the inhibition of various factors, including NS5B polymerase activity, HCV cell culture infection, TNF-alpha-induced NF-kappaB transcription, T-cell proliferation and virus-induced oxidative stress (56). Silymarin demonstrated a strong ability to prevent spontaneous hepatocellular carcinoma in a mouse model with HBV X protein transgenes. When administered orally, silymarin exhibited a dose-dependent effect, effectively reversing initial hepatic damage and lipid-related alterations, thereby promoting the restoration of healthy liver tissue (57). Another study also noted the ability of silymarin to inhibit cell proliferation, specifically targeting tumor cells while sparing healthy hepatic cells. In the G0/G1 phase of the cell cycle, silymarin led to an increase in the proportion of cells, whereas in the S-phase, it reduced the cell percentage. This effect was associated with the down-regulation of proteins like cyclin D1, cyclin E, phospho-Rb, and cyclin-dependent kinase 4 (CDK4), along with the up-regulation of p53, retinoblastoma protein (Rb), cyclin-dependent kinase inhibitor 1B (CDKN1B), also called as p27Kip1, and cyclin-dependent kinase inhibitor 1A (CDKN1A), also called as p21Cip1 (58).

Nigella sativa

Nigella sativa, an annual flowering plant originally hailing from South and Southwest Asia and Northern Africa, is cultivated in numerous regions across the globe. Throughout history, *Nigella sativa* seeds have held a significant place as a natural remedy within various ancient medicinal systems such as Unani, Ayurveda, Chinese, and Arabic medicines. This herb has yielded numerous active components through isolation. Research has revealed that *Nigella sativa* seeds, its oil, various extracts, and its primary compound, Thymoquinone (TQ), exhibit a range of pharmacological effects. These effects encompass immune system stimulation, anti-inflammatory properties, hypoglycemic and antihypertensive effects, relief from asthma symptoms, antimicrobial and antiparasitic activities, antioxidative properties, and potential anticancer effects (59,60). The potential of *Nigella sativa* (black cumin) to combat cancer was investigated through various in-vivo and in-vitro research studies. The administration of a methanolic extract obtained from *Nigella sativa*, also known as black seed, significantly reduced the development of liver tumours and protected liver cells from the harmful effects caused by diethyl nitrosamine (DENA) and carbon tetrachloride. In the group treated with both DENA and carbon tetrachloride (CCl4), there was a notable increase in the relative weight of the liver, the level of alpha-fetoprotein in the blood serum, and the activities of enzymes like glyceraldehyde phosphate dehydrogenase, hexokinase, and glucose 6-phosphate dehydrogenase in both the serum and liver tissue. Pre-treatment with the methanolic extract from *Nigella sativa* (MENS) effectively maintained these parameters close to normal levels (Table I). DENA and CCl4 treatment caused extensive liver damage, including necrosis, inflammatory infiltration, hepatocyte clusters, necrosis, and bile duct proliferation. The seeds of *Nigella sativa* demonstrated the potential to inhibit the development of liver tumours induced by DENA. Based on these findings, it can be concluded that MENS has a preventive effect against the progression of liver malignancy, possibly through its regulation of energy metabolic pathways such as glycolysis, which may be involved in the development of liver cancer (61). The silver nanocomposites produced from extracts of *Nigella sativa* seeds were created using an environmentally friendly method. These nanocomposites demonstrate the ability to hinder the growth of HepG2 cells in a manner dependent on their concentration. Additionally, they induce the fragmentation of apoptotic nuclei and lead to increased production of reactive oxygen species, indicating that *Nigella sativa* AgNCs possess significant anti-cancer properties against human hepatocellular carcinoma, while leaving normal cells unaffected (62). The *Nigella sativa* extract was found to hinder the growth of HepG2 cells in a laboratory setting. The HepG2 cells in the control group remained unchanged in appearance and formed a continuous layer. Conversely, the cells exposed to the *Nigella sativa* extract displayed various alterations in their appearance, such as cell shrinkage and membrane damage, ultimately leading to cell death and a significant reduction in cell count (Fig. 3) (63).

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(06), 3567-3580 | ISSN: 2251-6719

Glycyrrhiza glabra

Glycyrrhiza glabra, also recognized as licorice, has been observed to exhibit various pharmacological effects such as anti-viral, hepatoprotective, anti-tumor, antioxidative, anti-inflammatory, and immunomodulatory properties (64–66). The presence of a triterpenoid saponin called glycyrrhizin is closely associated with *Glycyrrhiza glabra*, making it the predominant and most plentiful compound (comprising 10–30%) within the root extract of this plant (67,68). Glycyrrhizin and other components found in *Glycyrrhiza glabra* have been verified for their potential to combat various types of cancer, including liver, skin, and breast cancer, by impeding the growth and development of cancer cells. For instance, the alcoholic root extract from *Glycyrrhiza glabra* effectively restrains the proliferation of the MDA-MB-231 breast cancer cell line in a dosage-dependent manner. Similarly, the ethyl acetate root extract significantly hinders the growth of breast cancer cell lines (T47D, MCF7, MDA-MB-231, and MDA-MB-361), the SiHa cervical cancer cell line, and the A2780 ovarian cancer cell line, demonstrating its anti-cancer properties against A549 lung cancer cells as well (69–71). GA has the potential to decrease stem-like characteristics and promote the differentiation of cells in both HepG2 and PLC/PRF/5 cell lines (72). In contrast to a placebo, glycyrrhizin exhibited a significant decrease in serum aminotransferase levels and improved liver histology. Furthermore, prolonged usage of glycyrrhizin has been associated with a decreased likelihood of developing hepatocellular carcinoma in individuals with chronic HCV. In vitro studies have shown that glycyrrhizin modifies the internal mobility of cells and has the potential to hinder the HBV surface antigen (73,74). Glycyrrhizic acid, found primarily in licorice extract, has the potential to inhibit the development of liver cancer in mice exposed to DEN (75). Licorice has the potential to restore functional indicators and mitigate liver damage caused by pathological factors. It also has the ability to prevent cell death in liver cells, and increase the levels of protective proteins like Bcl 2 and superoxide dismutase (SOD), while reducing the levels of harmful substances like cellular tumour antigen p53, caspase-3, malondialdehyde, high mobility group protein B1 (HMGB1), TNF-α, and interleukin 1β (IL-1β). Therefore, it can be considered an effective treatment for liver toxicity induced by cisplatin (76). Phytochemical investigations were conducted on the *Glycyrrhiza glabra* root, resulting in the isolation of 21 compounds. Among these, 10 compounds containing isoprenyl or dimethylpyran rings demonstrated superior efficacy in inhibiting tumour cells (77). Glycyrrhizic acid-modified O- carboxymethyl chitosan nanoparticles (CMCNP) with different levels of substitution effectively transport paclitaxel to HCC. CMCNP-GA significantly improved the accumulation of paclitaxel in liver tumour tissue and its targeted delivery to liver cancer cells. This led to a noteworthy increase in cytotoxicity in laboratory settings and enhanced antitumour effectiveness in animal models (78). Glycyrrhizin has been documented for its application in managing liver conditions such as chronic hepatitis C and B. An extract containing glycyrrhizin was found to decrease liver fat accumulation in genetically modified mice expressing the entire HCV poly-protein. This extract demonstrated the ability to impede the expression of the HCV core gene and the production of full-length HCV viral particles, both at the protein and RNA levels. Furthermore, it exhibited a cooperative effect when combined with interferon therapy (79–81) (Table I).

Lycium barbarum

Wolfberry, a renowned traditional Chinese remedy, consists of the fruit of the *Lycium barbarum* plant, which belongs to the *Solanaceae* family. It offers significant advantages for both ocular and hepatic health (82). The most essential component of *Lycium barbarum*, known as *Lycium* polysaccharide portion (LPP), possesses a wealth of biological functions, including antioxidative, neuroprotective, immune-boosting, anti-tumour, and regulation of glucose metabolism. Notably, LPP has been shown to restrain the growth of liver cells and induce apoptosis in liver hepatoma cells, underscoring its potential role in fighting cancer. The outcome of a clinical study indicated that the intake of LPP juice resulted in increased levels of interleukin (IL)-2, immunoglobulin G, serum antioxidants, and lymphocyte count in humans, while also reducing lipid peroxide levels (82–84). The concurrent use of LPP alongside ethanol exposure significantly intensified liver damage in a rat model designed to mimic alcohol-induced liver injury. This effect was achieved by reducing oxidative stress levels and diminishing the buildup of lipids within the liver (85). The apoptotic effects of two distinct *Lycium barbarum* polysaccharide (LBP) fractions, namely LBP- d and LBP-e, were investigated in hepatoma SMMC-7721 cancer cells. Both LBP-d and LBP-e fractions inhibited the proliferation of SMMC-7721 cells during the G0/G1 and S phases, accompanied by an increase in intracellular calcium levels (86). In cases of acute liver injury, it was observed that LPP (presumably a substance or treatment) maintained the usual liver tissue structure, reduced liver inflammation and the attraction of harmful substances, promoted partial liver regeneration by activating the nuclear factor kappa B pathway, and lowered oxidative stress when administered before exposing mice to CCl4 intoxication (87). Zeaxanthin dipalmitate (ZD), extracted from wolfberries, safeguards the liver from acute fatty liver disease by focusing on the converging mitophagy-Nod-

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 3567-3580 | ISSN: 2251-6719

like receptor 3 (NLRP3) inflammasome pathway, stemming from purinergic receptor P2X, ligand-gated ion channel 7 (P2X7) and adiponectin receptor 1 (AdipoR1) on hepatocyte cell membranes (88). ZD might trigger protective mechanisms beyond P2X7/adipoR1-mediated mitophagy since blocking membrane receptors and general autophagy didn't completely nullify ZD's effects. Because ZD is an antioxidant with a high affinity for lipids, it's likely that it also directly inhibits lipid peroxidation, independently of mitophagy signalling pathways, which contributes to liver protection (Fig. 4). Additionally, there's a known connection between lipid peroxidation and inflammation in alcohol-induced liver injury. Considering ZD is the primary component responsible for the orange color of wolfberries and a key part of their carotenoid fraction, regular wolfberry consumption is expected to have a beneficial impact on both treating and preventing alcoholic liver disease (89). *Lycium chinensis* polysaccharides (LCP) led to an increase in the spleen and thymus indices, enhanced antioxidant enzyme activities, and reduced oxidative damage. Moreover, LCP had a significant impact on the expression of VEGF and cyclin D1 proteins in rats with liver cancer induced by diethylnitrosamine. In summary, LCP demonstrated impressive protective properties against DEN-induced oxidative liver injury in rats with liver cancer (90).

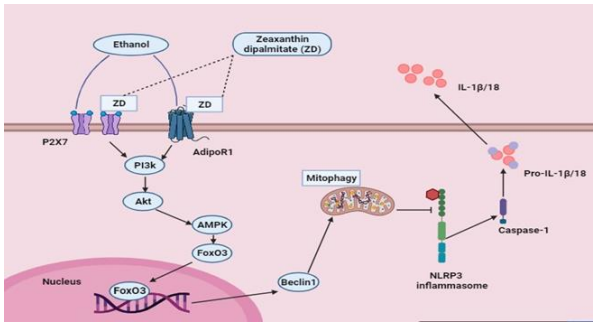

Fig. 4. Zeaxanthin dipalmitate (ZD) attenuates liver damage induced by ethanol by modulating the activity of P2X7 and adiponectin receptor 1 (adipoR1) at the cellular membrane.

Xanthorrhizol

Xanthorrhizol is a combination of sesquiterpenoids derived from the rhizome of *Curcuma xanthorrhizza*, which is a member of the *Zingiberaceae* family. It is widely recognized for its diverse range of biological effects, including but not limited to antimicrobial, antioxidant, anti-inflammatory, anticancer, antihyperglycemic, antiplatelet, antihypertensive, hepatoprotective, nephroprotective, estrogenic, and anti-estrogenic properties (91). Xanthorrhizol, in various *in-vivo* studies, successfully inhibited the formation and expansion of tumours. It reduced the expression of COX-2 and ornithine decarboxylase while suppressing the activity of NF-kB signalling. Furthermore, in an *in-vivo* examination, xanthorrhizol demonstrated its effectiveness in preventing metastasis in a mouse lung model by inhibiting MMP-9 and COX-2 (92). In a mouse leukemic monocyte-macrophage cell system stimulated by lipopolysaccharide, xanthorrhizol was found to exhibit anti-inflammatory properties. It significantly reduced the activity of inducible nitric oxide synthase and inhibited the production of nitric oxide and prostaglandin E2, consequently lowering cyclooxygenase-2 levels (93). In activated microglial cells, xanthorrhizol has demonstrated the ability to inhibit the production of pro-inflammatory molecules such as IL-6, COX-2, TNF-α, and iNOS (94). In both laboratory-based experiments and within living organisms, XTZ was found to impact various kinases, inflammatory cytokines, apoptosis-related proteins, and transcription factors. This resulted in the inhibition of processes such as angiogenesis and metastasis, while also triggering apoptosis and halting the cell cycle (95). Xanthorrhizol exerts a potent anti-proliferative effect on HepG2 cells by triggering apoptosis through the involvement of Bcl-2 family members (96). The application of xanthorrhizol to HepG2 cells led to observable apoptotic changes, such as DNA fragmentation, cell contraction, and the development of elongated lamellipodia. The induction of apoptosis by xanthorrhizol in HepG2 cells was linked to the activation of the tumour suppressor p53 and a reduction in the expression of the antiapoptotic protein Bcl-2, while the levels of Bax remained unchanged. Following a 24-hour exposure to xanthorrhizol, Bcl-2 protein expression decreased and remained lower than the control group throughout the experiment, this led to a change in the ratio of Bax to Bcl-2, tipping the balance in favour of apoptosis (Fig. 3). Furthermore, the activation of the initiator procaspase-9 and caspase-3 was observed, but not caspase-7. In summary, xanthorrhizol exerts antiproliferative effects on HepG2 cells by promoting apoptosis through the mitochondrial pathway (97). The XNT treatment exhibited a noteworthy decrease in the survival of A549 non-small cell carcinoma cells, and this reduction was directly proportional to the concentration of XNT used. This effect was primarily attributed to XNT's ability to trigger apoptotic cell death through oxidative stress, marked by an elevation in intracellular ROS production, depletion of antioxidants, heightened lipid peroxidation, an increase in characteristic apoptotic cell changes, and an upsurge in DNA damage in human lung cancer cells. Additionally, XNT induced apoptosis by suppressing the phosphorylation of PI3K and AKT while inhibiting the transcriptional signalling activity of NF-κBp65. Furthermore, the XNT therapy modifies the Mitochondrial Membrane Potential (ΔΨm), leading to

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(06), 3567-3580 | ISSN: 2251-6719

the initiation of apoptosis. This process is tightly linked to the activation of pro-apoptotic indicators such as Bax, Bad, caspase-3, caspase-9, and cytochrome c, while simultaneously inhibiting the expression of anti-apoptotic proteins like Bcl-2 and Bcl-XL. Hence, XNT could potentially serve as a chemotherapy option for managing lung cancer (98).

Table I. Table summarizes the herbs and their mechanism of action in HCC.

Herbs	Mechanism of action	Reference
Curcuma longa	Reduces VEGF expression and PI3K/AKT signalling substantially, suppresses tumour cell adhesion, inhibits proliferation; induces apoptosis; inhibits p21(ras).	[19–21]
Resveratrol	Suppresses cell growth, lowers ROS generation, promotes apoptosis, induces cell-cycle arrest in G1 and G2/M phases, boosts NO/NOS, protects the liver from NAFLD, and reduces MLCK expression.	[23,26,99]
Camellia sinensis	Down-regulated Bcl-2α and Bcl-xl through inactivating NF-κB, exert anti-proliferative, cytotoxic, and pro-apoptotic action against HepG2, antioxidant, anti-inflammatory.	[27,30]
Zingiber officinale	Control the apoptosis process by forming Bax/Bax homodimers and Bax/Bcl-2 heterodimers, reduces growth factors and α -fetoprotein level, anti-tumor properties, produces antioxidant benefits.	[33,34,36]
Broccoli sprouts	Antioxidative properties have major cell-protective effects, inhibit NF-κB, and effectively decrease oxidative stress.	[38–40,100]
Silymarin	Reduces COX-2 expression, elevates expression of proapoptotic proteins, reduces the expression of antiapoptotic proteins, positive impact on AFP, CEA, and CA19.9, exhibit antiviral properties against HCV infection, inhibits various factors like TNF-α-induced NF-kappaB transcription, and T-cell proliferation.	[53–56]
Nigella sativa	Anti-inflammatory properties, potential anticancer effects, protected liver cells from DENA, hinder the growth of HepG2 cells.	[59–62]
Glycyrrhiza glabra	Anti-tumor, antioxidative, anti-inflammatory, Release of cytochrome C, Bcl-2; inhibit the development of liver cancer	[64–66,75,76]
Lycium barbarum	Increased lymphocytes, IL-2, IgG and serum antioxidants level, the proliferation of SMMC-7721 cells during the G0/G1 and S phases, activating the nuclear factor kappa B (NF-κB) pathway, decreased lipid peroxide level;	[82–84,86,87]
Xanthorrhizol	Reduces COX-2 expression, NF-kB signalling, inhibits the production of IL-6, TNF-α, and iNOS, exerts an anti-proliferative effect on HepG2 cells, reduction in Bcl 2 protein.	[94,96]

3. Conclusion

Hepatocellular carcinoma (HCC) is a widespread disease observed in many countries worldwide, and it is strongly associated with a rise in mortality rates. The progression of HCC involves various intermediate stages, encompassing molecular and transcriptional events that ultimately lead to the transformation of hepatocytes into malignant cells. Several factors contribute to these stages, including conditions such as non-alcoholic fatty liver disease (NAFLD), hepatitis C (HCV), hepatitis B (HBV), oxidative stress, chronic inflammation, inborn metabolic disorders, exposure to environmental toxins, and certain medications, among others. A growing body

Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(06), 3567-3580 | ISSN: 2251-6719

of evidence indicates that numerous dietary and natural products have the potential to serve as resources for preventing and treating liver cancer. These natural products (as summarized in Table I) along with their active components, can impede the development and progression of liver cancer by targeting the key risk factors associated with HCC. One noteworthy advantage of these natural compounds is their low toxicity, ready availability, and affordability, making them promising candidates for use in cancer therapy. Research into various natural compounds and dietary items is essential to elucidate their role in cancer prevention. They operate by hindering processes such as tumour cell proliferation, invasion, metastasis, angiogenesis, inflammation, and mutation, and by promoting apoptosis. These actions align with inhibiting cancer cell self-renewal and survival mechanisms. We suggest that the concurrent use of these natural substances alongside conventional chemical medications and, in some cases, as maintenance therapy after discontinuing chemical treatments. This approach aims to hinder the progression of HCC and reduce its global incidence.

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