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Review

Herbal management of hepatocellular carcinoma through cutting the pathways of the common risk factors

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ARTICLE INFO

Keywords:

Hepatocellular carcinoma
 Non-alcoholic fatty liver
 Inflammation
 Oxidative stress
 Hepatitis
 Cytotoxic agents
 Herbal therapy

ABSTRACT

Hepatocellular carcinoma (HCC) is considered the most frequent tumor that associated with high mortality rate. Several risk factors contribute to the pathogenesis of HCC, such as chronic persistent infection with hepatitis C virus or hepatitis B virus, chronic untreated inflammation of liver with different etiology, oxidative stress and fatty liver disease. Several treatment protocols are used in the treatment of HCC but they also associated with diverse side effects. Many natural products are helpful in the co-treatment and prevention of HCC. Several mechanisms are involved in the action of these herbal products and their bioactive compounds in the prevention and co-treatment of HCC. They can inhibit the liver cancer development and progression in several ways as protecting against liver carcinogens, enhancing effects of chemotherapeutic drugs, inhibiting tumor cell growth and metastasis, and suppression of oxidative stress and chronic inflammation. In this review, we will discuss the utility of diverse natural products in the prevention and co-treatment of HCC, through its capturing of the common risk factors known to lead to HCC and shed the light on their possible mechanisms of action. Our theory assumes that shutting down the risk factor to cancer development pathways is a critical strategy in cancer prevention and management. We recommend the use of these plants side by side to recent chemical medications and after stopping these chemicals, as a maintenance therapy to avoid HCC progression and decrease its global incidence.

1. Introduction

The mortality rate due to hepatocellular carcinoma (HCC) increased rapidly during the past decade. Unluckily, the clinically satisfactory and successful treatment for HCC patient is still absent [1]. Several risk factors are involved in hepatocarcinogenesis like non-alcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcoholism, obesity, aflatoxin B1, iron accumulation and diabetes [2]. There are several protocols used in the treatment of HCC, including, surgical resection, ablation, chemotherapy and embolization. The use of these methods is limited due to their side effects and the development of resistance to the available chemotherapy and their complexities. Due to the limited treatment options to HCC, other than surgery and the poor prognosis of the disease, there is a critical need for additional therapies to enhance the survival or the quality of life. Complementary and alternative medicine (CAM) is considered as one way that may improve the anticancer drug efficacy and reduce their toxic effects [3]. The use of herbal medicines can be traced back to

more than 4000 years ago in ancient China and Egypt. Over recent decades, an increasing number of herbal products, including medicinal herbs and phytochemicals, have been used for treating chronic liver diseases worldwide due to cost effectiveness, higher safety margins, long-lasting curative effects and few adverse effects. According to the previous studies, medicinal herbs and phytochemicals could protect the liver by several mechanisms such as eliminating the virus, blocking fibrogenesis, inhibiting oxidative injury and suppressing tumorigenesis [4].

In this review, we discuss several factors that lead to HCC development, focusing on the role of different herbal medicines that used in the treatment of HCC by alleviating these risk factors.

2. Non-alcoholic fatty liver disease (NAFLD) AND treatment to prevent HCC development

Non-alcoholic fatty liver disease (NAFLD), or alternatively, non-alcoholic steatohepatitis (NASH), is a condition of liver pathology, which

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is similar to the fatty liver damage that caused by alcoholism, but, it happens in non-alcohol abuse people. NAFLD is characterized by the accumulation of triglycerides within hepatocytes, which is usually associated with metabolic syndrome and obesity [5]. The prevalence of NAFLD was established by the histological features found in ~70% of obese individuals suffering from steatosis, while steatosis was present in ~ 35% of lean individuals. NAFLD was also present in about 18.5% of obese individuals and in about 2.7% of leans [6]. Fatty liver is also found in about 13–22% of lean non-alcoholic individuals through several studies based on ultrasound imaging [7,8]. NAFLD is present in 20–35% of adult individuals and 5–17% of children in the Western world [9]. NAFLD is considered as one of the important reasons leading to chronic liver diseases in Hong Kong (~27.3%) [10] and China (~15%) [11]. This is because of the high-fat content in the modern diet and individual's lifestyle. NAFLD is considered as one of the most important reasons that cause chronic liver disease in developing and developed countries. NAFLD increases the risk of hepatocarcinogenesis similar to other pot cirrhotic liver diseases. HCC is now the end stage as a leading cause of obesity-related cancer deaths in middle-aged men in the USA [12]. An increasing number of case reports showed that HCC arises in non-cirrhotic individuals suffering from NAFLD [13].

Other HCC risk factors may be synergistically involved in HCC development besides NAFLD, such as alcoholic liver injury and chronic hepatitis C. Several mechanisms are involved in NAFLD-related HCC development (Fig. 1) [14–16]. Obesity participates in increasing the risk of cancer development through a low-grade, chronic inflammatory impact [17,18]. The expansion of adipose tissue stimulates the generation of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) [19]. TNF and IL-6 derived from adipose tissue play an important role in HCC development. This role has been supported in an experimental model, assuming that obesity enhances the growth of diethylnitrosamine-induced malignant liver tumor in mice [20]. The prevalence of HCC due to NAFLD is increasing around the world [21], where, 4–22% of HCC patients in Western countries are attributable to NAFLD [22]. In Asia, viral hepatitis remains endemic, so

that, 1–2% of HCC patients are attributed to NAFLD [23,24].

2.1. Herbs with anti NAFLD activity used in HCC treatment

2.1.1. Lycii fructus (wolfberry)

Wolfberry, a famous traditional Chinese supplement or drug, is the fruit part of Lycium barbarum plant, family Solanaceae. It has valuable benefits in both eyes and liver [26]. The most important part of wolfberry is the Lycium polysaccharide portion (LPP), which has a numerous biological actions, like immunoregulation, antioxidant effect, neuroprotection, control of glucose metabolism and anti-tumor activities. The lymphocyte number, interleukin-2 and immunoglobulin G level, were found to be increased upon the intake of polysaccharide juice in human beings in one of the clinical trials. It was reported also that it increases the levels of serum antioxidants and decreases the lipid peroxide level [27,28].

In the liver, LPP was found to inhibit hepatocyte proliferation and induce apoptosis of hepatoma cells, which indicate its possible application as anti-tumor [29,30]. Another study demonstrated that LPP causes a restoration of the activities of antioxidant enzymes and reduction of oxidative stress products caused by high-fat diet induced liver injury [31]. The co-treatment of LPP with ethanol administration markedly enhanced the liver injury in an alcohol-induced liver injury rat model by decreasing the oxidative stress and the accumulation of lipid in the liver [32]. In acute liver injury, LPP was found to keep the normal hepatic histology, decrease the hepatic inflammation/chemoattraction, stimulate the partial regeneration of the liver through the nuclear factor kappa B (NF-κB)-dependent pathway, and reduce the oxidative stress when used prior CCl₄ intoxication in mice [33].

LPP is helpful in NAFLD due to its useful properties in decreasing the inflammation and the oxidative stress. The co-treatment with LPP, orally, in NAFLD in rats, showed a significant improvement in the hepatic histology, reduction in the fibrosis, oxidative stress, inflammation, accumulation of fats and apoptosis, through modulating the transcriptional factors NF-κB and activator protein-1 (AP-1). Furthermore, the

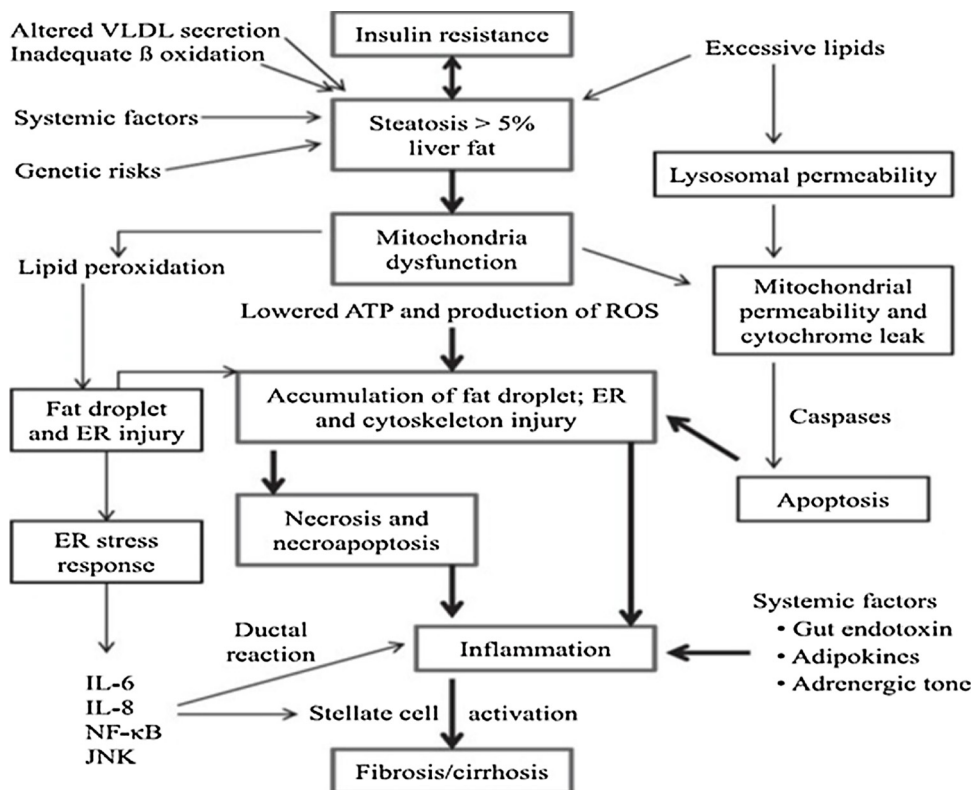


Fig. 1. Molecular mechanisms of NAFLD [25].

uptake of LPP for long-term did not have any unwanted side effects on the liver of healthy rats. So LPP can be useful in NAFLD treatment with minimal side effects [25].

2.1.2. Green tea

Green tea (*Camellia sinensis*) leaves, has been reported to be used in the prevention of liver diseases. The origin of green tea is China, which then distributed to Asian countries, including Korea, Vietnam and Japan. In the last years, green tea also spread to Western countries that traditionally consume black tea. The beneficial or therapeutic properties of green tea extracts have been reported by several studies. The major polyphenol of green tea, epigallocatechin-3-gallate (EGCG), was used in CCl₄-treated mice and showed a significant therapeutic potential in hepatic damage, inflammation and oxidative stress induced by CCl₄ in a dose-dependent manner at both biochemical and histological levels [34]. It was also reported that co-treatment of the whole green tea extract with alcohol administration showed an effective reduction of the hepatic oxidative stress and reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase systems in experimental alcohol-induced liver injury [35].

Green tea extract also showed an enhancement of the NASH features, such as oxidative stress, inflammation and lipid accumulation in obese mice [36]. A recent study also demonstrated that green tea extract showed significant improvement in inflammatory, chemical, metabolic, and radiological parameters of NAFLD patients who were dyslipidemic and non-diabetic [37]. It also showed an improvement in the liver enzymes of NAFLD patients in another study [38].

Numerous *in vitro* studies demonstrated the chemoprevention and anti-tumor properties of green tea in HCC [39]. The growth and cell proliferation of HCC-derived cells are inhibited by EGCG by induction of apoptosis [40]. The human HCC cell line, HepG2, growth was also inhibited by EGCG, through suppressing the phosphorylation of insulin-like growth factor-1 receptor (IGF-1R) and reducing the activation of its signaling molecules like extracellular signal-regulated kinase (ERK), STAT-3, Akt and GSK-3 β [41]. Drinking of EGCG caused a significant inhibition of liver cell adenoma development in contrast to the EGCG-untreated control group. This is related to decreased phosphorylation of ERK, Akt and IGF-1R proteins, activation of the hepatic AMP-activated kinase protein and the treatment of liver steatosis. The administration of EGCG in drinking water also caused a significant reduction of serum levels of insulin, IGF-1, IGF-2, tumor necrosis factor (TNF)- α , and free fatty acid. It also caused a decrease in the hepatic expression of *TNF- α* , *interleukins(IL-1 β ,IL-6)*, and *IL-18* mRNAs [42]. The development of glutathione S-transferase placental form (GST-P⁺) foci was also inhibited after the administration of EGCG in drinking water through the reduction of hepatic fibrosis, triglyceride content, inflammation, oxidative stress and inhibition of excessive hepatocyte proliferation [43].

2.1.3. Resveratrol

Resveratrol (RSV; 3, 5 4'-trihydroxystilbene), a phytoalexin that extracted from red grapes, is considered as one of the most accepted and recognized herbal derivatives worldwide as it has a powerful antioxidant and anti-inflammatory properties [44]. Recently, RSV has been found to be helpful in the treatment of NAFLD. When RSV is given after NAFLD induction by using high fat-diet, it causes a reduction of lipogenic genes as SREBP-1c and FAS [45]. The treatment with RSV also reduced the inflammation and oxidative stress in rats [46]. RSV causes a dysregulation in the metabolism of lipids in NAFLD through sirtuin 1 (SIRT1) pathway [47] and the up-regulation of hepatic low-density lipoprotein receptor [48]. RSV increases apoptosis in HCC cells, which is associated with the reduction of hexokinase 2 expression. Additionally, RSV improved the inhibition of cell growth induced by sorafenib in aerobic glycolytic HCC cells. The inhibition of hexokinase 2 by RSV can be considered to be a new trend to treat HCC and prevent its progression [49]. RSV was also found to decrease the expression of myosin light chain kinase (MLCK), which inhibited liver tumorigenesis and

promoted cell apoptosis in HCC rats induced by DENA. The expression of MLCK was found to be higher in HCC rats than normal rats, which is responsible for the proliferation and anti-apoptotic properties [50].

3. Inflammation and anti-inflammatory treatment to prevent HCC development

The Latin word "inflammation" means set a light or ignite, which describes exactly its effect on cancer. Inflammation increases the resistance to chemotherapy and promotes oncogenes and genes that convert healthy cells to tumors. It also stimulates cancer cell spreading and improves the cancer cells' ability for angiogenesis. Because cancer is defined as an inflammation, the anti-inflammatory drugs can be useful in treating cancers as the relation between cancer development and inflammation has been appreciated [51,52].

The hepatic damage may be due to either chronic or acute inflammation. In response to inflammation, several kinds of hepatic cells are activated, such as hepatic stellate cells (HSCs), liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs) and dendritic cells (DCs) to produce several types of cytokines, immune mediators and chemokines. One of the important pro-inflammatory cytokines is interleukin-6 (IL-6) that can inhibit apoptosis and tissue inflammation [53]. The inflammatory response mediates a defense mechanism against the microbial infection and stimulates tissue regeneration and repair. There is a relation between the inflammation and cancer development as chronic inflammation stimulates the development of dysplasia. About 15% of cancer occurrence is associated with microbial infection. In immunocompetent patients, chronic inflammation, like hepatitis B and C viral infection or human papilloma virus may result in the development of hepatocellular and cervical carcinoma, respectively [54].

Cancer also may result from an opportunistic infection like Kaposi's sarcoma, which results from human herpes virus (HHV)-8 infection. Inappropriate immune responses to microbes may also lead to cancer development as gastric cancer, which may result from chronic inflammation due to *Helicobacter pylori* colonization. The long-standing inflammatory bowel disease may lead to colon cancer. Long-term exposure to asbestos, silica and cigarette smoke, may lead to chronic irritation and subsequent inflammation that result in cancer development [51,52]. The promotion of tumor cells requires both the survival of the initiated cells and their expansion. Numerous inflammatory mediators like chemokines, eicosanoids, and cytokines have the ability to stimulate the proliferation of both untransformed and tumor cell [51]. Inflammation plays an important role in tumor growth through angiogenesis mediation. It also plays a critical role in other aspects of tumor progression like metastasis and tissue invasion. Matrix metalloproteinases and their inhibitors are important for remodeling of extracellular matrix and angiogenesis, which enhances vascular invasion of migrating cells [55]. The mechanisms contributed to the role of inflammation in hepatocarcinogenesis was showed in Fig. 2 [56].

3.1. Herbal plants with anti-inflammatory activity used to cut HCC progression pathways

3.1.1. Xanthorrhizol

Xanthorrhizol (XNT), a sesquiterpenoid complex, obtained from *Curcuma xanthorrhizae* rhizome, family Zingiberaceae. The anti-inflammatory effect of XNT was reported for the first time in lipopolysaccharide-mediated mouse leukemic monocyte macrophage cell RAW 264.7. It caused a significant reduction in the activities of inducible nitric oxide synthase (iNOS) and reduced cyclooxygenase-2 (COX-2), through the inhibition of nitric oxide (NO) and prostaglandin E₂ (PGE₂) production [57]. XNT was also found to inhibit pro-inflammatory cytokine interleukin-6 (IL-6), TNF- α , iNOS and COX-2 in activated microglial cells [58]. The anti-inflammatory property of XNT was also postulated in another study as it blocks the inflammatory and neurogenic pain response in pain test that induced by formalin in rats [59].



Fig. 2. Non-resolving inflammation contributes to the hallmarks of hepatocellular carcinoma [56].

XNT has also anticancer activities, which may be due to its anti-inflammatory effect by inhibiting the activity of NF- κ B, COX-2 and iNOS release [60]. It also inhibited the tumor development and formation in different *in vivo* studies. It decreased the expression of COX-2, ornithine decarboxylase and suppressing NF- κ B signaling activity. An *in vivo* study also demonstrated that xanthorrhizol has anti-metastatic activity through inhibiting matrix metalloproteinase 9 and COX-2 in a mice lung metastasis model [61]. It has a potent anti-proliferative effect on HepG2 cells through apoptosis induction via Bcl-2 family members [62].

3.1.2. Berberine

Berberine is a small alkaloid molecule isolated from *Coptidis rhizome*. It possesses anti-inflammatory and anticancer activities [63]. It down-regulates numerous hepatic pro-inflammatory genes such as IL-6, serum amyloid A3 (SAA3), NF- κ B and TNF- α . These genes play a vital role in steatohepatitis development [64]. It was reported that berberine has an anti-inflammatory activity for hepatic cells in different animal models. It has also been showed to decrease TNF- α and COX-2 expression in cyclophosphamide-induced hepatotoxicity in a rat model [65]. It also has the ability to inhibit TNF- α and IL-6 production in HepG2 cells. The anti-inflammatory effect of berberine may be due to the inhibition of ERK1/2 activation [66]. Its anti-inflammatory effect was postulated through the inhibition of LPS-induced inflammatory response in macrophages [64].

Berberine has anti-cancer activity on the human HCC cell lines through the induction of apoptosis and inhibition of tumor cell proliferation [67]. Berberine induces both cell death and apoptosis in HepG2 cells. This is related to the down-regulation of CD147, which is highly expressed in HCC cells [68]. It was shown to selectively inhibit the human hepatocellular cancer cell growth through the induction of AMPK-mediated caspase-dependent mitochondrial pathway cell apoptosis in addition to suppressing p53 [69]. The expression of p53 was found to be up-regulated by berberine through suppression of MDM2, the inner p53 inhibitor, at the post-transcriptional level [70]. The combination of berberine and vincristine showed a helpful effect against hepatoma cell lines through the potentiation of the pro-apoptotic effect of the single drug [71].

3.1.3. *Alpinia officinarum*

Alpinia officinarum, known as lesser galangal, belongs to family Zingiberaceae. It has a variety of pharmacological actions as

antioxidant, anti-inflammatory, antimicrobial, antiemetic and cytotoxic properties [72]. Different mechanisms are involved in the anti-inflammatory effect of *Alpinia officinarum*, including the regulation of NF- κ B, MAPKs pathway and the inhibition of prostaglandin E2 synthase and COX-2, the important enzymes involved in the inflammation. This effect is usually due to its content of diarylheptanoids and flavonoids [73]. Two compounds of *Alpinia officinarum* rhizome extract, galangin and 5-hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone, exhibited antioxidant and anti-inflammatory activities due to their phenolic content. These compounds showed a high affinity toward COX-2 active site through a molecular docking study [74]. Our recent study also demonstrated that five compounds isolated from the *Alpinia officinarum* rhizome extract showed a powerful anti-inflammatory effect on HepG2 cells stimulated by lipopolysaccharide. These compounds are galangin, isorhamnetin, two diarylheptanoids and kaempferol. These compounds down-regulated the gene expression of IL-6, IL-1 β , pro-inflammatory cytokines and TNF- α in a dose-dependent manner. This indicates that these isolated compounds may be a promising treatment for other inflammatory diseases [75].

Alpinia officinarum rhizome extract and its components showed anti-cancer activities against numerous cancer cell lines, such as breast, neuroblastoma, lung, and liver [76–78]. Our previous study suggested that *Alpinia officinarum* rhizome extract can be used as a promising natural chemopreventive agent against HCC in rats. It is also a helpful chemosensitizing agent when used in combination with cisplatin in the treatment of HCC. Additionally, *Alpinia officinarum* rhizome extract improved hepatic functions and decreased alpha-fetoprotein concentration in experimental HCC model. It also protected the hepatic tissue of the treated rats [79].

4. Oxidative stress and capturing to prevent HCC development

Oxidative stress (OS) occurs when the body is exposed to either a harmful exogenous or endogenous per-oxidative stimuli. One of these stimuli is free radicals, including reactive nitrogen species (RNS) and reactive oxygen species (ROS). Free radicals are produced during numerous oxidation-reduction (redox) reactions that happened in the cells. OS is usually associated with the development of various diseases as cardiovascular and nervous system diseases, diabetes and cancer through the induction of oxidative damage of DNA and abnormal expression of proteins [80]. OS may be a risk factor for HCC as it elevates hepatocyte DNA oxidative damage [81]. Chronic viral infections may

increase the production of ROS and RNS by causing inflammation and necrosis of hepatocytes that accompany immune cell infiltration [82]. The main cause of DNA damage is mutation, caused by increasing ROS and the failure in DNA repair resulting in an increase in the mutation of cancer-related genes, meaning that chronic inflammation is considered the main risk factor for HCC [83,84]. Increasing OS and the degree of DNA damage has elevated the incidence of HCC related to viral infection [85]. The elevated level of transforming growth factor beta (TGF- β) and also TNF- α in patients with chronic hepatitis C is mainly related to oxidative stress. TGF- β is used as an indicator of how tissues are damaged and the extent to which they are injured [86]. ROS is elevated due to increased oxidative stress, which stops the electron transport chain in damaged mitochondria. The excessive release of TNF- α not only causes severe damage to the mitochondrial respiratory chain but also causes damage to cytochrome oxidase. The high level of ROS increases lipid peroxidation and inhibits the respiratory electron transport chain [87]. ROS not only alter the mitochondrial metabolic activity but also affects the apoptotic pathways, changes the membrane permeability and causes damage to mitochondrial DNA [88]. Telomere shortening is accelerated by OS that leads to an increase in the cytoplasmic migration of reverse transcriptase telomerase subunits [89]. Damaging of the cells, mainly by OS, causes the release of a unique type of DNA that is called free circulating DNA (fcDNA), produced as oxides released by DNA from dead cells. It can be used as an indication for a wide group of diseases like cancer. Fc DNA also can be present by low value in normal cells [90]. During the exposure to OS, different types of genes and immune system mediator expression is altered. Among these mediators, is micro RNA (miRNA), which is a small non-coding RNA molecule (containing about 22 nucleotides) found in plants, animals and some viruses, that functions in RNA silencing and post-transcriptional regulation of gene expression. MiRNA dysfunction is related to different types of cancer including HCC [91]. The mechanisms of HCC development caused by OS can be summarized in Fig. 3 [89].

4.1. Herbal plants with antioxidant activity useful in HCC treatment

4.1.1. Vitamin C and diallyl sulfide

Vitamin C, (L-ascorbate, L-ascorbic acid), is known by its antioxidant activity and the ability to capture free radical with singlet oxygen such as OH⁻ or HOO⁻ and superoxide ion O₂⁻ and produce dehydroascorbate. Vitamin C activity is related to its free electron that interacts with electron deficient ions. Several in vitro studies reported the antioxidant activity of vitamin C [92]. In vivo studies also showed the antioxidant properties of vitamin C in a dose-dependent manner. Vitamin C administration protects guinea pigs, that do not form vitamin C, and osteodystrophy syndrome rats from oxidative stress when given oxidizing agents as endotoxin [93] and carbon tetrachloride [94]. It also protects rats exposed to cigarette smoke [95]. Parquet is highly toxic nitrogen herbicide and has strong oxidizing stress. The administration of vitamin C reduces oxidative stress before (not after) parquet administration [96]. Vitamin C has a promising role in cancer treatment through its selective cytotoxic activity for diverse cancer cell lines [97,98]. In 1970s, a clinical study was performed and proved that ascorbate has an important role in increasing the survival of cancer patients at late stages [99]. Combination of methotrexate with vitamin C is promising in cancer treatment through the reduction of H₂O₂ produced from methotrexate in Hep3B cells [100]. It was shown that vitamin C helped in the treatment of hepatotoxicity induced by DENA in Smp30 KO mice [101].

Garlic contains diallyl sulfide (DAS) as a major active constituent. DAS is characterized by its anti-inflammatory activity through the modulation of cytokines as it inhibits the activity NF- κ B [102]. DAS' anti-inflammatory activity is related to the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription activation and it also has antioxidant activity. Nrf2 is an emerging regulator of cellular resistance to oxidants [103]. A combination of vitamin C and DAS was shown to

offer several benefits, as inhibition of circulatory TNF- α and IL-6 in DENA-induced HCC in rats [104] and increases the sensitivity to chemotherapy as cisplatin in the treatment of HCC [105].

4.1.2. Ginger root

Ginger (*Zingiber officinale*) is one of the predominant herbaceous plants. It is a perennial plant and the main active part is the rhizome. Ginger not only used as a condiment but also it has antiemetic and anticancer activity [106]. Ginger has strong antioxidant and cell protection activity. This action of ginger is due to its potent active constituents as sesquiterpenoids, tannin, gingerols, shogaols and anthocyanin. Several in vitro and in vivo studies documented the antioxidant activity of ginger. The protective effect of ginger was showed against several toxic agents, like bromobenzene and cisplatin [107]. Another study displayed the chemopreventive effect of ginger against cancer [108]. Ginger has a great activity in the treatment of experimental cancer in a rat model. It decreased the level of growth factors and α -fetoprotein (liver tumor marker) after giving rats a daily dose about 50 mg/kg of ginger extract [109]. The anticancer effect of ginger is due to its proapoptotic and anti-inflammatory properties. The anti-inflammatory activity of ginger was confirmed by inhibiting NF- κ B and TNF- α after administration of 100 mg/kg of ginger in HCC rat model [110]. Ginger contains other different constituents as clavacol, pinostrobin, and geraniol. These active components were detected by gas chromatography and mass spectrometry. Ginger was found to inhibit the proliferation of cells in HepG-2 cell line (IC₅₀, 900 μ g/ml) [111]. One of the most popular active components in ginger is 6-shogaol which showed an anticancer effect against hepatoma cell line through the activation of ROS-mediated caspase-dependent apoptosis in a multidrug resistance [112].

4.1.3. Broccoli sprouts

One of the most popular cultivated plants is broccoli which is distinguished by its high content of the antioxidant content. The most active antioxidant components in this plant are vitamins, flavonoids and carotenoids. Isothiocyanates, the hydrolytic product of glucosinolate, is considered one of the antioxidant components, which motivates DNA protection from damage through its antioxidant activity [113,114]. The antioxidant property of broccoli may be direct by contributing in biochemical, cellular and physiological steps that inhibit free radical production, or indirect by inducing phase II enzymes that have a protective effect against OS [115]. The antioxidant activity of broccoli was observed in the human colon mucosa that exposed to oxidative stress [115]. Broccoli showed a potential anticancer activity due to its high content of glucosinolates [116]. Broccoli also contains a distinct component, sulforaphane, which is characterized by its activity as antioxidant and its ability to protect DNA from breaking down by highly reactive electrophiles through increasing the antioxidant system activity and inhibition of inflammation [117]. Antioxidant activity of sulforaphane is related to certain pathways, including the reduction of inflammation through inhibiting NF- κ B and overexpression of transcription of Nrf2, which has a very important role in keeping healthy cells and protect them from toxic chemicals and lifestyle-related factors [118]. Previous in vivo studies registered that sulforaphane has abroad activity against different types of liver diseases related to toxic chemicals [119,120], consumption of alcohol [121] and using high calorie food [122]. Broccoli has a major role in the suppression of different types of cancers, including liver HEP-G2 and colon cancer. Sulforaphane has different pathways related to its anticancer effect as it has anti-inflammatory, proapoptotic and cell cycle arresting action [123].

5. Hepatitis B, C infection and treatment to prevent HCC development

HBV and HCV infections are considered the chief reasons for HCC. Usually, there are no symptoms for people with chronic infection but

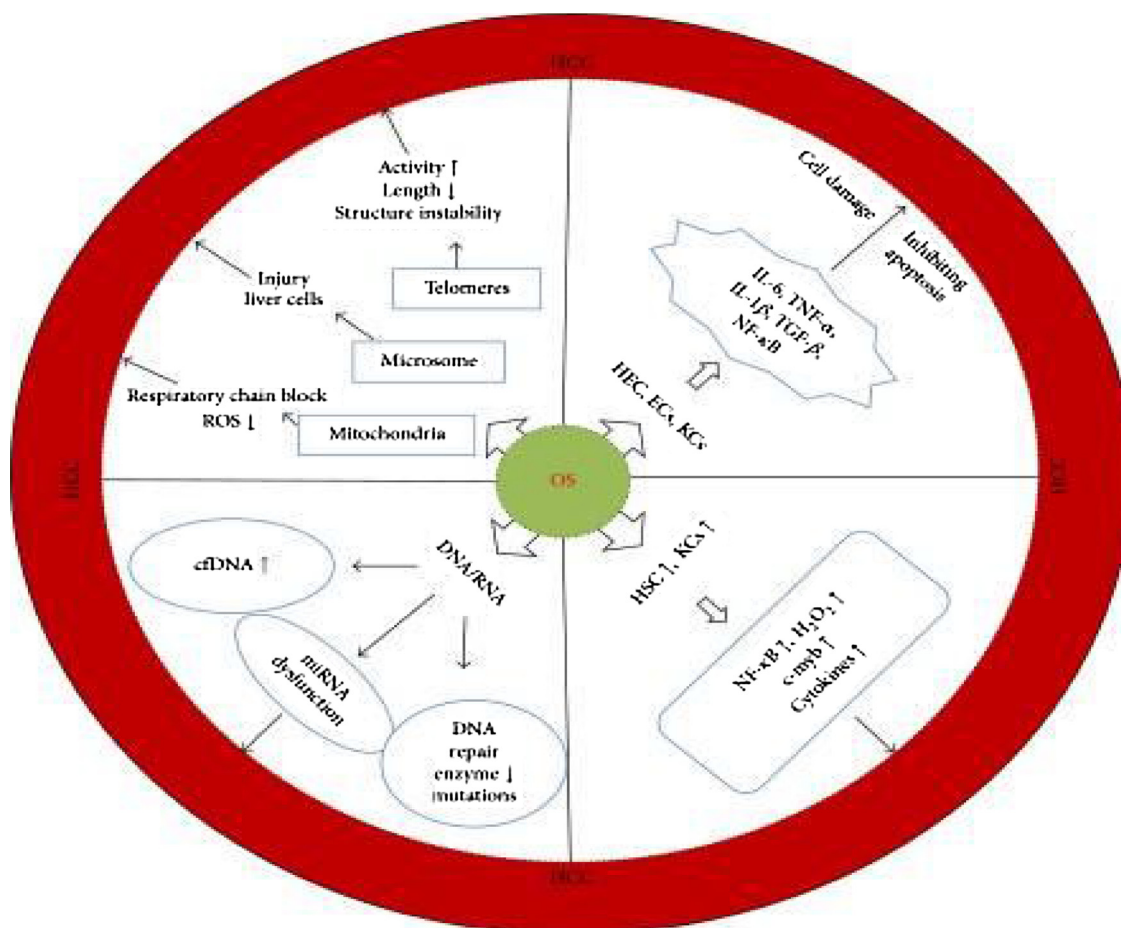


Fig. 3. The mechanism of HCC development due to oxidative stress [89].

lately; cirrhosis and HCC are developed [124]. Treating and overcoming HCV and HBV infection can help in the prevention of HCC development as they are oncogenic viruses [125]. The association between HCV infection and HCC varies worldwide. In Western countries and Africa, HCV is considered as the main cause of HCC, it also contributes to 80% to 90% of HCC cases in Japan [126,127]. As well as, 80% of patients infected with HCV can progress to chronic hepatitis, with about 20% developing cirrhosis [128]. The HCV-related liver cirrhosis can increase the risk of liver cancer, with 17-fold higher risk of developing HCC than in chronic hepatitis C infection alone, although this risk differs and depends on the degree of liver fibrosis caused by HCV [129]. The elevation of the risk of HCC development in patients infected with HCV arises from chronic inflammation, which results from the progression of liver fibrosis and cirrhosis. These inflammations cause alteration of the architecture of hepatocyte and defects of both cellular functions and the microcirculation of liver. HCV RNA does not integrate into the host genome. Alternatively, HCV viral proteins like HCV core protein and their induced host response have been involved in reactive oxygen species (ROS) production, apoptosis, activation of transcription and modulation of immunity through up-regulation of TNF- α , IL-6, and IL-1, which participate in the transformation into malignancy [130].

Hepatitis B virus (HBV) is a circular genome. Chronic HBV infection can be confirmed by the presence of serum HBsAg for a period not less than 6 months [131]. About 10%–25% of hepatitis B patients have a high risk of HCC development during their life. Chronic hepatitis differs than other causes of HCC, as HCC occurs in the absence of cirrhosis [132]. After tobacco smoking, HBV is considered the second environmental carcinogen that affects individuals, resulting in about 55% of all HCC cases around the world [133]. The association of chronic HBV

infection and HCC that now widely recognized was first explained by Beasley and colleagues in 1981 [134] in Taiwanese patients with positive serum HB surface antigen (HBsAg). Serum HBsAg can be detected in 24%–27% of patients with HCC in Japan, 41% of patients with HCC in the United States and 70% of patients with HCC in China in the absence of other risk factors [135]. Once HBV arrives at the liver cell, transcription of messenger viral RNAs occurs, followed by a translation into viral proteins and then, synthesis of DNA of the virus. DNA of the virus is then capable of integrating into the host genome in infected hepatocytes. Cancer can be facilitated via this process through numerous ways, like rapid cell cycling of hepatocytes and viral DNA integration into the host genome which causes instability and it may insert into, or adjacent to, genes that code proteins required for cancer development. It also leads to a chronic inflammation with fibrosis and proliferation of hepatocyte, which ultimately result in cirrhosis and cancer development [136–138].

5.1. Herbal with antiviral activity

5.1.1. *Andrographis paniculata*

Andrographis paniculata Nees (A. paniculata) is a medicinal plant, which belongs to family Acanthaceae. It is used in Japan, India, Korea, China and other Asian countries for a long time in the treatment of several diseases like inflammations, viral and bacterial infections and high blood pressure [139]. The most abundant di-terpene lactone found in the leaves and stems of A. paniculata is andrographolide. The andrographolide treatment was found to reduce the replication of HCV markedly and have a synergistic effect with the clinical trial drug PSI-7977 or current antiviral drugs like telaprevir and IFN- α when used in combination to treat HCV. The mechanism of action of andrographolide

may be due to its ability to induce the p38 MAPK/Nrf2/HO-1 pathway, where, MAPK stands for mitogen activated protein kinase and HO-1 is heme oxygenase-1. It was shown that andrographolide can be used as natural product or potential drug that is helpful in the treatment of HCV [140]. The treatment with *A. paniculata* aqueous extract was found to enhance the activity of hepatic enzymes and normalizes histopathological changes of malignant hepatic tissue induced by hexachlorocyclohexane [141]. It showed indirect and direct effects on tumor cells by inducing apoptosis and cancer cell necrosis, improving body's own immune system against tumor cells and inhibiting cell-cycle arrests and cancer cells proliferation [142]. The ethanolic extract of *A. paniculata* showed a cytotoxic effect against diverse human cancer cell lines like PC-3 (prostate), HepG2 (hepatoma), colon 205 (colonic) cancer cells and Jurkat (lymphocytic) [143]. The inhibitory effect of andrographolide and its analogs on tumor cells may be due to their ability to depress cyclin-dependent kinase and induce the expression of inhibitory proteins of the cell cycle that result in blocking the cell cycle progression at G0/G1 [144]. Andrographolide causes induction of apoptosis by several mechanisms including, the activation of caspase cascade, the release of cytochrome C from mitochondria and the activation of proapoptotic Bcl-2 family members Bax conformational change [145]. It also causes activation of ROS-dependent c-Jun NH₂-terminal kinase (JNK) resulting in the activation of tumor suppressor p53 and thereby increasing p53 phosphorylation and protein stabilization [146].

5.1.2. *Silybum marianum*

Silymarin is extracted from milk thistle seeds, *Silybum marianum* L. Gaertn., which belongs to Asteraceae family [147]. The extract of silymarin contains silibinin, which consists of a mixture of two flavonolignans called silybin A (SA) and silybin B (SB). It has diverse pharmacological activities including, antioxidant, antiproliferative, immunomodulatory, antiviral activities and antifibrotic in different tissues and organs [148–150]. Silymarin and its component silibinin possess antiviral activity against HCV infection in cell culture. Their antiviral activity is due to their ability to block the entry of the virus, the synthesis of viral RNA and protein, viral fusion, virus transmission and the activity of HCV NS5B RNA dependent RNA polymerase [148,149,151,152]. One study showed that the treatment with a soluble form of silibinin in the form of daily intravenous injection causes a significant inhibition of HCV viral loads by 3–4 logs in 1–2 weeks in previous IFN non-responder patients [153].

Several studies reported that silymarin has a potential anticancer effect against HCC. In a dose-dependent manner, silymarin inhibits the population growth of the human hepatocellular cancer cells (HepG2) as it elevates the percentage of apoptotic cells [154]. The antiproliferative activity of silymarin was also reported by another study without affecting the nontumor hepatic cells. In the G0/G1 phase, silymarin caused an increase in the percentage of cells, while in the S-phase it decreased the cell percentage associated with down-regulation of cyclin E, cyclin D1, phospho-Rb and CDK4 and up-regulation of p53, retinoblastoma protein (Rb), p27Kip1, and p21Cip1 [155]. Silymarin also showed in vivo preventive and therapeutic efficiency against liver cancer. Ramakrishnan et al. [156] reported that silymarin has a protective effect against DENA-induced HCC in rats. Silymarin also showed a potent preventive effect against spontaneous HCC in HBV X protein transgenic mouse model. Oral silymarin in a dose-responsive manner causes a restoration of the early stage hepatic damage and fatty changes that lead to the recovery of hepatic tissue [157]. The oral administration of silibinin showed a significant reduction of HCC xenograft growth by inducing histone acetylation, apoptosis and expression of SOD1 and inhibiting cell cycle progression, cell proliferation (Ki-67 expression), ERK and PTEN/P-Akt signaling [158].

5.1.3. *Glycyrrhiza glabra*

Glycyrrhiza glabra, a perennial herb, originates from South-Western and central Asia and the Mediterranean region. It showed numerous

pharmacological activities like antioxidant, anti-inflammatory and immunomodulatory activities. The main constituent of *Glycyrrhiza glabra* root is glycyrrhizin 1–9%, w/w [159]. Glycyrrhizin has anti-viral, anti-inflammatory, hepatoprotective and anti-tumor activities [160]. The antiviral activity was reported for glycyrrhizin and other components that isolated from *Glycyrrhiza* species against different viruses, such as herpes simplex, HIV, severe acute respiratory syndrome, influenza virus, coronavirus, enteroviruses and hepatic viruses [161–163]. Glycyrrhizin has been reported to be used in the treatment of hepatic diseases like chronic hepatitis C and B [164]. A preparation that contains glycyrrhizin was reported to reduce hepatic steatosis in transgenic mice expressing the full-length HCV poly-protein [165]. It was shown to have an inhibitory effect on HCV core gene expression and HCV full-length viral particle both at protein and RNA level and have a synergistic effect with interferon [166].

Glycyrrhizin and other components of *Glycyrrhiza glabra* showed antitumor activity in different kinds of cancers such as skin, liver and breast cancer, through inhibition of cellular proliferation, development and growth of cancer cells [167]. Glycyrrhizinic acid, a major bioactive component of the extract of *Glycyrrhiza glabra*, has the ability to inhibit HCC occurrence in DENA-treated mice [168]. Another study showed that *Glycyrrhiza glabra* extract has a potent effect in the treatment of HCC induced by DENA/CCl₄ in rats and this effect is more potent than the effect of cisplatin alone or cisplatin combined with *Glycyrrhiza glabra*, so that cisplatin has several side effects and *Glycyrrhiza glabra* is not associated with that side effects [169].

6. Cytotoxic agents, apoptosis and HCC

Apoptosis, or programmed cell death, has a great interest in the field of oncology [170]. The recognition of each pathway of apoptosis is very important not only in understanding cancer development but also in the prevention and treatment of the disease. The normal tissue homeostasis maintained by keeping the balance between the proliferation of cells and their death. The imbalance between these two processes may lead to dysregulated clonal expansion, the cause of all neoplastic diseases [171,172]. The mechanism of action of numerous cytotoxic agents includes apoptosis. Several experimental approaches aimed to stimulate apoptosis that leads to the improvement of therapeutic response. Numerous natural products play a vital role in the regulation of cellular proliferation and differentiation. The chemopreventive and chemotherapeutic activities of natural products may be due to their role in mediating different pathways involved in cancer development and progression [173].

6.1. Herbs with cytotoxic activity

6.1.1. *Nigella sativa*

Nigella sativa (*N. sativa*), an annual flowering plant, originates from South and Southwest Asia and Northern Africa is grown almost all over the world [174]. *N. sativa* and its main constituent thymoquinone (TQ) possess numerous therapeutic and pharmacological activities like anti-inflammatory [175], anticancer [176], antioxidant [177] and immunomodulatory activities [178]. It has cytotoxic activity, as the ethyl acetate column chromatographic fraction of the ethanolic extract of *N. sativa* showed a cytotoxic effect against diverse cell lines such as Molt4, Hep G2 and LL/2 [179]. Another in vitro studies showed about 50% cytotoxicity of a crude methanolic extract of *N. sativa* against Dalton's lymphoma ascites (DLA), Ehrlich ascites carcinoma (EAC) and Sarcoma-180 cells (S-180 cells) [180]. Its anti-cancer activity is due to its ability to exhibit powerful pro-apoptotic, anti-proliferative, anti-mutagenic, anti-metastatic and anti-oxidant effects. It also can inhibit tumor initiation and progression and has an anti-inflammatory and immunomodulatory effect. *N. sativa* can regulate signaling pathways like p53, iNOS and caspases [181]. The anti-tumor activity of *N. sativa* was reported in several in vivo and in vitro studies. A decoction that consists

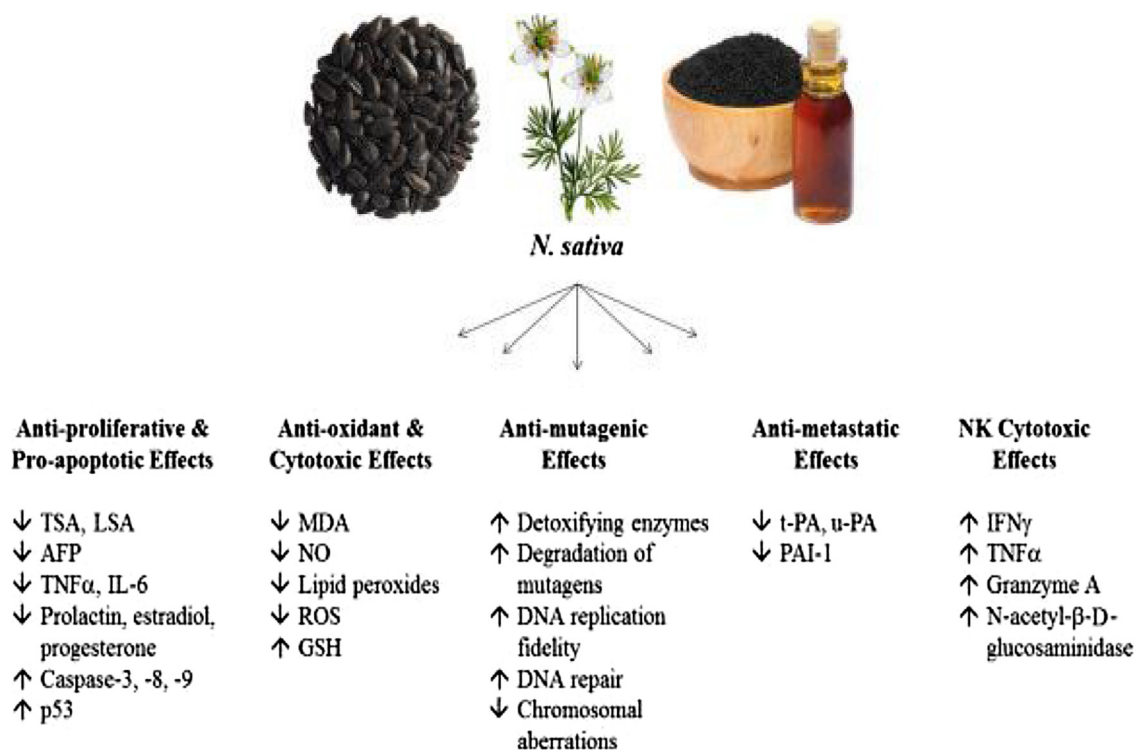


Fig. 4. The cellular and molecular mechanisms of *N. sativa* that explain its pro-apoptotic, antiproliferative, cytotoxic, anti-oxidant, anti-metastatic, anti-mutagenic and NK-mediated effects. (LSA: lipid-bound sialic acid, TSA: total sialic acid, TNF α : tumor necrosis factor α , MDA: malondialdehyde, AFP: α -fetoprotein, IL-6: interleukin-6, ROS: reactive oxygen species, NO: nitric oxide, GSH: glutathione, t-PA: tissue-type plasminogen activator, IFN- γ : interferon- γ , u-PA: urokinase-type plasminogen activator, PAI-1: plasminogen activator inhibitor type 1) [186].

of seeds of *N. sativa*, *Smilax glabra* rhizome, and *Hemidesmus indicus* roots showed a significant improvement in the hepatocarcinogenesis induced by DENA(4–6 g/kg/day) in rats [182]. The ethanolic extract of *N. sativa* showed a marked enhancement of DENA-induced histopathological variations of the hepatic tissue [183]. Another *in vivo* study showed that the administration of a methanolic extract of *N. sativa* in HCC albino rat model showed modulation of gluco-regulatory enzymes [184]. Aqueous extract of *N. sativa* showed *in vitro* antiproliferative activity and morphological changes like membrane damage and cell shrinkage in HepG2 cells, which lead to DNA damage, cell death and a decrease in cell proliferation [185]. The mechanisms that explain the pharmacological effects of *Nigella sativa* can be summarized in Fig. 4 [186].

6.1.2. *Illicium verum*

Illicium verum (*I. verum*) hook belongs to family Illiciaceae. It is commonly known as Chinese star anise or star anise. It is an aromatic evergreen tree that originates from Pakistan, China and other Asian countries. Due to its low toxic effects to humans, it was classified as “food and medicine” in 2002 by the Ministry of Health, People’s Republic of China [187]. The main active constituents that present in *I. verum* are sesquiterpenoids, monoterpenoids, lignans, phenylpropenoids, volatile compounds, and flavonoids. It also contains tannins, bitter principles and essential oils. These essential oils include trans-anethole, limonene, α -pinene, β -phellandrene, farnesol, safrol and α -terpineol [188]. It also possesses antimicrobial, antioxidant, antifungal, analgesic, anti-inflammatory, sedative, insecticidal and anticonvulsive activities [189]. Its cytotoxic activity was also reported in several studies [190–192]. It showed numerous mechanisms that involved in cell death such as apoptosis induction, scavenging of free radicals and tumor metastasis inhibition [191]. It was reported that alcoholic extract of *I. verum* showed a significant *in vitro* antiproliferative activities [190]. Similar *in vitro* study also showed a marked inhibition of cell proliferation by its alcoholic extract by promoting apoptosis, growth

inhibition and modulating the pro-apoptotic gene expression like Bax and p53 [193].

Separately, the cytotoxic effect of *I. verum* extract was studied in liver cancer model, it exhibited a significant anticancer outcome in hepatic tissue of rats with a significant improvement of tumor burden (decrease of nodule incidence, multiplicity, size, volume and liver weight). It also up-regulated phase II detoxifying enzymes (glutathione-S-transferase) and decreased oxidative stress by restoration of superoxide dismutase activity [194].

7. Miscellaneous causes of HCC and its herbal management

Sex has a vital role in HCC development as males are more diagnosed for HCC than females, with a ratio of 2:1–4:1. This may be due to the higher susceptibility of males to be infected with viral hepatitis, smoking, consuming higher amounts of alcohol and have a higher body mass index than females. The higher level of testosterone is associated with advanced hepatic fibrosis in males infected with HCV and HCC in hepatitis B carriers [195,196]. Another potent hepatocarcinogen is aflatoxin, which produced by *Aspergillus* species found on corn, grains, soybeans or peanuts that stored in warm humid conditions [197]. Several genetic and metabolic diseases are associated with HCC development such as Wilson’s disease, hemochromatosis, α -1 antitrypsin disease, glycogen-storage disease types I and II, porphyrias and tyrosinemia [198]. Other factors are also reported to be associated with the marked elevation of HCC development such as cigarette smoking and prolonged use of contraceptive pills [199]. Diabetes mellitus is now considered as an independent risk factor for HCC [200,201]. It causes liver cell damage through hyperinsulinemia and insulin resistance [202]. Hyperinsulinemia induces HCC through inflammation, cellular proliferation and apoptosis inhibition. As well, the increase in insulin levels can lead to a decline in the synthesis of insulin growth factor binding protein 1 by the liver, which is supposed to cause an increase in the bioavailability of insulin-like growth factor 1, in addition to the

Table 1

It summarizes the plants and their activities mentioned throughout this review.

Herbal plant	Activity	Reference
Wolfberry	NAFLD treatment, immunoregulation, antioxidant effect	[27,28,32].
Green tea	NAFLD treatment, antioxidant, induction of apoptosis and anti-inflammatory.	[35,36,38,40]
Resveratrol	NAFLD treatment, antioxidant, and anti-inflammatory.	[44,45,46].
Xanthorrhizol	Inflammation treatment and antiproliferative effect.	[57,62]
Berberine	anti-steatotic, Anti-inflammatory effect induction of apoptosis and inhibition of tumor cell proliferation.	[64,67]
<i>Alpinia officinarum</i>	Anti-inflammatory, antioxidant and cytotoxic properties	[72,73,75,79]
Vitamin C and diallyl sulfide	Antioxidant, chemosensitizers to chemotherapy and anti-inflammatory	[75,79,92,102,105]
Ginger root	Anti-inflammatory, antioxidant and promote apoptosis	[107,110]
Broccoli sprouts	Anti-inflammatory, antioxidant and promote apoptosis	[115,123]
<i>Andrographis paniculata</i>	Antiviral activity, induce apoptosis and necrosis of cancer cells and cytotoxic activity.	[140,142,144]
Silymarin	antioxidant, immunomodulatory, antiproliferative, antifibrotic, promote apoptosis and antiviral activities	[148,149,150,154]
Glycyrrhiza glabra	Antiviral activity, anti-inflammatory, antioxidant and immunomodulatory activities	[160,161,162,163,167]
Nigella sativa	The anti-inflammatory, anti-oxidant, cytotoxic and immunomodulatory	[175,176,177,178,179]
Illicium verum	cytotoxic activity, antioxidant, anti-inflammatory, induction of apoptosis, and inhibition of tumor metastasis	[189,190,191,192]

increase in apoptosis inhibition and cellular proliferation [203]. Insulin has also been related to increased oxidative stress and the ROS production, participating in DNA mutation [204].

Efficient storage of cereals liable to *Aspergillus* attack, continuous inspection of both male and female sex hormones in suspected individuals, managing storage diseases as Wilson's and hemochromatosis and controlling diabetes mellitus and other leading diseases will certainly contribute to a decline in HCC liability among risky individuals.

8. Summary

The plants and their activities mentioned in this review could be summarized in Table 1:

9. Conclusions

HCC is a prevalent disease in many countries around the world. It is highly related to the increase in deaths rate. The development of HCC passes through several intermediate steps such as molecular and transcriptional events that end finally to malignant transformation of hepatocytes. Several factors are involved in these steps including; NAFLD, HCV, HBV, oxidative stress, chronic inflammation, some inborn metabolic errors, environmental toxins and some drugs, etc. Accumulating evidence suggested that many dietary and natural products could be potential sources for prevention and treatment of liver cancer. These natural products (summarized in Table 1) and their active ingredients can inhibit the liver cancer development and progression, through cutting the roads in front of the known leading risk factors for HCC. We here call Urge the Ministry of Health in each country to establish records of liver patients, especially liver tumors. We recommend the use of these plants side by side to recent chemical medications and after stopping these chemicals, as a maintenance therapy to avoid HCC progression and decrease its global incidence. We also draw attention of specialists in the food industry to add some of these natural products in different recipes to reduce the probabilities of liver diseases infections.

Conflict of interest

None.

Funding

None.

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