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Review

Role of natural antioxidants in the therapeutic management of hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is a growing health problem in humans. HCC is considered the most common of internal malignancy which cause the death of human, but in the developed Western world, HCC is less common accompanied by increasing essentially in incidence, due to it occurs specially in chronic liver disease. HCC associated with various risk factors including hepatitis B virus infection; hepatitis C virus infection; prolonged aflatoxin exposure; and alcoholic cirrhosis. Overall, one-third of cirrhosis patients will develop HCC during their life time. Also, chemical carcinogens cause tumor promotions through free radical metabolites result in many biochemical and molecular changes that induces oxidative stress. The identify of HCC stage and underlying liver status then choosing the most appropriate line of therapy (surgical, loco regional, radiological and medical) can be improve the survival and/or the quality of life of the patient. Taken into the account of the nutritional value of some natural antioxidant agents that support the function of the body resulting an improvement of the health and protection from different diseases, our review will provide an up-dated status of the different aspects of HCC management through covering the efficacy and the beneficial effects of different natural agents and their mechanism of action against HCC for the future therapy modalities.

Key words: Hepatocellular carcinoma; risk factors; natural antioxidants

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INTRODUCTION

Hepatocellular carcinoma (HCC) incidence is the most common tumor in worldwide.[1] HCC involves major changes in multiple molecular pathways, genetic and epigenetic factors, which consequently leads to the malignant transformation and HCC progression.[2] Chronic liver disease and cirrhosis of patients cause HCC. HCC has major risk factors for developing cirrhosis such as, alcoholic consumbtion, hepatitis B virus (HBV) and hepatitis C virus (HCV) and nonalcoholic steatohepatitis.[2] Additionally, the contamination of water by chemicals, diabetes, obesity and genetic factors including hemochromatosis, and some physiological disorders act as risk factors for developing HCC.[3] Cirrhosis is the most dangerous factors for HCC, especially cirrhosis which caused by hepatitis virus infections.[4] Therefore, increasing HCC risks occur in the acquired HBV during the childbirth and early childhood.[5] The patients with HCC present with one or more of several clinical features as weight loss, right upper. HCC causes acute disaster of abdominal by bleeding intra-abdominal or extra hepatic appearance.[6] Also, patients have HCC with cirrhosis cause palmarerythema, obstractive jaundice, gynecomastia and portal hypertension.[7,8] HCC is associated with hypoglycemia, erythrocytosis, hypercalcemia, hypercholesterolemia and diarrhea.[9]

ETIOLOGY OF HCC

The distributions of HCC are largely result from various

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risk factors particularly the majority of hepatitis B and C viral infection and alcoholic liver disease.[10] Chronic HBV infection cause of HCC in different area, where the virus is largely endemic and vertical transmission common.[11,12] High alcohol consumption; smoking of cigarette; obesity; and diabetes have also been associated with an increased risk of developing HCC.[13-15] Previous studies have reported a close correlation with obesity and diabetes and an increased risk of HCC progression.[16] Also, there are common environmental factor associated with HCC development such as aflatoxin, a product of the Aspergillus fungus.[17] Several physiological disorders of the liver have been implicated in the HCC development, including α-1 antitrypsin deficiency; certain porphyrias; Olchi's disease; and hereditary hemachromatosis, each typically in the setting of cirrhosis.[18] Additionally, an automimmune disorders have been implicated in HCC pathogenesis, including primary biliary cirrhosis and autoimmune hepatitis.[19]

PATHOPHYSIOLOGY OF HCC

HCC majority occurs in the setting of liver cirrhosis. The accumulations of genetic and epigenetic changes related to hepatocarcinogenesis disease are well known. However, the regulating cell cycle and suppressing apoptosis used for maintenance the survival of cancerous cells. Retinoblastoma and *p53* genes responsible for the oncogenes activation and tumor suppressor genes are the good markers that understand the molecular, physiological mechanisms and disorders in the cellular signaling pathways of HCC incidence growing.[20] When the liver gets injured, necrosis will appear in the liver accompanied by the subsequent hepatocyte proliferation, after continuous cycles of destructive-regenerative process. The hyperplastic nodules will turn into dysplastic nodules inducing a high risk of developing HCC.[21]

Furthermore HCC well associated with various metabolic changes including biochemical alterations. Alfa-fetoprotein (AFP) is a glycoprotein in serum that was first recognized as a major marker for HCC. AFP elevation indicating to malignant after pathological diagnosis and endodermal lining tumor of the stomach, pancreas, and biliary tree.[22] Moreover, HCC development has also been associated with plasma lipid and lipoprotein alterations.[23] This alterations result in cellular dysfunction, reduction in the membrane integrity, fluidity and regulation of cellular processes related to growth and cell survival causing cancer development.[24,25] The cirrhosis and HCC characterized by a decrease of total protein and impair hepatic function indicating by increasing hepatic enzymes (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, and gamma glutamyl transferase) activity through the loss of functional integrity of the cell membrane in liver resulting liver damage.[26-28] Furthermore, the development and progression of HCC are well associated with the oxidative stress status that produced by increasing level of reactive oxygen species (ROS) resulting distortion and decrease the antioxidant activity in the tissues.[29,30] Lipid peroxidation (LPO) is responsible for formation of many toxic products, such as 4-hydroxynonenal and malondialdehyde MDA which attack cellular targets, thereby inducing carcinogenicity.[31-33] Many biochemical and molecular changes leads to free radical metabolites causing the chemical carcinogens induce oxidative stress leading to tumor promotion.[34,35] The failure of antioxidant defense mechanism and tissue damage were enhanced by increasing LPO. Glutathione (GSH) is present in high concentration of liver and widely distributed in cells.[36] It has many properties as, protects the cell against free radical, peroxides and other toxins, so after decreased of GSH level in tissue causing DNA damage, protein oxidation and LPO of the cell membrane biomolecules lead to hepatocyte damage.[37] However, the decrease of the antioxidant enzymes activity (superoxide dismutase and catalase) caused the increase of hepatocytes in the cirrhotic livers. The production of cytokines, ROS, and inflammation-mediated events leads to tumor formation.[38] The inflammatory diseases of cell, is produced by many pro-inflammatory cytokine as TNF-α and structural cells especially the pathogenesis of asthma.[39] Liver cirrhosis causes elevated in the pro-inflammatory cytokine TNF-α as a major marker for inflammatory state in the cirrhotic liver.[40] HCC has an anti-apoptotic genes expression and rapid cell proliferation,[41] due to apoptosis resistance under conventional therapies and incomplete cell cycle arrest.[42] HCC increased apoptosis by the down-regulation of the Bcl2 level, the activation of caspase cascade, and the up-regulation of Bax and the *p53* level.[43-45] Additionally, HCC contains various histological changes such as: (1) pseudoglandular pattern including gland-like dilatation of the canaliculi in tumor cells; and (2) trabecular pattern of growth.[46] Cytologically; polygonal and displaying of tumoral hepatocytes; smaller tumor cell; granular eosinophilic cytoplasm; vesicular nuclei; giant tumor cells; and conspicuous nucleoli are associated with HCC.[46-48]

MANAGEMENT AND PROGNOSIS OF HCC

There is a wide heterogeneity in HCC pattern, patient variations as candidates for recommended treatments, and increasingly complex available therapeutic options with diverse responses to these therapies in clinical practice.[49] Also HCC is highly associated with variable biologic behavior and the frequent coexistence of chronic liver disease and cirrhosis.[50] So, it is important to manage HCC patients by multidisciplinary HCC teams including hepatologists; medical and surgical oncologists; transplantation surgeons; diagnostic and interventional radiologists; pathologists; nurses and nurse practitioners.[51] The most commonly used treatment by the enhancement of latent antitumor immune response through chemotherapy.[52] Chemotherapy has varying effects, and work is underway in the search for active chemotherapy and appropriate for chemo-embolization, an intensive localized chemotherapy method by using improvement prognosis.[53] However, chemotherapy still has severe side effects and low survival rates.[54] As a recent reports, a large number of natural antioxidant extracts

have been suggested to induce beneficial effects on human health and disease control.[55] The beneficial effects of many medicinal plants may be due to the presence of antioxidative, antibacterial and antimicrobial components. Antioxidants such as flavonoids, phenolic acids and diterpenes can be used to treat the undesirable and harmful action of the free radicals related to various diseases.[30]

THERAPEUTIC MANAGEMENT OF HCC BY NATURAL ANTIOXIDANTS

Natural agents are alternative therapeutic agents to control different diseases including cancer progression through their antioxidant activity. They stimulate the normal metabolic function in cancer cells and regulate the tumor suppressor genes and immunity. These natural products control the over expression of metabolic enzymes and tumor growth factors in cancer cell.[56] Also they have the ability to control DNA damaging factors in cancer cells and regulate DNA transcription in tumors. Moreover, they possess numerous therapeutic benefits such as anti-obesity effects; anti-diabetic effects; immune enhancement; and anti-inflammatory effects.[57] Previous studies recorded that natural extracts, herbs and spices have been used for controlling diseases, including cancer through different mechanisms such as prevention of tumor initiation; delay or arrest of the development of tumors; extension of cancer latency periods; reduction in cancer metastasis and mortality and prevention of recurrence of secondary tumors.[58,59] Vegetables and fruits rich with polyphenol plays a crucial role in the protection of liver against hepatitis due to its potential activity in the reduction of early pro-inflammatory cytokines, activation of anti-inflammatory IL-10, and inhibition of lipo-polysaccharide induced activation of nuclear factor kappa B (NF-κB) in hepatocytes.[60-62] Furthermore, flavonoids are a group of polyphenolic compounds, different in chemical structure and characteristics, naturally founded in plants. They showed versatile health benefits such as anti-inflammatory; antioxidant; anti-proliferative and anticancer activity; free radical scavenging activity; and antihypertensive effects.[63,64]

Chicory

Chicory (Cichorium intybus L.) has been reported in medicine from North Africa to South Asia for several 100 years.[65] It contains many useful compound such as anthocyanins, vitamins A and C , potassium, calcium, and phosphorus and rich chioric acid.[66] It act as anti-inflamatory, anti-bacterial agent as well as it has immune-modulatory effects.[67] Many types of edible plants and vegetables contain high level of chicoric acid.[68] Chicoric acid have essential properties as antioxidant, antivirus and immunoregulation.[69] Chicory has a many properties as antioxidant, hepatoprotective, hypoglycemic, diuretic, and anti-testicular toxicity.[70-73] Also, chicory is a good source for inulin.[74,75] Inulin is a hepatoprotective compound that prevent of the tissue from demolition by inhibited oxidative degradation of DNA in liver mice.[74] In addition, inulin has hypolipidemic effect where it is not affected by digestive enzymes due to it is expected to behave like a soluble fiber.[76] Moreover it has prebiotic effect by decreasing the activity of growth pathogens and harmful microorganisms as well as increase the activity of growth colonic of beneficial bacteria to the host.[77,78]

Milk thistle

Milk (Silybum marianum) is one of the most famous herbal agents that act as hepato-reno protective agent from 16th century due to it contains approximately 4-6% silymarin and 20-35% fatty acids, particularly linoleic acid.[79,80] Silymarin composed of both polyphenolic molecules, including flavonolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, and silydianin) and one flavonoid (taxifolin), silibinin, a semipurified. These components have the beneficial effects, including liver protection and antioxidant, anti-viral, and anti-inflammatory properties.[81] Silybum is effective in the treatment of liver diseases (cirrhosis, jaundice and hepatitis).[82] Various studies including *in vitro* and animal research suggest that silybum may have hepatoprotective and antihepatotoxic properties that protect liver cells against toxins through its ability in the reduction of ROS and LPO production, as well as the rebalancing of cellular REDOX status.[81,83] Moreover its role in inhibition of pro-inflammatory signals, cellular proliferation and expression of survival proteins, resulting a significant protecting the liver.[81]

Glycyrrhizin

Glycyrrhizin is the active constituent obtained from aqueous extraction of root liquorice (Glycyrrhiza glabra). It has been used in traditional medicine to reduce bronchitis, jaundice as well as gastritis. Its major constituents are glycyrrhetic acid; flavonoids; hydroxycoumarins; and beta-sitosterol.[84] Licorice and their products have been reported to be useful in the treatment of human hepatitis; animal inducible hepatocarcinogenesis; and attenuating titanium dioxide nanoparticles-induced hepatotoxicity.[85] Glycyrrhizin has pharmacologic roles such as anti-inflammatory; antiviral; antioxidant; immunomodulatory; hepatoprotective and cardioprotective activities through the inhibition of beta-hydroxysteroid dehydrogenase enzyme.[86] Also it blinded to high mobility group box 1 (HMGB1) directly to suppress HMGB1-induced injury, inhibit toll-like receptor-4 pathway, lower uclear factor-κB (NF-κB) concentration and inhibit the production of inflammatory cytokines.[87,88]

Ginseng

Ginseng (Panax ginseng), a valued Chinese and Korean traditional medicinal herb, has been clinically used in China, Europe, United States and North America for thousands of years.[89-91] Ginseng is one of the well-known medicines in alleviating the development of HCC in chronic hepatitis patients.[92,93] Ginseng extract has an antioxidant activity due to its ability to scavenge free radicals and suppression of lipid peroxidation.[94] It has been shown to improve general conditions and non-specific complaints due to the exhaustive and feverish illness through enhancement of

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