

Role of natural antioxidants in the therapeutic management of hepatocellular carcinoma

Hanaa A. Hassan¹, Nermin E. El-Gharib¹, Anmar F. Azhari²

¹Physiology Division, Zoology Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt.

²Ministry of Health, Makkah Region, Makkah 21514, Saudi Arabia.

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

Corresponding Author:

Prof. Hanaa A. Hassan, Physiology Division, Zoology Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt.
E-mail: drhanaahassan@mans.edu.eg

Received: 30-04-2016, **Accepted:** 04-07-2016

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 consumption, 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, obstructive 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

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: service@oaeublish.com

How to cite this article: Hassan HA, El-Gharib NE, Azhari AF. Role of natural antioxidants in the therapeutic management of hepatocellular carcinoma. Hepatoma Res 2016;2:216-23.

Access this article online	
Website: http://www.hrjournal.net/	Quick Response Code 
DOI: 10.20517/2394-5079.2016.12	

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 hemochromatosis, each typically in the setting of cirrhosis.^[18] Additionally, an autoimmune 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- κ B) 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-inflammatory, 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, antiviral 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- κ B (NF- κ B) 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

- experimental liver disease. *J Ethnopharmacol* 2005;100:198-204.
36. Ahmad A, Pillai KK, Najmi AK, Ahmad SJ, Pal SN, Balani DK. Evaluation of hepatoprotective potential of jigrine post-treatment against thioacetamide induced hepatic damage. *J Ethnopharmacol* 2002;79:35-41.
 37. Chilakapati J, Korrapati MC, Hill RA, Warbritton A, Latendresse JR, Mehendale HM. Toxicokinetics and toxicity of thioacetamide sulfoxide: a metabolite of thioacetamide. *Toxicology* 2007;230:105-16.
 38. Cervello M, Montalto G. Cyclooxygenases in hepatocellular carcinoma. *World J Gastroenterol* 2006;12:5113-21.
 39. Coward WR, Okayama Y, Sagara H, Wilson SJ, Holgate ST, Church MK. NF-kappa B and TNF-alpha: a positive autocrine loop in human lung mast cells? *J Immunol* 2002;169:5287-93.
 40. Zaret KS, Grompe M. Generation and regeneration of cells of the liver and pancreas. *Science* 2008;322:1490-4.
 41. Lee S, Lee HJ, Kim JH, Lee HS, Jang JJ, Kang GH. Aberrant CpG island hypermethylation along multistep hepatocarcinogenesis. *Am J Pathol* 2003;163:1371-8.
 42. Nishikawa H, Kato T, Tawara I, Ikeda H, Kuribayashi K, Allen PM, Schreiber RD, Old LJ, Shiku H. IFN-gamma controls the generation/activation of CD4+ CD25+ regulatory T cells in antitumor immune response. *J Immunol* 2005;175:4433-40.
 43. Huether A, Hopfner M, Sutter AP, Baradari V, Schuppan D, Scherubl H. Signaling pathways involved in the inhibition of epidermal growth factor receptor by erlotinib in hepatocellular cancer. *World J Gastroenterol* 2006;12:5160-7.
 44. Hu S, Chen SM, Li XK, Qin R, Mei ZN. Antitumor effects of chishen extract from *Salvia miltiorrhiza* and *Paeoniae radix* on human hepatocellular carcinoma cells. *Acta Pharmacol Sin* 2007;28:1215-23.
 45. Youle RJ, Strasser A. The BCL-2 protein family: opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* 2008;9:47-59.
 46. Paradis V. Histopathology of hepatocellular carcinoma. In: Vauthey JN, Brouquet A, editors. Multidisciplinary treatment of hepatocellular carcinoma. Berlin: Springer; 2013. p. 21-32.
 47. Omata M, Peters RL, Tatter D. Sclerosing hepatic carcinoma: relationship to hypercalcemia. *Liver* 1981;1:33-49.
 48. Kojiro M, Sugihara S, Kakizoe S, Nakashima O, Kiyomatsu K. Hepatocellular carcinoma with sarcomatous change: a special reference to the relationship with anticancer therapy. *Can Chemother Pharmacol* 1989;23:S4-8.
 49. Guy J, Kelley RK, Roberts J, Kerlan R, Yao F, Terrault N. Multidisciplinary management of hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2012;10:354-62.
 50. Kaseb AO, Abaza YM, Roses RE. Multidisciplinary management of hepatocellular carcinoma. *Recent Results Cancer Res* 2013;190:247-59.
 51. Gish RG, Lencioni R, Di Bisceglie AM, Raoul JL, Mazzaferro V. Role of the multidisciplinary team in the diagnosis and treatment of hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2012;6:173-85.
 52. Osaki A, Suda T, Kamimura K, Tsuchiya A, Tamura Y, Takamura M, Igarashi M, Kawai H, Yamagiwa S, Aoyagi Y. A safe and effective dose of cisplatin in hepatic arterial infusion chemotherapy for hepatocellular carcinoma. *Cancer Med* 2013;2:86-98.
 53. Mok TS, Leung TW, Lee SD, Chao Y, Chan AT, Huang A, Lui MC, Yeo W, Chak K, Johnston A, Johnson P. A multi-centre randomized phase II study of nolatrexed versus doxorubicin in treatment of Chinese patients with advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1999;44:307-11.
 54. Leichman CG, Jacobson JR, Modiano M, Daniels JR, Zalupski MM, Doroshow JH, Fletcher WS, Macdonald JS. Hepatic chemoembolization combined with systemic infusion of 5-fluorouracil and bolus leucovorin for patients with metastatic colorectal carcinoma: a Southwest Oncology Group pilot trial. *Cancer* 1999;86:775-81.
 55. Hassan HA, El-Gharib NE. Obesity and clinical riskness relationship: therapeutic management by dietary antioxidant supplementation-a review. *Appl Biochem Biotechnol* 2015;176:647-69.
 56. Kuppusamy P, Yusoff MM, Maniam GP, Ichwan SJ, Soundharrajan I, Govindan N. Nutraceuticals as potential therapeutic agents for colon cancer: a review. *Acta Pharm Sinica B* 2014;4:173-81.
 57. Sousa GT, Lira FS, Rosa JC, de Oliveira EP, Oyama LM, Santos RV, Pimentel GD. Dietary whey protein lessens several risk factors for metabolic diseases: a review. *Lipids Health Dis* 2012;11:67.
 58. Kapadia GJ, Azuine MA, Takayasu J, Konoshima T, Takasaki M, Nishino H, Tokuda H. Inhibition of epstein-barr virus early antigen activation promoted by 12-O-tetradecanoylphorbol-13-acetate by the non-steroidal anti-inflammatory drugs. *Cancer Lett* 2000;161:221-9.
 59. Kelloff GJ. Perspectives on cancer chemoprevention research and drug development. *Adv Cancer Res* 2000;78:199-334.
 60. Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. *Nutr Rev* 1998;56:317-33.
 61. Yamashita H, Goto M, Matsui-Yuasa I, Kojima-Yuasa A. Ecklonia cava polyphenol has a protective effect against ethanol-induced liver injury in a cyclic AMP-dependent manner. *Mar Drugs* 2015;13:3877-91.
 62. Manach C, Scalbert A, Morand C, Rémésy C, Jiménez L. Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 2004;79:727-47.
 63. Xiao ZP, Peng ZY, Peng MJ, Yan WB, Ouyang YZ, Zhu HL. Flavonoids health benefits and their molecular mechanism. *Mini Rev Med Chem* 2011;11:169-77.
 64. Donfack JH, Simo CC, Ngameni B, Tchana AN, Kerr PG, Finzi PV, Vidari G, Giardina S, Buonocore D, Ngadjui BT, Moundipa PF, Marzatico F. Antihepatotoxic and antioxidant activities of methanol extract and isolated compounds from *Ficus chlamydocarpa*. *Nat Prod Commun* 2010;5:1607-12.
 65. Jamshidzadeha A, Khoshnooda JM, Dehghanib Z, Niknaha H. Hepatoprotective activity of *Cichorium intybus* L. leaves extract against carbon tetrachloride induced toxicity. *Iran J Pharm Res* 2006;1:41-6.
 66. Mulabagal V, Wang H, Ngouajio M, Nair MG. Characterization and quantification of health beneficial anthocyanins in leaf chicory (*Cichorium intybus*) varieties. *Eur Food Res Technol* 2009;230:47-53.
 67. Nayeemunnisa A. Alloxan diabetes-induced oxidative stress and impairment of oxidative defense system in rat brain: neuroprotective effects of *Cichorium intybus*. *Int J Diabetes Metabol* 2009;17:105-9.
 68. Lee J, Scagel CF. Chicoric acid found in basil (*Ocimum basilicum* L.) leaves. *Food Chem* 2009;115:650-6.
 69. Dalby-Brown L, Barsett H, Landbo AK, Meyer AS, Mølgaard P. Synergistic antioxidative effects of alkamides, caffeic acid derivatives, and polysaccharide fractions from *Echinacea purpurea* on *in vitro* oxidation of human low-density lipoproteins. *Agric J Food Chem* 2005;53:9413-23.
 70. Hassan HA. The prophylactic role of some edible wild plants against nitrosamine precursor's experimentally-induced testicular toxicity in male albino rats. *J Egypt Soc Toxicol* 2008;38:1-11.
 71. Pool-Zobel B, van Loo J, Rowland I, Roberfroid MB. Experimental evidences on the potential of prebiotic fructans to reduce the risk of colon cancer. *Br J Nutr* 2002;87:273-81.
 72. Cavin C, Delannoy M, Malnoe A, Debeve E, Touché A, Courtois D, Schilter B. Inhibition of the expression and activity of cyclooxygenase-2 by chicory extract. *Biochem Biophys Res Commun* 2005;327:742-9.
 73. Kim JH, Mun YJ, Woo WH, Jeon KS, An NH, Park JS. Effects of the ethanol extract of *Cichorium intybus* on the immunotoxicity by ethanol in mice. *Int Immunopharmacol* 2002;2:733-44.
 74. Kolida S, Tuohy K, Gibson GR. Prebiotic effect of inulin and oligofructose. *Br J Nutr* 2002;87:S193-7.
 75. Van Beek TA, Maas P, King BM, Leclercq E, Voragen AGJ, De Groot A. Bitter sesquiterpene lactones from chicory roots. *Agric J Food Chem* 1990;38:1035-8.
 76. Kim M, Shin HK. The water-soluble extract of chicory influences serum and liver lipid concentrations, cecal short-chain fatty acid concentrations and fecal lipid excretion in rats. *J Nutr* 1998;128:1731-6.
 77. Roberfroid MB. Inulin-type fructans: functional food ingredients. *J Nutr* 2007;137:S2493-502.
 78. Buriti FCA, Cardarelli HR, Filisetti TMCC, Saad SMI. Synbiotic potential of fresh cream cheese supplemented with inulin and *Lactobacillus paracasei* in co-culture with *Streptococcus thermophilus*. *Food Chem* 2007;104:1605-10.
 79. Greenlee H, Abascal K, Yarnell E, Ladas E. Clinical applications of *silybum marianum* in oncology. *Integr Cancer Ther* 2007;6:158-65.
 80. Kroll DJ, Shaw HS, Oberlies NH. Milk thistle nomenclature: why it

- matters in cancer research and pharmacokinetic studies. *Integr Cancer Ther* 2007;6:110-9.
81. Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. *Phytother Res* 2010;24:1423-32.
 82. Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, Blazevic T, Schwaiger S, Rollingner JM, Heiss EH, Schuster D, Kopp B, Bauer R, Stuppner H, Dirsch VM, Atanasov AG. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPAR γ): a review. *Biochem Pharmacol* 2014;92:73-89.
 83. Al-Anati L, Essid E, Reinehr R, Petzinger E. Silibinin protects OTA-mediated TNF- α release from perfused rat livers and isolated rat Kupffer cells. *Mol Nutr Food Res* 2009;53:460-6.
 84. Fiore C, Eisenhut M, Ragazzi E, Zanchin G, Armanini D. A history of the therapeutic use of liquorice in Europe. *J Ethnopharmacol* 2005;99:317-24.
 85. Orazizadeh M, Fakhredini F, Mansouri E, Khorsandi L. Effect of glycyrrhizic acid on titanium dioxide nanoparticles-induced hepatotoxicity in rats. *Chem Biol Interact* 2014;220:214-21.
 86. Asl MN, Hosseinzadeh H. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. *Phytother Res* 2008;22:709-24.
 87. Gwak GY, Moon TG, Lee DH, Yoo BC. Glycyrrhizin attenuates HMGB1-induced hepatocyte apoptosis by inhibiting the p38-dependent mitochondrial pathway. *World J Gastroenterol* 2012;18:679-84.
 88. Furuta K, Sato S, Miyake T, Okamoto E, Ishine J, Ishihara S, Amano Y, Adachi K, Kinoshita Y. Anti-tumor effects of cimetidine on hepatocellular carcinomas in diethylnitrosamine-treated rats. *Oncol Rep* 2008;19:361-8.
 89. El Denshary ES, Al-Gahazali MA, Mannaa FA, Salem HA, Hassan NS, Abdel-Wahhab MA. Dietary honey and ginseng protect against carbon tetrachloride-induced hepatonephrotoxicity in rats. *Exp Toxicol Pathol* 2012;64:753-60.
 90. Soldati F. Panax ginseng: standardization and biological activity. In: Cutler SJ, Cutler HG, editors. Biologically active natural products: pharmaceuticals. Boca Raton, FL: CRC Press, 2000. p. 209-32.
 91. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;27:1-19.
 92. Oka H, Yamamoto S, Kuroki T, Harihara S, Marumo T, Kim SR, Monna T, Kobayashi K, Tango T. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer* 1995;76:743-9.
 93. Abdel-Wahhab MA, Gamil K, El-Kady AA, El-Nekeety AA, Naguib KM. Therapeutic effects of korean red ginseng extract in egyptian patients with chronic liver diseases. *Ginseng J Res* 2011;35:69-79.
 94. He SX, Luo JY, Wang YP, Wang YL, Fu H, Xu JL, Zhao G, Liu EQ. Effects of extract from Ginkgo biloba on carbon tetrachloride-induced liver injury in rats. *World J Gastroenterol* 2006;12:3924-8.
 95. Nishino H, Tokuda H, Ii T, Takemura M, Kuchide M, Kanazawa M, Mou XY, Bu P, Takayasu J, Onozuka M, Masuda M, Satomi Y, Konoshima T, Kishi N, Baba M, Okada Y, Okuyama T. Cancer chemoprevention by ginseng in mouse liver and other organs. *J Korean Med Sci* 2001;16:S66-9.
 96. Yun TK, Choi SY. Preventive effect of ginseng intake against various human cancers: a case-control study on 1987 pairs. *Cancer Epidemiol Biomarkers Prev* 1995;4:401-8.
 97. Hasegawa H, Sung JH, Matsumiya S, Uchiyama M. Main ginseng saponin metabolites formed by intestinal bacteria. *Planta Med* 1996;62:453-7.
 98. Lee BM, Lee SK, Kim HS. Inhibition of oxidative DNA damage, 8-OHdG, and carbonyl contents in smokers treated with antioxidants (vitamin E, vitamin C, beta-carotene and red ginseng). *Cancer Lett* 1998;132:219-27.
 99. Choi HH, Jong HS, Park JH, Choi S, Lee JW, Kim TY, Otsuki T, Namba M, Bang YJ. A novel ginseng saponin metabolite induces apoptosis and down-regulates fibroblast growth factor receptor 3 in myeloma cells. *Int J Oncol* 2003;23:1087-93.
 100. Choi UK, Lee OH, Yim JH, Cho CW, Rhee YK, Lim SI, Kim YC. Hypolipidemic and antioxidant effects of dandelion (taraxacum officinale) root and leaf on cholesterol-fed rabbits. *Int J Mol Sci* 2010;11:67-78.
 101. Schütz K, Carle R, Schieber A. Taraxacum--a review on its phytochemical and pharmacological profile. *J Ethnopharmacol* 2006;107:313-23.
 102. Wichtl M. Herbal drugs and phytopharmaceuticals. A handbook for practice on a scientific basis. 3rd ed. Boca Raton, FL: CRC Press; 2004. p.704.
 103. Newall CA, Anderson LA, Phillipson JD. Herbal medicines: a guide for health-care professionals. London: Pharmaceutical Press; 1996. p. 296.
 104. Jeon HJ, Kang HJ, Jung HJ, Kang YS, Lim CJ, Kim YM, Park EH. Anti-inflammatory activity of Taraxacum officinale. *J Ethnopharmacol* 2008;115:82-8.
 105. Williams CA, Goldstone F, Greenham J. Flavonoids, cinnamic acids and coumarins from the different tissues and medicinal preparations of Taraxacum officinale. *Phytochemistry* 1996;42:121-7.
 106. Hu C, Kitts DD. Antioxidant, prooxidant, and cytotoxic activities of solvent-fractionated dandelion (Taraxacum officinale) flower extracts *in vitro*. *J Agric Food Chem* 2003;1:301-10.
 107. Al-Malki AL, Abo-Golayel MK, Abo-Elnaga G, Al-Beshri H. Hepatoprotective effect of dandelion (Taraxacum officinale) against induced chronic liver cirrhosis. *Med Plants Res* 2013;7:1494-505.
 108. Park JY, Park CM, Kim JJ, Song YS. Hepatoprotective activity of dandelion (Taraxacum officinale) water extract against Dgalactosamine-induced hepatitis in rats. *Korean J Soc Food Sci Nut* 2008;32:177-83.
 109. Hudec J, Burdová M, Kobida L, Komora L, Macho V, Kogan G, Turianica I, Kochanova R, Ložek O, Habán M, Chlebo P. Antioxidant capacity changes and phenolic profile of Echinacea purpurea, nettle (Urtica dioica L.), and dandelion (Taraxacum officinale) after application of polyamine and phenolic biosynthesis regulators. *Agric J Food Chem* 2007;55:5689-96.
 110. Seo SW, Koo HN, An HJ, Kwon KB, Lim BC, Seo EA, Ryu DG, Moon G, Kim HY, Kim HM, Hong SH. Taraxacum officinale protects against cholecystokinin-induced acute pancreatitis in rats. *World J Gastroenterol* 2005;11:597-9.
 111. Rana SV, Pal R, Vaiphei K, Sharma SK, Ola RP. Garlic in health and disease. *Nutr Res Rev* 2011;24:60-71.
 112. Herman-Antosiewicz A, Singh SV. Signal transduction pathways leading to cell cycle arrest and apoptosis induction in cancer cells by Allium vegetable-derived organosulfur compounds: a review. *Mutat Res* 2004;555:121-31.
 113. Chu Q, Lee DT, Tsao SW, Wang X, Wong YC. S-allylcysteine, a water-soluble garlic derivative, suppresses the growth of a human androgen-independent prostate cancer xenograft, CWR22R, under *in vivo* conditions. *BJU Int* 2007;99:925-32.
 114. Gapter LA, Yui OZ, Ng KY. S-Allylcysteine reduces breast tumor cell adhesion and invasion. *Biochem Biophys Res Commun* 2008;367:446-51.
 115. Tang FY, Chiang EP, Chung JG, Lee HZ, Hsu CY. S-allylcysteine modulates the expression of E-cadherin and inhibits the malignant progression of human oral cancer. *J Nutr Biochem* 2009;20:1013-20.
 116. Welch C, Wuarin L, Sidell N. Antiproliferative effect of the garlic compound S-allyl cysteine on human neuroblastoma cells *in vitro*. *Cancer Lett* 1992;63:211-9.
 117. Tang FY, Chiang EP, Pai MH. Consumption of S-allylcysteine inhibits the growth of human non-small-cell lung carcinoma in a mouse xenograft model. *J Agric Food Chem* 2010;58:11156-64.
 118. Chu YL, Ho CT, Chung JG, Raghur R, Lo YC, Sheen LY. Allicin induces anti-human liver cancer cells through the p53 gene modulating apoptosis and autophagy. *J Agric Food Chem* 2013;61:9839-48.
 119. Bryja V, Gradl D, Schambony A, Arenas E, Schulte G. Beta-arrestin is a necessary component of Wnt/beta-catenin signaling *in vitro* and *in vivo*. *Proc Natl Acad Sci U S A* 2007;104:6690-5.
 120. Zhang CL, Zeng T, Zhao XL, Yu LH, Zhu ZP, Xie KQ. Protective effects of garlic oil on hepatocarcinoma induced by N-nitrosodiethylamine in rats. *Int J Biol Sci* 2012;8:363-74.
 121. Sundaresan S, Subramanian P. Prevention of N-nitrosodiethylamine-induced hepatocarcinogenesis by S-allylcysteine. *Mol Cell Biochem* 2008;310:209-14.

122. Darvesh AS, Aggarwal BB, Bishayee A. Curcumin and liver cancer: a review. *Curr Pharm Biotechnol* 2012;13:218-28.
123. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. *Altern Med Rev* 2009;14:141-53.
124. Aggarwal BB, Sundaram C, Malani N, Ichikawa H. Curcumin: the Indian solid gold. *Adv Exp Med Biol* 2007;595:1-75.
125. Reyes-Gordillo K, Segovia J, Shibayama M, Vergara P, Moreno MG, Muriel P. Curcumin protects against acute liver damage in the rat by inhibiting NF-kappa B, proinflammatory cytokines production and oxidative stress. *Biochim Biophys Acta* 2007;1770:989-96.
126. Hsu FT, Liu YC, Liu TT, Hwang JJ. Curcumin sensitizes hepatocellular carcinoma cells to radiation via suppression of radiation-induced NF-kB activity. *Biomed Res Int* 2015;2015:363671.
127. Soliman MM, Baiomy AA, Yassin MH. Molecular and histopathological study on the ameliorative effects of curcumin against lead acetate-induced hepatotoxicity and nephrotoxicity in Wistar rats. *Biol Trace Elem Res* 2015;167:91-102.
128. Skommer J, Wlodkowic D, Pelkonen J. Gene-expression profiling during curcumin-induced apoptosis reveals downregulation of CXCR4. *Exp Hematol* 2007;35:84-95.
129. Dai XZ, Yin HT, Sun LF, Hu X, Zhou C, Zhou Y, Zhang W, Huang XE, Li XC. Potential therapeutic efficacy of curcumin in liver cancer. *Asian Pac J Cancer Prev* 2013;14:3855-9.
130. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res* 2003;23:363-98.
131. Hamzawy MA, El-Denshary ES, Hassan NS, Manaa F, Abdel-Wahhab MA. Antioxidant and hepatorenoprotective effects of Thyme vulgaris extract in rats during aflatoxicosis. *Glob J Pharmacol* 2012;6:106-17.
132. Hamzawy MA, El-Denshary ESM, Abdel-Wahhab MA. Effects of natural compounds in treatment and prevention of hepatotoxicity and hepatocellular carcinoma. *Hepatoma Res* 2015;1:111-8.
133. Hosseinzadeh S, Kukhdan AJ, Hosseini A, Armand R. The application of Thymus vulgaris in traditional and modern medicine: a review. *Global J Pharmacol* 2015;9:260-6.
134. Marculescu A, Vlase L, Hanganu D, Dragulescu C, Antonie I, Neli-Kinga O. Polyphenols analyses from Thymus species. *Proc Rom Acad Series B* 2007;3:117-21.
135. Thompson JD, Chalchat JC, Michet A, Linhart YB, Ehlers B. Qualitative and quantitative variation in monoterpene co-occurrence and composition in the essential oil of Thymus vulgaris chemotypes. *J Chem Ecol* 2003;29:859-80.