OAE Publishing Inc.

Topic: Natural Products and Hepatocellular Carcinoma

Beneficial and detrimental effects of natural dietary products on the risk of hepatocellular carcinoma, and their roles in its management

Rodolfo Sacco[1], Caterina Conte[2], Sara Marceglia[3], Valeria Mismas[1], Giampaolo Bresci[1], Antonio Romano[1], Roberto Eggenhoffner[4], Luca Giacomelli[4]

[1]*Department of Gastroenterology, Cisanello University Hospital, 56127 Pisa, Italy.*
[2]*Endocrinology and Metabolic Disease, Università Cattolica del Sacro Cuore, 00168 Rome, Italy.*
[3]*Department of Engineering, University of Trieste, 34100 Trieste, Italy.*
[4]*Department of Surgical Sciences and Integrated Diagnostics, School of Medicine, University of Genoa, 16163 Genoa, Italy.*

ABSTRACT

Hepatocellular carcinoma (HCC) is a common solid malignancy and a leading cause of cancer-related death worldwide. The mechanisms underlying the pathogenesis and development of HCC are complex and heterogeneous. Although mainly related to hepatitis B and C chronic infection; HCC may also arise from diet-associated conditions such as non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Furthermore, toxins and nutrients such as mycotoxins and alcohol have an established role in the pathogenesis of chronic liver diseases, whereas specific diet patterns or foods have been associated with a reduction in HCC risk. The aim of this review is to provide a thorough overview of the clinically relevant effects - either beneficial or detrimental - of natural products consumed by humans on HCC risk and management.

Key words: Hepatocellular carcinoma; natural products; diet; dietary supplements

Address for correspondence:
Dr. Rodolfo Sacco, Department of Gastroenterology, Cisanello University Hospital, 56127 Pisa, Italy.
E-mail: r.sacco@ao-pisa.toscana.it

Received: 10-11-2015, **Accepted:** 19-01-2016

INTRODUCTION

The risk of hepatocellular carcinoma (HCC), associated with nutritional and metabolic factors, has been underestimated until recently. HCC may represent a late complication of non-alcoholic steatohepatitis-related cirrhosis,[1] which in turn is strongly related to diet-associated conditions such as obesity, type 2 diabetes mellitus and dyslipidemia.[2] Furthermore, several foods, beverages and food contaminants are known to affect the risk of developing HCC. Nutritional compounds that display anti-inflammatory and antioxidant effects may have specific applications in preventing oxidative stress-induced injury, which characterizes the pathogenesis of cirrhosis and steatosis.[3] The pivotal role of diet is highlighted by the results of two large case-control

Access this article online	
Website: http://www.hrjournal.net/	Quick Response Code
DOI: 10.20517/2394-5079.2015.64	

How to cite this article: Sacco R, Conte C, Marceglia S, Mismas V, Bresci G, Romano A, Eggenhoffner R, Giacomelli L. Beneficial and detrimental effects of natural dietary products on the risk of hepatocellular carcinoma, and their role in its management. Hepatoma Res 2016;2:53-61.

studies conducted in Italy and Greece, indicating that strong adherence to the Mediterranean diet may be protective against HCC (approximately a 50% reduction in risk), with potential benefits also in patients with chronic viral hepatitis.[4] As for patients with established chronic liver disease, nutritional interventions to support sufficient energy intake significantly improve patient survival.[5-8] A better knowledge of the detrimental or beneficial effects of foods is therefore important in the prevention and management of HCC, and the evaluation of dietary supplements potentially able to reduce the risk and/or the progression of cirrhosis and steatosis is of the highest interest.

The potential protective and therapeutic mechanisms of natural compounds in the prevention and treatment of hepatotoxicity and HCC have been recently reviewed.[9] The aim of the present review is to provide an insight on the clinically relevant effects-either beneficial or detrimental-of natural products consumed by humans on HCC risk and management.

DETRIMENTAL NATURAL PRODUCTS

Foods and beverages

Alcohol

The detrimental effects of alcohol on the liver are well known; ethanol exerts toxic effects that can cause cell injury and a reactive response culminating in alcohol-induced hepatic cirrhosis. More in detail, reactions catalyzed by the main enzymes involved in alcohol metabolism, namely alcohol dehydrogenase and aldehyde dehydrogenase, lead to the production of reactive oxygen species (ROS) that can exert toxic effects such as lipid peroxidation, enzymes inactivation, DNA mutations, and destruction of cell membranes; in addition, in conditions of chronic alcohol abuse there is an increased production of acetaldehyde from ethanol, due to induction of the microsomal system and in particular of the Cytochrome P450 enzyme Cytochrome P450 2E1.[10] Acetaldehyde is one of the main mediators of alcohol-induced fibrogenesis in the liver, as it can stimulate synthesis of fibrillar-forming collagens and structural glycoproteins of extracellular matrix in hepatic stellate cells, and increase the secretion of transforming growth factor-β. Eventually, these events may lead to hepatic cirrhosis, which is associated with a 5-year cumulative risk for HCC of 8%.[10] The immunosuppressive effects of alcohol[11,12] and alcohol-induced epigenetic modifications[13] may also contribute to the development of HCC in patients with alcoholic liver disease.

Red meat

Red meat consumption has been reported to be associated with an increased risk of HCC.[14] Meat processing, e.g. curing and smoking, can in fact result in the formation of carcinogenic chemicals, including *N*-nitroso-compounds and polycyclic aromatic hydrocarbons. cooking, especially if high-temperature, can also produce known or suspected carcinogens, including heterocyclic aromatic amines and polycyclic aromatic hydrocarbons.[15] The International Agency for Research on Cancer has recently classified red meat and processed meat as "probably carcinogenic to humans" (Group 2A) and "carcinogenic to humans" (Group 1), respectively.[15] However, the strongest association appears to be with colorectal cancer, pancreatic cancer and prostate cancer,[15] and currently available evidence supporting a causative role for red meat in HCC is inconsistent.[16,17]

Pickled foods

A possible carcinogenic effect of pickled vegetables was first reported in 1992.[18] Traditionally, pickled vegetables are prepared by packing moist vegetables in a jar for weeks to months, allowing fermentation and growth of fungi and yeasts. This process can potentially yield carcinogenic compounds such as the *N*-nitroso compound Roussin's red (dimethylthiot etranitrosodiiron).[19] Consistently, a large systematic review and meta-analysis revealed that those who consume pickled vegetables/foods have an about 50% increase in risk of gastric cancer *vs*. those who consume little or no pickled vegetables/foods.[20] An association between pickled food and HCC has also been reported.[21]

Sugar

Non-alcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome. It is characterized by an increase in intrahepatic triglyceride content (i.e. steatosis), with or without inflammation and fibrosis [i.e. non-alcoholic steatohepatitis (NASH)]. Hepatic *de novo* lipogenesis (DNL) has been suggested to be abnormally increased in NAFLD, and to contribute to its development.[22] As glycolysis and the metabolism of carbohydrates are the main providers of substrates for DNL, a high-carbohydrate diet can prime the DNL pathway with a large substrate load and increase rates of DNL.[23] Dietary fructose may contribute to NAFLD by promoting DNL, insulin resistance, oxidative

stress, bacterial overgrowth, and inflammation.[24] Both NAFLD and NASH can further progress to hepatic fibrosis and eventually to cirrhosis,[25] older age and deterioration of metabolic status being major risk factors for fibrosis progression.[26] NAFLD/NASH that progresses to cirrhosis carries the highest risk for HCC, due to the erratic liver remodeling with repeated cycles of hepatocellular destruction and compensatory regeneration that characterizes cirrhosis. However, there is increasing concern that NAFLD-associated HCC may also occur in non-cirrhotic liver, due factors specifically associated with NAFLD (e.g. lipotoxicity associated with DNL and increased levels of proinflammatory adipokines/cytokines).[27] Recent findings indicate that the incidence rate of HCC in NAFLD and NASH is 0.44 and 5.29 cases per 1,000 person-years, respectively.[28] Although these rates are lower than those reported for patients with hepatitis B virus (HBV) or hepatitis C virus (HCV), the number of patients with NAFLD and NASH-related HCC is projected to increase, given the increasing prevalence of these conditions. Epidemiological evidence linking dietary sugar, and specifically, fructose consumption, with cancer derives from case-control studies that found an association between high dietary glycemic load and increased risk for HCC, especially in patients with chronic viral hepatitis.[16,17] However, a recent analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort revealed an association between higher total sugar intake and risk of HCC, but not between glycemic index/glycemic load and HCC.[18]

Overnutrition

Hepatic cirrhosis and an associated increased risk of developing HCC independent of viral hepatitis frequently occurs secondary to NASH and NAFLD,[29] which often has a nutritional basis. NAFLD is very common in obesity and is present in 60-75% of obese persons and 85-95% of morbidly obese persons.[30] Furthermore, it has been proposed that obesity, diabetes, and insulin resistance may predispose to HCC in patients with cirrhosis.[31-33] Thus, in the case of HCC arising from NAFLD, it appears that overnutrition is leading to obesity and its complications may increase the risk of developing HCC, rather than specific nutrients in the diet.

Food contaminants

Mycotoxins

Aflatoxin B1 (AFB1) is a mycotoxin (i.e. toxic compounds produced by fungal secondary metabolism) produced by *Aspergillus flavus* and *Aspergillus parasiticus*, widely represented in nature. The mycotoxin is found in many foods such as corn, rice, oil seeds, dried fruits, and peanuts that have been improperly stored in hot, humid, and unsanitary conditions.[34] Metabolism of aflatoxins by hepatic enzymes may generate reactive epoxide species with the potential of forming a covalent bond with guanine,[35] generating adducts that can promote cellular and macromolecule damage, including mutations in the *p53* tumor-suppressor gene.[36] Exposure to AFB1 has been associated with HCC in several cohort studies, supporting a role of AFB1 in liver cancerogenesis-particularly among subjects who are carriers of hepatitis B surface antigen.[37] It has been estimated that aflatoxin exposure may account for 5-28% of total HCC cases worldwide.[38]

Fumonisins are ubiquitous mycotoxins that contaminate cereal grains, primarily maize. More than 10 compounds have been isolated and characterized; fumonisin B1 is believed to be the most toxic among them, as it has been shown to be hepatocarcinogenic in rodents.[39-41] Fumonisins are thought to impair the de novo synthesis of ceramide and sphingolipid metabolism due to a structural resemblance with ceramide; this may lead to disruption of signal transduction pathways in the target cells.[42] A pathogenic role of exposure to fumonisins through consumption of moldy corn in human HCC has been suggested by studies carried out in China.[43-45]

Ochratoxin A is another mycotoxin that may have a role in the development of HCC.[46] It may be found in cacao and derived products, dried fruits, wine, cereals, green coffee, and spices (mainly nutmeg, paprika, coriander, and pepper powder).[47] The carcinogenic effect of ochratoxin A is the result of both direct genotoxic (covalent DNA adduct formation and mutagenicity)[48] and epigenetic mechanisms leading to protein synthesis inhibition, oxidative stress and the activation of specific cell signaling pathways.[49] In a recent case-control study, high performance liquid chromatography analysis of serum samples from HCC patients and controls indicated that the incidence of elevated ochratoxin A was highest in the HCC group, being 5-fold higher than in the control group.[50] These findings support a strong association between the presence of ochratoxin A and HCC. Ochratoxin A is a stable compound that is not destroyed by common food preparation procedures.

Available data on the presence of mycotoxins in grains and foods indicate that there may be a continuous low-level exposure to these toxic metabolites.[47] Foods mainly contributing to the intake of mycotoxins with diet are cereals, maize being the most risky commodity due to the potential co-occurrence of more than one mycotoxin. It has been postulated that individuals with increased maize-based products consumption such as celiac patients could be particularly at risk of mycotoxin exposure. However, studies have shown that the intake of mycotoxins in these potentially vulnerable populations is generally below the tolerable daily intake.[51,52]

Pyrrolizidine alkaloids

Pyrrolizidine alkaloids such as riddelliine, which is found in *Senecio riddellii* (Riddell groundsel) and *Senecio longilobus* (also known as woolly groundsel and thread-leaf groundsel),[37] can be found as a contaminant in foods such as meat, grains, seeds, milk, herbal tea and honey.[53] In hepatocytes, Cytochrome P450s convert dehydropyrrolizidine alkaloides to 6,7-dehydropyrrolizine esters, i.e. the toxic metabolites. Dehydroretronecine and dehydroheliotridine that are produced from the initial toxic metabolites via ROS react rapidly with the SH, OH, NH groups on nucleotides, as well as with proteins to form adducts, eventually leading to DNA damage and carcinogenesis.[54] There is a large body of evidence from studies in animals supporting the carcinogenicity of pyrrolizidine alkaloids.[37] Of note, there are published reports of primary liver tumors in natives of Central and South Africa associated with the consumption of traditional medicinal plants containing of pyrrolizidine alkaloids.[55-58] Honey and tea have been reported to be a significant source of pyrrolizidine alkaloids in Western countries.[59] Although health impairment due to chronic intake of pyrrolizidine alkaloids is improbable for adult consumers with average amounts of consumption of honey and tea,[60,61] longer-term regular consumption of products with containing high amounts of pyrrolizidine alkaloids could be associated with a risk of health impairment.

BENEFICIAL NATURAL PRODUCTS

Foods and beverages

Coffee

A protective effect of coffee against HCC was first suggested by Gallus *et al*.[62] in 2002. Since then, several other studies have confirmed this hypothesis. Meta-analyses of epidemiological studies found that an increased consumption of coffee may reduce the risk of liver cancer.[63-65] In a recent analysis of EPIC, a large epidemiological study designed to investigate the association between diet, lifestyle and environmental factors and the incidence of various types of cancer and other chronic diseases, coffee consumers in the highest compared to the lowest quintile had 72% lower risk of developing HCC.[66] Consistently, high levels of coffee consumption were associated with reduced risk of incident HCC and chronic liver disease mortality in a population-based prospective cohort study of more than 215,000 men and women from Hawaii and California.[67] Coffee has been shown to exert beneficial effects on body weight, development of diabetes, the prevention of hepatic fibrosis in NAFLD, and other chronic liver diseases, including chronic hepatitis C.[68] There are approximately 1,000 substances in coffee, including caffeine, diterphenoic alcohols and chlorogenic acid [(CGA), a polyphenol].[68] It is uncertain which are the exact substances and mechanisms responsible for the beneficial effects of coffee on the liver. Several substances as well as the method of preparation are thought to be of importance. As an example, filtered coffee may provide the most benefit due to a reduction in cafestol and kahweol, which can raise serum cholesterol, while maintaining CGA and caffeine content.

Fish

By virtue of its high content in omega-3 fatty acids, which may have anti-carcinogenic and anti-inflammatory effects,[69] fish might be protective against HCC. Evidence supporting a protective role of fish comes from the EPIC study. In EPIC, total fish intake was inversely associated with HCC risk (20% reduction in risk per 20 g/day of fish, after calibration).[70] Lean/white fish (cod, haddock, and plaice), fatty fish (salmon, tuna, trout, herring, kippers, and mackerel, and crustaceans and mollusks were independently associated with lower HCC risk, even after adjusting for HBV/HCV status and liver function biomarkers.[70]

Olive (Oleaeuropaea)

Epidemiological studies have shown that intake of virgin olive oil is associated with low incidences of several types of cancer,[71] likely due to its high content in phenolic antioxidants. These include hydroxytyrosol and oleuropein.[72] Hydroxytyrosol (HT) is a natural polyphenolic compound with significant antioxidant properties.[73] It has been recently demonstrated

that HT inhibited the proliferation and induced apoptosis in HCC *in vitro* and in a tumor model of HCC,[74] and exerted antiproliferative, antioxidant and anti-inflammatory effects on human hepatoma HepG2 and Hep3B cell lines.[75,76] Oleuropein, a major constituent of *O. europaea*, was shown to effectively inhibit cell viability and to induce apoptosis in HepG2 human hepatoma cells in a dose -dependent manner, through activation of the caspase pathway.[77]

Oleanolic acid (3β-hydroxyolean-12-en-28-oic acid) is a pentacyclic triterpenoid found in olive leaves. Antitumor effects of oleanolic acid have been investigated recently both *in vitro* and *in vivo*. It exhibited inhibitory effect on HCC through induction of apoptosis and cell cycle arrest both in transplanted tumors in mice and in HepG2 cells, indicating that oleanolic acid has significant antitumor activities on HCC both *in vitro* and *in vivo* models.[78] Olive fruit pulp is a rich source of antioxidants and possesses very good hepatoprotective activity against CCl_4-induced hepatic damage in mice.[79]

Other foods and beverages

Several other foods and beverages have been reported to have a protective role against HCC, including tea polyphenols (i.e. green and black tea),[80] tomatoes and tomato-based products[81] (a rich source of lycopene, an antioxidant carotenoid that has even been shown to prevent HCC metastases in animal studies[82]), dietary fiber,[18] green-yellow vegetables and fruit.[83]

Nutraceuticals and dietary supplements

A large proportion of HCC patients use dietary supplements.[3] However, only in few cases their use is supported by clinical evidence.

Branched chain amino acids

Branched chain amino acids (BCAA) may suppress hepatocarcinogenesis by several mechanisms, including improvement of immune function, reduction of oxidative stress and improvement of insulin resistance.[84] Supplementation of BCAA for 2 years in patients with cirrhosis (Child-Pugh class A) has been associates with increases albumin synthesis in a multicenter, randomized controlled trial.[85] However, another randomized controlled trial did not find an improvement in serum albumin levels with BCAA supplementation, possibly due to different patient characteristics (patients were Child-Pugh class B or C).[86] Clinical trials have reported that long-term oral supplementation with BCAAs is associated with decreased frequency of development of HCC in obese patients with cirrhosis and hepatitis C virus infection,[87] significant reduction in HCC incidence rate and improvement of event-free survival rate in patients with cirrhosis,[88] and reduced HCC recurrence after treatment with radiofrequency ablation in patients with cirrhosis.[84,89] Finally, BCAAs have been also shown to improve health-related quality of life[85,86] and sleep disturbances in patients with cirrhosis.[90]

Milk thistle (Silybum marianum)

Milk thistle is an herbal agent that has been used to treat liver diseases for centuries. Silymarin, the main active constituent of milk thistle, is a mixture of polyphenols, including flavonolignans and flavonoids. Despite a strong anticancer activity against human HCC cells are demonstrated *in vitro*,[91] clinical studies supporting the use of silymarin as a hepatoprotective agent have yielded conflicting results.

A Cochrane systematic review revealed that the evidence supporting a role of milk thistle for the treatment of patients with alcoholic and/or hepatitis B or C virus liver diseases is scanty, and that milk thistle *vs*. placebo or no intervention had no significant effect on mortality, complications of liver disease or liver histology.[92] Milk thistle was not associated with increased risk of adverse events.[92] Silymarin use in 1,049 patients with advanced fibrosis or cirrhosis unsuccessfully treated with peginterferon plus ribavirin has been associated with reduced progression from fibrosis to cirrhosis.[93] In a 24-week multicenter, double-blind, placebo-controlled trial that included 154 patients with chronic HCV infection and elevated serum alanine aminotransferase (ALT) unsuccessfully treated with interferon-based therapy, silymarin did not significantly reduce serum ALT levels.[94] Silymarin has also been used as an adjuvant therapy in conjunction with chemotherapy and other supplements (α-tocopheryl acetate and a product containing stem cell differentiation stage factors) in a case report of a patient with locally advanced HCC, with encouraging results.[95]

Omega-3 fatty acids

Preclinical data indicate that omega-3 polyunsaturated fatty acids (PUFAs) inhibit HCC cell growth and might therefore be useful for the chemoprevention and treatment of human HCC.[96] This hypothesis is supported by the results of a population-based prospective cohort study of 90,296 Japanese subjects, in which consumption of omega-3 PUFAs, particularly

eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, protected against the development of HCC, irrespective of HCV or HBV status.[97] The effect of treatment with high dose purified long chain omega-3 fatty acids on liver fat percentage and scores for liver fibrosis in patients with NAFLD is currently being investigated in a randomized double blind placebo controlled trial.[98]

Spirulina platensis

Spirulina is a blue-green alga (cyanobacterium) available as a dietary supplement. *In vitro* studies have demonstrated that spirulina may exert hepatoprotective effects.[99] In patients with chronic hepatitis C infection, viral load and ALT levels tended to improve after 6 months of treatment with spirulina in a small, active-controlled trial.[100] Another small, uncontrolled trial reported significant improvements in aspartate aminotransferase, alanin aminotransferase, gamma-glutamyltransferase, triglycerides, low-density lipoprotein-cholesterol, total cholesterol, and the ratio of total cholesterol to high-density lipoprotein cholesterol after 6 months of treatment in patients with NAFLD. According to the authors, spirulina supplementation resulted also in a significant reduction in weight and insulin resistance, and a significant improvement in health-related quality of life was observed. However, no changes in sonographic findings were observed.[101]

Antioxidants

Reduced glutathione (GSH) is a potent antioxidant naturally occurring in the body, and is available for parenteral administration. Very few studies have assessed the therapeutic role of GSH in liver diseases. In an Italian study that compared the effects of reduced GSH and vitamin K in patients with alcoholic liver disease, those treated with reduced GSH showed a greater improvement of hepatic function *vs*. patients treated with vitamin K.[102] A study published several years ago assessed the effect of GSH treatment on HCC in 8 patients with biopsy-proven HCC not amenable to surgery, but results were inconclusive.[103] Besides direct GSH supplementation, hepatic GSH deposits can be restored by administering compounds such as *S*-adenosyl-*L*-methionine and *N*-acetylcysteine. Both compounds are generally very well tolerated, although of limited clinical value in improving liver function in chronic liver diseases.[104-106]

Finally, it has been observed that patients with HCC have low levels of serum vitamin B[107] and vitamin D,[108] which suggests that these patients might benefit from supplementation with these vitamins.

Traditional Chinese medicines

It has been suggested that use of Chinese herbal medicines might result in the protection of liver function during chemotherapy.[109] The herbal formulation PHY906 consists of four commonly used herbs, i.e. Scutellaria baicalensis Georgi, Paeonia lactiflora Pall, Glycyrrhiza uralensis Fisch, and Ziziphus jujube Mill, at a ratio of 3:2:2:2. Studies have shown that PHY906 not only reduces gastrointestinal toxicity and enhances the antitumor efficacy of some anticancer drugs but also alleviates chemotherapy-induced side effects, such as diarrhea.[109] Preliminary clinical data indicate that PHY906 can serve as an adjuvant to chemotherapy in the treatment of advanced HCC.[110] Other traditional Chinese medicines that may have a role in the treatment of HCC are bufotoxin (toad skin secretion), astragalus and products containing ginseng (Panax ginseng), astragalus and mylabris (dried body of the Chinese blister beetle).[111]

CONCLUSION

Identifying modifiable risk factors such as diet is important to counteract HCC. Dietary patterns are complex to assess, and are entangled with other aspects of lifestyle. To date, conclusive evidence supporting a detrimental or beneficial role in the prevention of chronic liver diseases is available only for few products. Available information on coffee, fish and BCAAs supplementation is of acceptable quality and supports a beneficial role for these products in the prevention and management of HCC. On the other hand, the detrimental effects of alcohol and aflatoxins are widely recognized. Excessive sugar and calorie consumption should also be avoided.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;123:134-40.
2. Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis* 2001;21:17-26.
3. Sacco R, Sivozhelezov V, Pellegrini L, Giacomelli L, Longo V. Dietary supplementation in cancer patients: a personal view of current status and future perspectives. *Future Oncol* 2014;10:1523-5.

4. Turati F, Trichopoulos D, Polesel J, Bravi F, Rossi M, Talamini R, Franceschi S, Montella M, Trichopoulou A, La Vecchia C, Lagiou P. Mediterranean diet and hepatocellular carcinoma. *J Hepatol* 2014;60:606-11.
5. Cabre E, Gonzalez-Huix F, Abad-Lacruz A, Esteve M, Acero D, Fernandez-Banares F, Xiol X, Gassull MA. Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial. *Gastroenterology* 1990;98:715-20.
6. Ciuni R, Biondi A, Grosso G, Nunnari G, Panascia E, Randisi L, Volpes R, Arcadipane A, Basile F, Gridelli B, Gruttadauria S. Nutritional aspects in patient undergoing liver resection. *Updates Surg* 2011;63:249-52.
7. de Ledinghen V, Beau P, Mannant PR, Borderie C, Ripault MP, Silvain C, Beauchant M. Early feeding or enteral nutrition in patients with cirrhosis after bleeding from esophageal varices? A randomized controlled study. *Dig Dis Sci* 1997;42:536-41.
8. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992;102:200-5.
9. 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.
10. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;127:S35-50.
11. Balbo S, Meng L, Bliss RL, Jensen JA, Hatsukami DK, Hecht SS. Time course of DNA adduct formation in peripheral blood granulocytes and lymphocytes after drinking alcohol. *Mutagenesis* 2012;27:485-90.
12. Pascual M, Fernandez-Lizarbe S, Guerri C. Role of TLR4 in ethanol effects on innate and adaptive immune responses in peritoneal macrophages. *Immunol Cell Biol* 2011;89:716-27.
13. Miranda RC, Pietrzykowski AZ, Tang Y, Sathyan P, Mayfield D, Keshavarzian A, Sampson W, Hereld D. MicroRNAs: master regulators of ethanol abuse and toxicity? *Alcohol Clin Exp Res* 2010;34:575-87.
14. Freedman ND, Cross AJ, McGlynn KA, Abnet CC, Park Y, Hollenbeck AR, Schatzkin A, Everhart JE, Sinha R. Association of meat and fat intake with liver disease and hepatocellular carcinoma in the NIH-AARP cohort. *J Natl Cancer Inst* 2010;102:1354-65.
15. Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K, International Agency for Research on Cancer Monograph Working G. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* 2015;16:1599-600.
16. Lagiou P, Rossi M, Tzonou A, Georgila C, Trichopoulos D, La Vecchia C. Glycemic load in relation to hepatocellular carcinoma among patients with chronic hepatitis infection. *Ann Oncol* 2009;20:1741-5.
17. Rossi M, Lipworth L, Maso LD, Talamini R, Montella M, Polesel J, McLaughlin JK, Parpinel M, Franceschi S, Lagiou P, La Vecchia C. Dietary glycemic load and hepatocellular carcinoma with or without chronic hepatitis infection. *Ann Oncol* 2009;20:1736-40.
18. Fedirko V, Lukanova A, Bamia C, Trichopolou A, Trepo E, Nothlings U, Schlesinger S, Aleksandrova K, Boffetta P, Tjonneland A, Johnsen NF, Overvad K, Fagherazzi G, Racine A, Boutron-Ruault MC, Grote V, Kaaks R, Boeing H, Naska A, Adarakis G, Valanou E, Palli D, Sieri S, Tumino R, Vineis P, Panico S, Bueno-de-Mesquita HB, Siersema PD, Peeters PH, Weiderpass E, Skeie G, Engeset D, Quiros JR, Zamora-Ros R, Sanchez MJ, Amiano P, Huerta JM, Barricarte A, Johansen D, Lindkvist B, Sund M, Werner M, Crowe F, Khaw KT, Ferrari P, Romieu I, Chuang SC, Riboli E, Jenab M. Glycemic index, glycemic load, dietary carbohydrate, and dietary fiber intake and risk of liver and biliary tract cancers in Western Europeans. *Ann Oncol* 2013;24:543-53.
19. Cheng SJ, Sala M, Li MH, Courtois I, Chouroulinkov I. Promoting effect of Roussin's red identified in pickled vegetables from Linxian China. *Carcinogenesis* 1981;2:313-9.
20. Ren JS, Kamangar F, Forman D, Islami F. Pickled food and risk of gastric cancer-a systematic review and meta-analysis of English and Chinese literature. *Cancer Epidemiol Biomarkers Prev* 2012;21:905-15.
21. Zhao X, Cheng M, Zhang Q, Chen S, Tan J, Wang W, Luo X, Liu S, Lin S, Wang W, Li Z, Sun H, Ning J, Chen R. [A case-control study on the risk factors of hepatocellular carcinoma in Guizhou Province]. *Zhonghua Gan Zang Bing Za Zhi* 2014;22:33-7.
22. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ. Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest* 2005;115:1343-51.
23. Schwarz JM, Linfoot P, Dare D, Aghajanian K. Hepatic de novo lipogenesis in normoinsulinemic and hyperinsulinemic subjects consuming high-fat, low-carbohydrate and low-fat, high-carbohydrate isoenergetic diets. *Am J Clin Nutr* 2003;77:43-50.
24. Longato L. Non-alcoholic fatty liver disease (NAFLD): a tale of fat and sugar? *Fibrogenesis Tissue Repair* 2013;6:14.
25. Harrison SA, Torgerson S, Hayashi PH. The natural history of nonalcoholic fatty liver disease: a clinical histopathological study. *Am J Gastroenterol* 2003;98:2042-7.
26. Stål P. Liver fibrosis in non-alcoholic fatty liver disease - diagnostic challenge with prognostic significance. *World J Gastroenterol* 2015;21:11077-87.
27. Baffy G. Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease: Epidemiology, Pathogenesis, and Prevention. *J Clin Transl Hepatol* 2013;1:131-7.
28. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. *Hepatology* doi: 10.1002/hep.28431.
29. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* 2010;51:1820-32.
30. Fabbrini E, Conte C, Magkos F. Methods for assessing intrahepatic fat content and steatosis. *Curr Opin Clin Nutr Metab Care* 2009;12:474-81.
31. Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. *Gastroenterology* 2004;127:S97-103.
32. Lagiou P, Kuper H, Stuver SO, Tzonou A, Trichopoulos D, Adami HO. Role of diabetes mellitus in the etiology of hepatocellular carcinoma. *J Natl Cancer Inst* 2000;92:1096-9.
33. Nair S, Mason A, Eason J, Loss G, Perrillo RP. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology* 2002;36:150-5.
34. Kensler TW, Roebuck BD, Wogan GN, Groopman JD. Aflatoxin: a 50-year odyssey of mechanistic and translational toxicology. *Toxicol Sci* 2011;120 Suppl 1:S28-48.
35. Wild CP, Turner PC. The toxicology of aflatoxins as a basis for public health decisions. *Mutagenesis* 2002;17:471-81.
36. Bressac B, Kew M, Wands J, Ozturk M. Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa. *Nature* 1991;350:429-31.
37. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 82. Available from: http://monographs.iarc.fr/ENG/Monographs/vol82/index.php. 2002.
38. Liu Y, Wu F. Global burden of aflatoxin-induced hepatocellular carcinoma: a risk assessment. *Environ Health Perspect* 2010;118:818-24.
39. Gelderblom WC, Kriek NP, Marasas WF, Thiel PG. Toxicity and carcinogenicity of the Fusarium moniliforme metabolite, fumonisin B1, in rats. *Carcinogenesis* 1991;12:1247-51.
40. Hard GC, Howard PC, Kovatch RM, Bucci TJ. Rat kidney pathology induced by chronic exposure to fumonisin B1 includes rare variants of renal tubule tumor. *Toxicol Pathol* 2001;29:379-86.
41. Howard PC, Eppley RM, Stack ME, Warbritton A, Voss KA, Lorentzen RJ, Kovach RM, Bucci TJ. Fumonisin b1 carcinogenicity in a two-year feeding study using F344 rats and B6C3F1 mice. *Environ Health Perspect* 2001;109 Suppl 2:277-82.
42. De Ruyck K, De Boevre M, Huybrechts I, De Saeger S. Dietary mycotoxins, co-exposure, and carcinogenesis in humans: short review. *Mutat Res Rev Mutat Res* 2015;766:32-41.
43. Li FQ, Yoshizawa T, Kawamura O, Luo XY, Li YW. Aflatoxins and

fumonisins in corn from the high-incidence area for human hepatocellular carcinoma in Guangxi, China. *J Agric Food Chem* 2001;49:4122-6.
44. Sun G, Wang S, Hu X, Su J, Huang T, Yu J, Tang L, Gao W, Wang JS. Fumonisin B1 contamination of home-grown corn in high-risk areas for esophageal and liver cancer in China. *Food Addit Contam* 2007;24:181-5.
45. Ueno Y, Iijima K, Wang SD, Sugiura Y, Sekijima M, Tanaka T, Chen C, Yu SZ. Fumonisins as a possible contributory risk factor for primary liver cancer: a 3-year study of corn harvested in Haimen, China, by HPLC and ELISA. *Food Chem Toxicol* 1997;35:1143-50.
46. Felizardo RJ, Camara NO. Hepatocellular carcinoma and food contamination: aflatoxins and ochratoxin A as a great prompter. *World J Gastroenterol* 2013;19:3723-5.
47. Marin S, Ramos AJ, Cano-Sancho G, Sanchis V. Mycotoxins: occurrence, toxicology, and exposure assessment. *Food Chem Toxicol* 2013;60:218-37.
48. Pfohl-Leszkowicz A, Manderville RA. An update on direct genotoxicity as a molecular mechanism of ochratoxin a carcinogenicity. *Chem Res Toxicol* 2012;25:252-62.
49. Marin-Kuan M, Cavin C, Delatour T, Schilter B. Ochratoxin A carcinogenicity involves a complex network of epigenetic mechanisms. *Toxicon* 2008;52:195-202.
50. Ibrahim AS, Zaghloul H, Badria FA. Case report evidence of relationships between hepatocellular carcinoma and ochratoxicosis. *PLoS One* doi: 10.1371/journal.pone.0071423.
51. Brera C, Debegnach F, De Santis B, Di Ianni S, Gregori E, Neuhold S, Valitutti F. Exposure assessment to mycotoxins in gluten-free diet for celiac patients. *Food Chem Toxicol* 2014;69:13-7.
52. Cano-Sancho G, Ramos AJ, Marin S, Sanchis V. Occurrence of fumonisins in Catalonia (Spain) and an exposure assessment of specific population groups. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2012;29:799-808.
53. Edgar JA, Colegate SM, Boppre M, Molyneux RJ. Pyrrolizidine alkaloids in food: a spectrum of potential health consequences. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2011;28:308-24.
54. Neuman MG, Cohen L, Opris M, Nanau RM, Hyunjin J. Hepatotoxicity of Pyrrolizidine Alkaloids. *J Pharm Pharm Sci* 2015;18:825-43.
55. Pavlica D, Samuel I. Primary carcinoma of the liver in Ethiopia. A study of 38 cases proved at post-mortem examination. *Br J Cancer* 1970;24:22-9.
56. Schoental R. Toxicology and carcinogenic action of pyrrolizidine alkaloids. *Cancer Res* 1968;28:2237-46.
57. Schoental R, Coady A. The hepatotoxicity of some Ethiopian and East African plants, including some used in traditional medicines. *East Afr Med J* 1968;45:577-80.
58. Williams AO, Edington GM, Obakponovwe PC. Hepatocellular carcinoma in infancy and childhood in Ibadan, Western Nigeria. *Br J Cancer* 1967;21:474-82.
59. Bodi D, Ronczka S, Gottschalk C, Behr N, Skibba A, Wagner M, Lahrssen-Wiederholt M, Preiss-Weigert A, These A. Determination of pyrrolizidine alkaloids in tea, herbal drugs and honey. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 2014;31:1886-95.
60. Bundesinstitut für Risikobewertung. Scientific opinion [Internet]. [cited 2015 Nov 06]. Available from: http://www.bfr.bund.de/cm/349/chemical-analysis-and-toxicity-of-pyrrolizidine-alkaloids-and-assessment-of-the-health-risks-posed-by-their-occurence-in-honey.pdf.
61. Risikobewertung Bf. Scientific opinion [Internet]. [cited 2015 Nov 06]. Available from: http://www.bfr.bund.de/cm/349/pyrrolizidine-alkaloids-in-herbal-teas-and-teas.pdf.
62. Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, Lagiou P, Trichopoulos D. Does coffee protect against hepatocellular carcinoma? *Br J Cancer* 2002;87:956-9.
63. Bravi F, Bosetti C, Tavani A, Gallus S, La Vecchia C. Coffee reduces risk for hepatocellular carcinoma: an updated meta-analysis. *Clin Gastroenterol Hepatol* doi: 10.1016/j.cgh.2013.04.039
64. Larsson SC, Wolk A. Coffee consumption and risk of liver cancer: a meta-analysis. *Gastroenterology* 2007;132:1740-5.
65. Sang LX, Chang B, Li XH, Jiang M. Consumption of coffee associated with reduced risk of liver cancer: a meta-analysis. *BMC Gastroenterol* 2013;13:34.
66. Bamia C, Lagiou P, Jenab M, Trichopoulou A, Fedirko V, Aleksandrova K, Pischon T, Overvad K, Olsen A, Tjonneland A, Boutron-Ruault MC, Fagherazzi G, Racine A, Kuhn T, Boeing H, Floegel A, Benetou V, Palli D, Grioni S, Panico S, Tumino R, Vineis P, Bueno-de-Mesquita HB, Dik VK, Bhoo-Pathy N, Uiterwaal CS, Weiderpass E, Lund E, Quiros JR, Zamora-Ros R, Molina-Montes E, Chirlaque MD, Ardanaz E, Dorronsoro M, Lindkvist B, Wallstrom P, Nilsson LM, Sund M, Khaw KT, Wareham N, Bradbury KE, Travis RC, Ferrari P, Duarte-Salles T, Stepien M, Gunter M, Murphy N, Riboli E, Trichopoulos D. Coffee, tea and decaffeinated coffee in relation to hepatocellular carcinoma in a European population: multicentre, prospective cohort study. *Int J Cancer* 2015;136:1899-908.
67. Setiawan VW, Wilkens LR, Lu SC, Hernandez BY, Le Marchand L, Henderson BE. Association of coffee intake with reduced incidence of liver cancer and death from chronic liver disease in the US multiethnic cohort. *Gastroenterology* doi: 10.1053/j.gastro.2014.10.005
68. Torres DM, Harrison SA. Is it time to write a prescription for coffee? Coffee and liver disease. *Gastroenterology* 2013;144:670-2.
69. Larsson SC, Kumlin M, Ingelman-Sundberg M, Wolk A. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. *Am J Clin Nutr* 2004;79:935-45.
70. Fedirko V, Trichopolou A, Bamia C, Duarte-Salles T, Trepo E, Aleksandrova K, Nothlings U, Lukanova A, Lagiou P, Boffetta P, Trichopoulos D, Katzke VA, Overvad K, Tjonneland A, Hansen L, Boutron-Ruault MC, Fagherazzi G, Bastide N, Panico S, Grioni S, Vineis P, Palli D, Tumino R, Bueno-de-Mesquita HB, Peeters PH, Skeie G, Engeset D, Parr CL, Jakszyn P, Sanchez MJ, Barricarte A, Amiano P, Chirlaque M, Quiros JR, Sund M, Werner M, Sonestedt E, Ericson U, Key TJ, Khaw KT, Ferrari P, Romieu I, Riboli E, Jenab M. Consumption of fish and meats and risk of hepatocellular carcinoma: the European Prospective Investigation into Cancer and Nutrition (EPIC). *Ann Oncol* 2013;24:2166-73.
71. Perez-Lopez FR, Chedraui P, Haya J, Cuadros JL. Effects of the Mediterranean diet on longevity and age-related morbid conditions. *Maturitas* 2009;64:67-79.
72. Waterman E, Lockwood B. Active components and clinical applications of olive oil. *Altern Med Rev* 2007;12:331-42.
73. Visioli F, Poli A, Gall C. Antioxidant and other biological activities of phenols from olives and olive oil. *Med Res Rev* 2002;22:65-75.
74. Zhao B, Ma Y, Xu Z, Wang J, Wang F, Wang D, Pan S, Wu Y, Pan H, Xu D, Liu L, Jiang H. Hydroxytyrosol, a natural molecule from olive oil, suppresses the growth of human hepatocellular carcinoma cells via inactivating AKT and nuclear factor-kappa B pathways. *Cancer Lett* 2014;347:79-87.
75. Goya L, Mateos R, Bravo L. Effect of the olive oil phenol hydroxytyrosol on human hepatoma HepG2 cells. Protection against oxidative stress induced by tert-butylhydroperoxide. *Eur J Nutr* 2007;46:70-8.
76. Tutino V, Caruso MG, Messa C, Perri E, Notarnicola M. Antiproliferative, antioxidant and anti-inflammatory effects of hydroxytyrosol on human hepatoma HepG2 and Hep3B cell lines. *Anticancer Res* 2012;32:5371-7.
77. Yan CM, Chai EQ, Cai HY, Miao GY, Ma W. Oleuropein induces apoptosis via activation of caspases and suppression of phosphatidylinositol 3-kinase/protein kinase B pathway in HepG2 human hepatoma cell line. *Mol Med Rep* 2015;11:4617-24.
78. Wang X, Bai H, Zhang X, Liu J, Cao P, Liao N, Zhang W, Wang Z, Hai C. Inhibitory effect of oleanolic acid on hepatocellular carcinoma via ERK-p53-mediated cell cycle arrest and mitochondrial-dependent apoptosis. *Carcinogenesis* 2013;34:1323-30.
79. Kang H, Koppula S. Olea europaea Linn. Fruit pulp extract protects against carbon tetrachloride-induced hepatic damage in mice. *Indian J Pharm Sci* 2014;76:274-80.
80. Darvesh AS, Bishayee A. Chemopreventive and therapeutic potential of tea polyphenols in hepatocellular cancer. *Nutr Cancer* 2013;65:329-44.
81. Mandair DS, Rossi RE, Pericleous M, Whyand T, Caplin M. The impact of diet and nutrition in the prevention and progression of hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2014;8:369-82.

82. Huang CS, Liao JW, Hu ML. Lycopene inhibits experimental metastasis of human hepatoma SK-Hep-1 cells in athymic nude mice. *J Nutr* 2008;138:538-43.
83. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer* 2003;88:689-94.
84. Kawaguchi T, Izumi N, Charlton MR, Sata M. Branched-chain amino acids as pharmacological nutrients in chronic liver disease. *Hepatology* 2011;54:1063-70.
85. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H, Long-Term Survival Study G. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. *Clin Gastroenterol Hepatol* 2005;3:705-13.
86. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F, Abbiati R, Italian BSG. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology* 2003;124:1792-801.
87. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, Kato M, Nakamura T, Higuchi K, Nishiguchi S, Kumada H, Ohashi Y, Long-Term Survival Study G. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. *Hepatol Res* 2006;35:204-14.
88. Hayaishi S, Chung H, Kudo M, Ishikawa E, Takita M, Ueda T, Kitai S, Inoue T, Yada N, Hagiwara S, Minami Y, Ueshima K. Oral branched-chain amino acid granules reduce the incidence of hepatocellular carcinoma and improve event-free survival in patients with liver cirrhosis. *Dig Dis* 2011;29:326-32.
89. Tsuchiya K, Asahina Y, Izumi N. Long time oral supplementation with branched-chain amino acids improves survival and decreases recurrences in patients with hepatocellular carcinoma. *Nihon Shokakibyo Gakkai Zasshi* 2008;105:808-16. (in Japanese)
90. Ichikawa T, Naota T, Miyaaki H, Miuma S, Isomoto H, Takeshima F, Nakao K. Effect of an oral branched chain amino acid-enriched snack in cirrhotic patients with sleep disturbance. *Hepatol Res* 2010;40:971-8.
91. Varghese L, Agarwal C, Tyagi A, Singh RP, Agarwal R. Silibinin efficacy against human hepatocellular carcinoma. *Clin Cancer Res* 2005;11:8441-8.
92. Rambaldi A, Jacobs BP, Gluud C. Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. *Cochrane Database Syst Rev* 2007;(4):CD003620.
93. Freedman ND, Curto TM, Morishima C, Seeff LB, Goodman ZD, Wright EC, Sinha R, Everhart JE; HALT-C Trial Group. Silymarin use and liver disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. *Aliment Pharmacol Ther* 2011;33:127-37.
94. Fried MW, Navarro VJ, Afdhal N, Belle SH, Wahed AS, Hawke RL, Doo E, Meyers CM, Reddy KR, Silymarin in N, Group CHS. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: a randomized controlled trial. *JAMA* 2012;308:274-82.
95. Moroni M, Zanlorenzi L. Complete regression following sorafenib in unresectable, locally advanced hepatocellular carcinoma. *Future Oncol* 2013;9:1231-7.
96. Lim K, Han C, Dai Y, Shen M, Wu T. Omega-3 polyunsaturated fatty acids inhibit hepatocellular carcinoma cell growth through blocking beta-catenin and cyclooxygenase-2. *Mol Cancer Ther* 2009;8:3046-55.
97. Sawada N, Inoue M, Iwasaki M, Sasazuki S, Shimazu T, Yamaji T, Takachi R, Tanaka Y, Mizokami M, Tsugane S; Japan Public Health Center-Based Prospective Study Group. Consumption of n-3 fatty acids and fish reduces risk of hepatocellular carcinoma. *Gastroenterology* 2012;142:1468-75.
98. Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Calder PC, Byrne CD, Investigators WT. Design and rationale of the WELCOME trial: a randomised, placebo controlled study to test the efficacy of purified long chainomega-3 fatty acid treatment in non-alcoholic fatty liver disease [corrected]. *Contemp Clin Trials* 2014;37:301-11.
99. Kepekci RA, Polat S, Celik A, Bayat N, Saygideger SD. Protective effect of Spirulina platensis enriched in phenolic compounds against hepatotoxicity induced by CCl4. *Food Chem* 2013;141:1972-9.
100. Yakoot M, Salem A. Spirulina platensis versus silymarin in the treatment of chronic hepatitis C virus infection. A pilot randomized, comparative clinical trial. *BMC Gastroenterol* 2012;12:32.
101. Mazokopakis EE, Papadomanolaki MG, Fousteris AA, Kotsiris DA, Lampadakis IM, Ganotakis ES. The hepatoprotective and hypolipidemic effects of Spirulina (Arthrospira platensis) supplementation in a Cretan population with non-alcoholic fatty liver disease: a prospective pilot study. *Ann Gastroenterol* 2014;27:387-94.
102. Bresci G, Piccinocchi M, Banti S. The use of reduced glutathione in alcoholic hepatopathy. *Minerva Med* 1991;82:753-5. (in Italian)
103. Dalhoff K, Ranek L, Mantoni M, Poulsen HE. Glutathione treatment of hepatocellular carcinoma. *Liver* 1992;12:341-3.
104. Chayanupatkul M, Liangpunsakul S. Alcoholic hepatitis: a comprehensive review of pathogenesis and treatment. *World J Gastroenterol* 2014;20:6279-86.
105. de Oliveira CP, Stefano JT, de Siqueira ER, Silva LS, de Campos Mazo DF, Lima VM, Furuya CK, Mello ES, Souza FG, Rabello F, Santos TE, Nogueira MA, Caldwell SH, Alves VA, Carrilho FJ. Combination of N-acetylcysteine and metformin improves histological steatosis and fibrosis in patients with non-alcoholic steatohepatitis. *Hepatol Res* 2008;38:159-65.
106. Guo T, Chang L, Xiao Y, Liu Q. S-adenosyl-L-methionine for the treatment of chronic liver disease: a systematic review and meta-analysis. *PLoS One* 2015;10:e0122124.
107. Lin CC, Yin MC. B vitamins deficiency and decreased anti-oxidative state in patients with liver cancer. *Eur J Nutr* 2007;46:293-9.
108. Chiang KC, Yeh CN, Chen MF, Chen TC. Hepatocellular carcinoma and vitamin D: a review. *J Gastroenterol Hepatol* 2011;26:1597-603.
109. Qi F, Li A, Inagaki Y, Gao J, Li J, Kokudo N, Li XK, Tang W. Chinese herbal medicines as adjuvant treatment during chemo- or radio-therapy for cancer. *Biosci Trends* 2010;4:297-307.
110. Yen Y, So S, Rose M, Saif MW, Chu E, Liu SH, Foo A, Jiang Z, Su T, Cheng YC. Phase I/II study of PHY906/capecitabine in advanced hepatocellular carcinoma. *Anticancer Res* 2009;29:4083-92.
111. Wu P, Dugoua JJ, Eyawo O, Mills EJ. Traditional Chinese Medicines in the treatment of hepatocellular cancers: a systematic review and meta-analysis. *J Exp Clin Cancer Res* 2009;28:112.