REVIEW

Dietary Agents and Phytochemicals in the Prevention and Treatment of Hepatocellular Carcinoma: Review Article

Ahmad Mohammad*[1], Mishra Anuradha[1], Usmani Afreen[1], Ahmad Md. Parwez[2]

[1] Department of Pharmacology, Faculty of Pharmacy, Integral University, Lucknow, India
[2] Department of Pharmacology, National Medical College, Birgunj, Nepal

ABSTRACT

Amongst all types of primary liver cancers, hepatocellular carcinoma (HCC) is the commonest form of liver cancer in the world. Cancer chemoprevention using dietary supplements and phytochemicals has attracted increasing attention in recent years. Numerous study reports suggest the role of phytochemicals and dietary compounds in the prevention and treatment of liver cancer. Certain dietary agents and related phytochemicals present in grapes, pomegranate, vegetables, beans, turmeric, soy, rice bran, and fish oils are reported to have chemopreventive potentials against hepatocellular carcinoma. Phytochemicals such as Carotenoids, Epigallocatechin gallate (EGCG), Curcumin, Resveratrol, Rutoside, Quercetin, Chrysin and Silibinin have possible therapeutic importance in tumor suppression during the initial phases of carcinogenesis. Many phytochemicals which are still under investigation lack the scientific data in support of anticancer properties of these compounds rather than anti-oxidant mechanism. So, emphasis should be given on the investigation of plausible molecular mechanism behind anticancer activity. This review summarizes the use of these dietary agents and phytochemicals in the treatment and prevention of HCC and also highlights the mechanisms responsible for their effects.

Keywords: Chemoprevention, Dietary supplements, Hepatocellular Carcinoma, Phytochemicals

***Corresponding Author:** Mohammad Ahmad, Department of Pharmacology, Faculty of Pharmacy, Integral University, Lucknow, India. Email: mahmadd@iul.ac.in

INTRODUCTION

Liver Cancer

Cancer is the major public health related problem and a leading cause of deaths worldwide.[1] Mostly caused by environmental factors including lifestyle practices and specific occupations, no age group is immune to this disease.[2] Environmental pollutants including certain chemicals, industrial effluents, therapeutic drugs, mutagenic agents and ionizing radiation may increase the incidence of cancer.[3] Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to the conversion of normal cells to fully malignant tumor cells.[4] Moreover the cancer of liver is a critical health risk related with high mortality, accounting for more than 600,000 deaths each year.[5] Liver cancer, also known as hepatic cancer, develops in the liver. There are many types of liver cancer depending upon the type of cells that are affected and becomes cancerous.

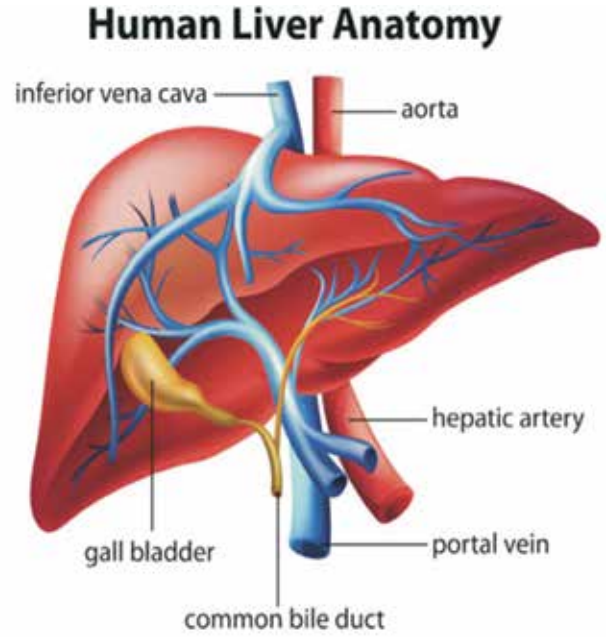

Figure 1 : Human Liver Anatomy

Liver Cancer Risk Factors

Chronic infection with Hepatitis B virus or Hepatitis C virus is the common risk factor for liver cancer. Hepatitis B and C viruses can spread from one person to another person through sharing of contaminated needles and through blood transfusion.[6,7] These infections can lead to cirrhosis of the liver. This risk can be minimized by blood testing for these viruses prior to blood transfusion. On the other hand alcohol abuse is a common cause of cirrhosis of the liver leading to cancer of liver.[8] Use of tobacco, smoking and obesity can also increase the chances of developing liver cancer.[9] Chronic exposure to heavy metal through drinking water increases the risk of developing some forms of liver cancer.[10] Long-term exposure to Aflatoxins is risk to liver cancer, especially in people with viral hepatitis infections.[11] Exposure to certain chemicals such as vinyl chloride and X-ray testing chemical thorium dioxide can increase the risk of developing liver cancer.[12] Other factor like metabolic diseases such as obesity and diabetes can cause cirrhosis and increase the chances of developing liver cancer.

Staging of Liver Cancer and Prognosis

TNM system of staging liver cancer by the American Joint Committee on Cancer (AJCC) is highly used method.[13] TNM system is based on the three criteria on the evaluation. In this system T stands for Tumor describes the number and size of the original tumor. N stands for Lymph Node indicates whether the lymph nodes are involved are not and M refers to Metastasis describing whether cancer has spread to distant parts of the body.[14] Score number (0-4) or letter is assigned to each criterion. A higher number score indicates increasing severity. T1 score indicates a smaller tumor than a T2 score but the letter X means the information cannot be assessed. Finally the T, N, and M scores are assigned for overall liver cancer staging.[15]

Different Stages of Liver Cancer

Liver Cancer (Stage I)

In stage one liver cancer, the single primary tumor has not grown into any blood vessels. The cancer has not spread to nearby lymph nodes or distant sites referred as T1, N0, and M0.[16]

Liver Cancer (Stage II)

In stage II, a single primary tumor of any size has grown into the blood vessels, but there are many small tumors, all less than 2 inches (5 cm) in diameter. The cancer has not spread to other nearby lymph nodes or distant sites referred as T2, N0, M0.[17]

Liver Cancer (Stage III)

There are three sub classes of stage III liver cancer described as follows: Stage IIIA: There are many tumors but at least one is larger than 2 inches (5 cm). This cancer has not spread to nearby lymph nodes or distant sites staged as: T3A, N0, M0. Stage IIIB: This has many tumors but at least, one tumor is rising into a branch of the portal vein or the hepatic vein. In this stage liver cancer has not spread to nearby lymph nodes or distant sites are referred as: T3B, N0, M0. While in Stage IIIC, the tumor has grown into a nearby organ (other than the gallbladder) or the tumor has grown into the outer surface of the liver. But the cancer has not spread to nearby lymph nodes or distant sites are referred as: T4, N0 and M0.[18]

Liver Cancer (Stage IV)

This Stage of the liver cancer is the highly developed form and the cancer has spread to the nearby lymph nodes and may have grown into nearby blood vessels or organs. Mostly advanced

form of liver cancer does not often metastasize to distant organs but it may spread to the lungs and bones. Stage IV liver cancer may be any T, N1 and M0, denoting that there may be any number or size of tumors in the liver. It has spread to nearby lymph nodes, but there is no evidence the cancer has spread to distant organs or tissue. Any T, any N and M1, meaning there may be any number or size of tumors in the liver, the cancer may or may not have grown into the lymph nodes, and it has spread to another part of the body.[19]

DIAGNOSIS AND TREATMENT OPTIONS

Liver cancer diagnostics options are advanced imaging and laboratory tests that takes about three to five days. Diagonostic tests includes alpha fetoprotein level and Carcino-embryonic antigen (CEA) level but complete blood count, hematocrit, platelet count, liver function tests and liver biopsy are also useful in patients with liver cancer.[20, 21, 22] Abdominal ultrasound and CT scan and MRI helps the doctor to identify the tumor, their size and location in the liver.[23, 24] Common treatments for stage IV liver cancer are chemotherapy, may be a recommended. Targeted therapy and systemic therapy using many chemotherapeutic agents such as sorafenib may be helpful to slow the growth of tumor.[25, 26, 27] Surgery to remove the tumor(s) by minimally-invasive laparoscopic surgeries and combined radiotherapy is advocated.[28] Other approaches for the treatment of liver cancer are liver transplantation, local ablative therapy and transarterial chemoembolisation.[29]

Hepatocelular Carcinoma

The most common type of the liver cancer is hepatocellular carcinoma (HCC). HCC starts in the main type of liver cells, called hepatocellular cells.[30] Hepatocellular carcinoma (HCC) is a major public health problem in both developed and underdeveloped countries.[31] The estimated worldwide number of new cases of liver cancer in 2012 is 782,000, of which more than 80% are from developing countries.1 Most cases of HCC are the result of infection with hepatitis B or C, or cirrhosis of the liver caused by alcoholism. HCC mainly occurs in liver cirrhosis patient and also in the patient with chronic liver diseases. Amongst all types of primary liver cancers, HCC is the most common and it is considered to be the 5th commonest cancer on the globe.[32] HCC represents 75–90% of primary liver cancer cases with a very high mortality.[33] Carcinogenesis of liver is a multi-step process that starts from preneoplastic lesions to malignant neoplasms associated with several genetic and epigenetic changes.[34,35] Hepatocellular carcinoma patients have many symptoms including abdominal pain or tenderness, especially in the upper-right part, enlarged abdomen, unexplained weight loss, loss of appetite and feelings of fullness blood in the stool, yellow skin or eyes, nausea and vomiting, fatigue, fluid in abdomen and worsening liver enzymes in a patient. Sometimes acute abdominal catastrophe from rupture of HCC with intra-abdominal bleeding.[36] Additionally signs of cirrhosis such as jaundice, palmar erythema, gynecomastia and portal hypertension may leads to to ascites, varices. The major risk factors for hepatocellular carcinoma are chronic viral (hepatits B and hepatitis C), toxins such as alcohol or aflatoxins, cirrhosis of the liver, metabolic disorders such as obesity, diabetes and non-alcoholic fatty liver disease.[37] Whereas the primary risk factor for hepatocellular carcinoma is cirrhosis of the liver and chronic liver disease. These risk factors vary widely from country to another but in many countries where hepatitis B is predominant cause of hepatocellular carcinoma. The risk of hepatocellular carcinoma in type 2 diabetics is greater than the non diabetic people.[38] Though the hepatocellular carcinoma most commonly affects adults, children with liver disorders and other cirrhotic diseases of the liver are prone to develop hepatocellular carcinoma. Neoplastic transformation is relatively a lengthy process giving ample opportunity to intervene in the pathogenesis of HCC in the early stages.[39] Therapeutic intervention at the early stage is significantly important for the prevention and treatment of cancer. Recent years a lot of focus is given on chemoprevention using dietary agents and the role of these dietary compounds in well documented.

Dietary Agents for Prevention of HCC

Due to the high amount of polyphenols presence in many fruits, a significant antioxidant activity may be useful to solve the risk of cancer.[40]

Major bioactive constituents present in fruits demonstrate anticancer potential animal models. Grape derived products are well known for their dietary components. Stilbenes, anthocyanins, and procyanidins, which are abundant in grape are reported to have antioxidant and anti-inflammatory properties.[41] Black currant (Ribes nigrum L.) fruits are known to possess strong antioxidant and anti-inflammatory activities due to high content of anthocyanins.[42] Many other fruits such as Pomegranate is potent antioxidant because of polyphenol contents. Pomegranate bioactive constituents were capable of suppressing hepatocarcinogenesis in rats.[43] On the other hands many vegetables and spices from the Cruciferae family are widely consumed to lower the risk of cancers. These include broccoli, cauliflower, sprouts having high contents of glucosinolates and isothiocyanates.[44] Garlic contains organo-sulphur compounds such as alliin, allicin, diallyl disulfide, diallyl sulfide, allyl mercaptan, and S-allylcysteine. These are reported to have anti-tumor properties. Allicin induces apoptotic and cell death through overproduction of ROS in human HCC cell line.[45] Turmeric (Curcuma longa L.) extracts delayed pathogenesis and may be a good candidate against HBV–related liver cancer. The yellow pigment curcumin found in Curcuma longa are reported to have antioxidant, anti-inflammatory and anticancer activities.[46] Vitamin E intake has also been shown to decrease the risk of HCC. Vitamin E has a potent anti-oxidant effect, and prevents DNA damage, also promotes inactivation of carcinogens.[47]

Figure 2 : Fruits and vegetables with numerous health claims

Table: 1 Lists of dietary factors in the prevention of HCC.[48-88]

Dietary factors	Types of study
Fish or n-3 polyunsaturated fatty acids (n-3 PUFA)	Case control study
White meat	Cohort study, case control study
Eggs	Population based case-control
Milk	Case control study
Yogurt	Population based case-control
Cereals	Case control study
Green tea	2-amino-6- methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) induced rat hepatocarcinogenesis
Vegetables and fruits	Case control study, cohort study
Apple	In-vitro
Pomegranate	In vivo
Mango	In vivo
Citrus fruit	In vivo
Grapes	In vitro, in vivo
Black currant	In vivo
Radish	In vitro
French bean	In vitro
Broccoli	In vitro
Tomato	In vivo
Bitter guard	In vitro and in vivo
Garlic	In vitro and in vivo
Turmeric	In vitro and in vivo
Ginger	In vitro and in vivo
Saffron	In vitro and in vivo
Cinnamon	In vitro
Star anise	In vivo
Basil	In vitro and in vivo
Rosemary	In vitro

Role of Phytochemicals in the Prevention of HCC

Evidence indicates that many polyphenols found in plants may delay the process of carcinogenesis.[89] Resveratrol is naturally occurring in a number of plants, including strawberries and grapes.[90] Resveratrol exhibited a potent chemopreventive effect in respect to hepatocarcinogenesis.[91] Resveratrol also have anticancer properties, including antioxidant and anti-inflammatory properties.[92] Quercetin which belongs to the chemical class of flavonoid, is abundantly found in citrus fruits and vegetables.[93] Quercetin is an anti-cancer compound which is also demonstrated a wide array of biological effects.[94] It is considered to be beneficial to health, including antioxidative, free radical scavenging and antiviral activities.[95] Rutoside (rutin) also belongs to the chemical class of flavonoid found in many plants the buckwheat plant Fagopyrum esculentum Moench.[96] Other rich dietary sources of rutin include black tea and apple peels.[97] Rutoside may have anticarcinogenic activity along with antioxidant, anti-inflammatory, antithrombotic activities.[98] Epigallocatechin-3-gallate (EGCG) a key active catechin in green tea

has cancer inhibitory activity against HCC both in vitro and in vivo studies.[99] EGCG effectively inhibited experimental liver carcinogenesis and slow down the development and progression of HCC.[100] The polyphenolic compound curcumin demonstrated similar profile to Epigallocatechin-3-gallate.[101] Various other studies also suggest chemopreventive potentials of phytochemicals compounds in hepatocellular carcinoma. Furthermore the supplementation with dietary phytochemicals may have potential therapeutic benefits in human subjects of liver HCC.

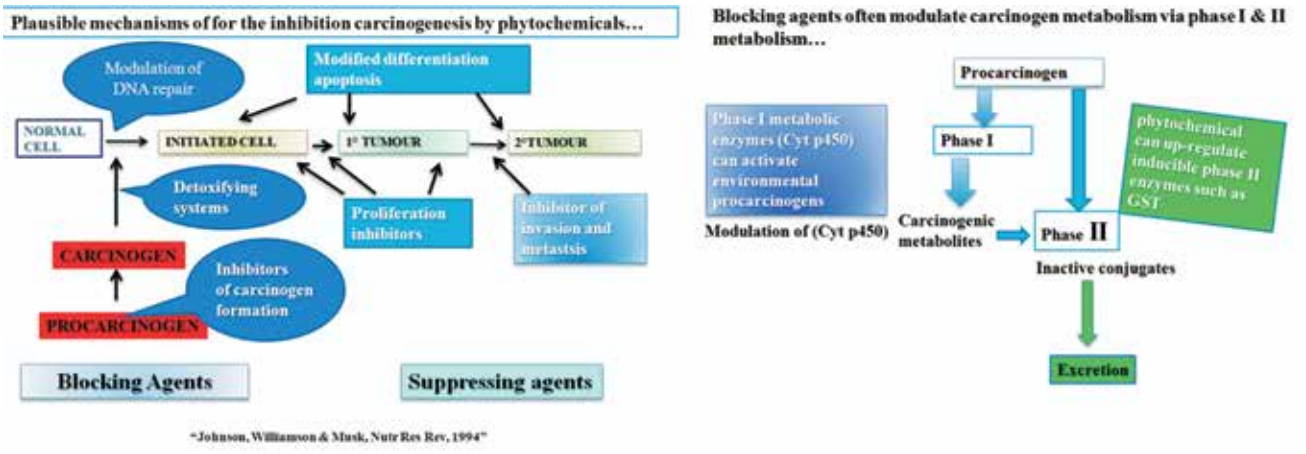

Figure 3 : Plausible mechanisms for inhibition of carcinogenesis by Phytochemicals.[102]

Table: 2 Lists of Phytochemicals in the Prevention of HCC.[103-109]

S. No.	Active compounds	Mechanism
1	Curcumin	-↓ DEN induced hepatocarcinogenesis -↑ apoptosis in Huh7 cells -↑ apoptosis and autophagy in HepG2 cells
2	Berberine	↓ DEN + Phenobarbital induced hepatocyte proliferation
3	Saikosaponin-D	↓DEN induced hepatocarcinogenesis
4	Tea polyphenols and tea pigments	↓ DEN induced hepatocarcinogenesis
5	Penta acetyl geniposide	↓ Aflatoxin B1 induced hepatocarcinogenesis
6	Ursolic acid	↓ DEN induced hepatocarcinogenesis
7	Astragalosides, astragalus polysaccharide and salvianolic acids	↓ DEN induced hepatocarcinogenesis
8	Gomisin A	↓ 3'-methyl-4-dimethylaminobenzene induced hepatocarcinogenesis
9	Salvia miltiorrhiza	↓ HepG2 cell proliferation
10	β-Elemene	↓H22 tumor growth
11	Raddeanin A	↓ H22 tumor growth
12	Ardipusilloside-I	↓ SMMC-7721 tumor growth
13	Gypenoside	↑apoptosis in Hep3B and HA22T cells
14	Icariin	↑ apoptosis in SMMC-7721 cells
15	Icaritin	↑ apoptosis in HepG2 cells
16	Scutellarin	↓ proliferation, ↑ apoptosis in HepG2 cells
17	Sarasapogenin	↓ proliferation, ↑ apoptosis, arrest cell cycle at G2/M Phase in HepG2 cells
18	Resveratrol-4-o-D-(2'-galloyl)-glucopranoside	↓ proliferation, ↑ apoptosis in SMMC-7221 cells
19	Quercetin	↓ proliferation, ↑ apoptosis in HA22T/VGH cells
20	Allicin	↓ proliferation, ↑ autophagy in HepG2 cells
21	Kaempferol	↓ proliferation, ↑ autophagy, arrest cell cycleat G2/Mphase in SK-Hep-1 cells
22	Arecolin	↑ anoikins in HA22T/VGH cells
23	Epicatechin gallate and epigallocatechin gallate	↑ intracellular DOX accumulation and ↑ DOX indced cekk killing against BEL-7404
24	Hesperidine	↓ acetaldehyde induced cell invasion in HepG2 cells
25	Resveratrol	↓ proliferation, ↑ apoptosis in Hepa 1-6 cells, -↓ proliferation, ↑ apoptosis and autophagy, arrest cell cycle at S phase in HuH7 cells, -↑ invasion in HCC cells

Future Prospects

Due to the rising incidence and mortality rates associated with hepatocellular carcinoma (HCC), efforts should be made to investigate the chemopreventive potentials of dietary phytochemicals against HCC. Although, the utilization of dietary chemopreventive agents in hepatocellular carcinoma is mainly based on their potential antioxidant and anti-inflammatory activities. Therefore, the scientific evidence in the support of anticancer properties of many bioactives compounds other than anti-oxidant mechanism is highly desired. Emphasis should also be given on the investigation of plausible molecular mechanism behind anticancer activity.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer. GLOBOCAN 2012 v1. 0, 2013.
2. Parsa N. Environmental factors inducing human cancers. Iranian J Publ Health. 2012; 41(11):1-9
3. Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Nat Cancer Inst. 1981; 66 (6):1192-308.
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144 (5): 646-74.
5. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65: 87-108.
6. Tsukuma H, Hiyama T, Tanaka S. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med. 1993; 328(25):1797–1801.
7. Nalpas B, Martin S, Fontaine H. Impact of medical recommendations on alcohol consumption in HCV positive patients. J Hepatol. 2001; 35(2):312-3.
8. Guptan RC, Thakur V, Sarin SK, Banerjee K, Khandekar P. Frequency and clinical profile of precore and surface hepatitis B mutants in Asian–Indian patients with chronic liver disease. Am J Gastroenterol. 1996; 91(7):1312-7.
9. Marrero JA, Fontana RJ, Fu S, Conjeevaram HS, Su GL, Lok A.S. Alcohol, tobacco and obesity are synergistic risk factors for hepatocellular carcinoma. J Hepatol. 2005; 42:218–24.
10. Hong YS, Song KH, Chung JY. Health effects of chronic arsenic exposure. J Prev Med Pub Health. 2014; 47(5):245-52.
11. Barrett JR. Liver cancer and aflatoxin: New information from the Kenyan outbreak. Environmental health perspectives. 2005;113(12):A837.
12. Hardell L, Ohlson CG, Fredrikson M. Occupational exposure to polyvinyl chloride as a risk factor for testicular cancer evaluated in a case-control study. Cancer. 1997; 73(6):828-30.
13. Pons F, Varela M, Llovet JM. Staging systems in hepatocellular carcinoma. Hpb. 2005; 7(1):35-41.
14. Sobin LH, Gospodarowicz MK, Wittekind Ch. Eds. TNM Classification of Malignant Tumors, 7th ed. Wiley-Blackwell, Oxford 2009; 978-1-4443-3241-4.
15. Levy I, Sherman M. Staging of hepatocellular carcinoma: assessment of the CLIP, Okuda, and Child-Pugh staging systems in a cohort of 257 patients in Toronto. Gut. 2002; 50(6):881-5.
16. Katyal S, Oliver III JH, Peterson MS, Ferris JV, Carr BS, Baron RL. Extrahepatic metastases of hepatocellular carcinoma 1. Radiology. 2000; 216(3):698-703.
17. Vauthey JN, Lauwers GY, Esnaola NF, et. al. Cleary KR. Simplified staging for hepatocellular carcinoma. J Clin Oncol. 2002; 20(6):1527-36.
18. Poon RT, Fan ST. Evaluation of the new AJCC/UICC staging system for hepatocellular carcinoma after hepatic resection in Chinese patients. Surg Onco Clin NA. 2003; 12(1):35-50.
19. Chambers AF, Groom AC, MacDonald IC. Metastasis: dissemination and growth of cancer cells in metastatic sites. Nat Rev Can. 2002; 2(8):563-72.

20. Hansen HJ, Snyder JJ, Miller E, et al. Carcinoembryonic antigen (CEA) assay: A laboratory adjunct in the diagnosis and management of cancer. Human Pathol. 1974; 5(2):139-47.
21. Soresi M, Magliarisi C, Campagna P, et al. Usefulness of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma. Anticancer research. 2002; 23(2C):1747-53.
22. Farinati F, Marino D, De Giorgio et al. Diagnostic and prognostic role of α-fetoprotein in hepatocellular carcinoma: both or neither?. AM J Gastroenterol. 2006; 101(3):524-32.
23. Calvet X, Bruix J, Gines P, et al. Rodés J. Prognostic factors of hepatocellular carcinoma in the west: a multivariate analysis in 206 patients. Hepatology. 1990; 12(4):753-60.
24. Foroutani A, Garland AM, Berber E, et al. Laparoscopic ultrasound vs triphasic computed tomography for detecting liver tumors. Arch Surg. 2000; 135(8):933-8.
25. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nature reviews Drug discovery. 2006; 5(10):835-44.
26. Gish RG, Baron A. Hepatocellular carcinoma (HCC): current and evolving therapies. IDrugs. 2008; 11(3):198-203.
27. Kudo M. Treatment of advanced hepatocellular carcinoma with emphasis on hepatic arterial infusion chemotherapy and molecular targeted therapy. Liver Cancer. 2012; 1(2):62-70.
28. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. Worlds Surg. 1991; 15(2):270-85.
29. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53(3):1020-22.
30. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. Hepatology. 2008; 48:S20-37.
31. Yang JD, Roberts LR. Hepatocellular carcinoma: a global view. Nat Rev Gastro Hep. 2010; 7(8):448-58.
32. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA: a cancer journal for clinicians. 2005; 55(2):74-108.
33. El-Serag, H B, Rudolph K L. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastro. 2007; 2557-76.
34. Wang GG, Allis CD, Chi P. Chromatin remodeling and cancer, part I: covalent histone modifications. Trends Mol Med. 2007; 13:363–72.
35. Liu M, Jiang L, Guan XY. The genetic and epigenetic alterations in human hepatocellular carcinoma: a recent update. Protein & Cell. 2014; 5(9):673-91.
36. Yang T, Zhang J, Lu JH, Yang GS, Wu MC, Yu WF. Risk factors influencing postoperative outcomes of major hepatic resection of hepatocellular carcinoma for patients with underlying liver diseases. World J Sug. 2011; 35(9):2073.
37. Caldwell S, Park SH. The epidemiology of hepatocellular cancer: from the perspectives of public health problem to tumor biology. J Gastroent. 2009; 44: 96-101.
38. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology. 2002; 36(5):1206-13.
39. Sakamoto M, Hirohashi S, Shimosato Y. Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Path.1991; 22(2):172-8.
40. Brat P, George S, Bellamy A, et al. Daily polyphenol intake in France from fruit and vegetables. J Nutr. 2006; 136(9):2368-73.
41. Leifert WR, Abeywardena MY. Grape seed and red wine polyphenol extracts inhibit cellular cholesterol uptake, cell proliferation, and 5-lipoxygenase activity. Nutr Res. 2008; 28(12):842-50.
42. Kapasakalidis PG, Rastall RA, Gordon MH. Extraction of polyphenols from processed black currant (Ribes nigrum L.) residues. J Agric Food chem. 2006; 54(11):4016-21.

43. Bhandari PR. Pomegranate (Punica granatum L). Ancient seeds for modern cure? Review of potential therapeutic applications. Int J Nutr Pharmacol Neurol Dis. 2012; 2(3):171.
44. Cartea ME, Velasco P. Glucosinolates in Brassica foods: bioavailability in food and significance for human health. Phytochem Rev. 2008; 7(2):213-29.
45. Santhosha SG, Jamuna P, Prabhavathi SN. Bioactive components of garlic and their physiological role in health maintenance: A review. Food Bioscience. 2013; 3:59-74.
46. Basnet P, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. Molecules. 2011; 16(6):4567-98.
47. Ha HL, Shin HJ, Feitelson MA, Yu DY. Oxidative stress and antioxidants in hepatic pathogenesis. World J Gastroenterol. 2010 Dec 28; 16(48):6035-43.
48. Fedirko V, Trichopolou A, Bamia C, et al. 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
49. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med.1989; 320: 265-71.
50. Freedman ND, Cross AJ, McGlynn KA, et al. 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.
51. Talamini R, Polesel J, Montella M, et al. Food groups and risk of hepatocellular carcinoma: A multicenter case-control study in Ital. Int J Cancer. 2006; 119: 2916-21.
52. Kurozawa Y, Ogimoto I, Shibata A, et al. Dietary habits and risk of death due to hepatocellular carcinoma in a large scale cohort study in Japan. Univariate analysis of JACC study data. Kurume Med J. 2004; 51: 141-9.
53. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Franceschi S. Risk factors for hepatocellular carcinoma in northern Italy. Int J Cancer. 1988; 42: 872-6.
54. Hirose M, Hasegawa R, Kimura J, et al. Inhibitory effects of 1-Ohexyl- 2,3,5-trimethylhydroquinone (HTHQ), green tea catechins and other antioxidants on 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1)-induced rat hepatocarcinogenesis and dose dependent inhibition by HTHQ of lesion induction by Glu-P-1 or 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx). Carcinogenesis. 1995; 16:3049-55.
55. Zhang W, Xiang YB, Li HL, et al. Vegetable-based dietary pattern and liver cancer risk: results from the Shanghai women's and men's health studies. Cancer Sci. 2013; 104: 1353-61.
56. Kurahashi N, Inoue M, Iwasaki M, Tanaka Y, Mizokami M, Tsugane S. Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: a prospective cohort study in Japan. Br J Cancer. 2009; 100: 181-4.
57. 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.
58. Sudan S, Rupasinghe HP. Flavonoid-enriched apple fraction AF4 induces cell cycle arrest, DNA topoisomerase II inhibition, and apoptosis in human liver cancer HepG2 cells. Nutr Cancer. 2014, 66, 1237-46.
59. Bishayee A, Thoppil RJ, Darvesh AS, Ohanyan V, Meszaros JG, Bhatia D. Pomegranate phytoconstituents blunt the inflammatory cascade in a chemically induced rodent model of hepatocellular carcinogenesis. J Nutr Biochem. 2013; 24:178–87.
60. Bishayee A, Bhatia D, Thoppil RJ, Darvesh AS, Nevo E, Lansky EP. Pomegranate mediated chemoprevention of experimental hepatocarcinogenesis involves Nrf2-regulated antioxidant mechanisms. Carcinogenesis. 2011; 32: 888-96.

61. Prasad S, Kalra N, Shukla Y. Hepatoprotective effects of lupeol and mango pulp extract of carcinogen induced alteration in Swiss albino mice. Mol Nutr F Res. 2007; 51:352-9.
62. Hara A Sakata K, Yamada Y, et al. Suppression of mutation by dietary exposure of auraptene, a citrus antioxidant, in N,N-diethylnitrosamine-induced hepatocellular carcinomas in rats. Oncol Rep. 2005; 14:345–51.
63. Jo JY, de Mejia EG, Lila MA. Cytotoxicity of bioactive polymeric fractions from grape cell culture on human hepatocellular carcinoma, murine leukemia and non-cancerous PK15 kidney cells. Food Chem Toxicol. 2006; 44:1758–67.
64. Feng LL, Liu BX, Zhong JY, Sun LB, Yu HS. Effect of grape procyanidins on tumor angiogenesis in liver cancer xenograft models. Asian Pac J Cancer Prev. 2014;15:737-41.
65. Zhang CZ, Fang EF, Zhang HT, Liu LL, Yun JP. Momordica charantia lectin exhibits antitumor activity towards hepatocellular carcinoma. Investig New Drugs. 2015;33:1-11.
66. Thoppil RJ, Bhatia D, Barnes KF, et al. Black currant anthocyanins abrogate oxidative stress through Nrf2-mediated antioxidant mechanisms in a rat model of hepatocellular carcinoma. Curr Cancer D Tar. 2012; 12:1244–57.
67. Abdull RA, De Nicola GR, Pagnotta E, Iori R, Ioannides C. 4-Methylsulfanyl-3-butenyl isothiocyanate derived from glucoraphasatin is a potent inducer of rat hepatic phase II enzymes and a potential chemopreventive agent. Arch Toxicol. 2012; 86:183-94.
68. Dong M, He X, Liu RH. Phytochemicals of black bean seed coats: Isolation, structure elucidation, and their antiproliferative and antioxidative activities. J Agric Food Chem. 2007; 55:6044-51.
69. Mohamed AA, El-Kadi AO. Sulforaphane induces CYP1A1 mRNA, protein, and catalytic activity levels via an AhR-dependent pathway in murine hepatoma Hepa 1c1c7 and human HepG2 cells. Cancer Lett. 2009; 275:93-101.
70. Hwang ES, Jeffery EH. Induction of quinone reductase by sulforaphane and sulforaphane N-acetylcysteine conjugate in murine hepatoma cells. J Med Food. 2005; 8:198-203.
71. Gupta P, Bansal MP, Koul A. Evaluating the effect of lycopene from Lycopersicum esculentum on apoptosis during NDEA induced hepatocarcinogenesis. Biochem Biophys Res Commun. 2013; 434: 479-85.
72. Friedman M, Levin CE, Lee SU, et al. Tomatine-containing green tomato extracts inhibit growth of human breast, colon, liver, and stomach cancer cells. J Agric Food Chem. 2009; 57:5727-33.
73. Fang EF, Zhang CZ. Wong JH, et al. The MAP30 protein from bitter gourd (Momordica charantia) seeds promotes apoptosis in liver cancer cells in vitro and in vivo. Cancer Lett. 2012; 324: 66-74.
74. Belloir C, Singh V, Daurat C, Siess MH, Le Bon AM. Protective effects of garlic sulfur compounds against DNA damage induced by direct- and indirect-acting genotoxic agents in HepG2 cells. Food Chem Toxicol. 2006; 44:827-34.
75. De Martino A, Filomeni G, Aquilano K, Ciriolo MR, Rotilio G. Effects of water garlic extracts on cell cycle and viability of HepG2 hepatoma cells. J Nutr Biochem. 2006; 17:742-74.
76. Ishikawa H, Saeki T, Otani T, et al. Aged garlic extract prevents a decline of NK cell number and activity in patients with advanced cancer. J Nutr. 2006; 136:816S-20S.
77. Sreepriya M, Bali G. Chemopreventive effects of embelin and curcumin against N-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats. Fitoterapia. 2005; 76:549–55.
78. Kim J, Ha HL, Moon HB, et al. Chemopreventive effect of Curcuma longa Linn on liver pathology in HBx transgenic mice. Integr Cancer Ther. 2011; 10:168-77.
79. Habib SH, Makpol S, Abdul HN, Das S, Ngah WZ, Yusof YA. Ginger extract (Zingiber officinale) has anti-cancer and anti-inflammatory effects on ethionine-induced hepatoma rats. Clinics. 2008; 63:807-13.

80. Weng CJ, Wu CF, Huang HW, Ho CT, Yen GC. Anti-invasion effects of 6-shogaol and 6-gingerol, two active components in ginger, on human hepatocarcinoma cells. Mol Nut Food Res. 2010; 54:1618-27.
81. Afshari TJ, Brook A, Mousavi SH. Study of cytotoxic and apoptogenic properties of saffron extract in human cancer cell lines. Food Chem Toxicol. 2008; 46:3443-7.
82. Amin A, Hamza AA, Bajbouj K, Ashraf SS, Daoud S. Saffron: A potential candidate for a novel anticancer drug against hepatocellular carcinoma. Hepatology 2011; 54:857-67.
83. Chen CY, Yiin SJ, Hsu JL, Wang WC, Lin SC, Chern CL. Isoobtusilactone A sensitizes human hepatoma HepG2 cells to TRAIL-induced apoptosis via ROS and CHOP-mediated up-regulation of DR5. J Agric Food Chem. 2012; 60:3533-9.
84. Chen CY, Liu TZ, Chen CH, et al. Isoobtusilactone A-induced apoptosis in human hepatoma HepG2 cells is mediated via increased NADPH oxidase-derived reactive oxygen species (ROS) production and the mitochondria-associated apoptotic mechanisms. Food Chem Toxicol. 2007; 45:1268-76.
85. Yadav AS, Bhatnagar D. Chemo-preventive effect of Star anise in N-nitrosodiethylamine initiated and phenobarbital promoted hepato-carcinogenesis. Chem Biol Interact. 2007; 169: 207-14.
86. Jeurissen SM Pun, A, Delatour T, Rietjens IM, Basil extract inhibits the sulfotransferase mediated formation of DNA adducts of the procarcinogen 1'-hydroxyestragole by rat and human liver S9 homogenates and in HepG2 human hepatoma cells. Food Chem Toxicol. 2008; 46:2296-2302.
87. Costa S, Utan A, Speroni E, et al. Carnosic acid from extracts: A potential chemoprotective agent against aflatoxin B1. An in vitro study. J Appl Toxicol. 2007; 27:152–9.
88. Lee KW, Lee HJ, Lee CY. Vitamins, phytochemicals, diets and their implementation in cancer chemoprevention. Crit Rev Food Sci Nutr. 2004; 44(6):437-52.
89. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009; 2(5):270-8.
90. Chang YH, Jiang M, Liu KG, Li XQ. Curcumin inhibited hypoxia induced epithelial-mesenchymal transition in hepatic carcinoma cell line HepG2 in vitro. Chin J Integr Tradit. West Med. 2013; 33:1102-6.
91. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997; 275(5297):218-20.
92. Lakhanpal P, Rai DK. Quercetin: a versatile flavonoid. Internet Journal of Medical Update. 2007; 2(2):22-37.
93. Murakami A, Ashida H, Terao J. Multitargeted cancer prevention by quercetin. Cancer letters. 2008; 269(2):315-25.
94. Formica JV, Regelson W. Review of the biology of quercetin and related bioflavonoids. Food Chem Toxicol. 1995; 33(12):1061-80.
95. Bowen IH, Cubbin IJ. Fagopyrum esculentum Moench.(Buckwheat): In vitro culture and the production of rutin. Medicinal and Aromatic Plants . 1993:202-17.
96. Golding JB, McGlasson WB, Wyllie SG, Leach DN. Fate of apple peel phenolics during cool storage. J Agric Food Chem. 2001; 49(5):2283-9.
97. Dar MA, Tabassum N. Rutin-potent natural thrombolytic agent. Int Current Pharm J. 2012; 1(12):431-5.
98. Darvesh AS, Bishayee A. Chemopreventive and therapeutic potential of tea polyphenols in hepatocellular cancer. Nutr Cancer. 2013; 65(3):329-44.
99. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol. 2011; 82(12):1807-21.
100. Bertl E, Becker H, Eicher T, et al. Inhibition of endothelial cell functions by novel potential cancer chemopreventive agents. Biochem Biophys Res Commun. 2004; 325(1):287-95.
101. Johnson IT, Williamson G, Musk SR. Anticarcinogenic factors in plant foods: a new class of nutrients. Nutr Res Rev. 1994; 7(01):175-204.

102. Chuang SE, Kuo ML, Hsu CH, et al. Curcumin-containing diet inhibits diethylnitrosamine-induced murine hepatocarcinogenesis. Carcinogenesis. 2000; 21(2):331-5.
103. Wang WZ, Li L, Liu MY, et al. Curcumin induces FasL-related apoptosis through p38 activation in human hepatocellular carcinoma Huh7 cells. Life sciences. 2013; 92(6):352-8.
104. Qian H, Yang Y, Wang X. Curcumin enhanced adriamycin-induced human liver-derived Hepatoma G2 cell death through activation of mitochondria-mediated apoptosis and autophagy. Eur J Pharm Sci. 2011; 43(3):125-31.
105. Chang YH, Jiang M, Liu KG, Li XQ. Curcumin inhibited hypoxia induced epithelial-mesenchymal transition in hepatic carcinoma cell line HepG2 in vitro. Chin J Integr Tradit West Med. 2013; 33:1102-06.
106. Zhao X, Zhang JJ, Wang X, et al. Effect of berberine on hepatocyte proliferation, inducible nitric oxide synthase expression, cytochrome P450 2E1 and 1A2 activities in diethylnitrosamine and phenobarbital-treated rats. Biomed Pharmacother. 2008; 62:567-72.
107. Lu XL, He SX, Ren MD, et al. Chemopreventive effect of saikosaponin-d on diethylinitrosamine - induced hepatocarcinogenesis: Involvement of CCAAT/enhancer binding protein and cyclooxygenase - 2. Mol Med Rep. 2012; 5:637-44.
108. Jia X, Han C, Chen J. Studies on the inhibitory effects of tea polyphenols and tea pigments on liver precancerous lesion in rats. J Hyg Res. 2001; 30:168-9.
109. Lin YL, Hsu JD, Chou FP, et al. Suppressive effect of penta-acetyl geniposide on the development of -glutamyl transpeptidase foci-induced by aflatoxin B1 in rats. Chem Biol Interact. 2000; 128:115-26.