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. Mostly caused by environmental factors including lifestyle practices and specific occupations, no age group is immune to this disease. Environmental pollutants including certain chemicals, industrial effluents, therapeutic drugs, mutagenic agents and ionizing radiation may increase the incidence of cancer. 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. Moreover the cancer of liver is a critical health risk related with high mortality, accounting for more than 600,000 deaths each year. 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.
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. 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. Use of tobacco, smoking and obesity can also increase the chances of developing liver cancer. Chronic exposure to heavy metal through drinking water increases the risk of developing some forms of liver cancer. Long-term exposure to Aflatoxins is risk to liver cancer, especially in people with viral hepatitis infections. Exposure to certain chemicals such as vinyl chloride and X-ray testing chemical thorium dioxide can increase the risk of developing liver cancer. 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. 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. 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.

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.

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.

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 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.

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. Diagnostic 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

**Hepatocellular 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.26 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. Black currant (Ribes nigrum L.) fruits are known to possess strong antioxidant and anti-inflammatory activities due to high content of anthocyanins. Many other fruits such as Pomegranate is potent antioxidant because of polyphenol contents. Pomegranate bioactive constituents were capable of suppressing hepatocarcinogenesis in rats. 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. 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. 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. Vitamin E intake has also been shown to decrease the risk of HCC. Vitamin E has a potent antioxidant effect, and prevents DNA damage, also promotes inactivation of carcinogens.

Table: 1 Lists of dietary factors in the prevention of HCC

<table>
<thead>
<tr>
<th>Dietary factors</th>
<th>Types of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish or n-3 polyunsaturated fatty acids (n-3 PUFA)</td>
<td>Case control study</td>
</tr>
<tr>
<td>White meat</td>
<td>Cohort study, case control study</td>
</tr>
<tr>
<td>Eggs</td>
<td>Population based case-control</td>
</tr>
<tr>
<td>Milk</td>
<td>Case control study</td>
</tr>
<tr>
<td>Yogurt</td>
<td>Population based case-control</td>
</tr>
<tr>
<td>Cereals</td>
<td>Case control study</td>
</tr>
<tr>
<td>Green tea</td>
<td>4-amino-6-methylidipyrido[1,2-a:3,2′-d]imidazole (Glu-P-1) induced rat hepatocarcinogenesis</td>
</tr>
<tr>
<td>Vegetables and fruits</td>
<td>Case control study, cohort study</td>
</tr>
<tr>
<td>Apple</td>
<td>In-vitro</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>In vivo</td>
</tr>
<tr>
<td>Mango</td>
<td>In vivo</td>
</tr>
<tr>
<td>Citrus fruit</td>
<td>In vivo</td>
</tr>
<tr>
<td>Grapes</td>
<td>In vitro, in vivo</td>
</tr>
<tr>
<td>Black currant</td>
<td>In vivo</td>
</tr>
<tr>
<td>Radish</td>
<td>In vitro</td>
</tr>
<tr>
<td>French bean</td>
<td>In vitro</td>
</tr>
<tr>
<td>Broccoli</td>
<td>In vitro</td>
</tr>
<tr>
<td>Tomato</td>
<td>In vivo</td>
</tr>
<tr>
<td>Bitter guard</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Garlic</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Turmeric</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Ginger</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Saffron</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>In vitro</td>
</tr>
<tr>
<td>Star anise</td>
<td>In vivo</td>
</tr>
<tr>
<td>Basil</td>
<td>In vitro and in vivo</td>
</tr>
<tr>
<td>Rosemary</td>
<td>In vitro</td>
</tr>
</tbody>
</table>

Figure 2 : Fruits and vegetables with numerous health claims

Role of Phytochemicals in the Prevention of HCC

Evidence indicates that many polyphenols found in plants may delay the process of carcinogenesis. Resveratrol is naturally occurring in a number of plants, including strawberries and grapes. Resveratrol exhibited a potent chemopreventive effect in respect to hepatocarcinogenesis. Resveratrol also have anticancer properties, including antioxidant and anti-inflammatory properties. Quercetin which belongs to the chemical class of flavonoid, is abundantly found in citrus fruits and vegetables. Quercetin is an anti-cancer compound which is also demonstrated a wide array of biological effects. It is considered to be beneficial to health, including antioxidative, free radical scavenging and antiviral activities. Rutoside (rutin) also belongs to the chemical class of flavonoid found in many plants the buckwheat plant Fagopyrum esculentum Moench. Other rich dietary sources of rutin include black tea and apple peels. Rutoside may have anticarcinogenic activity along with antioxidant, anti-inflammatory, antithrombotic activities. Epigallocatechin-3-gallate (EGCG) a key active catechin in green tea...
has cancer inhibitory activity against HCC both in vitro and in vivo studies.\textsuperscript{99} EGCG effectively inhibited experimental liver carcinogenesis and slow down the development and progression of HCC.\textsuperscript{100} The polyphenolic compound curcumin demonstrated similar profile to Epigallocatechin-3-gallate.\textsuperscript{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.\textsuperscript{102}

Table: 2 Lists of Phytochemicals in the Prevention of HCC.\textsuperscript{103-109}

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

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


