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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

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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

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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

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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.