Herbal and Hepatocellular Cancer

Subjects: Gastroenterology & Hepatology

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Cirrhosis is the most important risk factor for the development of Hepatocellular cancer (HCC). Thus, it is estimated that one out of three patients with cirrhosis will suffer from HCC during their lifetime. Although chronic viral hepatitis, chronic alcohol intake and metabolic-associated fatty liver disease (MAFLD) are responsible for most cases of cirrhosis, any other cause of cirrhosis (such as herbal causes) might result in hepatocellular carcinoma.

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1. Introduction

Hepatocellular cancer (HCC) is the sixth most frequently diagnosed cancer and the third cause of cancer-related death worldwide, according to the recent registries. In 2020, approximately 724,800 new cases of HCC were diagnosed, with a total of 664,000 deaths in 185 countries from all over the world [1]. Therefore, HCC represents a sizeable contributor to the global cancer-related burden [2]. The incidence of HCC increases substantially in advanced aging population, with a peak in seventh decade of life, except for Chinese and black African patients, whose mean ages at diagnosis are considerably low [3][4]. Regarding the sex preponderance, there is a ratio of around 2.5:1 (male:female) [1]. Only 10% of HCCs occur in patients without any known etiology of liver disease, whilst approximately 90% are associated mainly with chronic viral hepatitis, alcohol abuse, aflatoxin exposure and metabolic-associated fatty liver disease (MAFLD) [5]. Nowadays, hepatitis B (HBV) infection has become the main cause of HCC, accounting for roughly 54% of cases globally. Nevertheless, the incidence and prevalence of MAFLD-related HCC are expected to rise dramatically due the growing obesity pandemic [5][6]. The estimated annual incidence of HCC among patients with non-alcoholic-steatohepatitis-related cirrhosis is 0.5–2.6%. Thus, MAFLD may soon become the foremost global cause of HCC [6].

Cirrhosis is the most important risk factor for the development of HCC [7]. Thus, it is estimated that one out of three patients with cirrhosis will suffer from HCC during their lifetime [7]. Although chronic viral hepatitis, chronic alcohol intake and MAFLD are responsible for most cases of cirrhosis, any other cause of cirrhosis (e.g., drugs or herbal causes) might result in hepatocellular carcinoma [4]. It is well-known that chronic liver damage caused by conventional drugs can lead to severe liver fibrosis and even liver cirrhosis. Once this state has been reached, it is not unlikely to develop into HCC due to the patient's natural history of cirrhosis [8]. However, neither in the case of conventional medications nor the illicit use of recreational drug or herbs is there robust evidence regarding their associations with the risk of HCC.

Illicit drug and tobacco use, together with alcohol intake, are major contributors to the universal morbidity rate worldwide [9]. Despite the well-known risks of systemic diseases (such as malignancies, lung and cardiovascular disorders, etc.), tobacco consumption remains a serious public health concern [10]. According to World Health Organization (WHO), cigarette smoking kills more of the European population than any other preventable cause [10]. Likewise, substance use disorders, along with mental illnesses, are the first cause of the health burden in young people, accounting for nearly 20% of all disability-adjusted life years. Furthermore, illicit substance consumption carries the risk of significant physical and social disturbances, such as traffic accidents, violent behaviors, and increased suicide rates, among others [11][12]. Thus, among injection drug addicts, the proportion of chronic hepatitis cases is not negligible, causing an important burden of liver cirrhosis and, consequently, of virus-related hepatocellular carcinoma [13].

On the other hand, in modern society, physical appearance is increasingly acquiring an overestimated value, favoring the popularity of illegal and illicit substances used to strengthen and enlarge the muscles for aesthetic purposes [14]. Anabolic androgenic steroids (AAS), nowadays, have very limited medical indications [15]. However, AAS are typically used by 20–40-year-old people, predominantly males, who illicitly consume these drugs for recreational purposes in the context of gym practice or weight training [16][17].

2. Herbal and HCC

2.1. Khat and HCC

Khat (*Catha edulis*) is a plant with psychoactive effects similar to those of amphetamine. Indeed, it is popularly known as the “natural amphetamine”. Specifically, this herb is one of the most widely consumed herbs in the whole world, with users usually chewing its leaves [18]. The mean age of khat users is approximately the second decade of life, with a significant predominance of the male gender [19]. Khat is a legal and socially accepted substance used recreationally in East African and Middle Eastern countries (mainly Somalia, Ethiopia and Yemen) [19]. It is estimated that it has a daily consumption by more than 20 million people [20]. However, Khat is considered a drug of abuse by the WHO, and its sale is forbidden in almost all Western countries, including the United States of America (USA) and European Union [19].

Khat is a well-established hepatotoxic agent, with case reports and case series implicating the herb in acute and chronic liver injury, and it is defined as category B in terms of its hepatotoxicity potential in LiverTox (this xenobiotic has been reported and is known or highly likely to cause idiosyncratic liver damage, with 12–50 previously published cases) [21][22]. Although it is not clear whether this toxic potential is due to its constituents or a direct effect of the pesticides/preservatives used for cultivating and transporting the herb [23]. The mechanism of khat-related liver injury remains to be elucidated. Animal model studies have shown that khat can cause acute hepatitis, and that chronic active hepatitis and fibrotic liver disease are linked to long-term khat exposure in rats [24]. On the other hand, vasoconstriction due to cathinone, one of its components, has been suggested as a plausible mechanism of the liver injury [25]. It is worth mentioning that, in humans, the pattern of liver damage associated with khat typically has autoimmune features, with frequent autoantibody presentation and, histologically, chronic

hepatitis and fibrosis [26][27][28][29][30]. Indeed, a cross-sectional study carried out in Ethiopia—one of the countries with the highest prevalence of khat intake—showed, interestingly, an eye-catching ratio of cirrhosis of apparently unexplained causes (55%). The authors noted that the widespread consumption of khat in this area, together with histological features of toxic injury in the liver biopsy performed among a subgroup of patients without an established etiology, suggest a probable causal association [31]. Similar data have been published in other regions with a high prevalence of khat use, such as Somaliland [32]. Nonetheless, a careful review of all the published reports on khat-induced liver injury does not provide sufficient evidence to link khat consumption with the development of HCC [21][23][26][27][28][29][31][32][33][34][35][36].

2.2. Kava and HCC

Kava (or kava-kava) is a herb extracted from the roots of the plant named *Piper methysticum.* Kava has been taken as a recreational beverage in Oceania for centuries, and more recently, it has been used in its concentrated form or as an infusion to alleviate anxiety disorders [37][38].

The hepatotoxicity of kava has been recognized in recent decades, with an important fraction of sever and fatal cases, and it is thus included in category A (highest hepatotoxic potential) in LiverTox (the xenobiotic is well-known, with more than 50 cases published in the literature) [39][40]. Several experimental studies on in vivo mouse models have shown the liver oncogenic potential of kava. In 2011, Behl et al. found an increase in the incidence of hepatoblastoma (dose-dependent) in male mice and an increment in hepatocellular carcinoma and adenoma detection (non-dose-related) in female mice. Moreover, non-neoplastic lesions (such as hepatocellular hypertrophy) were detected in the livers of mice, and such findings were confirmed in an independent study, which also identified a considerable rise in the rates of liver cancer and non-malignant liver lesions in mice of both sexes after kava exposure [41][42]. In contrast, in humans, there is no convincing published evidence linking kava intake to HCC thus far [39][43][44][45][46][47][48][49][50][51][52][53][54]. This apparent discrepancy could be related to the low quality of the design of these studies (observational, lacking long-term follow-up) that precluded the drawing of firm conclusions.

2.3. Other Herbs and HCC

Other herbs have been associated with chronic liver damage, even causing liver fibrosis and cirrhosis. In a recent review of the published case reports on herbal-induced liver injury in Latin America, a case of chronic hepatitis with a cholestatic and granulomatous pattern and cirrhotic processing due to *Centella asiatica* was identified [55][56]. *Centella asiatica* (or *Gotu kola*) is a traditional Chinese plant frequently used in Southeast Asia that occasionally is taken to facilitate weight loss, among other applications [57]. In the same systematic review, another case of herb-induced hepatotoxicity with a chronic course due to *Crotalaria juncea* was also included [55]. This herb is traditionally used as household remedy for several medical conditions, and it is known to cause sinusoidal obstruction syndrome [58]. *Crotalaria juncea* contains pyrrolizidine alkaloids among its components [55], which have been clearly related to veno-occlusive disease and, hence, to cirrhosis [55][59]. Nevertheless, there is no published evidence to associate these herbs with the risk of HCC.

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