

Coffee, Traditional Chinese Medicine and cannabinoids as potential tools for prevention and treatment of hepatocellular carcinoma

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ABSTRACT

In the last decade, the incidence of hepatocellular carcinoma (HCC) is growing in both Europe and United States. Conventional therapies such as liver resection, transplantation, ablation, chemoembolization and sorafenib are not enough to avoid a significant mortality. Many studies suggested the positive effect of caffeine for prevention of HCC. Nevertheless, the amount of therapeutic caffeine and the high-dose safety are unknown. Many authors proposed Traditional Chinese Medicine as preventive and/or curative approach. Although it reveals limits such as the uncertain safety profile and the lack of evidence about a unique product, it shows interesting results in terms of survival and quality of life if given in combination with standard loco-regional therapy. Among the future promises, cannabinoids show interesting background mechanisms of blocking cell proliferation and neoangiogenesis. It is conceivable that in the next years, some natural products may have a role in improving the standards of care of HCC.

Key words: Hepatocellular carcinoma; caffeine; Traditional Chinese Medicine; cannabinoids

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INTRODUCTION

Liver neoplasm represents the sixth most common cancer and the third cause of cancer-related mortality worldwide.^[1] Hepatocellular carcinoma (HCC) is the main liver cancer,

accounting for more than 90% of cases of liver tumors. In the last decades, the HCC incidence and HCC-related mortality are increasing in both United States and Northern Europe.^[2] Cirrhosis due to chronic hepatitis B and C, is the major risk factor for the HCC development. However, also other

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potentially risky conditions such as alcohol intake, tobacco habit, overweight, diabetes, aflatoxin consumption and oral contraceptives use, should be considered.^[3]

Barcelona-Clinic Liver Cancer (BCLC) staging system is a widely used set of criteria to guide management of patients with HCC. It takes into account tumor stage, liver functional status, physical status and cancer-related symptoms.^[4] Surgical treatment of HCC is a potentially curative approach, including liver transplantation (LT) and liver resection. LT is the best treatment option for patients fitting the “Milan criteria” since it removes both neoplasm and underlying liver disease. For patients with single tumor < 2 cm, with a Child-Turcotte-Pugh class A, without clinically significant portal hypertension and with normal bilirubin, liver resection represents a feasible strategy.^[4] Ablation with ethanol or acetic acid or thermal, is another potentially curative option. It is practicable in patients with single, small tumors not candidates for surgery.^[4] Many HCC cases are diagnosed in stage B of BCLC algorithm, for which the standard of care is the transcatheter arterial chemoembolization (TACE).^[4] Lastly, sorafenib is the unique universally approved systemic palliative drug for BCLC C patients.^[4]

In the European^[5] and in the North-American^[6] guidelines, no natural product is mentioned neither for the prophylaxis nor for the treatment of HCC. On the contrary, in the Asian-Pacific ones,^[7] natural products are cited for both primary and secondary prophylaxis.

Literature data are available regarding the coffee-derived substances as prevention tools in high-risk populations, the possible prevention or adjuvant effect of many kinds of Traditional Chinese Medicine (TCM), and possible utility of cannabinoids as antineoplastic drugs.

Hereby, we sought to review the current knowledge on the role of some natural products in the prevention and treatment of HCC. The research included published articles (peer reviewed original articles, review articles and meta-analyses). The search terms included “natural products and hepatocellular carcinoma”, “natural products and liver”, “hepatocellular carcinoma treatment options”, “coffee and HCC”, “Traditional Chinese Medicine and HCC”, and “cannabinoids and HCC”.

COFFEE

Many data are available about the dose-dependent protective effect of coffee respect to the development of liver disease and HCC.^[8] Both *in vitro* and *in vivo* studies showed that several coffee compounds such as diterpenes, cafestol and kahweol, may act on some enzymes involved in carcinogenesis.^[9,10] Diterpenes, cafestol and kahweol seem to modify the xenotoxic metabolism via induction of glutathione-S-transferase and inhibition of N-acetyltransferase.^[11] Caffeine and antioxidant substances from coffee beans, may improve some liver enzymes, such as γ -glutamyltransferase and

aminotransferase. Interestingly, this positive effect of caffeine is mainly relevant in heavy drinkers.^[12,13] Notably, coffee consumption would be inversely related to the hazard of cirrhosis, which is the main risk factor of HCC.^[14,15]

Although some authors^[16,17] suggested a not statistically significant association between coffee consumption and risk of HCC, many other studies reported positive results.

In an Italian case-control study (including 250 HCC),^[18] coffee intake showed a significant protective role against HCC. In all patients, ten-year coffee intake was associated with a decreased risk of HCC with a dose-effect relation (double with 3-4 cups/day respect to 1-2 cups/day).

In a further Italian study (185 HCC),^[19] patients drinking ≥ 4 cups/day (no decaffeinated) had a lesser risk of HCC respect to the others.

Tanaka *et al.*^[20] developed a Japanese case-control study (209 HCC) showing that coffee consumption during the last 1-2 years, was associated with a decreased risk of HCC. Another Japanese case-control study including 73 HCC, analyzed the role of coffee in patients with hepatitis C.^[21] Coffee drinking ≥ 1 cup/day significantly reduced the risk of HCC compared to the abstinence. The same data were found for hepatitis B chronic carriers^[22] with a risk reduction of 30-80%.

Two large Japanese prospective studies^[23,24] including hepatitis B, C and sieronegative subjects, reported that drinkers of ≥ 5 cups/day had a lower dose-dependent HCC risk respect to abstinent patients.

The relationship between coffee and risk of HCC was studied also by Johnson *et al.*^[25] through a large prospective study including 63,257 patients. The authors reported that subjects consuming ≥ 3 cups/day experienced a 44% of HCC risk reduction.

Hu *et al.*^[26] firstly analyzed the possible association between coffee consumption, serum gamma-glutamyltransferase and HCC. The study cohorts included 60,323 patients without cancer. During a median follow-up period of 19.3 years, 128 participants developed HCC. According to the author's data, a combination of very low coffee consumption and high level of serum GGT was associated with nearly nine-fold increased risk of HCC.

In 2007, Bravi *et al.*^[27] performed a meta-analysis based on 10 studies (both European and Asian) and a total of 2,260 HCC cases. Authors reported a 41% of reduction in HCC risk among coffee drinkers compared to non-drinkers. In the same year, Larsson *et al.*^[28] published another meta-analysis with similar conclusions. In 2013, Bravi *et al.*^[29] conducted a further meta-analysis including more recent studies. According to the authors, coffee drinkers had a decrease of 40% in the risk of HCC compared to abstinent patients. Moreover, high coffee drinkers showed more than 50% of risk drop. Notably,

the protective effect of coffee was reliable across different subgroups at increased HCC risk.

After the publication of these meta-analyses, other studies regarding the protective role of coffee in the HCC setting have been published. The first one, was a multicentre study by Bamia *et al.*^[30] including 201 HCC cases. Authors demonstrated that coffee intake was associated with a decrease of 72% in HCC risk. Setiawan *et al.*^[31] conducted a large population-based prospective cohort study (451 HCC) showing that drinkers of 2-3 cups/day respect to abstinent subjects, had a 38% of HCC risk reduction. In addition, patients drinking 4 or more cups/day had a 41% of risk drop. Feld *et al.*^[32] again suggested that regular ingestion of coffee in patients with chronic liver disease can make slower the progression of liver fibrosis, preventing both cirrhosis and HCC. Petrick *et al.*^[33] developed the Liver Cancer Pooling Project based on North-American data and including 1,212,893 patients (with 860 HCC cases). A high caffeinated coffee consumption (≥ 4 cups/day) was associated with a lower risk of HCC in comparison to a lesser intake. In a Japanese cohort-study^[34] including 258 cases, an inverse association was reported between coffee and mortality associated to HCC. Interestingly, the hazard of HCC-related death for abstinent patients was two-fold higher compared to coffee drinkers, and this was true also for few consumption (≥ 1 cup/day).

TCM

Many authors proposed TCM-based therapy alone or in combination with standard loco-regional therapies for prevention or treatment of HCC [Table 1]. The main TCM products include combinations of different herbal medicines or animal/insect extracts. Astragalus shows immunomodulatory properties and anti-tumor activity. It seems to reinforce Lymphokine Activated Killer cell activity restoring the T-cell function suppressed in cancer patients.^[35,36] The Panax Ginseng has inhibitory effects on cell proliferation and angiogenesis^[37] restraining tumor cell

invasion and defeating sister chromatid interactions in human lymphocytes.^[38] Toad skin secretion bufalin (Bufotoxin) could induce apoptosis in human-leukaemia cells modifying the expression of some apoptotic genes.^[39] Other toad skin secretions such as 3-formyloxyresibufogenin, 19-oxobufalin, 19-oxodesacetylcinobufagin, 6-hydroxycinobufagin and 1-hydroxybufalin seem to have inhibitory properties on KB, human promyelocytic leukemia cells (HL-60) and MH-60 cancer cell lines.^[40] *Mylabris phalerata* (Mylabris) can lead to the apoptosis of tumor cells^[41] while *Atractylodes* might bring apoptosis and have cytotoxic effects against tumor cells.^[42] *Bupleurum falcatum* shows a significant anti-cell adhesive activity on solid tumor cells^[43] and *Curcuma longa* has a relevant immunostimulatory activity.^[44]

Concerning the prevention ability of herbal products, a Japanese herb called Sho-saiko-to has to be cited since it is reported in the Asian-Pacific guidelines.^[7] In a randomized controlled trial (RCT),^[45] Sho-saiko-to was shown to improve liver function in patients with chronic hepatitis. Also Oka *et al.*^[46] reported that Sho-saiko-to may prevent the development of HCC in cirrhotic subjects. Successive studies with liver cell lines confirmed the above-cited suggestions.^[47,48]

In 2013, Zhai *et al.*^[49] compared in a RCT the efficacy of TCM and TACE in preventing recurrence of small HCC after resection. Authors tested TACE or TCM as adjuvant therapy for patients who underwent surgery without evidence of recidivism. One hundred and eighty-eight patients received Cinobufacini injection (extract from *Bufo bufo gargarizans* Cantor) and Jiedu Granule (a compound herbal medicine). The other patients (191 cases) were assigned to the TACE subgroup. TCM was associated with decreased HCC recurrence after resection in comparison to TACE, with similar adverse events.

Regarding the use of TCM alone as therapeutic tool, Tian *et al.*^[50] demonstrated that it may be effective in subjects affected by middle/late stage HCC. In this RCT, 97 patients were treated with *Oleum fructus bruceas*, Ganji Decoction and external application of Ailitong, and 48 patients received

Table 1. The main natural products from Traditional Chinese Medicine

Product	Type	Main property/ies	Studies in humans	RCTs	Meta-analysis	Ref.
Astragalus	Herb	Restores T-cell	Yes	Yes	Yes	[35,36,53,55]
Panax	Herb	Anti-proliferation and angiogenesis	Yes	Yes	Yes	[37,38,55]
Ginseng						
Bufotoxin	Toad skin secretion	Induces apoptosis	Yes	Yes	Yes	[39,55]
Atractylodes	Herb	Induces apoptosis	No	No	No	[42]
Bupleurum falcatum	Herb	Anti-adhesive activity	No	No	No	[43]
Curcuma longa	Herb	Immunostimulatory activity	No	No	No	[44]
Cinobufacini	Bufo skin extract	Induces apoptosis	Yes	Yes	No	[49]
Jiedu	Herb	Unreported	Yes	Yes	No	[49]
Sho-saiko-to*	Herb	Decreases collagen type 1	Yes	Yes	No	[7,45-48]
Bruceas	Fruit extract	Unreported	Yes	Yes	No	[50]
Ganji	Herb	Unreported	Yes	Yes	No	[50]
Ailitong	Herb	Unreported	Yes	Yes	No	[50]
Kanglaite	Herb	Immunomodulation	Yes	Yes	Yes	[56]

*It comes from the Japanese Tradition

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