Natural products and hepatocellular carcinoma: a review

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ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth commonest cause of malignancy and the third cause of cancer mortality. There are different treatment options for HCC ranging from loco-regional therapy to surgical treatment. Different regimen of systemic chemotherapy has been tried with a poor response. Several studies aimed at discovering more molecules for the management of HCC. Those studies aimed at recognizing and targeting several signaling and molecular pathways that lead to cellular proliferation and tumor formation. In this review, we discussed the role of several agents found in natural and dietary products such as curcumin, resveratrol, flavonoids, *Rubus aleaefolius* Poir total alkaloids, *Livistona chinensis* seed, and crocetin. We had used the names of the above-mentioned products as key words in addition to "HCC" on PubMed to find studies that discussed their roles in HCC. Articles were downloaded for reviewing and discussing natural products that had adequate studies in treating HCC.

Key words: Hepatocellular carcinoma; molecular signaling; natural products

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth commonest cause of malignancy and the third cause of cancer mortality.[1,2] Most patients with HCC were diagnosed in advanced stage that carried poor outcome with an overall 5-year survival rate of < 9%.[3,4] An estimation of 21,000 deaths related to HCC was reported in the US in 2012.[5] HCC has been frequently reported in Sub-Saharan Africa, Europe, North America, and Asia.[6,7] Most HCC occurs in the patients with liver cirrhosis mainly related to hepatitis B and C infections, hemochromatosis, non-alcoholic steatohepatitis, alcohol consumption, nitrosamines, and aflatoxins.[8-11]

Hepatic carcinogens, viral hepatitis, and liver cirrhosis induce inflammation and oxidative stress.[12] Production of free radicals (such as oxygen and nitrogen species) as well as cytokines and chemokines lead to cellular injury.[12] Following that, cellular proliferation happens, leading to malignant transformation.[13,14] Moreover, signaling processes at the cellular and molecular levels are involved throughout the development of HCC.[15-17]

Management of HCC is rather complex compared to other malignancy; it happens mostly in the setting of liver cirrhosis, and the treatment option largely depends on the stage of liver disease, the patient's functional status, number, size and location of tumor, and the presence or

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absence of vascular invasion.[18] Several staging systems have been developed for HCC, but the best and most widely used is Barcelona Clinic Liver Cancer classification; added to the staging, it has prognostic and treatment implication.[19]

There are different treatment options for HCC ranging from loco-regional therapy (radiofrequency ablation, arterial chemoembolization, intra-tumor ethanol injection, yttrium-90 intra-arterial delivery as microspheres, and microwave coagulation) to surgical treatment (surgical resection and liver transplantation) and sorafenib.[9,20,21] Distinctive regimen of chemotherapy has been tried with poor response.

Surgical treatment is the best present-day management options for HCC, but not all patients are eligible for it.[12] Surgical resection cannot be performed if the tumor is present in multiple sites, in advanced liver disease (Child's B and C) and in the presence of vascular invasion,[21] and only about 20% of patients are candidates for surgical resection.[22] Early on, HCC was a contraindication for liver transplantation due to poor result. Mazzaferro *et al.*[23] published Milan criteria, in which patients with early disease have a good outcome. A significant number of HCC patients do not meet Milan criteria on presentation or drop out due to disease progression while waiting for liver transplantation due to the shortage of donors.[23] Sorafenib, a tyrosine kinase inhibitor and vascular endothelial growth factor, is presently used in managing unresected HCC.[24] It increases the average survival time by 3 months in patients with late-stage HCC.[18] However, sorafenib can be used in Child's A and selected Child's B patients, in addition to the side effect and high cost.[25,26]

Clearly, the available treatment option is far from optimal, either due to limited efficacy or contraindication due to advanced liver disease (resection and loco-regional therapy for Child's C), this reiterates the need for new treatment option.

Several studies aimed at discovering more molecules for the management of HCC. Those studies aimed at recognizing and targeting several signaling and molecular pathways that lead to cellular proliferation and tumor formation.[12,27-29]

In this review, we discussed the role of several agents found in natural and dietary products such as curcumin, resveratrol, flavonoids, *Rubus aleaefolious* Poir total alkaloids, *Livistona chinensis* seed, and crocetin. We had used the names of the above-mentioned products as key words in addition to "HCC" on PubMed to find studies that discussed their roles in HCC. Articles were downloaded for reviewing and discussing natural products that had adequate studies in treating HCC.

CURCUMIN

Curcumin is a polyphenol, a diferuloylmethane and it is among the three main curcuminoids present in turmeric.[18] Curcumin is a potent anti-inflammatory agent.[30] Curcumin has been proven to be effective in treating a variety of conditions such as allergy, psoriasis, diabetes, rheumatoid arthritis, asthma, and neurodegenerative diseases.[18] Moreover, it is cardioprotective, hepatoprotective, carcinoprotective, and neuroprotective.[18] As mentioned earlier, free radicals generation is an important step in tumor formation, and curcuminoids are known to inhibit oxidation owing to their methoxy group, 1,3 β-diketone moiety, and phenolic hydroxyl group.[31] Curcumin was found to inhibit nuclear factor-kB (NF-kB), which activated inflammatory cytokines and chemokines, leading to several inflammatory conditions.[32-34] NF-kB activation promotes cellular proliferation, angiogenesis, and invasion and inhibits apoptosis.[35,36] In addition, curcumin also inhibits interleukin-1 (IL-1), IL-1B, IL-6, IL-8, tumor necrosis alpha, and cyclo-oxygenase pathways.[35,37-39] Several studies have supported curcumin's anti-oxidant and anti-inflammatory, particularly in HCC. Dai *et al*.[27] studied the anti-tumor effects of curcumin *in vitro* and *in vivo*. Curcumin inhibited HepG2's proliferation in a dose and time dependent fashion, with the most potent inhibition at a concentration of 8 umol/L for 48 h, it leads to HepG2 induced cells apoptosis at high doses, the apoptosis rate increased up to 20% at a curcumin concentration of 16 umol/L. In addition, high doses of curcumin have been shown to elevate casepase-3, an essential protein for apoptosis.[27] Curcumin has restricted liver tumor growth in HepG2 xenograft mice models *in vivo*; the greatest reduction in tumor volume was around 3740 mm^3 at a high curcumin dose of 60 mg/kg.[27] Curcumin also mediated apoptosis in HL60, SGC7901, and Bel7402 cells by inhibiting telomerase activity.[40]

In another study by Lin *et al*.,[41] curcumin caused a decline migration and invasion of SK-Hep-1 cells as well as matrix metalloproteinase-9 (MMP-9) levels. Also, curcumin has an inhibitory effect of vasculogenic mimicry in SK-Heo-1 cells, a process in which hepatocytes act as endothelial cells and form blood vessels, by inhibiting the STAT3 and Akt pathways.[42] Moreover, curcumin decreases caveolin-1 levels and epidermal growth factor signaling, and therefore may prevent vascular invasion and metastasis.[40] Unfortunately, curcumin has poor pharmacokinetics as it undergoes poor

absorption and has low bioavailability.[43] Curcumin gets directly conjugated once it is absorbed, and only a small amount remains as free curcumin.[43] It has been suggested that its metabolite, curcumin glucuronide, is responsible for most of its therapeutically assumed action,[44] however, a recent study showed that curcumin glucuronide has a less potent effect than curcumin itself on HepG2 cells, as the expression of *GSTT1, CAT, IL-8, AREG,* and *ACOX1* genes was greatly downregulated by curcumin than by curcumin glucuronide.[43] In addition, curcumin is more rapidly absorbed than curcumin glucuronide.[43] Curcumin is the most studied natural product for HCC; it is clearly effective in HCC at different molecular mechanisms for inflammation, proliferation, and apoptosis, there is a lack of clinical data in humans to confirm the above.

RESVERATROL

Resveratrol (3, 4', 5-trihydroxy-trans-stilbene) is found in red wine, berries, grapes, and peanuts.[45] Resveratrol has been found to be anti-inflammatory in viral infections, neurodegenerative diseases, cardiovascular diseases, ischemia, and cancer. Resveratrol has anti-cancer effects by suppressing initiation, promotion, and progression of tumor formation.[46-49] Moreover, it has significant anti-cancer activity by inhibiting inflammation and free radicals generation.[50,51] Resveratrol has been found to hold rat hepatoma Fao cells and HepG2 cells in S and G2/M phase and prevent them from engaging in mitotic division.[52] Another study showed that cells exposed to resveratrol were held in G1 phase and had an upregulation in *Bax* and *p21* genes.[53] It also decreased the invasion of cancer cells by downregulating hepatic growth factor.[54] It inhibits vascular endothelial growth factor gene expression by inducing hypoxia in HepG2 cells.[55] In another study, HepG2 cells exposed to high concentrations of resveratrol reaching between 50 and 100 umol/L for more than 48 h were more prone to apoptosis, in a dose-dependent fashion.[56] In a study that exposed H22 cells to resveratrol with 5-fluorouracil (FU) *vs*. 5-FU alone; resveratrol and 5-FU had a greater anti-cancer activity compared to 5-FU alone.[57] Notas *et al.*[58] concluded that resveratrol has an anti-proliferative effect against HepG2 cells as well as inducing the production of nitric oxide. It has also been shown to downregulate NF-kB, caveolin-1, and MMP-9.[59,60] Several *in vivo* studies also support the anti-tumor activity of resveratrol in HCC. Resveratrol was administered to mice that had HCC tumor cells, hepatic tumor growth reduced and cell cycle proteins p34cdc2 and cyclin B1's expression was suppressed.[61] Resveratrol has shown to have both *in vivo* and *in vitro* effect against HCC though different pathways and appear to have a promising potential, yet there is no clinical data in humans.

FLAVONOIDS

Flavonoids are polyphenols found in vegetables, fruits, flowers, tea, wine, stems, and roots.[62] There are seven types of flavonoids: Anthocyanidins, flavanones, flavonols, flavones, flavanols, flavononol, and isoflavones.[63] They have been shown to be cardio-protective and hepato-protective and possess anti-viral and anti-cancer activity.[64-66] Flavonoids have found to induce apoptosis in HepG2 cells via activation of the mitochondrial pathway, along with the translocation of cytochrome c, activation of caspases such as 9, 8, and 3, abnormal changes in mitochondrial membrane potential, generation of reactive oxygen species, elevation in intracellular calcium, and upregulated transcription of endonuclease G and apoptosis inducing factor-related genes.[67] Flavonoids have also been found to inhibit HepG2 cells growth by inhibiting the NF-kB pathway via blocking tumor necrosis factor-alpha.[68] Administering epigallocatechin-3-gallate (EGCG), which is found in green tea, to HepG2 cells induces their apoptosis by suppressing epidermal growth factor receptor/c-Met signaling; therefore, suppress tumor cell proliferation and invasion.[69] Quercetin, found in flavonol, has shown to restrain the expression of heat shock proteins 27 and 40, which lead to resistance to chemotherapy, hence potentiating the effect of the chemotherapeutic agent.[70] Moreover, flavonoids have been found to be anti-hepatitis B virus (HBV) and hepatitis B core. EGCG inhibits HBV replication by altering its DNA synthesis.[71] Furthermore, hepatitis C virus is inhibited by catechin that interferes with NF-kB and COX-2 pathways.[72]

Like curcumin and resveratrol, flavonoids appear to have activity against HCC with different mechanisms, through different pathways but need to be tested in clinical trial.

TOTAL ALKALOIDS OF *RUBUS ALEAEFOLIOUS* POIR

R. aleaefolious is a plant used for the management of hepatitis in China.[73] Hong *et al.*[74] have reported that components of *R. aleaefolious*, such as butanol and ethylacetate, are hepatoprotective in mice with acute liver injury after exposure to carbon tetrachloride. Reports from the literature have discussed the protective and therapeutic role of *R. aleaefolious* Poir in carcinogenesis.[75,76] Zhao *et al.*[73] examined the therapeutic effects of total alkaloids in *R. aleaefolious* Poir (TARAP) on HCC both *in vitro* and *in vivo*. TARAP has been shown to affect HCC growth and induce apoptosis in HepG2 cells via mitochondrion-mediated apoptosis by causing the loss of mitochondrion potential and activation of caspases 9 and 3, apoptosis was dose dependent.[73] Bax and Bcl-2 are important proteins involved in the process of apoptosis.[77] Bcl-2 is known to be anti-apoptotic,[73] and BAX

is pro-apoptotic.[78] If the ratio of Bcl-2 to BAX is great, then apoptosis does not occur.[73] TARAP has downregulated the expression of Bcl-2 and upregulated the expression of BAX, decreasing the Bcl-2-BAX ratio, hence inducing apoptosis.[73] TARAP has been used in China for hepatitis and its use in HCC needs further studies.

LIVISTONA CHINENSIS SEED

L. chinensis seed has been used in China for cancer treatment.[79] Lin *et al.*[28] have evaluated the therapeutic role of ethanol extract of the *L. chinensis* seed (EELC) against HCC both *in vitro* and *in vivo*. EELC has inhibited tumor growth in HCC xenograft mice and decreased the tumor weight by 43%, moreover, EELC tumor inhibition was assessed *in vitro* on HepG2 cells, and the maximum reduction in cell viability was around 60% in a maximum time of 24 h, it also induced cell apoptosis in HCC xenograft mice and HepG2 cells.[28] Moreover, EELC has induced the loss of the mitochondrion membrane potential in HepG2 cells, leading to apoptosis and stimulates the release of caspases 9 and 3 in HepG2 cells and causes a rise in the BAX-Bcl-2 ratio, as what TARAP does.[28]

CROCIN

Derived from *Crocus sativus*, saffron exhibits a therapeutic effect against depression, cancer, and asthma.[80] It also acts like oxytocin and as a stimulant.[80] Three compounds are found in saffron: Picrocrocin, crocin, and safranal.[81] Crocins give saffron its color.[80] Several studies discussed the anti-cancer effect of saffron in different types of cancer such as pancreatic, gastric, bladder, and hepatic cancer.[82-85] Noureini and Wink[84] studied the anti-proliferative effects of crocin in HepG2 cells. HepG2 cells exposed to 3 mg/mL of crocin had almost a 59% decrease in telomerase activity. In addition, crocin and safranil have shown to increase the cleavage of caspase-3, arrest the cell cycle, and cause DNA damage in HepG2 cells.[85] Moreover, Tseng *et al.*[86] reported that crocetin, a major constituent in saffron, was an anti-oxidant and hepatoprotective by decreasing the synthesis of malondialdehyde in hepatocytes, a marker for fatty acid oxidation and oxidative stress. As concluded by other researchers, crocetin protects against cancer by inducing apoptosis and arresting the cell cycle.[86]

CONCLUSION

The potential chemo-preventive and therapeutic role of above discussed natural products in HCC is due to their potent anti-oxidant and anti-inflammatory properties as well as their ability to modulate different signaling mechanisms that are implicated in the process of carcinogenesis. They hold considerable promise as therapeutic agents for HCC. Most of these studies are preclinical with very limited clinical data; therefore, the clinical efficacy of these products is still far from being tested. There is a need to develop a dosing from using the available technology to overcome the low bioavailability and to have a standard dosage for future clinical trials. Once that is achieved, the safety of these products in high doses needs to be ascertained, although they have been in use for hundreds of years.

Lack of good clinical trials testing these products compared to sorafenib and other pharmacological therapy may be due to lack of financial support to conduct such trails.

There is a pressing need for governmental funding and collaboration between centers to conduct multicenter randomized open label studies using the standard of care, with or without these products either individualized or in combination.

Conflict of interest
There is no conflict of interest.

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