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Role of Herbal Medicines in Hepatocellular Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Mutation in several factors and pathways leads to the development of hepatic cancer i.e. Mutation in Wnt-β-Catenin Signalling Pathway , activation of the Insulin-Like Growth Factor (IGF) Signalling Pathway, The P13/PTEN/AKT, TP53 Tumour Suppressor Gene. Liver cirrhosis and fatty liver predispose the normal tissues to fibrosis leading to liver cancer. Excessive alcohol intake results in

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the inflammation of liver proceeding to cirrhosis and ultimately hepatic carcinoma. Hepatocellular Carcinoma (HCC) is multi-centric i.e. has huge variability in its spread which differs from person to person. Four approaches are practiced for treatment of hepatic cancer; surgery, transarterial intervention, percutaneous intervention, and drug approach. Surgery includes liver transplant and tumour resection. Transarterial approach includes chemoembolization and embolization. Percutaneous approach includes radiofrequency thermal ablation (RFTA) and ethanol injection. Drugs are various including herbal plant medicines, herbal formulae, synthetic drugs, immune, and gene therapies. *Zingiber officinal, Schinus molle L., Zerumbone, Curcuma longa* and *Mammea siamensis* are some of the plant medicines.

Keywords: HCC (Hepatocellular carcinoma); RFTA (Radiofrequency Thermal Ablation); liver transplant; mutations.

1. INTRODUCTION

Most common primary liver cancer is HCC. There are roughly one million new cases of liver cancer worldwide and is the fifth most leading cancer throughout world and third common cause of cancer related death [1]. Its treatment presents a major health issue due to its increasing emergence and complex management strategies [2]. The optimal surgical therapy for liver cancer is quite controversial topic. Biomarkers play the prominent role for safer liver excision. Transplantation in hepatic liver failure patients depends upon person to person in terms of individual benefits [3]. This review however focuses upon the pathogenesis of hepatic cancer underlying various physiological and genetic changes involving mutations in normal cellular pathways and events leading to liver cancer. The leading factors are the fatty liver, regular alcohol consumption, hepatitis B, C and liver cirrhosis. The possible treatment options are also pinpointed in this article [4].

2. PATHOPHISIOLOGY OF HEPATIC CANCER

The pathophysiology of HCC is growing topic and tends to depend upon multiple factors .In 1981, a study conducted linked hepatitis B infection to HCC development further research linked metabolic syndrome as a prominent cause of HCC predominantly arises in a cirrhotic liver where continuous inflammation occurs along with fibrogenesis [5]. Inflammation and fibrogenesis predispose the liver to dysplasia, proceeding to malignant transformation. All these factors plays a prominent part in starting the advancement towards HCC [6]. Liver cancer can appear in form of hepatic nodules which are either manifested as hypointense or non-hypervascular nodules having predictive potential for nature of tumor [7]. In normal individuals activated lymphocytes proliferation is regulated by CTLA-4 pathway but in cancer this pathway overcome the proliferation of T cells, which results in inhibitory signal transmission to cytotoxic T lymphocytes so their potency is reduced leading to immune tolerance [8]. Some alterations lead to liver cancer, of which few are irreversible and others are not. Out of many factors leading to liver cancer, the susceptibility of genome is major reason which is likely to be added in, removed of or mutated with genes. From mutational causes CTNNBI mutant is cause of alcoholic liver cancer, while epigenetic level alterations are irreversible [9]. Molecular mechanisms leading to development of HCC are not well known but studies performed showed the following molecular and genetic features; Mutation in Wnt-β-Catenin Signaling Pathway which plays a part in liver development and maturation [10,11], Activation of the IGF Signaling Pathway lead to cascade of molecular events such as cell proliferation, antiapoptosis and invasive behaviour [12]. The P13/PTEN/AKT Pathway is involved in several cellular processes such as proliferation, apoptosis, differentiation, cell motility, cell cycle progression, tumour growth [13] and angiogenesis TP53 Tumour Suppressor Gene mutation are strongly linked to HCC [14]. Hepatocellular carcinoma is also related to infection with hepatitis C virus (HCV) hereditary hemochromatosis, alpha1-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease [15].

Genetic alterations also leads to HCCs being divided into two main groups depending upon chromosome stability status HCCs without chromosome instability have frequent beta-catenin mutations as the single genetic alteration of large size and HBV negative, whereas HCCs with chromosome instability have frequent axin1 and p53 mutations and seems to be HBV

positive [16]. HCC is a multistep process hepatic nodules consists of precancerous lesions i.e. dysplastic foci, DNs and early HCC. Pathologically, dysplastic foci are clusters of hepatocytes showing precancerous traits i.e. small cell change, having <1 mm in diameter [17]. Liver cirrhosis is one of the factor leading to HCC contributing to second highest mortality rate worldwide [18]. In General, HCC is a multicentric tumour, and it has huge variability from nodule to nodule, within an individual patient [19]. Patients with HCC having family history of hepatitis C have advanced fibrosis [3,20]. TERT Promoter Mutations (telomerase reverse transcriptase) involve somatic mutations governing cellular processes leading to different types of cancers particularly hepatic [21,22]. Mac-2 Binding Protein Glycosylation Isomer (M2BPGi) are indicative of liver fibrosis leading to Liver cancer [23]. Large intake of alcohol leads to liver cirrhosis leading to the development of HCC [24].

3. ETIOLOGY OF LIVER CANCER

The most common factors accounting for the cause of liver cancer are excessive alcohol intake, fatty liver, liver cirrhosis, smoking, hepatitis B and particularly hepatitis C, fibrosis of normal liver cells [25,26].

4. LIVER CANCER TREATMENT

Treatment of liver cancer is done by many approaches mainly categorized into four options which are to be decided according to the status of the patient as well as disease progression.

4.1 Treatment Modalities

If surgery [7] is to be opted then it may include tumor resection [27] or liver transplantation [28], while opting a percutaneous intervention includes RFTA [29,30] and ethanol injection [31], if a transarterial intervention [32] is needed then chemoembolization and embolization are the procedures, but if drugs are to be looked for treating the liver cancer then there are synthetic as well as medicinal plant options or herbal preparations, then immune and gene therapies [33]. Currently for slowing down or stopping the progression of HCC in phase of patient waiting for liver transplantation local treatments has been mainly practiced. TACE, although not a primary curative procedure for liver cancer, still can be

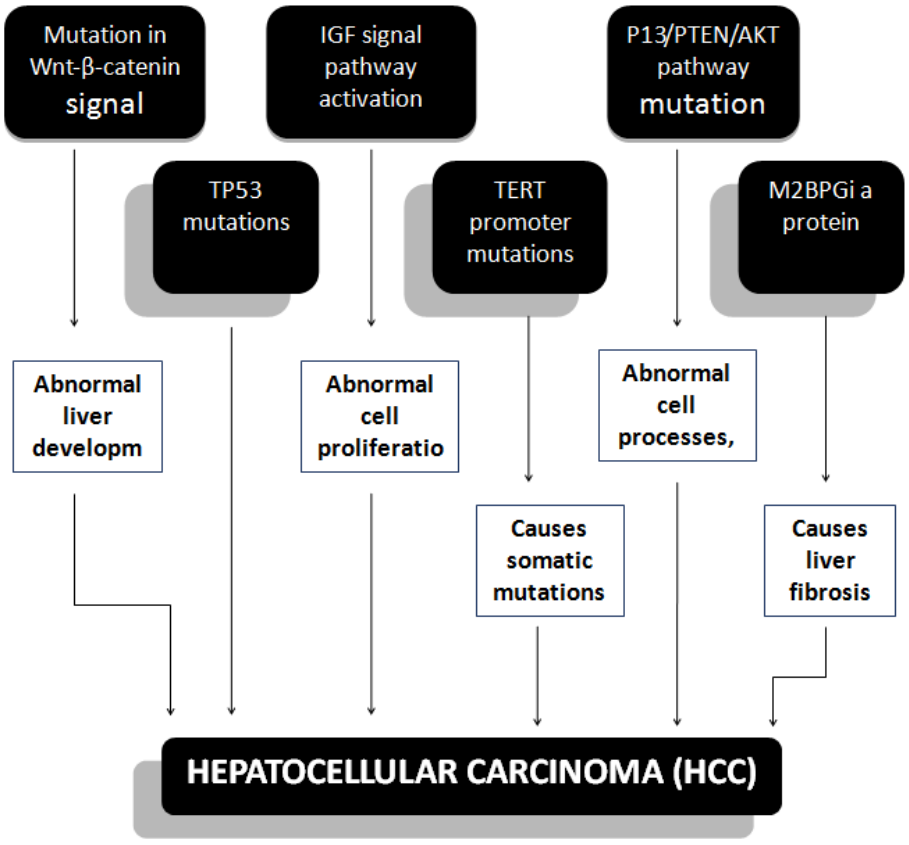

Fig. 1. Various factors contributing towards hepatocellular carcinoma

used in a relatively safe way to manage multifocal and unresectable HCC [34] and before liver transplantation it suppresses the lesions of cancer [35]. For Percutaneous intervention a percutaneous ethanol injection (PEI), e.g. RFA, is utilized in small HCC for patients who are poor candidates for resection with poor hepatic reserve, while candidates having good hepatic reserve can be cured with hepatic resection. Anti-androgens, Tamoxifen, herbal drugs and octeoride are not recommended for liver cancer but Sorafenib has shown mortality benefit as an exclusive treatment [36]. Beside treatment of liver cancer, prevention of factors which contribute towards liver cancer must also be controlled like chronic viral B and C infections [37]. These treatment and prevention options are again depending upon the vascular invasion, presence or absence of metastasis, or liver function, which may be a curative treatment with liver transplantation, surgical resection or percutaneous ablation [38]. With immunotherapy after resection of liver cancer patients, survival rate was increased with monoclonal antibody 17-1A, while prior treatment with interleukin 2 was effective in prevention of immunodepression after operative procedures [39]. Systemic chemotherapy, and hormonal compounds are some palliative approaches for liver cancer, preventing the blood supply to the HCC by closing the arterial system of liver [40]. Advanced-stage HCC with extrahepatic spread and vascular invasion is treated with sorafenib being a standard treatment and first survival agent, while Lenvatinib also gave good outcome for HCC [26]. Precancerous HCC cells are thought to be removed by an oral, acyclic retinoid, peretinoin [18]. Interstitial treatments, like microwave ablation (MWA), radiofrequency ablation (RFA), and irreversible electroporation (IRE), are introduced as new treatment options for HCC [41].

4.2 Herbs and Herbal Compounds

Among the oncologists the Herbs and their compounds are of prime interest. Previously, as an anti-HCC agent certain herbal composite formulas as well as compounds are present. Some Herbal compounds like. Curcumin showed three remarkable properties against liver cancer: antiangiogenesis of HCC, anti-metastatic property, and anti-HCC [42]. Resveratrol significantly is proved to be acting against HCC. It was known that it suppresses the invasion which is potentiated by ROS, inhibits the MMP-9 expression mediated by TNF-alpha, enhances

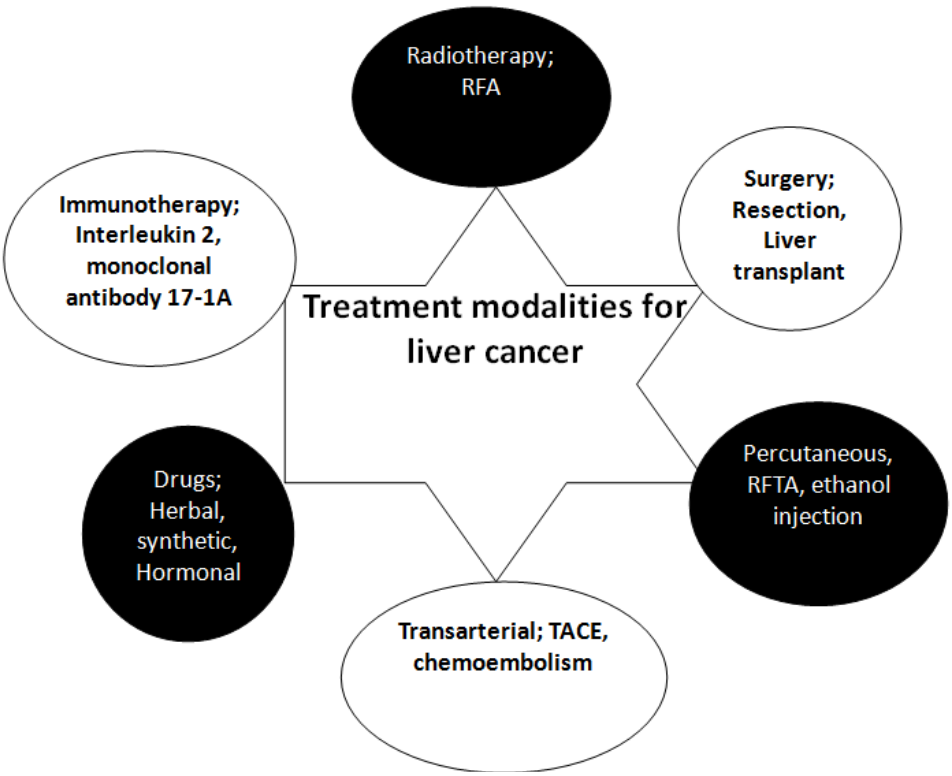

Fig. 2. Modalities present for Liver cancer

Table 1. Summary of all herbal medicines showing anti-HCC effect

Treatment drug		
Herbal plant medicines	**Effects**	**References**
Curcumin	antiangiogenesis of HCC, anti-metastatic property, anti-HCC	[42]
Resveratrol	Anti-HCC by multiple mechanisms	[43]
Silibinin	cell proliferation inhibited, anti-HCC	[45]
Tanshinone IIA	DNA synthesis inhibited, anti-HCC	[47]
Dracocephalum kotschyi	Tumoral cell selective, anti-HCC	[48]
Pra-Sa-Prao-Yhai	Anti-HCC	[49]
Mesua ferrea	Anti-HCC	[49]
Piper chaba	Anti-HCC	[49]
Zingiber officinal	Anti-HCC, most potent	[49]
Kaempferia galangal	Anti-HCC	[49]
Atractylodes lancea	Anti-HCC	[49]
23 plants from "MANOSROI III"	Anticancer recipes	[24]
Zingiber zerumbet smith	Zerumbone isolated from it causes apoptosis	[51]
Schinus molle L.	Inhibition of HepG2 cell line	[52]
L. Molleoides	Anti-HepG2 cell line	[52]
Ar. Macroura	Inhibition of HepG2 cell line	[52]
Ac. satureioides	Inhibition of HepG2 cell line	[52]
Silymarin	Treats chronic liver disease	[53].
Phyllanthus amarus	A viricide against hepatitis B	[54]
TJ-9	HCC prevention	[57]
Shikonin	Apoptosis of liver cancer cells	[58]
Glycyrrhizin	Normalizes plasma ALT level	[61]
Osthole	Reduces plasma ALT level	[61]

the mitochondrial membrane potential [43], also promotes the intercellular communication at gap-junction, NO/NOS is modulated too, G1 and G2/M phases are arrested in cell cycle, ROS is reduced, Bax expression is upregulated and Bcl-2 is downregulated by Resveratrol [44]. Silibinin showed anti-HCC characteristics by different mechanism, ERK ½ cascade, NO production, and cell proliferation are inhibited [45], histone H3 and H4 acetylation is increased, metalloprotein-2 is downregulated, Cyclin-dependent kinase (CDK2), CDK4, cyclin E, cyclin D3, and cyclin D1 are decreased by Silibinin [46]. Tanshinone IIA activity against HCC; DNA synthesis is inhibited, p53, bax, and fas are upregulated, c-myc and bcl-2 downregulated, G(0)/G(1) are arrested in cell cycle, and apoptosis is induced [47].

Extract of *Dracocephalum kotschyi* (250μg/mL) is tumoral cell selective and induces mitochondrial membrane permeabilization (MMP), cytochrome c release and mitochondrial swelling in tumoral cells only, so proposed as a future candidate for anticancer research [48]. Some anti-cancer herbal medicines as well as herbal formulae are Pra-Sa-Prao-Yhai recipe, *Mesua ferrea, Piper chaba, Zingiber officinal, Kaempferia galangal, Atractylodes lancea*. Out of these herbs and herbal preparations, *Zingiber officinal* is the most effective against human hepatic cancer cell line HepG2 (hepatocarcinoma). Two more crude extracts from Plants like *Curcuma longa* and *Mammea siamensis* showed remarkable activity against HepG2 cell. *Zingiber officinal* is the most potent and effective one with good selectivity against cancerous cells [49].

From the "MANOSROI III" database some 23 plants were also discovered to be with high frequency as anticancer recipes [24]. Chemopreventive strategies are always much helpful in decreasing HCC risk or delaying it [50]. Zerumbone a component isolated from *Zingiber zerumbet smith* causes the up and down regulation of Bax (proapoptotic) and Bcl-2 (anti-apoptotic) protein respectively and induces the apoptotic process in HepG2 cells [51]. Some methanolic extracts from plants showed inhibitory effect for growth of hepatic cancer cells; most effective one is *Schinus molle L*., while in a concentration-dependent manner *S. molle methanolic* extracts, *L. Molleoides, Ar. Macroura,* and *Ac. satureioides* inhibits growth of Hep G2

cell line [52]. Now some patients who have gone liver transplant also need post-transplant survival, so doxorubicin neadjuvant chemotherapy favourably alters that survival in patients with HCC [4].

Some risk factors which are directly or indirectly contributing to the liver cancer are treated by Silymarin such as chronic liver diseases, which are highly contributing towards HCC, so Silymarin is indirectly helpful for HCC [53]. An extract from *Phyllanthus amarus*, which is a viricide contributes towards eliminating hepatitis B virus, and thus theoretically decreases the risk of HCC [54]. Liver transplantation is contraindicated in patients with HCC which is poorly differentiated [55]. Although many phytochemicals were tested against HCC, but resveratrol was proved to be much effective against HCC and thus decreased the mortality rate [56]. In patients with no HBs antigen a herbal preparation TJ-9 helps for the prevention of HCC development when patients are also having liver cirrhosis [57]. Apoptosis in liver cancer cells was induced by shikonin, through oxygen reactive species, which is a Chinese plant-derived naphthoquinone [58]. Resveretrol is a potent agent against many human cancer cells [59]. It exerts anti-proliferative and proapoptotic effect on many human cancer cells [60].

Alanine aminotransferase (ALT) normalization is a strategy for prevention of HCC development in patients with HCV i.e. hepatitis C, so a plant medicine Glycyrrhizin normalizes the plasma ALT thus prevents the HCC. Another plant medicine, a simple coumarin, osthole strongly reduces plasma ALT levels as well as inhibits the activation of caspase-3 [61]. When HCC cannot be cleared by hepatic resection, and hepatic functions are poor then liver transplantation is the treatment of choice [62].

5. CONCLUSION

Transarterial approach includes chemoembolization and embolization. Percutaneous approach includes radiofrequency thermal ablation (RFTA) and ethanol injection. Drugs are various including herbal plant medicines, herbal formulae, synthetic drugs, immune, and gene therapies. *Zingiber officinal, Schinus molle L., Zerumbone, Curcuma longa* and *Mammea siamensis* are some of the plant medicines.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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