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Original Article

Updates on Traditional Medicinal Plants for Hepatocellular Carcinoma

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ABSTRACT

Aim: Hepatocellular carcinoma (HCC) is a major worldwide problem primarily caused by hepatitis B and C virus infection. End stage liver cancer treatment options are limited thus requiring expensive liver transplantation which is not available in many countries. **Methods:** Several herbal compounds and herbal composite formulas have been studied through *in-vitro* and *in vivo* as an anti-HCC agent, enhancing our knowledge about their biological functions and targets. In this article, arecent update on the herbal medicine has been provided with reference to liver cancer. **Results:** For the sake of clarity, the effective herbal compounds, clinical studies of herbal composite formula, cell culture, and animal model studies safety are discussed. The effects of many herbal active compounds of *Annona atemoya, Andrographis paniculata, Boerhaviadiffusa, Piper longum, Podophyllum hexandrum, Phyllanthus amarus,* and *Terminalia chebula*, and herbal composite formula on autophagy, apoptosis, antioxidant, and inflammation characteristicshave been provided. **Conclusion:** This will enhance our understanding on the prevention and treatment of HCC by herbal active compounds and herbal composite formulas.

Key words: Liver cancer, Herbs, Anticancer, Medicine, Treatment.

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INTRODUCTION

Hepatocellular carcinoma (malignant hepatoma; HCC) is an end-stage liver disease and is accompanied by yellowing of the skin, fluids build up in the abdomen, abnormalities in blood clotting, severe abdominal pain, vomiting/nausea and restlessness. While the majority of the cases of HCC occurs within injured or virally infected hepatocyte, other types of cells in the liver can route to the development of cancer, but they are less common. Cancers that arise in any other part of the body, such as lung, colon or breast and spread to the liver is called as metastatic cancer rather than liver cancer.[1] People acquire liver cancer in the context of chronic liver disease (cirrhosis), which increases the risk of liver cancer with scars. Conditions that cause liver cirrhosis are chronic hepatitis B, hepatitis C, alcohol usage, genetic predisposition, iron and copper overloads, and drug abuse (Figure 1). HCC is found more often in men compared to women and is commonly distributed in Southeast Asia and Sub-Saharan Africa than in the United States. Around 700,000 people are identified with HCC each in the world. HCC is the principal source of cancer deaths around the world that might cross 600,000 deaths every year.[2] Liver cancer gradually develops from the pre-malignant stages due to theaccumulation of a series of cellular and genetic alterations. Therefore, extremely damaged livers are more susceptible to various tumors.[3] Thus virally infected hepatocytes are predisposed to perturbed transcription regulation critical for gluconeogenesis and lipogenesis (e.g., C/EBP beta, CREB, HNF1/4, FoxO1, PGC1, CD36 activation), activation of kinases (e.g., Ras-Raf, JNK, p38MAPK) and accumulation of mutations due to defective DNA repair.[4,5] These variable factors that contribute for liver cancer eventually force the cells to lose its cell cycle growth and certain biomarkers are expressed which distinguish the different heterogeneous population of the cell from each other. The identification of such types has been cumber some and when the cancer is identified it is in the late stage and often hard to manage (Figure 2). Natural somatic mutations in any of these pathways and genes can increase the chance of liver cancer. As a consequence of these perturbations, cells are inflamed, injured and secrete stress molecules (ROS, and ATP) and this continuous insult lead to un-programmed cell growth which are all signs of the premalignant phenotype.

Current treatment options include psychosocial support, surgical operation, radiation therapy and chemotherapy and the use of a receptor tyrosine kinase inhibitor, Sorafenib, and all these points have limitations in success.[6] Presently, the most common method used in cancer chemotherapy is comprised of antimetabolites, alkylating agents, platinum analogs natural anticancer agents and antitumor antibiotics. Though with the rising pace of mortality related to cancer and its toxic side effects of irradiation therapy and cancer chemotherapy, finding of novel plant-derived anticancer agents offer an attractive choice. Medicinal plants have been screened as a potential anticancer source since the 1950s, with the discovery of vinblastine, vincristine, and vinca alkaloids.[7] In this review, selected medicinal plants that can aid in fighting against liver cancer are discussed along with their chief bioactive phytochemicals.

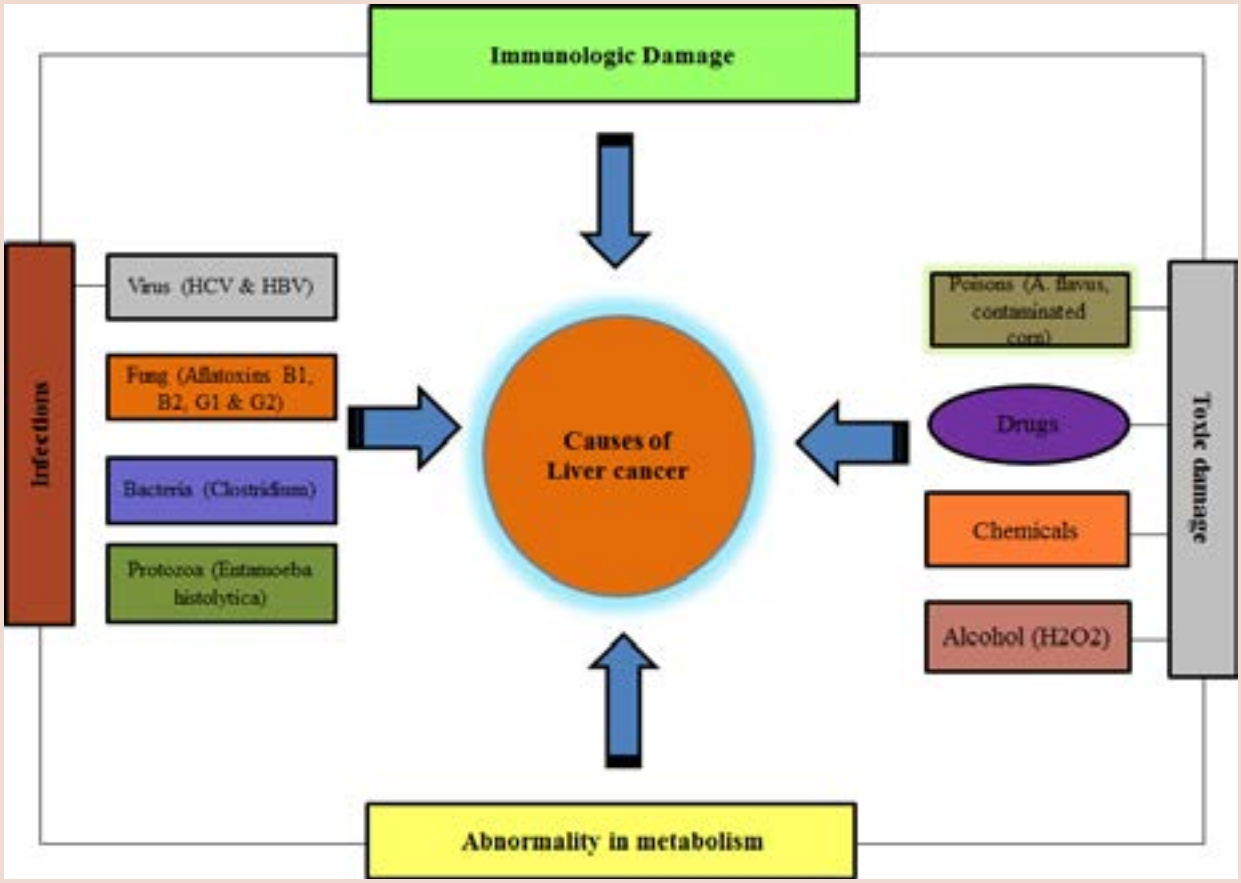

Figure 1: Causes of liver cancer.

Types of Liver Diseases

To maintain homeostasis and health liver plays hundreds of important functions in our body, hence it is predictable that liver injuries harshly affect health and may become perilous for the life. Liver diseases are characterized in mainly in 4 types: (a) Cirrhosis (b) Fatty liver disease (c) Hepatitis (d) HCC. Hepatitis and HCC are most serious health problem worldwide.

Cirrhosis

Cirrhosis is liver damaging and life-threatening disorder which develops slowly over years of liver inflammation. Cirrhosis most commonly caused by prolonged intake of alcohol, hepatitis B, hepatitis C, autoimmune hepatitis, steatohepatitis, obstructed bile ducts and several inherited diseases. Other factors like long contact with environmental toxin can cause cirrhosis and it is recognized that cirrhosis has been linked with HCC, particularly in themale. Generally, 1/3rd of HCC occurs in cirrhotic livers.[6]

Fatty Liver

Excessiveness of the fat in the liver of alcoholic or non-alcoholic people is the primary sign of FLD (Fatty liver disease). It never damages the liver itself but can cause liver cell inflammation to harsh liver scarring and cirrhosis. There may be different factors which may contribute in the development of FLD which includes the toxic inflammatory proteins release and production through its own inflammatory, fat, and liver cells, and apoptosis/necrosis oxidative stress.[8]

Fibrosis

Fibrosis occurs prior to cirrhosis in which unnecessary deposition of connective tissues including collagen takes place. It becomes mostly in chronic liver diseases. In the later stage, liver fibrosis changes into cirrhosis, liver collapse and portal hypertension, and frequently liver transplantation is needed. Chronic HCV infection, alcohol intake and non-alcoholic steatohepatitis are the main causes in developed countries.[9,10]

Hepatitis

Inflammation of the liver is known as hepatitis. The liver is composed of different cell types. And 80% of the liver consist of liver cells (hepatocytes). Cirrhosis is caused by scarring of the liver tissue which is a key risk factor for initiation of liver cancer. The major cause of cirrhosis is due to viral hepatitis, especially HBV and HCV, as well certain autoimmune diseases of the liver, hemochromatosis, alcohol abuse, and other diseases causing chronic liver inflammation.[11] When these liver cells are destroyed or damaged, the body has to continuously substitute them. Research shows that when cells are being replaced too repeatedly, there is abiggerrisk that mutations within the cells will be passed along until the cells lose their ability to control their own growth, which can result in liver cancer.[12] Interferon therapy can prevent these types of hepatitis from becoming chronic infections and can reduce the chance of developing liver cancer.[3]

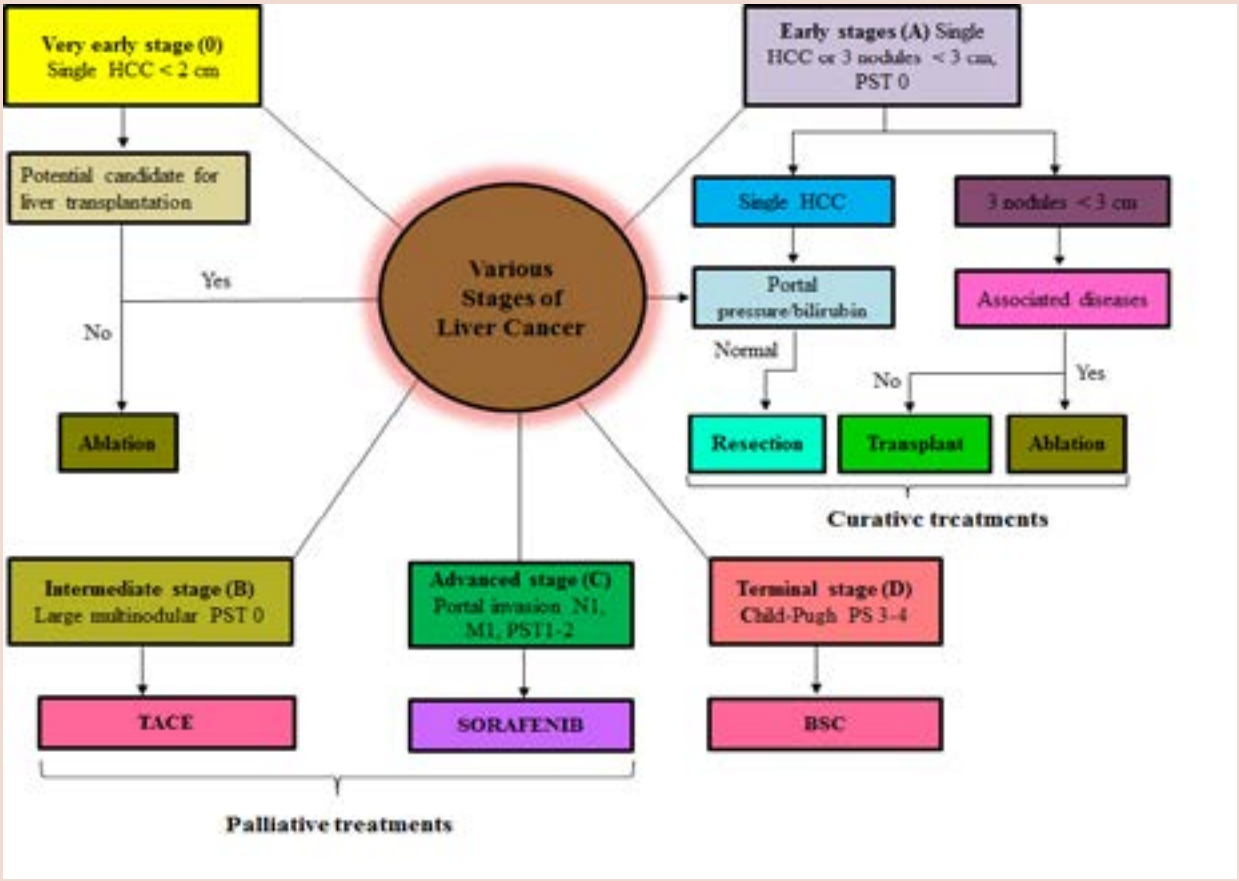

Figure 2: Different stages of liver cancer and its treatments.

Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a rising clinical problem and predominantly occurs in patients with underlying cirrhosis and chronic liver disease. The incidence of HCC is highest in Africa and Asia, where the high endemic prevalence of HCV and HBV strongly prompts to the development of chronic liver disease and the ensuing development of HCC.[13] HCC is commonly diagnosed at an advanced stage with weight loss, signs of decompensated liver disease and right-upper-quadrant pain, it is currently recognized at an earlier stage by screening of patients diagnosed with cirrhosis, serum alpha-fetoprotein (AFP) measurements and using cross-sectional imaging studies. The origin of HCC requires identification and characterization of Hepatic Caner Stem Cells (HCSs).[14] Thus, developing effective and efficient care for patients with end-stage liver disease and HCC should become an important focus, if the truth of the nature of HCSs is known.[15] Generally, only a few numbers of all patients have access to transplantation, and, even in the developed world, organ shortage remains a major limiting factor. In these patients, local ablative therapies, including chemoembolization, potentially novel chemotherapeutic agents and radiofrequency ablation (RFA), may provide palliation and extend life. With the emergence of extremely effective direct-acting antivirals (DAAs) for hepatitis,[1] it is expected to reduce the incidence of hepatitis-related HCC.[3] Overall, a combination of virus-specific, environmental, immune-related factors and host genetics are likely to determine the progression and treatment of HCC.[16]

Epidemiology of Liver Cancer

Liver Cancer is the second foremost cause of cancer deaths worldwide[17] and one of the only increasing causes of cancer-related mortality in the World.[18] Although hepatitis B still remains the most common risk factor worldwide, chronic HCV infection is the driving force for the increased incidence of HCC especially in Western countries and Japan.[19] In Asia-Pacific regions and sub-Sahara population, HBV is the major cause for HCC, in contrast chronic infection with HCV is the main cause of HCC in Pakistan, Egypt, and many developed countries.[20] The World Health Organization (WHO) estimates that more than 170 million people are currently chronic carriers of HCV and that 3% of the world's population has been infected with HCV.[21]

Risk Factors

The risk factors for HCC development are multifactorial, multistage and complicated and linked with chronic and persistent infection. Hepatitis B or C virus along with exposure to mycotoxins like aflatoxins and consumption of alcohol is commonly recognized etiological mediators in HCC. It is found that eighty percent HCC infected individuals have cirrhosis, generally it is the most dangerous form of liver fibrosis, finishing point of chronic liver damage. Additional factors which increase the progression of HCC are the lengthy use of oral contraceptives, occupational exposure to vinyl chloride (chloroethylene) or related toxins and angiogenesis therapy.

Molecular Variations Involved in HCC

It was reported by Ozturk (1999) that 4 genetic pathways play pivotal role in liver cells transformation into malignant cells; (a) involvement of p53 pathway in DNA damage and response (b) involvement of pRB/p16INK4A pathway in controlling the cell cycle (c) role of TGF-β1 pathway in growth inhibition (d), and the role of apoptosis and β-catenin/Axin1 pathway in morphogenesis and signal transduction. In addition, the involvement of above twenty genes has been reported during HCC progression.

Prevention of HCC

The first step in the prevention of HCC is its accurate early detection. Based on in-depth reviews of serological diagnosis of HCC, in addition to AFP, there are other biomarkers: descarboxyprothrombin (DCP), Lens culinaris agglutinin-reactive AFP(AFP-L3), epidermal growth factor (EGF), homology domains 2(TIE2)-expressing monocytes (TEMs), tyrosine kinase with Ig, Golgi protein 73 (GP73), glypican-3 (GPC3), squamous cell carcinoma antigen (SCCA) and interleukin-6(IL-6), are proposed for the early detection of HCC.[3,22,23] The diagnosis of HCC is mainly based on noninvasive standard imaging methods, such as dynamic multiphasic multidetector-row CT (MDCT), magnetic resonance imaging (MRI) and ultrasound (US).[24] Recent innovative procedures exhibit beneficial effects in HCC treatment by using drug-eluting-beads and radioembolization using Yttrium-90. Sorafenib is currently the only approved treatment for HCC. Regarding prevention of HCC recurrence after surgical resection, the addition of antiviral treatment has proven to be a rational strategy. Various Strategies aimed at eliminating the virus may provide opportunities for effective prevention of the development of HCC. Pegylated interferon plus ribavirin therapy appears to be effective at reducing the risk of HCC in patients who achieve sustained virological responses.[25]

Herbal Treatment of HCC

Herbal treasure options or complementary alternative medicine (CAM) offers a host of new phytochemicals that could be helpful as a preventive and clinical in managing the liver associated imbalances involving HCC. Several food items, as well as herbs that we use in our every-day life, could be protective agents against liver cancer. Studies have shown that traditional medicines could delay 1) tumor progression, 2) increase survival and life quality, and 3) improve the quality of life due to synergistically efficient chemotherapy/ radiotherapy options.[26] Plants such as *Annona atemoya*, *Andrographis paniculata, Boerhavia diffusa*, *Piper longum*, *Podophyllum hexandrum*, *Phyllanthus amarus*, and *Terminalia chebula* have showed their antitumor properties against humans. These plants comprise of certain chemicals that might Some of these plant products have been found to contain chemically defined components that can protect theliver from oxidative injury, enhance the elimination of virus, stop fibrogenesis and tumor growth. Dietetic powder like green tea has shown anti-proliferative property in hepatoma cells, and hypolipidemic property in the hepatomic rats.[26,27] Several natural compounds could enhance immunity and anti-tumor activities such as *Macarangatriloba*, leaves, food antioxidants like phenolic compounds, carotenoids, β-carotene, bilberry extract resveratrol, triterpenoids, polysaccharide-rich substance, saikosaponins, baicalin, organic germanium, rutin, and zinc, and compounds produced by the fermented milks.[28] Meta-analysis studies have shown that Chinese herbs are beneficial in regulating the virus stimulated HCC and reducing the chemotherapy side effects.[28] Dry powder rhizomes of *Acorus calamus* have been used with water in different areas of India. Beetle vine and *Andrographis paniculata* leaves are given to people suffering from jaundice.[27,29] A recent study has shown an entire HCC reversion after using herbal medicine but stillthemechanism of action is not clear.[29,30]

HCC Anticancer Herbs

Plumbago zeylanica

Plumbago zeylanica is isolated and extracted as plumbagin, whose major role is to inhibit spread and growth of cancers including liver cancer. *Plumbago zeylanica* has a robust neuroprotective, antioxidant, immunoenhancing and hepatoprotective properties. Results have confirmed a significant inhibition of metastasis liver cancer by introducing 1, 4-naphthoquinone extract derived from plumbagin medicinal plant.[7]

Psoralea corylifolia

Psoralea corylifolia also known as "Boh-Gol-Zhee" in Korea and its active components are ashoreline, corylfolnin and bavachinin which possess strong anticancer activity. The major role of *Psoralea corylifolia* as itimproves the immunity of the human body by exciting natural killer cell function and is reported to inhibit in the cell cycle of G2/M phase in the cancer cells. *Psoralea corylifolia* also owns strong immunoenhancing, hepatoprotective and antioxidant properties. Extract from *Psoralea* inhibits mitochondrial dysfunction and ROS production persuaded by oxidative stress in liver cells.[31]

Podophyllum hexandrum

The major lignans from *Podophyllum hexandrum* are podophylin and podophyllotoxin known as Himalayan Mayapple. The active ingredient role of podophyllotoxin among all natural anticancer components as it possesses hematopoietic and radioprotective properties. A study done by Ganie *et al* suggests that ethyl acetate extract of *P. hexandrum*possesses *in vitro* antioxidant functions and acts as aliver-protective agent against CCl_4-induced hepatotoxicity.[32]

Solanum nigrum

Solanum nigrum, herbal plant belongs to South East Asia and are reported to have an inhibitive role on liver cancer growth. Its active key molecules are solamargine and solasonine that hinder cell growth and spread of uncontrolled cancer cells. Glycoproteins extracted from *Solanum nigrum* have apoptotic and antiproliferative properties. *Solanum nigrum* prevents growth and spread of HCC by autophagy as well as apoptosis. A higher dose induces apoptotic programmed cell death and lowers dosage results in autophagocytosis death of cancer cells. *Solanum nigrum* is known as a potent agent to treat HCC, by targeting the G2/M phase as well induction of apoptosis thereby achieving cell growth inhibition.[33] Solamargine is the extracted and purified from *Solanum nigrum*, which has antineoplastic effects. A water soluble component from this plant of *Solanum nigrum* genus consists of 60-90 percent of solamargine and solasonine.[34] This water soluble component acts as an active component in the pharmaceutical composition, inhibiting the growth of tumor cells particularly the liver cancer cells. These compounds were screened to discern the effect on human tumor cell growth inhibition *in vitro* by MTT assay and in mice with H22 liver cancer. Solamargine had significantly inhibited six tumor cells *in vitro*, coupled with inhibition of liver cancer in H22 mice.[35]

Zingiber officinale

Gingerols that is extracted from *Zingiber officinale* helps in killing cancer cells by inducing apoptosis. Active components such as 6-shogaol, inhibit the hindering development of new blood vessels and by inducing autophagy and apoptosis. It is unique property of antioxidant, anti-inflammatory and antimutagenic helps it to fight the growth of cancer cells. Higherexpression levels of NFκB and TNF-α was reduced significantly in rat with liver cancer treated with ginger extract. *Zingiber* extracts may

act both as an anti-inflammatory and anti-cancer agent for inactivating NFκB through the suppression of TNF-α pro-inflammatory pathways.[36]

Emblica officinalis

Amla is otherwise known as *Emblica officinalis* rich in gallic acid, vitamin C, tannins, flavonoids, and have reported defending against hepatoxicity-induced liver injury. Effect of *Emblica officinalis* against alcohol stimulated hepatic damage in rats has been studied, which showed the fruit extracts from *Emblica officinalis* possess antioxidant and nitric oxide (NO) scavenging property *in vitro* study.[37] Damodara *et al*, also reported in their *in vitro* study that no scavenging compounds were present in *Emblica officinalis*, as this might protect from free radical-mediated oxidative stress in the hepatocytes of rats with alcohol stimulated liver damage.[38] Amla decreased autophagy presences through Beclin-1 and Bax/Bcl-2 down-regulation and decreased the level of *N*-nitrosodiethylamine-enhanced hepatic apoptosis. Thus, supplementation with amla counteracts *N*-nitrosodiethylamine stimulated liver damage through its anti-autophagy, anti-apoptosis, antioxidant and anti-inflammation characteristics.[37]

Stylogne cauliflora

The methanolic extract of *Stylogne cauliflora* plant comprises of two new oligo phenolic complexes to act as HCV NS3 protease inhibitors such as SCH 644342 and SCH 644343. *Stylogne cauliflora* has anti-HCV NS3 protease activity due to the presence of oligophenols.[39]

Elsholtzia rugulosa and *Thevetia peruviana*

Luteolin and apigenin are two natural flavonoids extracted from *Elsholtzia rugulosa* and *Thevetia peruviana* are recognized as anti-HCV agents targeting HCC cancer. A pharmacophore molecular feature was recognized from eight NS5B inhibitors nominated to inhibit it interactions. Finally, 20 chemical compounds exhibited important activity against HCV including luteolin and apigenin; thereby it acts as an active inhibition key molecule against NS5B polymerase enzymatic activity of HCV in liver cancer. A flavone subclass of flavonoids Luteolin-7-O-glucoside (LUT7G), has known to rise anti-inflammatory and anti-oxidant property, as the results from *in vitro* study suggests the anti-proliferative influence of LUT7G on HepG2 is related with G2/M phase cell cycle arrest via JNK stimulation.[40] Apigenin has also reported to stop the proliferation of liver cancer cells and results from Glaucio *et al* study suggests that apigenin stimulated apoptosis in HepG2 cells results in are duction of antioxidant defenses and might be mediated via H_2O_2-dependent pathway.[41]

Euphorbia antiquorum

The herbal extract of *Euphorbia antiquorum* plays a significant role *in vitro* inhibition and development of hepatoma cells and are known to possess the composition against the spread and growth of cancer cells.[42,43]

Stellera chamaejasme

The methanol extract of *Stellera chamaejasme* known as stelleramacrin has been evaluated for anti-tumor activity through active bioassay. Bioassay-based separation of the extract was performed to obtain seven diterpene compounds like pimelea factor stelleramacrin, gnidimacrin, huratoxin, stellerarin, sub-toxic, simplex in and neochemae-jasmin A and B.[43] Stelleramacrin A&B purified is active constituents having anticancer properties. Gnidimacrin or piemelea acts as a therapeutic agent against various cancers including liver cancer.[44]

Ginkgo biloba

Ginkgo biloba extract consists of 31.2% flavonolglycosides, 15.4% terpene lactones and 10.ppm of ginkgolic acid.[45] When this combination was applied, it constrains the growth as well as thespread of several potential cancers such as glioblastoma multiform, invasive estrogenreceptor as well as hepatocellular carcinoma by inducing apoptosis. It consists of ginkgolides (A&B) and ginkgetin known for its antioxidant activity. It is also known to reduce the side effects of radiotherapy and chemotherapy.[46]

Glycyrrhiza glabra

Glycyrrhiza glabra, a plant consists made up of various medicinal properties with pharmacological actions and could be used as a template for designing new herbal medicines. Flavonoids components derived from this herbal plant have strong antioxidant, antimutagenic, anticancer and hepatoprotective properties. Its active compound licochalone-A inhibits spread of various cancers and growth by arresting cancer cell division. Glycyrrhizic acid isolated from *Glycyrrhizaglabra* has powerful protection against aflatoxins and the value to cure varieties of ailments from a simple cough to hepatitis. Various studies have reported the chiefphytol constituents such as glabrin A&B, glycyrrhizin, triterpene sterols, glycyrrhizinic acid, and isoflavones saponin.[47]

Gossypium hirsutum

Gossypium hirsutum extract consists of asparagine, gossypol, arginine, resins, etc. The active component is gossypol which inhibits the spread and growth of various cancers including liver cancer by inducing cancer cell arrest and apoptosis. Gossypol is one of an active oxidative metabolite of various cancers plays a unique role from growth and spread.[48]

Nigella sativa

Black cumin seed oil also known as *Nigella sativa* inhibits cancer cell activity by eradicating few cancer cell types. Studies have shown that *Nigella sativa* is effective against cancer in animals, and could be effective like anti-cancer drugs.[49] Dithymoquinone and thymoquinone are isolated; have strong anticancer properties including HCC. Thymoquinone is very active in both hormone refractory and hormone sensitive to prostate cancer. Additionally, it possesses anti-inflammatory and immuno enhancing properties to protect liver cancer by enhancing the immune function of the body.[50]

Ocimum sanctum

Ocimum sanctum derivatives include eugenol, linoleic acid, and rosmarinine acid. It contains flavonoids such as vicein, orientin, cirismaritin, isothymusin, cirsilienol, apigenin & isothymonin. Vicenin and orientininhibit spread and growth of cancer like liver cancer especially by hindering supply of nutrients and oxygen to cancerous cells, thereby by causing cancer cell death.[51]

Oldenlandia diffusa

Oldenlandia diffusa extract consists of stigmasterol, oldenlandosides, oleanicoli acid, beta-sitosterol, flavonoid glycosides and p-coumaric acid. Urolic acids interact growth and spread of various cancers including liver cancer. Ursolic acid acts as typical cytotoxic effects on cancer growing cells and, therefore, promoting apoptosis.[52]

Aronia melanocarpa

Aronia melanocarpa belongs to eastern North America and are popular in Russia and Eastern Europe. Fruits of *Aronia melanocarpa* are the key plant source of phenolic ingredients, chiefly anthocyanin. Anthocyanin's is water-soluble pigments responsible for giving dark blue color to fruits, preventing the formation of n-nitrosamine in rats and thereby reduce the toxicity and growth of cadmium in kidneys and liver.[53] It has ahigh concentration of polyphenol and anthocyanin which stimulates circulation. It is highly rich in antioxidants that are reported to treat aconditions such as liver failure.[53]

Curcuma longa

Curcuma longa herb has an antioxidant property which helps in stimulating bile and acts as liver-protectant. Rhizome ethanolic extract of

Curcuma longa on thioacetamide stimulated liver cirrhosis into the rats showed hepatoprotective activity. The progress of liver cirrhosis might be prevented through anti-inflammatory and antioxidant properties of *Curcuma longa*.[54]

Hvdrastis canadensis

Berberine is an isoquinoline plant alkaloid produced from plant *Hvdrastis canadensis*, *Arcungelisia,* and *Berberineeris*. They exhibit anti-tumor activities in both *in-vitro* and *in vivo* studies and found effective against liver cancer.[55,56] Studies were conducted to evaluate the anti-tumor activity of berberine against Huh7 cancer, and WRL68 liver cellsdescribed that berberine stimulates Huh7 cells apoptosis through the mitochondrial pathway.[57]

Euphorbia antiquorum

The latex of *Euphorbia antiquorum* has reported having inhibitory effects on several different cancer cell lines. The hypothesis is that *Euphorbia antiquorum* cause's cell death via apoptotic pathway.[58] Their active compounds have demonstrated *in vitro* inhibition of hepatoma growth cells.[58]

Berberis vulgaris

Berberis vulgaris is a renowned plant with its herbal medical activity. Their root contains chelidone acid, berberine, berbamine, isotetrandrine, magnoflorine, columbamine, oxycanthine, and palmatine. It possesses immunoenhancing, anti-inflammatory, antioxidant and anticancer properties. It is known to interfere with the P-glycoprotein in the chemotherapy resistant cancer tissues. Abeer *et al* screened and compared the *in vitro* antidiabetic, antioxidant, cholinergic and anticancer activity of berberine active compound. Various concentrations of berberine chloride extract showed no inhibitory effect on normal blood cells butits ethanolic extract has shown an inhibitory effect against breast, colon, and liver cancer cell lines MCF7, CACO-2, and HepG2.[59]

Aloe vera

Aloe vera is also another natural plant that has to be processed correctly to maintain it cancer-fighting properties.[60] *Aloe vera* plant extract is acemannan that stimulates the immune system to accelerate wound healing as well as it possesses anticancer property. *Aloe vera* consists of super carbohydrates that protect against especially liver cancer. It plays a unique role of extraordinary antioxidant and thereby reduces side effects of radiotherapy and chemotherapy.[60]

Andrographis paniculata

The bioactive components of *Andrographis paniculata*are and rograholide which has strong anticancer and immuno enhancing activity. This extract directly exerts on tumor cells by stopping the G0/G1 phase of cell cycle thereby inducing apoptosis. *Andrographis paniculata* augments the activity of protective liver enzymes and thereby reducing side effects of radiotherapy & chemotherapy. Hepatoprotective effect of ethanolic *Andrographis paniculata* leaf extract in rats could lead to a reduced level of thioacetamide stimulated toxicity, the normalized level of reactive oxygen species, inhibited cellular proliferation, and stimulation of apoptosis in HepG2 cells.[61]

Bauhinia variegate

Bauhinia variegate inhibit the cell proliferation and spread of avarious type of cancer including liver cancer. It also known to poses significant hepatoprotective property. Rajkapoor *et al* studied the chemopreventive and cytotoxic effect of *Bauhinia variegata* was evaluated in *N*-nitrosodiethylamine stimulated human cancer cell lines and liver tumor in rats. Results showed the significant cytotoxic effect and chemopreventive ethanol extract of *Bauhinia variegata* against DEN-induced human cancer cell lines and liver tumor in rats.[62]

Rheum emodi

Emodin, a natural anthraquinone extracted from *Rheum emodi* possess antiproliferative properties in cancer cell lines. It is extracted from the rhizome of rhubarb and it reported to cause apoptosis of cancer cell types by several pathways in liver cance[63] and its active component 1, 3, 8-trihydroxy-6-methylanthraquinone is used in Chinese medicine for treating various diseases. It is also suggested that emodin induces apoptosis in liver cancer cell line through acomplex cascade of signaling pathways.[64]

Silybum marianum

Silybum marianum is isolated from seeds of milk thistle. It is known for its ancient herbal remedy method used to act as hepatoprotection thereby treating liver disease. It consists of flavonolignans that are composed of lignin moieties and flavonoid. Silymarin has two major roles in HCV infection at different levels as it exhibits immunomodulatory and anti-inflammatory actions that contribute to hepatoprotective effects as well as inhibits HCV replication in cell culture.[65] Numerous *in vitro* and *in vivo* studies have established the chemopreventive effect of silymarin against HCC; it exerts a positive influence on the balance of apoptosis cell persistence and by interfering with cytokines. It also possesses inhibitory effect and anti-inflammatory activity of silymarin metastases development. Silymarin could be administered as adjuvant therapy in some neoplastic diseases as well.[66]

Camellia sinensis

(−)-Epigallocatechin-3-gallate is the major constituent of green tea extracted from *Camellia sinensis*, which can induce apoptosis and inhibit cell proliferation in various types of human tumors. Studies have shown EGCG induced apoptosis and suppressed angiogenesis in liver metastases without hepatoxicity.[67] It was studied and concluded that the combination of ascorbic acid and EGCG strongly suppressed metastasis of liver cancer cells and proliferation, as it must be related to scavenging of reactive oxygen species.[67] The liver metastatic area was significantly reduced by EGCG administration and also reported to induce apoptosis in different HCC cells by down regulating P13K/AKT activity by affecting cell cycles and acting as a potential anticancer agent in the prevention of HCC.[68]

Ballotanigra

Studies have reported ladanein extracted from plant *Ballotanigra* inhibit post-attachment of HCV in HCC and prevent primary human hepatocytes from infection.[69] The antiviral activity of ladanein has been demonstrated effective against all HCV genotypes which lead to liver cancer.[1,70]

Melastomade cemfidum

Naringenin is a phylotexin extract from *Melastomade cemfidum* and is found in tomatoes and grape fruits known for its wide pharmacological effects. Studies reported by Lee *et al* have showed the shielding character of naringenin on hepatic damage caused by dimethyl nitro samine (DMN) in rats. Reports suggest that naringenin can be used to prevent the development of hepatic fibrosis. Pari *et al* studied the antioxidant property of naringenin to fight the damage cells in the liver as well as it decreases the lipid peroxidation against induced oxidative stress in the liver.[71]

Swietenia macrophylla

3-hydroxy caruilignan is extracted from *Swietenia macrophylla* stems. Studies have reported 3-hydroxy caruilignan-C, a potential anti-viral agent which interferes with HCV-replication via inducing IFN stimulated transcription element as well as IFN dependent anti-viral gene expression in the liver cells. 3-hydroxy caruilignan hindered HCV RNA-replication in Huh7 cells harboring a HCV subgenomic RNA replicon.[72]

Thereby, 3-hydroxy caruilignanis noted as apotential adjuvant to for anti-HCV therapy in liver cancer patients.

Magnolia officinalis

Honokiol is the lignin present in the bark, leaves, and cones of *Magnolia officinalis*. The extract of the plant is used earlier in Japanese medicine. Honokiol, like naringenin and EGCG, affects the HCV infection through cell entry and replication shown in Huh-7 cells.[73]

Blumea balsamifera

Blumea balsamifera also known as sambongis grown in South East Asia. Its leaves have different physiological actions, including antifungal, plasmin inhibitory and liver protect effects. It also decrease the level of proliferation related to ligands that in turn stimulate tumor cell growth. *Blumea balsamifera* is known to be effective against HCC cell in the liver and its extract induced growth-inhibitory activity HCC and in rats without cytotoxicity in rat hepatocytes used as cell model suggest that *Blumea balsamifera* has potential therapeutic property in hepatoma cancer patients and significant mechanism in the BME growth inhibitory.[74]

Panax Ginseng

Panax Ginseng is one of the known Chinese and Korean traditional herbal medicines used worldwide. It belongs to the family of Araliacea. The most chief bioactive component of ginseng is ginsenosides which are the secondary metabolite containing glucose moiety. Liver cancer tissue showed decreased odd ratios with increasing ginseng intake. It has been tested for their inhibiting putative carcinogens mechanism such as apoptosis, immunosurveillance, proliferation and angiogenesis.[75]

Astragalus membranaceus

Astragalus membranaceus is used to treat advanced cases of HCC by the Chinese medicines. One of the derivatives for *Astragalus membranaceus* is swainsonine which is known to prevent metastases. Research studies have also showed a high prevalence of patients administered with *Astragalus membranaceus* compared to the patients treated with conventional treatment alone. *Astragalus membranaceus* is also used with *Ligustrum lucidu*m herb in China. *Astragalus membranaceus* is combined with *Panax ginseng*, and has regulatory effect on natural killer cell and improves immune cells activity and regulate secretion of cortisol stress hormone, followed by antitumor activity *in vivo*, increasing host immune response, and effective for anti-tumor therapy.[76]

Betula utilis

The active constituents of *Betula utilis* obtained from the plant shows anticancer, anti-inflammatory, anti-HIV, antioxidant and antibacterial activity. Betulin is the plant extract of *Betula utilis* which is converted into betulinic acid, which has been revealed to inhibit the growth of liver cancer tissues.[77]

Camellia sinensis

This herb comprises polyphenolics compounds that are known to possess anticancer and antimutagenic action. Research experiments conducted have concluded that both the extract of green tea and black tea that have its major polyphenolic constituent (-)-epigallocatechin gallate inhibited liver tumor cells from synthesizing DNA. It inhibits the uncontrolled growth of cells by eradicating the free radicals present in the body.[78]

Fagopyrum esculentum

This herb is used to treat cancer as it a key component amygdalin as a chief role as ananticancer activity. Amygdalin is natural cyanide-containing substances in the liver by enzymes called beta-glucosidase to form as glucuronic acid. Glucuronidase is alternative important enzymes that are present in higher concentration in the cancerous cells, breaks the glucuronic acid to secret cyanide that in turn destroys cancer cells. Cancer cells donot contain enzyme rhodanese which is found in the normal cells. Rhodanese protects healthy cells from the killing effects of cyanide by changing cyanide into moderately harmless substance identified as thiocyanate.[79,80]

Glycine max

It is also known as Soya bean rich in selenium, zinc, amino acid, aprotease inhibitor, phytosterols, isoflavones and vitamins (A, B1, B2, B12, C, D, E and K). Studies have revealed isoflavones convert cancer cells to healthy cells by differentiating cells. Genistein is an isoflavone which are found higher concentrations in soy products, that causes apoptosis in cancer cells. It is also known to prevent platelet aggregation that promotes the spread of cancer cells, as it hinders the synthesis of DNA in cancer cells, thereby preventing the growth of cancerous cells. Experiments have shown genistein and its isoflavones prevent the growth of cancerous cells by inhibiting angiogenesis (formation of new blood vessels). Thereby enhancing immunity of the healthy cells and increasing the survival period in the liver cancer patients.[80]

Picrorrhiza kurroa

It is also known as Kutki and shown to reduce the formation of HCC due to exposures of the chemical as its active herbal constituent's icrosides-I, II and III and kutkoside. This herb has the property to lower the levels of hydroperoxides and lipid peroxidases, and facilitate recovery of antioxidant to prevent the liver from oxidative impairment.[80,81]

Foeniculum vulgare

Studies have evaluated the efficiency of *Foeniculum vulgare* seed methanolic extract for its antitumor antioxidant and cytotoxic, events and for its ability to serve as non-toxic radioprotector in Swiss albino mice. *Foeniculum vulgare* seed methanolic extract may defend mouse cells from injury via reduce oxidative stress due to reactive oxygen species. It is an effective, safe, and easily accessible source of natural antioxidants to recover the oxidative strength of fatty foods through storage. *Foeniculum vulgare* seed methanolic extract also presented an anti-tumor property through augmentation of antioxidant defense system modulating lipid peroxidation in EAC-bearing mice with or without radiation exposure.[82] Also known as wild pepper fennel, it has been reported to have remarkable anticancer property by targeting the HepG2 liver cells lines.[83]

Classic herbal composite formula and their clinical studies

Shi-Quan-Da-Bu-Tang (TJ-48, Juzen-taiho-to in Japanese) is a classic herbal composite formula comprises of ten herbs which include Cinnamon, Chinese angelica, Liquorice root, Mongolian milk vetch root, Ginseng root, Large head atractylodes rhizome, Radix rehmanniae root, Tuckahoe, White peony root, and Szechwan lovge rhizome. In Asia, an extensive use of TJ-48 has been observed in medical practice even without its clear mechanism of action. Protective role of TJ-48 has been observed in surgically treated HCC patient's against hepatocarcinogenesis. Studies have shown a significant recurrence-free survival of HCC patients treated with a group of TJ-48.[84] Xiao-Chai-Hu-Tang (TJ-9, Shosaiko-to in Japanese) is another classic herbal composite formula, usually given to chronic liver disease patients for their physical improvement and inhibition of liver cancer development. Crude extracts of TJ-9 comprises of seven herbs which include Bupleurum root, Ginger rhizome, Ginseng root, Glycyrrhiza root, Jujube fruit, Pinellia tuber, and Scutellaria root. The protective role of TJ-9 against HCC development was also investigated. Two hundred and sixty cirrhosis patients were divided into two groups according to age, sex, incidence of hepatitis-B surface antigen, and severity level of liver injury. Trial group patients have been given 7.5 g daily oral dose of TJ-9 along with conventional drugs given

to control patients with continuous monitoring of sixty months. A significant increase in the survival of trial group patients without hepatitis-B antigen was observed compared to control group. It was concluded that TJ-9 might inhibit HCC development in cirrhosis patients especially with negative hepatitis-B antigen.[85] Further studies has also shown the protective role of TJ-9 against two hundred and sixty cirrhosis HCC patients that were distributed according to their age, sex, and occurrence of hepatitis-B antigen. Results have shown that the HCC occurrence was considerably decreased in the trial group than the trial group. So, it was established that TJ-9 might inhibit or delay HCC development in cirrhosis patients.[86] But, there is a study limitation concerning the duplication of studied patients. Furthermore, these results presented by some authors with similar time-interval, and without any description of different or same patients. Hence, the promising role of TJ-9 might be considered but further studies are required by different authors/institutions to validate these findings.

Another herbal composite formula in Chinese herbal medicine is Bu-Zhong-Yi-Qi-Tang (BZYQT), encompassing of eight herbs which include Chinese angelica, Bupleurum root, Liquorice root, Ginseng root, Large head atractylodes rhizome, Mongolian milkvetch root, Skunk bugbane rhizome, and Tangerine. Studies have been conducted to investigate the BZYQT effects on granulocyte-colony stimulating factor (G-CSF) and the production of TNF-α through peripheral blood mononuclear cells (PBMC) in healthy individuals and HCC patients. It was observed that production of G-CSF and TNF-α was considerably activated by BZYQT in healthy individuals and HCC patients. But, G-CSF and TNF-α stimulation level was less in HCC patients compared to healthy individuals. It was concluded that BZYQT could play a distinctive role in the activation of PBMC to produce G-CSF and TNF-α. Also, it might enhance the defense mechanism of patients toward HCC.[87] Although, the study has limitations which include reduced BZYQT distribution of pharmacokinetics effects in HCC patients, and it might be the key limitation in clinical evaluation at large scale.

Experience Herbal Composite formula and their clinical studies

Generally, the herbal composite formula could be used as apalliative and adjuvant treatment against HCC instead a direct tumor cells killer. The objective of the use of this formula is alleviation of the symptoms, liver function recovery, and life quality improvement. Most of the work on theuse of this composite formula is retrospective, and acomponent of herbs in this formula has not been well-defined. This formula has been used with a combination of conventional palliative treatment like transcatheter arterial chemoembolization.

The study investigated Chinese crude drug effect on liver function and some post-transcatheter arterial chemoembolization (TACE) HCC patients. Forty-five post-TACE HCC patients have been treated with herbal crude whereas the rest thirty-seven patients being the control group were treated with routine therapy. Observed symptoms were abdominal distention, anorexia, nausea, lassitude together with α-fetoprotein (AFP) and liver function. Therapy was ended with improved hepatic function and symptoms. It was concluded that post-TACE HCC patients liver function and their life quality improved through the prescription of Chinese crude drugs.[88]

Another study has done meta-analysis for the comparison of efficiency and safety of Chinese crude drug and TACE (therapy-I) and with TACE alone (therapy-II). Overall, thirty-seven trials were carried out with 2653-patients. Results have shown that therapy-I enhanced life quality of patients and their survival, alleviated symptoms and an enhanced response against tumor response in comparison to the therapy-II. So, the therapy-I has shown therapeutic benefits without any side effects.[30]

Further studies investigated the efficacy of Chinese herbal medicine with a combination of chemotherapy. The study was included with a search of databases including PubMed, EMBASE, and TCMLARS. Also, bibliographies of studies that were recognized in a systematic search for possibly related study abstracts or titles in any language. Random effects meta-analysis have been applied in twenty-six studies involving 2079-patients. The results have shown an increased survival rate as well as tumor response against Chinese herbal medicine plus chemotherapy in comparison to chemotherapy alone.[89]

Shenqi mixture (SQM), an herbal composite formula composed of Ginseng root and Mongolian milkvetch root. An investigation was carried out to check the efficacy as well as the safety of SQM plus microwave coagulation for HCC treatment. The size of the tumor, symptoms, AFP serum level, and few immune factors have been estimated. Results have shown a reduced level of AFP, and tumor size. The $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ levels, Karnofsky scores, the activity of NK, and hepatic function have been enhanced with SQM plus microwave coagulation treatment in comparison to microwave coagulation alone. Survival rate, as well as symptoms like hepatic pain, jaundice, fever, poor appetite, and weakness, were improved due to SQM.[90]

Herbal Composite Formula and its Experimental Studies

Cell Culture Studies

An *in vitro* activity of herbal composite formula with adefinite constituent or indefinite constituent was checked extensively against HCC. Lycium barbarum (LBE), as well as the *Rehmannia glutinosa* (RGE) extracts, were used to check the apoptosis and cell proliferation in human (HA22T/VGH) HCC and rat (H-4-II-E) cells. Both cell lines have been treated with different concentrations of LBE and RGE, and their apoptosis, cell proliferation, and level of p53 protein measured. It was observed that both cell lines have prevented the proliferation of H-4-II-E and of HA22T/VGH cells whereas the apoptosis and p53 have improved in H-4-II-E cells treated with crude LBE and RGE.[91] Another study was carried out to check the chemopreventive role of *Cornus officinalis* extract toward HCC by three HCC-cell lines (HepG2, PLC/PRF/5, and SK-Hep1). The role of this extract as the herbal composite formula was considered due to the following reasons. First, single herb might be a composite formula as per Chinese herbal medicine, as in the case of Ginseng Decoction where Ginseng is the only content. Secondly, the C. officinalis Sieb. et Zuce is an extract of several compounds. The study has shown that growth of all HCC cells was inhibited due to the extract of this compound and it was described as a chemo-preventive agent toward HCC with anti-neoplastic effects.[92]

The study was performed to investigate Xiaoliu Pingyi Mixture (XLPY) induced apoptosis in the human HCC cell line H-7402. Serum pharmacologic method was used in the treatment of cells despite the direct addition of herbal agent in the culture medium. It was observed that XLPY loaded serum could considerably impede the growth of HCC and stimulate apoptosis process. The XLPY also stopped Bcl-2 expression in H-7402 cells.[93] Also, the anti-HCC role of TJ-9 which is classic composite formula was investigated. Efficacy of TJ-19 extracts was extensively explored against HCC. Also, its effects were analyzed on G-CSF and TNF-α in peripheral mononuclear cells of HCC plus liver cirrhosis patients which have shown an enhanced level of G-CSF and TNF-α. It was described that TJ-9 might increase defense mechanism through an enhanced level of G-CSF and TNF-α which consequently could improve the physical condition of HCC patients.[94]

Further studies explored the role of TJ-9 ingredients (baicalin, baicalein, ginsenoside Rb1, ginsenoside Rg1, saikosaponin-a, and saikosaponin-c)

on human hepatoma cells (HuH-7). Cell-cycle analysis has been performed by bromodeoxyuridine (BrdU) labeling method and flow cytometry. It was observed that baicalin, baicalein, and saikosaponin-a reduced the cell proliferation in a dose-dependent manner. However, saikosaponin-a showed cell-killing effect whereas ginsenoside Rb1, saikosaponin-c, and ginsenoside Rg1 had shown no influence over cell proliferation.[95] Chai-Hu-Jia-Long-Gu-Mu-Li-Tang (SGYMT; Saiko-ka-ryukotsu-boreito in Japanese) is a classic composite formula. Its extracts comprise of eleven herbs: Bupleurum root, Cassia twig, Dragon's bone, Ginseng root, Ginger rhizome, Jujube fruit, Glycyrrhiza root, Rhubarb, pinellia tuber, and Scutellaria root. The SGYMT extracts and its herbal constituents were analyzed to check their inhibitory effects on the tumor-specific matrix metalloproteinases-2 and 9 (MMP-2/9) properties in HCC cell line (SK-Hep1 cells). It was observed that SGYMT reduced the MMP-2 and 9 activities, but SGYMT and its ingredients cytotoxicity's checked on SK-Hep1 cells were lowest. Also, SGYMT has shown an effective inhibition against SK-Hep1 cells invasion in comparison to control groups. Hence, it the SGYMT might be described as a possible anti-tumor metastasis agent.[96]

Animal Model Studies

Qingrejiedu, Huoxuehuayu, Fuzhengguben (QHF) is an herbal composite formula comprises of Lentinan, Ginsenosides Rg3, Norcantharidin, and Tanshinone. The study was performed to investigate the role of QHF ingredients against HCC. Effects of QHF plus cisplatin has been observed in HCC cells implanted mouse model. Results have shown that growth of HCC cells was inhibited, and life span of HCC mice was also prolonged due to QHF treatment. Additionally, the combination of QHF and cisplatin could also ameliorate cisplatin-activated leucopenia, spleen, thymus atrophy, and other toxic reactions.[97] Effects of another composite formula called Fuzheng Jiedu Decoction (FJD) were investigated against HCC by male BALB/c athymic mouse model. The intrahepatic metastasis, survival rate, and tumors volume were investigated. Results showed a significant increase in the rate of survival and reduced tumor intrahepatic metastasis. Histochemical results have shown an enhanced intensity of phosphatase and tensin homolog deleted on chromosome ten (PTEN) stained in a tumor tissue with FJD treatment. It was concluded that rate of survival and reduced tumor intrahepatic metastasis could prolong with FJD treatment.[98] Another study analyzed theanti-cancer effect of Chinese herbal composite formula Star-99 against HCC mouse model.

Four injections of Star-99 have been given after every five days to a nude mice that were transplanted with human HCC SMMC-7721 cells. The value of tumor, growth index, and apoptosis has been calculated. It was observed that the Star-99 could reduce the size of the tumor, and considerably enhanced the apoptotic index. Also, Star-99 could be considered a better treatment of HCC.[99]

Bletillastriata was used as a TACE agent against HCC rats. The *Bletillastriata* has been crushed into micro-particles, and the rat HCC hepatically implanted model induced in the hepatoma cells. It was observed that *Bletillastriata* plus mitomycin using TACE have reduced tumor growth that was implanted in the liver. Also, thesurvival rate of HCC rats considerably increased, and Bletilla was described as an anti-HCC agent.[100] Another study was carried out to analyze theTJ-48 effect on HCC performed through DEN stimulated HCC mouse model. Inhibition activity of TJ-48 reduced the liver tumor development with decreased cytokine expression, oxidative DNA damage, and inflammatory cell infiltration.[101] Also, it was observed that TJ-9 decreased pre-neoplastic cells that have been identified as glutathione S-transferase-P (GST-P) positive hepatocytes, decreased liver tumors growth, and considerably decreased 8-hydroxy-2′-deoxyguanosine (8-OHdG) production.[102]

Safety and Future Study

There might be several potential herb derived drugs used against HCC as a chemopreventive and chemotherapeutic strategy. Several compounds obtained from herbs were *in vitro* and *in vivo* studied against HCC since long to enhance our knowledge regarding their biological roles and targets. But, still there are few concerns about the effectiveness of herbal medicines despite many years study and improvement in our understanding of molecular targets. To address this concern, herbs derived biological active compounds must be well defined and comprehensively standardized. Herbs and compounds of interactions have shown a better biological role. So, the herbal composite formulas are biologically more effective and one must be very careful while excluding the compound from herbal composite formula even if the compound has no role as itself.

Another concern is about the variation of *in vitro* and *in vivo* results. In China, several clinical trials were carried out with a focus on the use of herbal composite formulas against cancer. But, randomized, high quality and placebo-controlled clinical studies are required to get more knowledge and reduced the exaggerated effect of composite formula and herbal compounds. In contrast to this, these trials could provide a foundation to further explore the pharmacological effects of anti-HCC herbs that need a comprehensively validated data. Hence, there is a need for clinical trials that could analyze replicable herbs derived compounds for effective therapeutic applications.

Safe use of herbs without any side effect is another concern. Most of herbal experts usually recommend traditional herbs which are organic, unrefined, pure, traditionally prepared, and described in Chinese, Korean, and Japanese. Also, the toxic effects especially hepatotoxicity are contrary to the view that the herbs are harmless and natural. Hence, toxicity and safety studies must be focused prior to ultimate clinical guidelines. Hence, it is concluded that the herbs derived compounds are safe and effective against HCC and cirrhosis in small single-center studies. But, standardized preparation, purity, and active compounds with a combination of natural ingredients must be specified to achieve quality, and establishing Phase-2 and 3 trials which could validate these fascinating/positive results against this devastating disease.

CONCLUSION AND DISCUSSION

Several types of research are still going on the use of medicinal plants with anticancer properties, including liver cancer. Since many varieties of species are active in the different experimental system, the medicinal products from plants continue to be a rich source of biologically active compounds. Still there are a lot more steps for further studies on chemical characterization as well as standardization of the extract used. With the help of pharmacological studies, most of the test experiments are performed in a mice model. However, there are research studies in human system for various types of plant extract. This review discusses various medicinal herbs that have been examined for anti-liver cancer activity, presenting an important route into their use for the treatment of liver cancer. Although new research findings have shown extracts on potential phytotherapeutic ligands in advanced liver cancer therapy which could lead to greater safety and benefits for the people, resulting in better success in health care and thereby improving the quality of life in patients having liver cancer.

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CONFLICT OF INTEREST

All authors disclose no conflict of Interest.

ABBREVIATION USED

C/EBP bet: CCAAT-enhancer-binding proteins, **CRE**-: *cAMP response element-binding* protein, **HNF1/4**- Hepatocyte nuclear factor-1, **Fox O-:** Forkhead box protein O1, **PGC-:** Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, **CD3**-: Cluster of differentiation 36, **Ras:** Ras protein subfamily, **Ra**: oProto-oncogene serine/threonine-*protein* kinase, **JN**: c-Jun N-terminal kinases, **p38 MAP**-: Mitogen-activated protein kinase 14, **p5**: Tumor protein, **pRB/p16INK4-:** Tumor suppressor protein, **TGF-β-:** Transforming growth factor beta 1, **NFκ-:** Nuclear factor kappa-light-chain-enhancer of activated B cells, **TNF:** Tumor necrosis factor alpha, JNK-c-Jun -: Terminal kinases, **G-CS-:** Granulocyte colony-stimulating factor, **CD3$^+$, CD4$^+$, CD4$^+$/CD**: Cluster of differentiation, **Bcl:** (B-cell lymphoma 2, **PTE**: Phosphatase and tensin homolog.

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PICTORIAL ABSTRACT

SUMMARY

- In this article, a recent update on the herbal medicine has been provided with reference to liver cancer. For the sake of clarity, the effective herbal compounds, clinical studies of herbal composite formula, cell culture, and animal model studies safety are discussed.
- The effects of many herbal active compounds and herbal composite formula on autophagy, apoptosis, antioxidant, and inflammation characteristics have been provided.
- This will enhance our understanding on the prevention and treatment of HCC by herbal active compounds and herbal composite formulas.

ABOUT AUTHORS

Shilu Mathew graduated her Bachelorsin Industrial Biotechnology with distinction from Dr. MGR University (2004) and therefore she was awarded to study with scholarship from Department of Science & Technology (DST) from New Delhi to complete her Master in Engineering and Technology in Medical Nanotechnology at SASTRA University (2008) as well as Master's in Bioinformatics from Loyola College. She accomplished both her degree projects, by combination of both wet lab and insilico study, which had encouraged boosting her skills in Bioinformatics too. She is currently working at the Centre of Excellence in Genomic Medicine Research (CEGMR) as Research Assistant for 4 years in various cancer research projects, utilizing genetic and epigenetic up-to-date technologies and approaches. Her current research projects utilize next-generation sequencing technology to perform whole exome sequencing, mRNA sequencing, genome wide methylation analysis, gene expression, and cloning as well as methylation analysis for different types of cancer specific type of genes. Her research interest focuses on nanomaterials, biomaterials, drug delivery, bio polymers, polymer science, material science, bio sensors, toxicology and expertise in Ion torrent, Next generation sequencing-NGS, qPCR, multi-plex PCR, synthesis competent cells, Genescan, Microarray, Agilent, Molecular virtual docker, Schrödinger, Auto dock 4.0, Discoveries, NAMD, GROMACS, Modeler ACD Chemsketch, Oracle-molevol, Phylogeny related-PAUP and PAML.

Dr. Ishtiaq Qadri is a Professor at the King Fahd Medical Research Center King Abdul Aziz University, Jeddah Saudi Arabia where he is enthusiastically involved in the study of liver adaptive responses, nanosensor development, specific gene expression and regulation during insulin resistance and hepatic steatosis. He completed his PhD in 1989 from Imperial College of Science and Technology, London UK (1984-1988) and later carried out post-doctoral research at the University of California San Francisco, CA, US (1988-1993) , and University of Colorado Health Sciences Center, Denver CO USA (1994-1998) . He has published over 100 peer-reviewed research papers in international journals. He is the recipient of over 28 international R & D grants funded from NIH USA, American Liver Foundation, Colorado League of Cancer, US-State Dept, Bio-Safety Engagement Program of US, Pasteur Institute of France, Higher Education Commission, Ministry of Science and Technology Science Foundation.

The focus of his current research is on:

- Development of nanobiosensor for biological interactions.
- Understanding the key signaling pathways of viral induced HCC.
- Understanding the genetic control of HCC.
- Identification of novel Bio-markers for Fibrosis.
- Understanding the mechanism(s) of IFN resistance.