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Review Article

From Traditional Practices to Modern Interventions: Exploring Herbs Role in Treating Liver Cancer Following Its Signalling Pathways

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ABSTRACT

The foremost hepatocellular carcinoma is a primary reason for cancer-causing death globally. It ranks as the second main factor in male cancer-related mortality and the fourth nearly prevalent neoplasm overall. Compared to women, men are more likely to acquire hepatoma. Many risk factors have been related to liver cancer, which includes cirrhosis, NAFLD, NASH, viral hepatitis, intake of alcohol, aflatoxins, obesity & diabetes, iron overload, tobacco use, exposure to certain chemicals, family history, etc. Any chronic inflammatory liver disease can cause HCC, but cirrhosis is the pathophysiological process that is present in cases of the disease. There are several treatment approaches available for hepatocellular carcinoma (HCC), including surgery, immunotherapy, liver transplantation, and chemotherapy. However, these treatments have not significantly improved outcomes for HCC patients. An herbal medicine containing natural compounds has become a viable therapeutic choice for various diseases, including cancer. Among these, some herbal components are interested in treating HCC. All these below-mentioned plants have anticancer properties. They work against cancer cells through various pathways and are responsible for apoptosis, antiproliferation, cytotoxicity, etc. All this study has been conducted on multiple cell lines *in-vitro* studies. Herbal medicine is often more affordable and accessible than conventional cancer treatments, particularly in regions where access to healthcare is limited. Growing attention has been shown in researching and developing herbal medication used to treat cancer, leading to the discovery of new compounds and formulations with potential therapeutic benefits. In this aspect, we are highlighting various expected pathways to cure HCC.

INTRODUCTION

Cancer ranks among the most prevalent non-communicable illnesses globally. Cancer continues to be a major global reason for demise. In recent years, research efforts have increasingly aimed to develop new therapies to minimize the side effects of traditional cancer treatments.[1] Malignant growth, or unchecked cell development, is the precursor of cancer. Amongst all cancers worldwide, hepatic cancer is a commonly occurring hepatic primary carcinoma, particularly in areas where viral hepatitis infection is common. HCC can also start and progress as a result of autoimmune diseases, diabetes mellitus, obesity, alcohol use, and inflammation.[2] Cancer is ranked as the second most prevalent reason of death worldwide.[3] Recently, despite numerous challenges, there has been increasing promise in plant-derived drug research, presenting a viable alternative to synthetic medicine and therapeutics. The focus of research lies in uncovering and harnessing the potential of bioactive natural compounds extracted using different herb parts, which is a significant area of interest for chemists, biologists, pharmacists, and medical experts aiming to explore the potential of these remarkable molecules.[4] Natural products are valuable for drug development, particularly in cancer research. Between the 1940s and December 2010, approximately 48.6% of tiny molecules with anticancer properties were either derived by using natural compounds or inspired by them.[5] Conventional cancer treatments are recognized

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for their high toxicity and serious adverse effects that negatively impact patients' quality of life to a significant degree. Moreover, these treatments typically provide no more than a 6 month increase in life expectancy. Medicinal herbs have played an important role in traditional medicine and are increasingly studied for their potential therapeutic benefits.[6] These molecules should be non-toxic, selective in targeting, possess little adverse effects, and spare healthy host cells while targeting cancer cells. Natural ingredients have been found to impede cancer progression and promote mechanisms linked to disease prevention.[7]

Herbal Plants used in Hepatocellular Carcinoma Treatment

Annona muricata

Annona muricata L., another name is soursop and guanabana, is a perennial tree in subtropical regions. *A. muricata Lin.* Be held by the Annonaceae family, comprising more than 2300 species and around 130 genera. Many substances found in *A. muricata L*. have pharmacological action. Annonaceous acetogenins are potent phytochemicals found in the graviola plant (*A. muricata*) that are unique to the family.[8] The phytochemicals found in *A. muricata* were identified for their antioxidant, antimicrobial, anti-inflammatory, insecticidal, and larvicidal properties, as well as their ability to be cytotoxic to cancer cells. When investigating the impact of *A. muricata* extract on the PI3K/Akt pathway, that is discovered that the extract notably decreased the phospho-Akt level.[9]

Subin Varghese Thomas *et al.* have investigated the study of fruit extract of *A. muricata* in DEN-induced hepatoma in male Wistar rats. Annonaceous acetogenins induce cytotoxicity, partly by inhibiting mitochondrial complex I, which plays a role in respiratory chain phosphorylation and adenosine triphosphate synthesis. The aerial segments of the graviola plant have been extensively researched, demonstrating various activities related to pharmacology.[10]

Artemisia vulgaris

It is well known that the evergreen rhizomatous plant *Artemisia vulgaris L.,* sometimes known as mugwort, infests waste sites, roadsides, agronomic settings, and landscapes. It's a member of the Asteraceae family. The Greek queen of shooting animals is the source of the genus name, *Artemisia*. Introduced as a deciduous perennial. *A. vulgaris L*. has a well-developed rhizome that spreads rapidly.[11] Artemisinin and its derivatives have exhibited cytotoxic effects against cancer cells. Because of these qualities, artemisinin's selective toxicity makes it a potential anti-carcinoma agent. These qualities suggest that there will be fewer adverse consequences, which will protect users.[12] The extract from *A. vulgaris* is utilized as an immunomodulator to support a primary treatment.[13] The impact of *A. vulgaris* induces apoptosis by increasing intracellular ROS.[14]

Ponlawat Maki *et al*. conducted a study on Cancer cell lines of human liver hepatocellular carcinoma (HepG2) that were used in this experiment. In HepG2 cell lines, the ethanolic extract of *A. vulgaris L*. aerial portion exhibited cytotoxicity. According to the principle of Thai traditional medicine, this study supports using this plant to treat patients with liver cancer. Specifically, bitter Herbs are utilized to treat bitter organ illnesses, such as liver cancer.[15] Sharmila K *et al.* assess the effect of the extract made using methanol and *A. vulgaris* leaf on the growth of HepG2 cells using the *in-vitro* method, i.e., the MTT assay.[16] S. Ali *et al*. assessed the *A. vulgaris* extract's chemopreventive and chemotherapeutic potential against DEN-induced hepatoma in species balb c mice. In this study, biomarkers like lactate dehydrogenase, AST, ALT, and beta-glutamyl transferase were evaluated for their activity, showing a significant decrease in its level on the use of extract of AV in DEN-treated mice. The DMSO method measured the total bilirubin level (TBL). They performed a solid-phase ELISA test for the quantitative assessment of the cancer marker alpha-fetoprotein (AFP) antigen (CEA), which shows a remarkable decrease in the level of AFP and CEA on using *A. vulgaris* extract.[17]

Eclipta alba

Eclipta alba (L.) Hassk. which is from the family Asteraceae. It features mature, cylindrical, grayish roots. The roots, leaves, Panchanga (a term likely referring to different plant parts, including the stems, leaves, flowers, fruits, and seeds), and beeja (seeds) of *E. alba* are all utilized. *E. alba (L.)* contains a diverse range of active constituents, these include coumestan derivatives such as wedelolactone and alkaloids like desmethyl-wedelolactone-7 glucoside found in the leaves. Other components in the aerial portions include luteolin-7-O-glucoside, ß-amyrin, ecliptal, hen triacontanol, heptacosano in the roots, and stigmasterol.[18] Medicinal plants play a important role in drug discovery.[19] In Ayurveda, it is known as Bhringaraj and has been used particularly for conditions related to liver health and hair.

The anticancer properties of a hydroalcoholic extract from *E. alba* were assessed. The extract inhibited the growth of HepG2 cells dose-dependent.[20] It regulates the protein kinase-B signal transduction, encourages and deters the unnatural growth of cells of the liver, downregulates HIF-1A expression, and prevents liver cancer.[21]

This study investigates the potential of a hydroalcoholic extract of EAE in treating liver cancer and reversing multidrug resistance (MDR) through animal experiments. The extract reduced reactive oxygen species (ROS) levels and demonstrated ROS scavenging properties. In liver cancer-induced animals, EAE treatment normalized elevated alpha-fetoprotein levels, indicating its therapeutic

effect. Zymogram analysis revealed MMP inhibition, and RT-PCR showed reduced nuclear factor-kB RNA expression with EAE treatment.[22]

Allium sativum

Allium sativum's common name is garlic and it belongs to the family Alliaceae alongside onions and is widely utilized both in medicinal and culinary contexts. Its historical roots trace back more than 6000 years to central Asia. It continues to be used in folk medicine globally to treat various illnesses. Throughout history, garlic has been widely used for its preventive and healing properties. Additionally, there have been observed immunomodulatory and antitumor effects associated with garlic in laboratory and animal studies.[23-25] The anticarcinogenic activity of garlic is attributed to its capacity to modulate the metabolism of carcinogens. S-allyl cysteine (SAC), a garlic derivative on HCC cells, shows the activation of cleaved CPP32/Yama/apopain and cleaved Caspase-9, along with the apoptosis of cells.[26]
Wu and colleagues documented a study examining the influence of *A. sativum* oil and its chemical constituents, like DADS and DATS, on the liver detoxification system. Garlic oil and diallyl sulfide (DAS) markedly enhanced the activity of pentoxyresorufin O-alkylate. Conversely, diallyl disulfide and diallyl trisulfide significantly reduced the effect of N-nitroso dimethylamine demethylase.[27] As per findings from a conducted study by Godwin Offumobi Ogar *et al*., the NDEA-exposed group exhibited significant liver architecture distortion, including vascular congestion, liver cirrhosis, and nutmeg liver. In contrast, the treatment-provided groups showed reduced abnormalities and malignant formation. The ethanolic extract of *A. sativum* exhibits cancer-inhibiting effects by enhancing liver structure, boosting antioxidant defense mechanism, and activating the antioncogene gene TP53. Garlic extract's antiproliferative property makes it a potential alternative for treating and preventing hepatocellular carcinoma.[28]

Nigella sativa

The medicinal plant *N. sativa,* included in the Ranunculaceae family, is known through various names such as black seed, also known as black cumin, and belongs to the *N. sativa* species. Bisexual plant that typically grows between 20 to 90 cm in height. It is mainly found in regions of Asia, including the Middle East, as well as southern Europe and northern Africa.[29] Thymoquinone from *N. sativa* exhibits a potent inhibitory effect on EGFR phosphorylation and behaves as a chemopreventive agent against liver cancer actuation.[30] A study which was conducted by Aminah Suhaila Haron *et al*. suggests that thymoquinone (TMQ) and its lipostructured using nanotechnology carrier formulation (TQ-NLC) could be effective antiproliferative agents for liver cancer treatment and results obtained show that both compounds inhibit Hep3B proliferation this effect occurs in a manner dependent on both time and dosage, concomitant with caspases 3 and 7 activation. However, they differ in inducing cell cycle arrest and modulating Nrf2 and GSH levels, which are regulated by free radicals' production in Hep3B cells.[31] The findings came from the investigation that was done on a study conducted by Ahmed A. Abd Rabou *et al*. which illustrates the cytotoxic impacts of *N. sativa* oil on liver cancer cell lines through genetic assessments of its nanoemulsion. The ultrafine emulsion-formulation increased the essential oil's toxic nature toward cells, suppressing the growth of cells, and lowering IC_{50} values. Both *N. sativa* essential oil and the investigation revealed that nanoemulsions were deemed safe for healthy cells., indicating selective cellular toxicity. These findings suggest that *N. sativa* oil nanoemulsion could be a promising targeting of cells for treating hepatic carcinoma.[32] The given study indicates that the treatment significantly increased reactive oxygen species levels in Hep3B cells compared to HepG2 cells which Shah Jehan and colleagues observed that the hepatoblastoma cell line, when transformed with sh-p53 lentivirus, showed a more significant rise in ROS levels compared to those without the sh-p53 treatment. Additionally, their analysis of apoptotic markers *via* protein immunoblotting indicated a relatively higher level of apoptosis in Thymoquinone-treated cells lacking functional p53 compared to cells with intact p53, which serves as a renowned tumor suppressor, governing various processes crucial in tumorigenesis. The absence of functional p53 can lead to malignant transformations and the initiation of tumors, while mutations or deletions in p53 may occur at later stages of cancer, thereby fostering the progression of carcinoma and resistance to drug treatments.[33]

Alipinia officinarum

This plant's common name is galangal, is native to Southeast China. This plant is belonging to the Zingiberaceae family.[34] GA arrests the cell cycle of HCC. This led to the suppression of aberrantly up-regulated β-catenin response transcription in liver cancers.[35] The present study by Shimaa A. Abass *et al*. aimed to assess the possible treatment and preventative effects of AORE, either alone or in combination with CP, to reduce cisplatin-related effects. In this finding indicates that hepatoma animals treated with AORE, with or without cisplatin, exhibited a normalization of AFP levels comparable to the control group, along with a reversal of histopathological abnormalities to a normal state. Additionally, there was a drop in the percentage of mitotic figures. Furthermore, combining AORE with CP reduced the proportion of CP-toxic hepatocytes that have deteriorated. These effects are attributed to due existence of bioactive substances like galangin and diarylheptanoids.[36]

Aegle marmelos

Aegle marmelos (L.) Correa, commonly referred to as bael and part of the *Rutaceae* family, is utilized in old Indian

treatment for diverse medicinal attributes. While originally native to Northern India, it is extensively distributed across the Indian Peninsula, as well as in regions such as Ceylon, Burma, Bangladesh, Thailand, and Indo-China.[37] The protective effects of *Aegle marmelos* against liver carcinogenesis are believed to be multifaceted. This plant extract restores cellular antioxidant and detoxifying enzymes, such as glutathione (GSH), and influences DNA synthesis & ornithine decarboxylase (ODC) activity. In animal models, *A. marmelos* pretreatment countered the adverse effects of 2-acetylaminofluorene (2-AAF) with partial hepatectomy (PH) and increased detoxifying enzymes. It appears that *A. marmelos* extract inhibits oxidative damage by scavenging free radicals, protecting DNA sites, and blocking the uptake of mutagens. The results indicate that the extract from *A. marmelos* is a strong chemopreventive agent.[38] It indicates that *A. marmelos* could be considered a valuable addition to the array of medicinal plants used in phytotherapy to potentially reduce the occurrence of liver cancer. The extract has pro-apoptotic and anti-inflammatory properties, offering both curative and prophylactic benefits. It effectively modulates hemoglobin concentration, leukocyte, platelet count of lymphocytes, neutrophils, monocytes, and eosinophils in mice given MNU when compared to the control group. Additionally, HEAM treatment normalized the leukocyte, resulting in increased lymphocyte numbers but decreased neutrophil, monocyte, and eosinophil counts. This provides further proof of its advantages and effects, particularly emphasizing its immunomodulatory properties in this specific scenario.[39]

Curcuma longa

C. longa, which -belongs to the Zingiberaceae family, is characterized by its stemless and rhizome-less structure. It typically reaches heights of up to 2 m and features erect leafy shoots. These leaves, which can grow up to 1-m in length, are oblong, exhibiting a dark green hue on their upper surfaces and a paler green tone underneath.[40] Generally, curcumin from *C. longa* triggers cell death of cancer cells by making changes in the Wnt pathway.[41] Rats administered with curcumin had higher survival rates, lower blood aspartate aminotransferase (AST) activity and AFP levels, and higher serum albumin concentrations. Additionally, curcumin showed a strong ability to reduce oxidative stress in the liver and prevent apoptosis. Research conducted *in-vitro* showed that 50 µM of curcumin lowers hepatoblastoma cell viability. This suggests that curcumin inhibits the autophagic route and overrides programmed cell death to protect against HCC caused by TAA, especially up to the first dysplastic stage. Furthermore, curcumin's antioxidant qualities significantly lessen liver fibrosis.[42] *C. longa* oil was used to treat Hepa1-6 cells, and its effects on apoptosis and cell proliferation were also investigated. Curcuma oil pretreatment greatly decreased the oxidative damage and inflammation brought on by concanavalin A. Moreover, administration of *Curcuma* oil was linked to a reduction in the incidence of hepatocellular carcinoma (HCC). Studies conducted *in-vitro* showed that curcuma oil caused natural cell death in hepatic cells and decreased their growth. Furthermore, in mice with hepatic damage, curcuma oil showed protective benefits against oxidative stress and inflammation.[43] This study's main goal was to find out whether curcumin has any antiangiogenic effects on hepatocellular carcinoma (HCC). Curcumin was added in different quantities to H22HCC cells *in-vitro*. Furthermore, the expression levels of the proteins connected to the phosphoinositide 3-kinase/PKB /threonine kinase 1 pathway were evaluated using a mouse xenograft model. The results showed that curcumin administration is dose-dependent in its ability to inhibit H22 cell division. Furthermore, studies conducted on humans demonstrated that curcumin therapy inhibited the growth of tumors. Moreover, curcumin therapy significantly inhibits the phosphoinositide 3-kinase signaling pathway and reduces VEGF expression.[44]

Zingiber zerumbet

Zingiber is a genus within the Zingiberaceae family, encompassing approx 141 species. This is commonly known as wild ginger, is a member of this genus, and is recognized by various names and terms like "Jangli adha." This specific variety of wild ginger is said to have originated in India and the Malaysian Peninsula. It is usually found in lowland settings that are moist and dark. Ginger has been used in hangovers, nausea, motion and morning sickness, worm infestations in children, wounds, and bruises traditionally.[45] An active component of *Z. zerumbet* is a Zerumbone, which inhibits the potential of hepatoma HepG2 cells by targeting the MAPK signaling pathway. *In-vivo*, methanolic extract of *Z. zerumbet* rhizome significantly suppressed Ehrlich ascites carcinoma.

In EAC-bearing mice, treatment results in inhibited cell proliferation, diminished body weight gain, extended lifespan, and normalized abnormal hematological features. Additionally, MEZZR treatment induced nuclear condensation and fragmentation. Furthermore, *in-vitro* experiments showed that the cell growth inhibitory effect of MEZZR, as measured so is significantly reduction in the presence of caspase inhibitors.[46] ZER (*Zingiber zerumbet*) demonstrated *in-vivo* anti-hepatocellular carcinoma (HCC) effects. VEGF, matrix metalloproteinase-9, their levels were decreased in liver cancer tissues. The anticancer mechanisms of ZER on HCC involve both inhibiting and promoting cancer cell programmed death, indicating its promising potential for development as an anti-liver cancer chemotherapeutic agent (Table 1).[47]

Table 1: Summary of herbal plants

S. No.	*Plant name*	*Family*	*Other activity*	*Plant part used*	*Mechanism of anticancer activity*
1.	*Annona muricata*	Annonaceae	Antimicrobial, insecticidal, antioxidants	Leaves, fruits	PI3K/Akt pathway inhibition [9]
2.	*Artemisia vulgaris*	Asteraceae	Analgesic, hepatitis treatment, gastric ulcers	Rhizome	Apoptosis through increasing intracellular ROS [14]
3.	*Eclipta alba*	Asteraceae	Antihemorrhagic, analgesic, antiviral, antibacterial	Leaves, seeds, fruits, flowers stems	PI3K/Akt encouraged programmed cell death [21]
4.	*Allium sativum*	Alliaceae	Antidiabetic, anti-hypertensive, antithrombotic, antiobesity	Bulb	Activating gene TP53 [28]
5.	*N. sativa*	Ranunculaceae	Antibacterial, antifungal, anti-inflammatory	Seeds	Augmentation of Natural Killer Cells Activity [33]
6.	*Alpinia officinarum*	Zingiberaceae	Antidiabetic, hypolipidemic, antiplatelet	Rhizome, leaves	Wnt/β-catenin Pathway inhibition [35]
7.	*Aegle marmelos*	Rutaceae	Antidiarrheal, antibacterial, antiviral	Leaves, fruits	Free radicals scavenging activity [39]
8.	*C. longa*	Zingiberaceae	Anti-inflammatory, antioxidants	Rhizome	Reduction of expression of VEGF and PI3K/Akt pathway [44]
9.	*Zingiber zerumbet*	Zingiberaceae	Migraine, motion sickness, nausea treatment	Rhizome	Angiogenesis by VEGF level decreasing [47]

Pathways through which Herbal Components can show Liver Cancer Treatment

Patients with hepatocellular carcinoma (HCC) typically do not show symptoms and are often diagnosed in advance.[48] Consequently, there is a pressing need to discover new treatments for HCC and Liver cancer, characterized by high heterogeneity and involves the dysregulation of multiple signaling pathways. The mechanism's complete understanding of hepatocellular carcinoma (HCC) development and progression remains elusive.[49,50] Hepatic cancer is the result of a molecular variety caused by mutations and epigenetic changes in proto-oncogenes. Researchers have dedicated significant efforts to unraveling the molecular mechanisms underlying hepatocarcinogenesis. This ongoing research has paved the way for novel therapeutic approaches, such as targeted therapy and immunotherapy, which are particularly beneficial for advanced HCC cases.[51,52]

Receptor tyrosine kinase pathway

RTKs represent a group of enzymes within the tyrosine kinase category. They are pivotal in facilitating cell communication and controlling different intricate biological processes like cell proliferation, movement, specialization, and metabolic activities.[53] Disruption of RTK signaling pathways is implicated in numerous human diseases, with cancer being particularly prominent among them.[54] As receptors, they become activated upon binding to specific ligands. Additionally, they function as kinases, catalyzing the phosphorylation of tyrosine residues on target proteins, thereby initiating downstream signaling pathways.[55] The RTK family comprises several subfamilies, such as EGFR, FGFR, and VEGFR [56,57]. RTK monomers include 3 main domains.[58,59]

EGFRs

EGFR, a glycoprotein that is located at the transmembrane and which involves binding space for ligands and in cytoplasm, have domains for tyrosine kinase. Its main role in tissue, regulate the development and maintenance of tissues. Through integrating extracellular signals, EGFR is responsible for motility, multiplication, & differentiation.[60-62] EGFR contains six ligands.[63] HB-EGF stimulates the proliferation, invasion, and angiogenesis associated with HCC. Consequently, inhibitors targeting HB-EGF could be employed alongside sorafenib in personalized treatment approaches for HCC patients.[64]

FGFRs

Fibroblast growth factors (FGFs) derive their name from their capacity to stimulate the growth of fibroblasts. Beyond their mitogenic effects, FGFs frequently play roles in metabolic processes, the healing of tissues, and the regeneration of mature tissues by turning on signaling channels again.[65] The FGFR signaling pathway is crucial in controlling various aspects of tumor cellular function, including cancer cell multiplication, endothelial progenitor cells, response to therapy, and tumor metastasis.[66] FGF2, a potent mitogen, holds significance in developing and advancing HCC. This molecule promotes DNA formation within hepatic cancer cells and acts in the processes of invasion of tumors.[67,68]

VEGFRs

These receptors are involved in the formation of blood vessels.[69] The VEGF receptors corresponding to these functions are classified into three primary subtypes: VEGFR 1, VEGFR 2, and VEGFR3.[70] Its function is to safeguard against hepatocellular injury induced by hepatotoxicity who are also infected with the hepatitis B virus. In most cases of HCC, VEGF mRNA is overexpressed, correlating with the cancer's aggressiveness, vessel density, metastatic potential, recurrence rates, and prognosis. Moreover, heightened levels of VEGFR have been observed in both hepatoma cell lines and serum of carcinoma patients. Concurrently, blocking the signaling route has notably hindered the differentiation and moving from one place to another of hepatoma cells.[71-73]

RAS/MEK/RAF/ERK

This pathway functions in the development of tumors.[74,75] Expression of this pathway is observed in hepatic cancer. First, mutations in the Ras gene, an upstream component of this signaling pathway, have been found in 30% of liver cancers. Second, Raf kinases are often overexpressed in most HCC cases. Third, global activation of VEGF, PDGF-, and TGF-α leads to Ras/Raf/MEK activation along with RTK activation/ERK path.[76] Phosphorylation of ERK initiates the activation of various target molecules, thereby promoting liver cancer progression. Therefore, it's important to elucidate the relationship between ERK and gene expression[77] Fig. 1.

PI3K/AKT/mTOR

The transmission within the cell of signals cascade is responsible for controlling diverse processes, cellular multiplication, and angiogenesis. Dysregulated receptor tyrosine kinases (RTKs) often result in the activation of this pathway in many cancer types. This pathway communicates with its associated upstream and downstream molecules to exert its effects on cellular function.[78,79] Research indicates that in hypoxic microenvironments, HIF-2α expression is increased, which causes stimulation of lipogenesis.[80] Furthermore, the aberrant PDK1 (three-phosphoinositide-dependent protein kinase) expression, a critical agent that stimulates the phosphoinositide 3 kinase signaling cascade, is a distinctive feature of invading, hepatocellular carcinoma cells. This suggests that protein kinase could potentially be targeted as a molecular therapy for hepatic cancer[81] Fig. 2.

Wnt/β-catenin

This type of signaling pathway is evolutionarily hoarded and plays a crucial role in forming new tissue *in-vivo*. Dysregulation of this route is connected to the progression of various cancers, like CCA and hepatocellular carcinoma.[82,83] The signaling pathway is activated, observed in HCC patients. Wnt is a glycoprotein which secreted and attaches to the Frizzled N protein, which acts as a receptor.

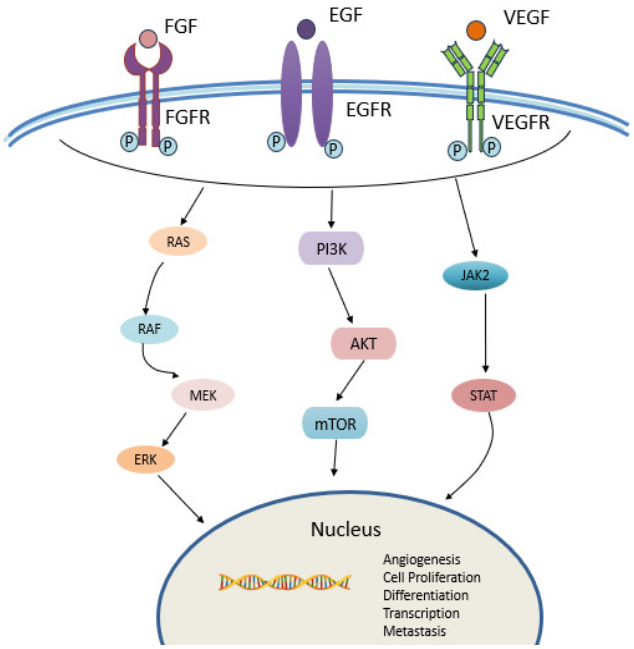

Fig. 1: RTKs and the downstream signaling pathways they are connected to. RTKs can activate their protein kinase function when they bind to their associated growth factors. This can increase signal transduction, control downstream signal transduction pathways, and initiate several biochemical events in cells. Research and development of anticancer medicines are focused on RTKIs. IGFR, FGFR, RTKs, inhibitors RTKIs, PTEN

This interaction causes signaling pathways downstream to become active.[84] This complex activation increases cytoplasmic β-catenin levels, resulting in its collection and nuclear relocation. Inside the nucleus, co-regulating downstream genes are involved in proliferation and cell survival.[85-87] Nuclear accumulation of catenin β-1 is closely linked with β-catenin mutations, with the majority being missense mutations occurring at exon 3. These mutations interfere with the phosphorylation and later deterioration of protein of this pathway[88,89] Fig. 3.

JAK/STAT

This pathway, extremely preserved across species, consists of Janus kinase 1-3, and TYK 2. It is for controlling stem cell maintenance, specialization, & immune/inflammatory responses. Cytokine binding to JAK receptors triggers pathway activation.[90] Numerous studies have highlighted the abnormal activation of JAK/STAT in hepatocellular carcinoma (HCC) generation, both being crucial components of the JAK/STAT signaling pathway and facilitators of canceration. Additionally, it has been demonstrated that the aberrant phosphorylation of STAT3 by JAK1 leads to increased augmentation, Moving, encroaching, and ontogenesis in hepatic cancer.[91] The dysregulated release of cytokines triggers JAK activation, leading to the phosphorylation of STAT3 at key 4-hydroxyphenyl alanine surplus Ser-727 in hepatocellular carcinoma. Overproduction of cytokines that promote

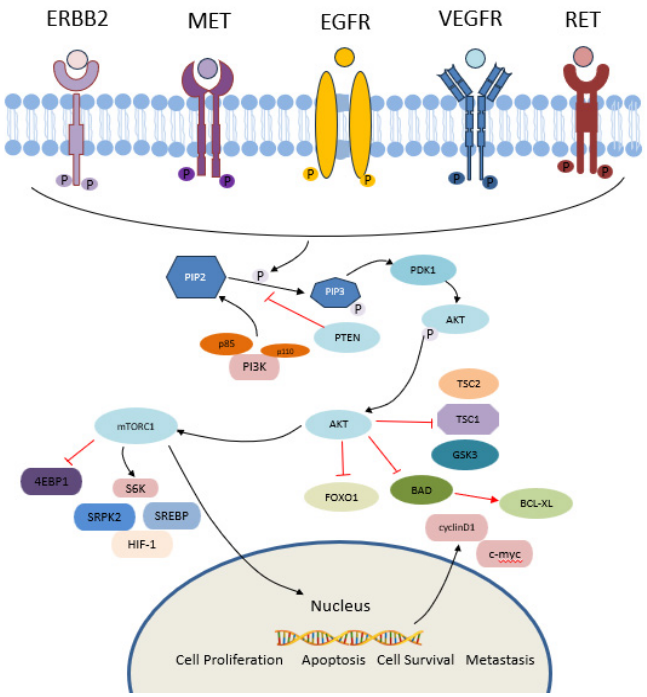

Fig. 2: mTOR/AKT/PI3K signaling pathway and inhibitor targets through the domain of pathway. This pathway regulates the multiplication inside the cells and the formation of new blood vessels

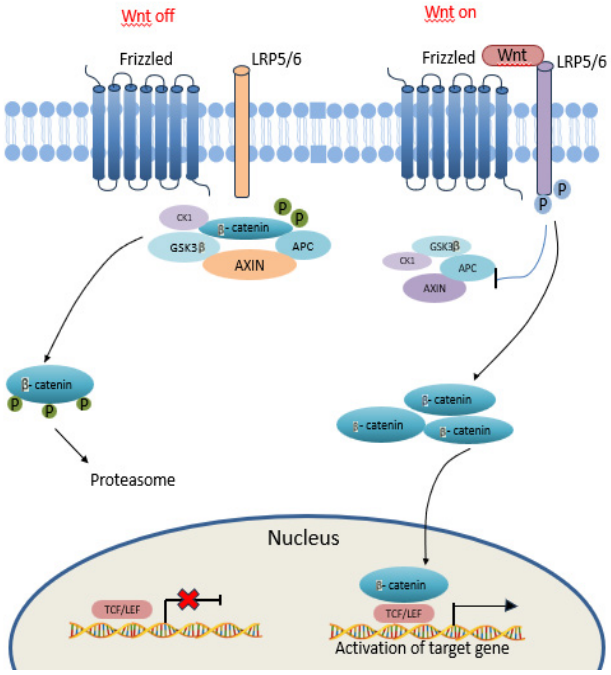

Fig. 3: The on and off states of the signaling pathway. Nonetheless, Wnt/β-catenin signaling is often overexpressed in the Wnt-on state and HCC

inflammation such as Interleukin-6, IL-10, IL-11, and TGF-α enhances the activity of JAK and STAT3. This alteration in the tumor microenvironment fosters oncogenic conditions, ultimately inhibiting apoptosis[92] Fig. 4.

Discussion

The script explores how herbal components affect hepatocellular carcinoma by influencing signaling pathways. The liver is crucial for detoxification and synthesizing essential substances. Other diseases with Hepatocellular carcinoma, hepatitis, liver cirrhosis, and hepatic fibrosis are important liver illnesses with global health concerns. So, we need to explore new therapeutic options for treating hepatic cancer. Various herbal components show activity against hepatocellular carcinoma by apoptosis, Cellular proliferation inhibition, Inhibition of metastasis, etc. The herbs which are described here are *A. muricata, A. vulgaris, E. alba, A. sativum, N. sativa, A. officinarum, A. marmelos, C. longa, Z. zerumbet*. These herbs catch hold of many components like annonaceous acetogenins, diallyl sulfide, thymoquinone, curcumin, galangin, and many more. These components show *in-vivo* and *in-vitro* anticancer activity by following various signaling pathways. The pathways that are responsible for this activity are RTK pathways (EGFRs, FGFRs, VEGFRs), pathway, and phosphatidylinositol 3-kinases/mTOR/STAT pathway. Because these paths have a crucial function in tumor development in hepatoma, these discoveries indicate that focusing on this signaling path is optimal for advancing anticancer drugs in future

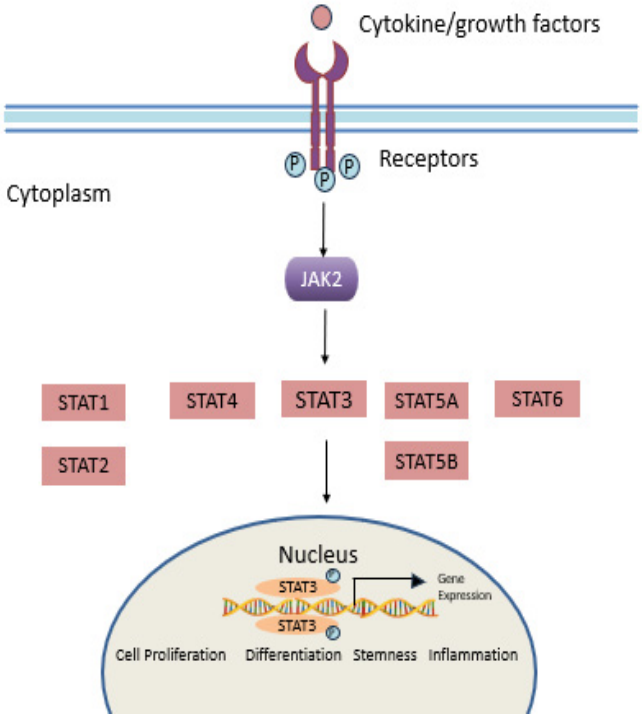

Fig. 4: Illustration of targeted inhibitors and JAK/STAT signaling. The Janus Kinase/STAT signaling pathways control the articulation of genes and functional processes in cells, including immune response, metabolism, differentiation, and proliferation. The primary targets of currently available inhibitors are JAK1-3, TYK2, STAT3, JAK, and the suppressor of cytokine signaling, TYK2

drugs averse to hepatocellular carcinoma.

Conclusion

In summary, the evolution from traditional to modern practices has highlighted the significance of herbs in treating liver cancer by influencing it signaling pathways. This investigation underscores the potential of herbal remedies as a valuable asset in cancer treatment. By understanding how herbs work, particularly on pathways like Janus kinase/signal transducer of activation of transcriptions, RTK, phosphoinositide 3-kinases/mTOR/PKB, Wnt/CTNNB1 protein, we gain insights that can shape new treatment approaches. Fusing traditional herbal wisdom with modern science provides a hopeful direction for more effective and tailored liver cancer therapies. Ongoing research is crucial to fully exploit the healing properties of herbs and enhance results for patients with liver cancer.

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