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Review Article

An Overview of Traditional Medicinal Plants Used in Treating Hepatocellular Carcinoma (HCC) with Emphasis on Mechanisms of Action

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ABSTRACT

Cancer is an incurable fatal disease wreaking havoc on the population of countries either developed or developing. Hepatocellular carcinoma (HCC) is the fifth most frequent type of cancer having a poor prognosis. Globally, HCC management and treatment intervention using medicinal plants from generation to generation is rapidly increasing and remains an area of promising research. This review provided insight into medicinal plants' ethnomedicinal use, photochemistry and mechanisms of action on HCC exhibiting anti-cancer potentials subjected to scientific investigations. Furthermore, clinical, toxicity studies and detailed mechanisms of action would provide an understanding of the development of lead compounds in drug discovery and development for HCC.

Keywords: Cancer, Hepatocellular carcinoma, Medicinal plants, Mechanisms

Introduction

Cancer remains one of the leading causes of death worldwide, and its prevalence is unabated with increasing early diagnosis, clinical intervention and increased public knowledge of common risk factors of this disease [1, 2] Cancer is a polygenic and multifactorial disease where multiple gene mutations cause normal cells to become abnormal or uncontrollable in growth patterns, ultimately leading to the evasion of cell cycle regulation and programmed cell death [3].

The cancer disease process happens during development when the human cells grow old, get damaged, and die; then new cells capture their position. The breakdown of the orderly process results in abnormal or damaged cell growth and multiplication without control. These cells will possibly form tumours, which are lumps of tissue and might be cancerous or not (benign). Tumours that are cancerous spread to or invade close by tissues and can travel in the body to distant places to form fresh tumours, a process known as metastasis [4]. Cancer is also known as a severe health predicament in all populations irrespective of social or wealth class. The global reaction to cancer has been irregular and discriminatory.

The trouble of neoplastic or cancer diseases is a considerable global health confront accounting for considerably high cases of deaths. In 2022, about 2 million new incidences of liver cancer were diagnosed in the US and an estimated 609,360 death cancer projections with the occurrence of 1,670 deaths/day [5]. These projections

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were based on the reported incidence of cancer and its mortality in 2018 and 2019, respectively, and do not account for the unknown effects of COVID-19 (coronavirus disease 2019) on cancer diagnoses and deaths [4]. The incidence of cancer in Uganda was about 32,617 cancers as reported in 2018 with 21,829 deaths [6].

Liver cancer is reported to be the second most common cause of death related to cancer globally after lung cancer [7]. In addition, hepatocellular carcinoma HCC is one of the most frequent cancers that affect the liver, and the incidence rate is 500,00 to 1 million new cases yearly [2]. In the United State of America, liver cancer is the second most frequent cause of death after cardiac disease [4]. Liver surgical resection and transplantation are the most common and proficient therapeutic strategies for treating HCC at an early stage. The current synthetic drugs are still not potent or effective in treating advanced HCC [8]. Hence, drug discovery and development must be aimed toward products having high efficiency and low toxicity for HCC.

Generally, cancer treatment and management strategies include surgery, radiotherapy, chemotherapy, and hormonotherapy. The relapse of cancer and side effects of conventional treatment procedures leading to reduced quality of life patients (QOL) [9] have been significant bane attributable to the strategies above in cancer treatment. However, there is an increase in demand for developing novel approaches and complementary therapies to cancer treatment. One critical complementary approach is using plant-derived products that have been in use thousands of years ago with characteristics of very low side effects in cancer treatment [10,11]. Plant-derived constituents, among other pharmacological importance, directly inhibit the proliferation of cancer cells and display broad activity that targets many pathways [12]. This review is thus aimed at providing comprehensive information on the need for different medicinal plants for treating HCC with some mechanism of action involved.

Hepatocellular Carcinoma (HCC)

Liver cancer is the foremost cause of death, which is cancer-related globally. Cancer-related death is worrisome, and data indicated a 4.7 % death rate for all cancer types. Liver cancer is positioned sixth in terms of incidence and ranks third position in death rate globally [13], as attested by the International Agency for Research on Cancer. An exceedingly aggressive and most common class of liver cancer, hepatocellular carcinoma (HCC), occurs in the fifth position. The incidence of HCC is topographically dependent, with most cases taking place in developing countries. Eastern Asia and Sub-Saharan Africa are where the highest incidence of HCC Occurs [14]. In developed countries like the United States, concern about the growing incidence of HCC is reported in the latest analysis from the Surveillance Epidemiology End Results (SEER). The projection revealed that the incidence might climax by 2030, especially among Hispanics, Blacks, Whites and Asian Americans, respectively. In many cases, liver cancer is caused by long-term damage and scars from the liver cirrhosis emanating from viral infections (Virus B or C) or non-viral causes such as autoimmune diseases, non-alcoholic Fatty Liver Disease (NAFLD), inflammation of the liver (chronic), diabetes, obesity, smoking, alcohol consumption, exposure to aflatoxin and iron overload in the body (hemochromatosis). The report confirmed that some of the ways of preventing HCC include vaccination and antiviral treatments. Hepatitis B vaccination remains the best intervention to reduce the incidence of HCC in places where hepatitis B virus (HBV) is highly prevalent, as demonstrated in Taiwan [15].

Risk factors/causative agents of HCC

HCC risk factors or causative agents are multifactorial, including gender, age, ethnicity, and geographical regions [16]. Chronic HBV infection and fungal toxin aflatoxins B1(AFB1) from contaminated food, are the most common factors [17]. HBV infection (Hepatitis B Virus) is regarded as a significant threat factor. Others, for example, are long-standing alcohol abuse, iron overload (either inherited or common in Sub Sahara African), cigarette smoking, membranous obstruction of the inferior vena cava (MOIVC), cirrhosis, alcoholic fatty liver disease (AFLD), obesity, diabetes, non-alcoholic fatty liver disease (NAFLD), some environmental chemicals that are carcinogenic leads to the development of HCC.

Virus and HCC

The burden of the virus as causative to the pathogenesis of HCC cannot be overemphasised. HBV is a partially double-stranded DNA virus belonging to the genus of Avihepadnavirus of the

Hepadnaviriae family. Out of the 240 million HBV infections in the world, HBV accounts for 75-80% of HCC [18]. HBV genetic material gets fused into the human genome, which induces inflammation, p53 inactivation, and oxidative stress, causing hepatocarcinogenesis. The proliferation and loss of growth control, sustained cycles of necrosis and regeneration, and activation of various oncogenic pathways such PI3K/Akt/STAT3 pathway and Wnt/β-catenin all lead to genomic instability associated with HCC [16].

Carcinogens and HCC

Carcinogens are cancer-causing agents involved in the aetiology of HCC. Aflatoxin, tobacco smoking (4-aminobiphenyl and polycyclic aromatic hydrocarbons), vinyl chloride, arsenic cadmium, lead, and nickel are carcinogens implicated when an individual is exposed to them, and they contribute to the pathogenesis of HCC [8]. For example, aflatoxin induces mutation in the P53 tumour suppressor gene and causes abnormal growth of the liver, resulting in HCC development [19]. Carcinogens could act independently or synergistically with the genetic material of viruses to cause DNA damage, thus inducing cirrhosis while contributing to HCC.

Alcoholic Fatty Liver Disease (AFLD)-Associated HCC

AFLD is a major cause of liver disease burden and is responsible for 30% of HCC-related deaths in the world [20]. The pathogenesis of AFLD resulting from the excessive intake of alcohol starts with hepatic injury from the fat build, progression to inflammation and scarring leading to HCC [16]. In the United States, the baseline of more than 14 drinks/week and seven drinks/week for men and women, respectively is responsible for AFLD [21]. Variations depend on factors such as gender, ethnicity, and genetics in determining the threshold level of alcohol that induces hepatotoxic effects.

Iron overload and associated HCC

Iron overload, known as iron accumulation in the liver, has emerged to be an essential risk factor for HCC pathogenesis. An iron level in the body exceeding 5 g is known as iron overload. Large amounts are released into the liver's cytoplasm when the safe level sequestration of metal is exceeded, resulting in the denaturing of protein and hepatic damage, bringing about HCC development [22].

Pathogenesis of HCC

The carcinogenesis mechanisms or pathogenesis of the diverse risk factors are complicated to be separated from the procedures leading to cirrhosis. Mechanistically, signalling pathways of related cellular oncogenes activation, unstable genome and tumour suppressor genes deactivation vis a vis DNA mismatch repair defects and impaired chromosomal segregation, overexpression of growth and angiogenic factors, and telomerase activation all contribute to HCC development [23, 24]. The mechanisms of hepatocarcinogenesis for the various risk factors are shown below. Common risk factors are indicated using the same colour. In addition to these mechanisms, hepatitis B virus (HBV) and aflatoxin B1 affect the genome — HBV can integrate into the host genome HCV, hepatitis C virus, and aflatoxin B1 is a mutagen. On the other hand, overexpression, or upregulation of rate-limiting enzymes (such as phosphofructokinase, hexokinase, lactate dehydrogenase and pyruvate kinase) in glycolytic pathway and increase in glucose uptake by overexpression of GLUTs enzymes have been attributed to HCC (Figure 1).

Detection and diagnosis of HCC

HCC is rarely detected early, and its fatality is much within a few months of its diagnosis. Imaging through multiphase computed tomography (CT) and/or multiphase magnetic image (MRI) scans forms the basis of HCC diagnosis. HCC are non-symptomatic until the advanced stage; hence, clinical features are seldom helpful in its diagnosis. Hence, combining abdominal ultrasound and diagnostic biomarkers helps increase the specificity and sensitivity of screening tests for HCC.

Treatment of HCC

Treatment options in HCC depend on the disease progression and the patient's state. Surgical resection, local ablation with radiofrequency, transcatheter arterial chemoembolization (TACE), radioembolization and targeted systemic therapeutic like the use of sorafenib are some of the available interventions [25]. The primary goal of treatment is probably finding the cure or prolonging life considerably. Another important goal is improving the patient's quality of life. This is achievable through psychosocial support and

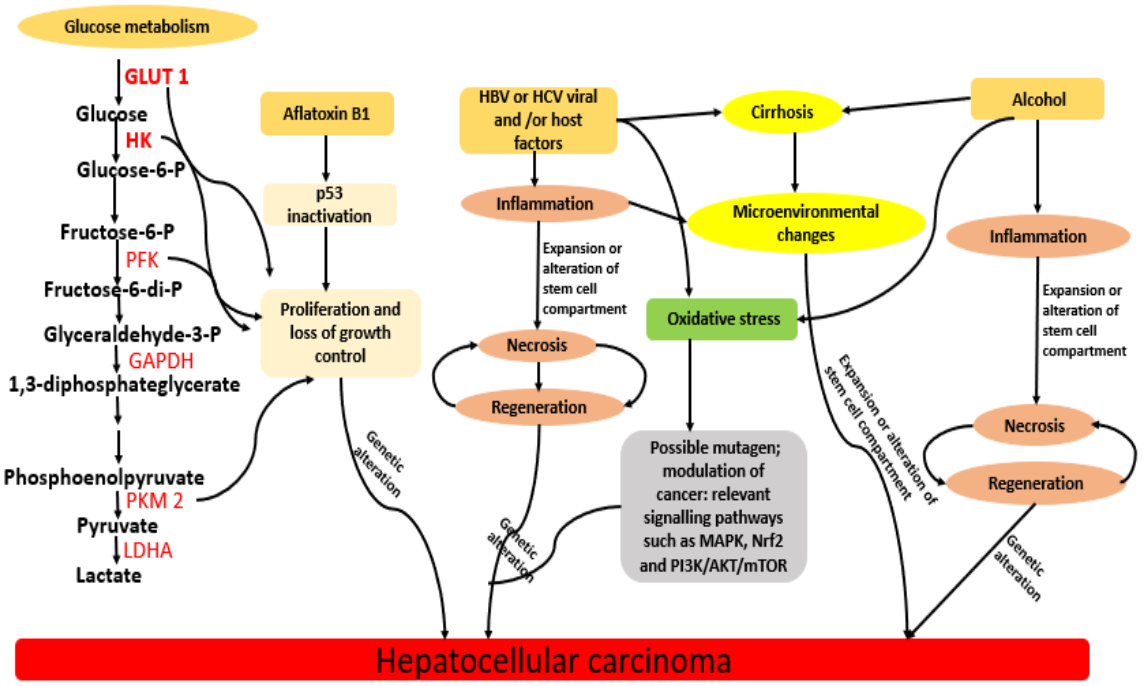

Figure 1. Different risk factors of HCC mechanisms or pathogenesis

supportive/palliative care. Multi-kinase inhibitors, for example, lenvatinib and sorafenib, are among the systemic drugs available for the treatment, and they are considered in patients with unresectable HCC cases.

Treatment through medicinal plant

Higher plants contribute more than 25% as natural products or derivatives out of the 50% of drugs already in use clinically [26]. Thus, plants remain the primary foundation of nearly all medicine in the world, which are important remedies for man. The knowledge of medicinal plants for their curative effects was accumulated over time from evidence-based observation [26]. In Africa, up to 80% of the population uses traditional medicines for Primary Health Care (PHC) (WHO, 2002). Adaptations of herbal medicines in developed countries are termed "Complementary" or "Alternative" Medicine [27,28]. In addition, to ascertain the importance of medicinal plants, 80% of the World's population has benefited in healthcare needs from phytomedicinal sources, according to the estimation of the World Health Organization WHO [27], and even in the USA, about 20% of people have taken some herbal supplementation because approximately 25% of common medications contain herbs nowadays.

Promoting the use of herbal products in research and clinical settings requires knowledge about the pharmacokinetics and tissue distribution behaviour that is dependent on the physiological status of the body such as gender, age and disease state. In addition, oral bioavailability, tissue distribution, halftime (t1/2), maximum plasma concentration (Cmax), and time to reach Cmax (Tmax), are factors of pharmacokinetic parameters that cause variations in their therapeutic effects [29]. Herbal medicines include vegetable medicines, botanical medicines, or phytomedicines as described by WHO (World Health Organization)—some of the anticancer drugs available for treatment emanate from medicinal plants. Examples include vincristine and Vinblastine which are used as anticancer drugs that were discovered in vinca plants (*Catharanthus roseus*).

Research has shown that several medicinal plants have anticancer properties against a comprehensive variety of cancers, in particular HCC, with these anticancer properties accredited to the active chemical constituents available in these plants, as revealed in Table 1. Medicinal plants play a major role as therapeutic agents in traditional medicine contributing a major role in the treatment of hepatocellular carcinoma as mentioned in different literature reviews with their

Table 1. Traditional medicinal plants used in treating hepatocellular carcinoma (HCC) with their mechanism of action

PLANT	PLANT PART	EXTRACTION SOLVENT	PHYTOCHEMICALS	MECHANISM IN LIVER CANCERS	REFERENCES
***NephaliumLappaccum* (Rambutan)**	Fruit	Aqueous Chloroform Ethyl acetate Hexane Methanol	Terpenoids, Alkaloids, Phenols, Anthocyanin, Carbohydrate, Triterpenoids, Cardiac glycosides, Coumarins, Flavonoids, Protein, Steroids, Saponins, Tannins,	cell proliferation controlling and caused shrinkage of HepG-2 cell-sto spherical shape from polygonal	[37]
Moringa Oleifera L.	Leaf	Aqueous; Dichloromethane; Ethanol	saponins, alkaloid, cyanogenic glycoside and flavonoid	Decreasing cell proliferation and exhibiting apoptosis cell death in liver HepG-2	[38,6]
Carica Papaya L.	Leaf	Aqueous; n-hexane; Methanol	Alkaloids, Flavonoids, Saponins, Steroids, Tannins, Phlobatannine	Activate apoptosis by activating caspase 3/7 on Jurket cells	[39,6]
Allium Sativum L.	Bulb	Ethanol	Alkaloid, saponins, flavonoids, glycoside, anthraquinones, tannin and terpenoids	Increasing apoptosis by activating tumor suppressor (TP53) gene	[30,31,40,41,6]
Abelmoschus Esculentus (L) Moench	Fruit, Seed	Methanol	carbohydrates, sterols, flavonoids, proteins, tannins, terpenoids, phenols, and alkaloids	Proliferation and migration inhibition probably due to vascular endothelial growth factor (VEGF) production inhibition, leading to both apoptosis and death	[42,43,6]
DioscoreaMembranacea		Ethanol	saponins, phenanthrenes, anthocyanins, steroidal, saponins, diosgenin, and dioscin	Its decrease glypican3 and reticulin expression	[44,45]
DracocephalumRiotschjiBoiss (Labeatae)	Aerial part	Ethanol, Methanol	Flavonoid, Luteolin	Induction of apoptosis via the opening of mitochondrial transition pore	[46,47,31]
EucomisAutumnalis (ML) Chitt	Root	Methanol	Flavonoid, Phenolic acid, Eucomic acid	_	[48,36]
Benja-ummarit		Ethanol	Pipericine, Piperine, Piperettine, Dehydropipernoline, Pipercide	Inhibit cell production via vascular endothelial growth factor (VEGF) production inhibition	[49]
Alisma Orientale	Tuber	Methanol	Terpenoids, including sesquiterpenoids, diterpenoids, and triterpenoids	Increase apoptosis via down-regulating the Bax, p-JNK family protein and activation of Bcl-2 family proteins	[50,51]
AristolochiaCucurbitifolia/ macroura Go´mez	Root, Stem	Methanol	Isoquinoline alkaloid and derivatives, phenanthrene derivatives, benzoate derivative	_	[51,53]
Polugonum sp.	Root		Resveratrol, flavonoids, quinones, phenylpropanoids, and terpenoids,	Resultinginapoptosis induction through the inhibition of integrins, cadherins and modulation of actin cytoskeleton organisation	[51,54]
Curtisia dentate (Burn F) C. A. Sn	Leaves	Acetone	Lupeol, betulinic acid, ursolic acid and β-sitosterol	Involvement in the induction of apoptosis in HepG2 cell line	[55,36]

Psidium Guajara	Leaves	Aqueous, Methanol	Glycosides, Phenols, Saponins, and Tannins, Flavonoids, and Terpenoids	Proliferation of cells are inhibited in HepG2 cell line	[56,57,31,58]
Pacific Yew (*Taxus brevifolia)*	stem, leaf, and bark		bioflavonoids, lignans, phytosterols, phytoecdysteroids.	–	[59]
Marsdeniatenacissima	Leaves, Root	Methanol	alkaloids, flavonoids, phenols, and saponins	Induces apoptosis by the up-regulation of caspase-9, Bax, and caspase-3 and inhibit anti-apoptotic which resulted to Bcl-2 and Bcl-XL expression down regulation. Is inhibit angiogenesis, promote apoptosis, improve immune function by targeting JAK-1, HIF1α and P53, respectively.	[60,61,62]
Coriolus versicolor (Trametesversicolor) mushrooms		Aqueous, Methanol, Ethanol	Phenols, isoflavone molecule and flavonoids	Its suppresses proliferation of cells by suppressing the expression of Th1 cytokinesIL-1β, IL-2, TNFα, and IFN-l	[63,64,65]
Basidiomycotina		Water, hexane, butanol, methanol and ethyl acetate	phenolic and fatty acids	Increasing expression of proteins that is responsible for apoptosis and cell cycle arrest	[66,67]
***Viscum album L.* (mistletoe)**			Flavonoid, Phenolic acid, Terpenoids, Lectin	It inhibits HCC cells proliferation through downregulation of c-Myc protein expression	[68,69]
Panax ginseng	Root, Leaves, Stem	Ethanol, Methanol	Ginsenosides, Phenolic, flavonoid, vitamin, Protopanaxadiol (PPD) Ginsenoside Rh2	Induction of anticancer activity via the instruction of apoptosis-related genes and the decrease the expression of cell cycle regulatory genes.	[70,71]
***TrametesrobiniophilaMurr* mushrooms (Huaier granule)**			Polysaccharides, steroids and alkaloids	It inhibits tumor cell proliferation, prevented metastasis, induced tumor cell death and interfered with angiogenesis via various signaling pathways.	[72,73,74]
Epimediiherba			Flavonoids	It possesses anticancer activities via cell cycle regulation, apoptosis, angiogenesis, and metastasis, and a variety of signaling pathways including JAK2-STAT3, MAPK-ERK, and PI3k-Akt-mTOR.	[75,76]
Camptotheca acuminate	Leaves, Root, Fruit		fatty acids, alkaloids, flavonoids, polyphenols, tannins, terpenes, sterols and ellagic acids	Its antiproliferative activity is via induction of apoptotic proteins including Bcl-2 family protein	[77,78,79]
Poppy oil (*Papaver somniferum L*)	Seed		alkaloids, phenolic compounds, and essential oil	–	[80]
Amaranthus spinosus	Leaves, Stem	Ethanol, Methanol	Etalains, hydroxycinnamates, saponins, steroids and flavonoids	Inhibition of cell proliferation, induces apoptosis through down regulation of the expression of Bcl-2 with surviving while Bax, caspase-9, caspase-3, Apaf-1 and PARP were up regulated.	[81,82,79]

Ziziphus jujube		Ethanol	Ursolic acid, Oleanolic acid, Flavonols, saponins	Induce apoptotic effect and differential cell cycle apprehension in HepG2 cell	[83,84]
Panax Ginseng				Induces anti–proliferative effect, cell death and autophagy.	[85]
Ardisia pusilla A. DC		Methanol	Ardipusilloside I, Triterpenoid, saponins, Phenylpropanoid, glycoside,	Inhibition the metastasis and invasion of HCC cell*in vivoandin vitro* via reduced metalloproteinase (MMP)-9 and MMP 2 proteins	[86,87,79,88]
Digitalis ferruginea		ethanol, acetone, water	LanatosideC, phenolic, flavonoid, tannin c	Inhibition of cell proliferation and induction of apoptosis and cell cycle arrest of G2/M phase by blocking MAPK/Wnt/PAM signaling pathways.	[89,90]
Diospyros kaki	Leaves	Ethanol	Non-specified terpenoids and flavonoids	induces cancer cell death andinhibits cell proliferation via PDGFR-Rac-JNKsignaling axis is triggered by EEDK.	[91,92]
Sanguisorba officinalis		Methanol	phenolic acids, flavonoids, Ziyuglycoside II (3β-3-α-1- arabinopyranosyloxy19-hydroxyurs-12- en-28-oicacid)	Inhibition of cell proliferation, apoptosis inducing and down-regulation of cell movement and invasion in various HCC cells via the EGFR/MAPK and EGFR/PI3K/AKT/NFκB signaling pathways	[93,94]
Bruceajavanica	Seed, Fruit	Ethanol	Bruceajavanica oil, sesquiterpenes, olein, pregnane glucosides, oleic acid, anthraquinones, linoleic acid, and tetracyclic triterpene quassinoids	inhibit tumor cell from growing, affect the autophagy, apoptosis of tumor cell, invasion, and migration processes and activate immunity via NF-κB, p38-mitogen-activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K)/protein kinase B (AKT), Wnt/β-catenin, and signal transducer and activator of transcription 3 (STAT3) pathways.	[31,95,96]
Artemisia annua			Artemisinin, coumarins, flavonoids and phenolic acid derivative	Promote anti- proliferative effect and induces apoptosis via reduction in activities of Akt/mTOR/anti-apoptotic proteins (likeBcl-XL and Bcl-2), that lead to increasing the activation of pro-apoptotic proteins (such as Bax and Bak) and tumor suppressor p53 via the Akt/mTOR signaling pathway.	[97,98]
Citrus bergamia	Fruit	Methanol	Eriocitrin, Neoeriocitrin, Naringin, Neohesperidin	Induces cell cycle arrest in G2 phase, activates the apoptotic machinery through both extrinsic and intrinsic pathways	[99,100]
Scutellariaebaicalensis			Oroxylin A, baicalin, baicalein, wogonoside, and wogonin	Induction of G2/M cell cycle, activate and arrest caspase system on liver cell by ERK pathway upregulation	[101,102]

Fagopyrum tataricum			Tatariside F, flavonoids and phenolics	Induces antitumor effects in vivo and in vitro by up-regulating the protein expressions of p53 and Bax, and down-regulating the Bcl-2.	[103,79,104]
Pulicariajaubertii	Whole plant, aerial part	Methanol	Pulicariajaubertii 1, hydroquinone, triterpenes		[105,106]
Jujube (*Ziziphus Jujuba*)	Leaves	Aqueous, Ethanol	terpenes, tannins, alkaloids, phenols, steroids, and cardiac glycosides	Induces apoptosis and promote differential cell cycle arrest via increased hyperphosphorylation of Rb and p27(Kip1).	[79,107,108]
Camellia sinensis	Leaves	Aqueous	Epigallocatechin-3- gallate, alkaloids, flavonoids, steroids, terpenoids, carotenoids, benzoic acid, ascorbic acid, tocopherols, folic acid, and tannins consisting of catechin (flavonol) and gallic acids	–	[31,79,109]
Garcinia mangostana	Fruits	Ethanol	xanthones and its derivatives (Mangostanaxanthone V, Mangostanaxanthone VI, Alpha-mangostin) and Flavonoid	inhibition of cell survival by induced caspase-9, caspase-8 and caspase-3 activities, increased pro-apoptotic protein (Bax, Bim, t-Bid) levels, and decreased anti-apoptotic protein (c-FLIP, Mcl-1) levels	[110,111,112]
Rhizomacoptidis			Berberine, alkaloids, volatile oils, organic acids, lignans, and flavones	Inhibition of the proliferation, migrating cancer cell and promote apoptosis. Suppressing the growth of the tumor in nude mice via up-regulating of the miR-122 expression	[113,114,115]
Nelumbo nucifera	Seed	Ethanol	Neferine, alkaloids, flavonoids, sesquiterpenoids, essential oils	Reduced mitochondrial membrane potential, increased intracellular calcium levels [Ca2+] increased expression of apoptotic proteins such as Bad, Bax, cleaved forms of PARP, caspase 9, caspase 3, through the downregulation of anti-apoptotic protein Bcl2.	[116,117,118]
Garcinia	fruits, leaves, and seeds	Methanol, Ethanol	Gambogic acid, anthones, flavonoids, phenolic acids, organic acids, and terpenoids	Induce cell cycle arrest at apoptotic effect and sub-G1 phase via up- regulation of Caspase-3	[119,120]
Poncirus trifoliate	Fruits	Methanol	Poncirus fructus, Syringin, Citric acid, Poncirin	Inhibition of the EMT process and down-regulating MMP-2 and MMP-9 activities.	[121, 179]
Alpinia galangal	Rhizome, Leaves	Methanol	1 0 –Acetoxychavicol acetate, Phenolic, Flavonoid	–	[122,123]
White Birch Trees (*Betula papyrifera*)	Bark	Methanol, Ethanol, Aqueous	Betulinic acid, Alkaloids, Phenols, Terpenoids	–	[79,124]
Huanglian decoction			CoptidisRhizoma, ZingiberisRhizoma, Folium ArtemisiaeArgyi, Mume Fructus, berberine, palmatine, baicalin and geniposide	Inhibition of cancer cell growth by down-regulations of the expression of CCNB1 in other to activate the signaling pathway of p53.	[76,125]

Allophylus cobbe	Leaves, bark, Root, Stem	methanol, hexane, ethyl acetate, dichloromethane	Tannins, Phlobatannins, Steroids, Terpenoids, Cardiac glycosides, Favonoids	——	[35,126,127]
Madhucalongiflora	Leaves, bark, Root, Stem	methanol, hexane, ethyl acetate, dichloromethane	sapogenins, triterpenoids, saponins, flavonoids and glycoside	_	[35,128]
Adenantherabicolor	Leaves, bark	hexane, dichloromethane, ethyl acetate, and methanol	phenolic and total flavonoid	_	[35]
Cycleapeltate	Leaves, bark	hexane, dichloromethane, ethyl acetate, and methanol	tannin, proteins, resins, carbohydrates, alkaloids and terpenoids	_	[35,129,130]
Munronia pinnata	Leaves, bark	methanol, hexane, ethyl acetate, dichloromethane	Saponin, Alkaloids, Tannins, Flavonoids, and Steroid Glycosides	_	[35,131]
Schumacheriacastaneifolia	Leaves, bark	methanol, hexane, ethyl acetate, dichloromethane	sulphated flavonoids	_	[35,132]
Caralliabrachiate	Leaves, bark	hexane, dichloromethane, ethyl acetate, and methanol	Alkaloids, Glycosides, Phenolic compounds and tannins, Flavonoids, Carbohydrates, Proteins, Fats and oils, Saponins	_	[35,133]
Asparagus Racemosus	Root	Aqueous	e steroidal saponins, essential oils, various amino acids, lavonoids, resin, steroidal tannin glycosides (asparaguses), and bitter glycosides	_	[134]
Solanum nigrum		Aqueous	alkaloids and steroid saponins glycoprotein,solasonine, steroidal glycosides,alpha, and beta solanigrinechez, alkaloidssolamargine,	Induction of apoptosis in cancer cells mainly through the downregulation the activation of MAPK and mTOR pathways.	[134,135]
Rubus AleafoliousPoir	Root	Butanol and ethyl acetate	Total alkaloids	Inhibition of the hepatocellular migration and invasion. In addition, it decreases the expression of SHH, PTCH, SMO, and Gli1 in HCC mouse tumors at both transcriptional and translational levels. It also inhibited the activity of MMP2 and MMP9. Finally, it reduces the expression of MMP2 and MMP9, as well as the tissue inhibitor of MMPs	[134, 180]
***Perilla frutescens* (commonly known as Korean perilla or Beefsteak vine)**	Leaf		Phenolic acids, policosanol, flavonoids, triterpenes, phytosterols, carotenoids, fatty acids, tocopherols, and essential oils	Induces apopotosis by expression of apoptosis-related genes	[134,136]
Ajwa Dates (*Phoenix dactylifera L.*)		Methanol	flavonoids glycosides, polyphenol, and phytosterols	Induces apoptosis, induces elevation of G2/M and S phases of cell cycle	[134,137,138]
Tumeric (*Curcuma longa*)	Rhizome	Ethanolic	Curcumin, cyclocurcumin	_	[30,32,41,139]

Ginger essential oil			camphene, zingiberene, ocimene, z-citral, e-citral.	Induces relevant antiproliferative and antitumor activities by important mediators and pathways of cell signaling, including Bax/Bcl2, p38/MAPK, Nrf2, p65/NF-κB, TNF-α, ERK1/2, SAPK/JNK, ROS/NF-κB/COX-2, caspases-3, -9, and p53	[30,41,140]
Saffron (Crocus sativus).	Flower		carotene, crocin, anthocyanin, and lycopene.	Inhibits the cell proliferation via inducting apoptosis, modulation of oxidative damage and suppression of inflammatory response	[30,41,141]
***Artemisia vulgaris* (Mugwort)**	Aerial part		flavonoids, coumarins, volatile oils, sesquiterpene, lactones, inulin, and traces of alkaloids		[30,142,143]
***Amorphophallus campanulatus* (Elephant foot yam)**	Tuber		Phenolic, tannins, sugar, starch, and total protein	Induces cytotoxic and apoptotic activities	[30,144,145,146]
Broussonetialuzonica	Leaves	Methanol	carbohydrates, reducing sugars, flavonoids, tannins, alkaloids, and sterols		[30,147]
Graptopetalumparaguayense	Stem	Ethanol	gallic acid, flavone, genistin, daidzin, and quercetin	Induced apoptosis in HCC cells by promoting the loss of mitochondrial membrane potential and the production of reactive oxygen species.	[30,148,149]
***Nigella sativa* (Black seed or black cumin)**	Seed		monoterpene, di-terpene, sesquiterpenes, monoterpenoid alcohols, and ketone	Induces apoptosis and controls Akt pathway.	[30,150,151]
Petasites japonicas	Root		Flavonoids, sesquiterpenes, triterpenes, phenol	Anti-proliferative activity through inhibiting the Akt/mTOR and Wnt signaling pathways	[30,152,153]
Asafoetida (Ferulaasafetida)			farnesiferols A, B and C, asaresinotannols, coumarin derivatives (e.g.umbelliferone),ferulic acid, coumarin-sesquiterpene complexes (e.g. asacoumarin A and asacoumarin B)	induction of apoptosis and altered TGF-β and NF-kB signaling with increase in TNF-α and caspase-3 expression	[32,154]
Cinnamomum (Cinnamomum sp.)	dry bark and twigs		2-methoxycinnamaldehyde and cuminaldehyde	_	[32]
Dandelion (Taraxacum officinale)	Root		α-amyrin, β-amyrin, lupeol and taraxasterol	Anti-proliferative by enhanced phosphorylation level of AMPK	[32,155]

Pomegranate (Punica granatum L.)	Leaf, fruit, peel, seed	Petroleum ether, dichloromethane, ethyl acetate, methanol and water	anthocyanins, 3-glucosides, cyanidin, pelargonidin, ellagitannins, delphinidin 3,5-diglucosides and other phenolic compounds, flavonoids, proanthocyanidin compounds, gallic acid, minerals and complex polysaccharides, ellagic acid and ethyl brevifolin-carboxylate, triterpene acids consisting of ursolic, oleanolic, asiatic acids and maslinic	Suppression of the inflammatory cascade through modulation of NFκB signaling pathway	[32, 181, 191]
Salvia miltiorrhiza			Tanshinones	Induces apoptosis for the sub-G1 proportion increase, down-regulation of Bcl-2, upregulation of p53 and Bax, and the activation of the caspases-3 and -9 pathways.	[32,156]
Plumbago zeylanica	Roots, stem, flower, and leaves	Petroleum ether, chloroform, ethyl acetate and methanol	1, 4-naphthoquinone	Cell cycle arrest at the G1 phase, apoptosis via the mitochondrial cell death pathway, and enhanced production of reactive oxygen species	[30,182,189]
***Psoralea corylifolia* (Boh-Gol-Zhee)**	Leaves, fruit	Petroleum ether, chloroform, ethanol and aqous	ashoreline, corylfolnin and bavachinin	Induction of a long noncoding RNA, RAD51-AS1, which bound to RAD51 mRNA, thereby inhibiting RAD51 protein expression	[30,188,190]
Podophyllum hexandrum		ethyl acetate	_odophyllin and podophyllotoxin	-	[30]
Emblica officinalis	Berry, fruit,Leaves, seeds	Ethanol	gallic acid, vitamin C, tannins, flavonoids,	- Prevent mutagenesis and lipid peroxidation in response to carcinogens and reactive oxygen species; Alkylating carcinogens generate DNA mutations through carbon oxidation or conjugation reactions with nucleic acids	[30,184,192]
Stylognecauliflora		Methanol	Oligophenolic compounds SCH 644343 and SCH 644342	-	[157,30]
Elsholtziarugulosa and Thevetia peruviana			Flavonoids (Luteolin and apigenin)	-	[30]
Euphorbia antiquorum	Leaves		Flavonoid and Triterpenoid	__-	[30]
Stellerachamaejasme		Methanol	gnidimacrin,pimelea factor stellerama-crin, stellerarin,huratoxin, simplex in, sub-toxic, and neochemae-jasminA and B.	Inhibit the proliferation of cancer cell via the down regulation of Smad4-mediated TGF-β signaling pathway	[30,158]
Ginkgo biloba			flavonolglycosides, terpene lactones andginkgolic acid	Inhibition of proliferation of the cancer cell and triggers apoptosis during the NF-kb/p53 signaling pathway	[30,159]

Glycyrrhiza glabra			Flavonoids(licochalone-A)	Induces apoptosis and cell cycle arrest and improves metabolism through via metabolism through regulation of MiRA.	[30,160]
Gossypium hirsutum	Seeds, roots, and stems	Petroleum ether, methanol and aqueous	Asparagine, gossypol, arginine, resins,	increasing antioxidant activity, altering gene expression, inducing apoptosis and inhibiting angiogenesis and metastasis	[30,185,193]
Ocimum sanctum	Leaves and stem	Methanol, hydroalcoholic, and aqueous	flavonoids (vicein, cirismaritin, orientin, cirsilienol, isothymusin, apigenin &isothymonin) eugenol, linoleic acid, and rosmarinine acid	Increasing antioxidant activity, altering gene expression, inducing apoptosis and inhibiting angiogenesis and metastasis	[30,186,187]
Oldenlandiadiffusa	Stem, Leaves	Methanol	oldenlandosides, stigmasterol, beta-sitosterol, flavonoid glycosides, oleanicoliacid, and p-coumaric acid	Inducing endoplasmic reticulum stress (ER stress) and activating the PERK-eIF2α-ATF4 signaling pathway	[30,194,195]
Aronia melanocarpa	Fruit		phenolic ingredients, chiefly anthocyanin	-	[30]
Hydrastis Canadensis	Rhizome/Root		Alkaloid (Berberine and hydrastine)		[161,30]
Berberis vulgaris	Root		berberine, isotetrandrine, berbamine, magnoflorine, columbamine, oxycanthine, chelidone acid and palmatine	-	[30]
Aloe vera	Leaves	Diethylether, Ethanol, Water	alkaloids, flavonoids, saponin, phenol, glycosides, and tannins	-	[30,162,163]
Andrographis paniculata	Whole plant	Ethanol	diterpenoids, flavonoids and polyphenols	-	[30,164]
Bauhinia variegate	Root, Stem bark, Flower bud	Ethanol	alkaloids, tannins, steroids, anthraquinones, coumarin, saponins, cardiac glycosides, flavonoids,	-	[30,165,166]
Rheum emodi			physcion, anthraquinone (rhein, chrysophanol, aloe-emodin, emodin, and their glycosides) and stilbene (picetannol, resveratrol and their glycosides	Inhibittumour formation by upregulating miR34a at the same time inhibiting EFK1/2, AKT and VEGFR2.	[30,167,168]
Ballota nigra	Root and stem	Ethanol, chloroform, and ethyl acetate	Ladanein, phenylpropanoid glycosides, diterpenes, flavonoids, oils and betaines	-	[30,169,196]
Melastomadecemfidum	Leaf	Methanol	Naringenin, flavonoids, tannins, phenylpropanoids, organic acids, terpenoids, and steroids	_	[30, 197]
Swietenia macrophylla	Stem		3-hydroxy caruilignan	__	[30]
Magnolia officinalis	bark, leaves, and cones		Lignin (Honokiol)	__	[30]
Blumea balsamifera (sambongis)	Leaves		ketones,terpenoids, phenols, fatty acids, alcohol, ethers, aldehydes, pyridines, furans, and alkanes) and non-volatile (flavonoids, flavanones, and chalcones)	__	[170,30,171]

Panax Ginseng	Root, Rhizomes, Leaves, Stem	Ethanol and methanol	Ginsenosides	Inhibiting cancer cell proliferation and promoting cancer cell apoptosis	[30,198,199]
Astragalus membranaceus	Root	Ethanol	Swainsonine, saponins, flavonoids and polysaccharides	Down-regulate MT1G through daidzein to promote ferroptosis of HCC cells and improve prognosis	[30,200,201]
Betula utilis	stem bark	Methanol	Betulin, triterpenoids, phenolics, and flavonoids	Activation of extrinsic apoptosis pathway via up regulation of DR4, DR5 and PARP cleavage in MCF-7 cells over non-tumorigenic MCF-10A cells	[30,202,203]
Picrorrhizakurroa (Kutki)	Rhizomes, root	Methanolic, alchol and aqueous	icrosides-I, II and III and kutkoside	Prevention of biochemical changes in the liver and serum of galactosamine-intoxicated	[30,204]
Foeniculum vulgare	Seed	Methanolic	proteins, cardiac glycosides,saponins, trace elements, flavonoids, sterols, triterpenes, coumarins, volatile oils, and vitamins	—	[30,172]
Achyroclinesatureioides (Dc.) Lam,		Methanolic	Flavonoids, chalcone, caffeoyl derivatives	—	[173,174]
Lithraeamolleoides (Vell.) Engl.,	fruit, leaves and aerial parts	Alcohol	limonene, α-pinene, β-pinene, α-terpineol, myrcene, sabinene hydrate, 4-terpineol, camphene, and Δ-3-carene	—	[173,175]
Schinusmolle L.,	trees and shrubs		Limonene, α-Phellandrene, Camphene, α-Pinene, β-Pinene, β-Myrcene and Caryophyllene	—	[173,176]
Cryptolepissanguinolenta	Leaves, Seed	Methanol	Alkaloid (Cryptolepine), tannins, and flavones	—	[177,178]

curative potential due to the presence of phytochemicals [30–35] Plants and herbs have been reported to be used to treat cancer and other diseases using leaf, root, fruit and bark extracts of the selected plants when investigated for cytotoxic properties on HepG2 cells [35].

Phytochemicals in the Treatment of HCC

Plants are vast sources of secondary metabolites that are shown to be potent chemotherapeutic that is used in treating different diseases including metabolic, chronic cardiovascular, neoplastic, and neurodegenerative. Although there is a hopeful indication, but many phytochemicals lack the appropriate solid scientific accuracy because of the difficulty in translating them. This is owing to high cost, expertise, and ethical issues among others complicating the successful clinical translation.

The dietary phytochemicals, such as resveratrol, curcumin, quercetin, N-trans-feruloyl octopamine, emodin, silybin, lycopene, phloretin and caffeine show anti-cancer properties against HCC. The cancer hallmarks are the key molecular targets of the phytochemicals to halt the pathogenesis of HCC [34]. Human health is improved or maintained with the therapeutic potential of several plant-derived compounds against various diseases, including HCC [35]. The delay in tumour progression, increased survival and life quality and improved quality of life are due to the synergistic actions of various medicinal plants and chemotherapy [30]. Many concoctions with different combinations of herbal plants have demonstrated improvement in liver function and promoted liver regeneration as well as prevented liver damage and have also been used to treat hepatitis, liver fibrosis and HCC Table 2 [32]. Plants have been shown to have a diversity of secondary metabolites such as phenolic (e.g., flavonoids, coumarins, phenolic acids, quinones, lignans, tannins, stilbenes), nitrogen-containing compounds (e.g., betalains, amines, alkaloids), terpenoids (e.g. carotenoids), vitamins, and many endogenous metabolites whereas phenolic acids and Flavonoid are important groups of secondary metabolites competent of promoting anti-ageing, scavenging free superoxide radicals, reducing the risk of cancer and advance plant flavour, colouration and aroma while Phenolic compounds serve as defensive agents against invading plant pathogens. Therefore, flavonoids and Phenolic are reported to demonstrate anti-depressant, cytotoxic, anti-ulcerative, antioxidant, anti-cancer, anti-inflammatory and anti-depressant activities. Antioxidant activity is a fundamental property of most of bioactive compounds with anti-carcinogenic and anti-ageing properties [30,32,36,35].

Herbal medicines are still being extensively used universally, but there persists a huge lag in the reception of their strength by the medical and scientific community owing to the deficient scientific evidence. Advance studies into the compounds are much desirable to assist in closing the current gap between clinical application and preclinical research. Plants are adjudged to be rich in secondary metabolites, effective chemotherapeutic and/or chemo-preventive agents used for several chronic metabolic, neoplastic, metabolic, neurodegenerative, and cardiovascular diseases.

Plant-derived products would continue to provide broad options in efficiently treating HCC since these products are essentially abundant in nature, more so they are assumed to lead to effects that are fewer or less toxic side. The medical field, in particular, cancer study is continuously evolving, and futuristically, there is a need for the exploration to understand the properties and potentials of phytochemicals in HCC and other cancer types. Several natural compounds derived from plant sources have been evaluated for their effectiveness as potential treatment options against hepatocellular carcinoma (Table 1).

***In-silico* analysis of plant-based phytochemicals against HCC**

Following rigorous analysis, a few pharmacologically active elements from plants can be used as the most promising therapeutic options for HCC. Chemicals produced by plants have demonstrated anticancer potentials for the treatment of a range of cancers [205]. Numerous plant-derived chemicals have been introduced and used as chemotherapeutic medicines, according to studies [205]. *In silico* methods such as pharmacokinetics, pharmacogenomics, molecular docking, and molecular dynamics simulations are commonly used for the mechanistic prediction of plant-based phytochemicals and target proteins. The predicting properties include absorption, distribution, metabolism excretion and (ADMET) as well as the drug-likeness or drug-ability (Lipinski's rule of five), which is very germane in the prediction of the drug properties of plant-based phytochemicals. To examine the ligands' capacity to bind to target

binding sites, molecular docking and molecular dynamics simulation techniques define the atomic-level interactions between plant phytochemicals as ligand molecules and various proteins as receptor or target molecules [206–209]. The molecular interaction of plant-based phytochemicals with several target proteins (such as Bcl2-associated X (BAX) proteins, glycolytic enzymes, caspase enzymes, human placenta aromatase, poly ADP-ribose polymerase (PARP), phosphoinositide-3-kinase, tumour necrosis factor alpha (TNF-α), epidermal growth factor receptor tyrosine kinase (EGFR), Human placental aromatase cytochrome P450 (CYP19A1), Cyclin D and p53) to revealed mechanism of HCC treatment by numerous plants have been reported [210 – 213]. Despite recent developments in medicines, technology, and screening techniques, HCC still has a low rate of survival and is the deadliest malignancy. It is more likely that ligand molecules identified through in-silico research, such as molecular docking, will advance to the next stage of the drug development process.

Conclusion

Despite the progressions in HCC incidence and prevalence, diagnosis and therapeutics, scientists have not discovered or developed lead compounds for HCC without major side effects. Consequently, advances in alternative therapies are desirable in order to overcome such setbacks. Over 50% of the already existing medicines or natural compounds are derived from plants. Hence, there is a need to offer an immeasurable source for diverse chemical structures with anticancer properties to sustain the drug discovery process. The recent growing applications of molecular biological techniques and combinatorial chemistry approaches provide access to novel natural compounds with anticancer properties for future drug development and discovery.

Medicinal plants are currently used in treating HCC due to their several phytochemical components and high antioxidant and anti-inflammatory properties inhibiting human HepG2 cell propagation. Additionally, these plants with their phytochemicals belong to different classes such as proteins, cardiac glycosides, saponins, trace elements, flavonoids, Phenolic, tannins, sugar, starch sterols, triterpenes, coumarins, volatile oils, and vitamins have shown the ability to affect several signalling pathways, signifying their anti-tumour potential. Therefore, there might be a superior option for preventing the progression or propagation of HCC.

Future Perspective

Several medicinal plants have shown insignificant side effects even with high safety profile and cost-effectiveness than some synthetic medicines and therapies if taken proportionally. Thus, apart from showing possible synergistic anticancer effects, they can also protect patients from the potential side effects of chemotherapies. However, a few shortcomings of this therapy still need to be addressed. The phytoconstituents or phytochemical low bioavailability, instability, and hydrophobicity hinder the practical clinical application of anticancer therapy to attain its full potential. Functionalized nanomaterials, micelles, liposomes, and phospholipid complexes would address these shortcomings or issues encountered. Therefore, further study must be done to understand their chemical kinetics and dynamic action to understand their therapeutic strategy better and determine the appropriate dose required for effective HCC treatment. Thus, the recent review summarized those medicinal plants that have phytochemicals with feasible natural product sources and promising candidates to be used as an adjuvant in treating HCC. These molecules can be developed into a novel anticancer molecule once their complete apoptotic action has been studied clinically.

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