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Review Article

The Role of Natural Products in Managing Hepatocellular Carcinoma

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ABSTRACT:
Objective: Hepatocellular carcinoma (HCC) is the most occurring cancer worldwide, responsible for approximately 1000000 deaths annually. There are many ways for the treatment of HCC such as; resection, liver transplantation, sorafenib and chemoembolization. Although all the previous treatments for hepatocellular carcinoma are good and may be fast but these methods are expensive and have many complications, so all the world is going to produce new drugs from natural origins to avoid these complications. Herbal medicine has become a very safe, non-toxic, and easily available source of cancer-treating compounds. Herbs are believed to neutralize the effects of diseases in a body because of various characteristics they possess. Although all the previous treatments for hepatocellular carcinoma are good and may be fast in their effects but it is more expensive and have many complications, so all the world is going to produce new drugs from natural origins and plants to avoid these complications A number of medicinal plants showed a cytotoxic effect on hepatocellular carcinoma due to the presence of bioactive secondary metabolites. Aim: This review aims to illustrate the role of natural products and their major bioactive constituents in the treatment of hepatocellular carcinoma, and discusses the possible mechanisms of action, to be used instead of synthetic medications which combined with undesired complications. Results: The current review showed that medicinal plants play a vital role in the management of hepatocellular carcinoma due to the presence of diversity of phytoconstituents that exert their effect via different mechanisms of action.

Keywords: Hepatocellular carcinoma, medicinal plants, cytotoxic, bioactive.

1. INTRODUCTION

The causes of cancer in many parts of world are primary attributed to the biological, chemical, and other environmental factors which lead to unorganized and uncontrolled proliferation of cells (carcinogens)[1]. Many types of cancer are exist cell for example; leukemia, lung cancer, breast cancer, ovarian cancer, prostate cancer, brain cancer and liver cancer[1].

Hepatocellular carcinoma (HCC) is the third cause of death from cancer and the world's fifth cause of malignancy. The diagnosis of HCC often comes in an advanced stage leading to a poor outcome [1]. In Egypt, HCC is considered as the most difficult health issue by the health authorities. The number of patients with HCC has doubled in a decade.The fourth common cancer in Egypt is HCC[2].

There are two major types of primary liver cancer which are; cholangiocarcinoma (CC) derived from the epithelium of the bile ducts and hepatocellular carcinoma (HCC) that is derived from hepatocytes. Furthermore, there is a rare type that is called combined hepatocellular-cholangiocarcinoma, when both CC and HCC are found in the same liver[2].

HCC are reported to be with higher rates in East and Southeast Asia, East and Western Africa. Due to the presence of bioactive secondary metabolites, a variety of medicinal plants have demonstrated a cytotoxic impact on hepatocellular carcinoma [3, 4].

So this review aims to illustrate the role of natural products and their major bioactive constituents in treating hepatocellular carcinoma, and discusses possible mechanisms of action.

1. Risk factors

There are many risk factors that play an important role in the development of HCC. These risk factors are summarized below

1.1. Environmental-related risk factors

1.1.1. Infectious risk factors

HCC risk is increased by both hepatitis C virus (HCV) and hepatitis B virus (HBV) **[5].**HBV is one of the infectious risk factors of HCC. There are two ways of HBV

transmission;horizontal transmission (parenteral and sexual routes) and verticaltransmission (from mother to newborns)[6]. In Egypt, successful nationwide vaccination strategy plays a vital role in decreasing the prevalence of HBV infection over the last 20 years [6].Another risk factor for HCC is HCV infection which leads to cirrhosis (93%). It causes both hepatic inflammation and fibrosis. Different HCV prevalence in Egypt was reported. The HCV prevalence in the age group (15–59 years) was 14.7% in 2008 while it became10% in 2015. This decline in prevalence was related to aging of infected people receiving anti-schistosomal injections [7].

1.1.2. Non-infectious risk factors

Many environmental risk factors which are non-infectious play role in HCC risk.

1.1.2.1. Chemical compounds

The exposure of the liver to organic and inorganic chemical compounds leads to adverse effects that cause HCC[8].

1.1.2.2. Alcohol

The known risk factor for HCC is chronic alcohol intake that increases HCC by fivefold. This effect is produced by complex mechanism under multi-factorial process [9].

1.1.2.3. Smoking

The carcinogenic effect of the tobacco ingredients is well-documented. Among cigarette smokers, there is an increase in the incidence of HCC risk and mortality [10].In Egypt, many studies showed that there is a direct relation between smoking and the increasing the risk of HCC [11].

1.2. Host- /genetic-related risk factors

1.2.1. Obesity

Obesity causes an increase in the HCC risk by 89%. It is a metabolic defect defined as body mass index (BMI) ≥ 30 kg/m2

1.2.2. Family history of HCC

Family history of HCC increases HCC risk. In Egypt, 21.4%of HCC patients have a family history (first and second degrees relatives) of HCC [11].

2. Diagnosis

During surveillance, finding a suspicious lesion using ultrasound in cirrhotic liver is followed by diagnostic confirmation using contrast enhanced helical computed tomography (CT) or dynamic magnetic resonance irradiation (MRI). Also, non-pathological confirmation of HCC diagnosis is achieved by AFP testing combined with previously mentioned imaging techniques [12].

3. Prevention of HCC

The prevention of HCC can be classified into; primary prevention that depends on early prevention of HCC risk factors,secondary prevention that based on the treatment of risk factors at an early stage, and tertiary prevention by decreasing HCC relapse after successful curative treatment [13].

4. Management of HCC

There are many factors that affect the way by which HCC can be treated such as; the functional status of the patient, the stage of liver disease, location and size of tumor, and the presence or absence of vascular invasion. There are manyoptions for the treatment of HCC such as; loco-regional therapy, surgical treatment and sorafenib[1]. As previous treatments for HCC are expensive and may have many complications, so,there is in need for new treatment option.

5. Natural Products against Hepatocellular Carcinoma

Herbal medicine has become a very safe, non-toxic, and easily available source of cancer-treating compounds. Herbs are believed to neutralize the effects of diseases in a body because of various characteristics they possess. Although all the previous treatments for hepatocellular carcinoma are good and may be fast in their effects but it is more expensive and have many complications, so all the world is going to produce new drugs from natural origins and plants to avoid these complications [14, 15].

Table 1.summarized most of the medicinal plants that reported to show activity against hepatocellular carcinoma with possible mechanisms of action.

5.1. Livistona chinensis

Previous study revealed that the ethanol extract of the *L. chinensis* seed (EELC) showed a potent anti tumor effect in HCC xenograft mice and cause 43% reduction in the weight of tumor, furthermore, EELC showed a potent cytotoxic effect against HepG2 cells, causing 60%reduction of the viability , it also showed cell apoptosis in both *in vivo* and *in vitro* studies. **[16].**

5.2. *Rubus aleaefolious* Poir

A study revealed that *R. aleaefolious* exhibited hepatoprotective effect in mice with acute liver injury after exposure to carbon tetrachloride**[17].**Studies showed that *R. aleaefolious* plays an important protective role in carcinogenesis[18,19]. The total alkaloids in *R. aleaefolious* Poir (TARAP) showed a potent effect on HCC, by causing mitochondrion-mediated apoptosis leading to effect on HCC growth and induce apoptosis in HepG2 cells [20].

5.3. *Crocus sativus*

Crocus sativus, saffron, contains different bioactive compounds as; safranal, crocin and Picrocrocin. The anti-proliferative effects of crocin in HepG2 cells were studied. Safraniland crocin have shown to cause DNA damage in HepG2 cells by increasing the cleavage of caspase-3 and causing arrest of the cell cycle. Furthermore, crocin caused 59% decrease in telomerase activity of HepG2 cells [1].

5.4. *Paris polyphylla*

Paris polyphylla (family Liliaceae) contains different constituents, where steroidal saponins are the main active components that exhibited analgesic, immune-stimulator and antitumor activities. Aqueous and ethanol extracts of *P. polyphylla* showed a potent cytotoxic activity against liver cancer cell line (HepG2) [14].

5.5. *Morus alba*

M. alba contains different biological active compounds like albanol,albafuran, calystegin,morusin, moranoline,

hydroxymoricin and kuwanol . The leaves contain some 1-deoxynojirimycin, apigenin, rutin and quercetin [21]. The study showed that methanolextract of the leaves exhibited a potent cytotoxic activity againstHepG2cell due to the presence of different phenolic compounds that showed an antiproliferative effect on the HepG2 cell line via the arrest of the cellcycle in G2/M phase [22].

5.6. *Scutellaria barbata*

Scutellaria barbata, family Lamiaceae, is rich inbioactive compounds as; polysaccharides, steroids, flavones and alkaloids . *In vitro*researches revealed a potent cytotoxic activity of *Scutellaria barbata against* skin cancer, hepatoma, lung cancerand colon cancer[23,14].

5.7. *Rabdosiae rubescens*

Rabdosiae rubescens(family Lamiaceae) showed different biological activities such as; anticancer, anti-parasitic, anti-inflammatoryand antibacterial.*R. rubescens* contains different bioactive compounds. The main active compound is oridonin, a tetracyclic terpenoid, it causes growth inhibition and apoptosis in cancer cells. as ingallbladder,colorectal, skin, gastric, breast and hepatocellularcarcinoma [24].

5.8. *Prunus armeniaca*

Prunus armeniaca belongs to family Rosacea. The seeds of *P. armeniaca* used against different types of cancers due to its cyanogenic glycosides . Amygdalin is one of the important glycosides of *P. armeniaca*, used for the treatment of prostate cancer. Furthermore, *P. armeniaca* kernels showed a potent cytotoxic activity against different cancers as HepG2, human breast (MCF-7) and colon (HCT-116) cell lines, where the highest cytotoxicity was against HepG2 cells [14].

5.9. *Perilla frutescens*

*Perilla frutescens*belongs to Labiatae family. Multiple *in vivo* and *in vitro* studies have been conducted to evaluate the anticancer and antitumor potential of *P. frutescens*. The ethanol extract of the leaves exhibited the highest anticancer activity against HepG2 cells via inhibition of the cell proliferation and upregulation of apoptosis-related gene expression **[25].**

5.10. *Curcuma longa*

Curcuma longa (Turmeric) ,family Zingiberaceae , exhibited different biological activities includinganticancer, anti-inflammatory, anti-bacterial, antioxidant effects and anti-HIC(human immunodeficiency virus) activities . The main component of *C. longa*is Curcumin, it showed anti-inflammatoryand anticancer activities [1].It inhibited the cell proliferation and induced cells apoptosis [14].

5.11.*Pleiogynium timorense* (DC.) Leenh.

*Pleiogynium timorense*belongs to Anacardiaceae family.The volatile constituents of *P. timorense* fruits exhibited a moderate cytotoxic effect on human hepatoma cells [15]. Seven phenolic compounds were isolated from The bark of the plant contains different phenolic compounds which showed a promising cytotoxic effect against HepG2 cell line [26].

5.12. *Clitoria ternatea*

The methanol extractof the flowers of *Clitoria ternatea* (family Fabaceae) showed a potent cytotoxic activity against human liver cancer cell line (HepG2),and results revealed that it increased the mean survival timeand non-viable cell count . Also, it decreased tumor volume, packed cell volume and viable count [27].

5.13.*Cestrum nocturnum*

Cestrum nocturnum L. belongs to family Solanaceae. Polysaccharides extracts of *C. nocturnum* had antitumor effects.The plant possess different bioactive compounds such as; apigenin, protocatechuic acid, stigmasterol,β-sitosterol and coumarins which could contribute to a potent cytotoxicity against hepatocellular carcinoma, colon and lung cell lines.**[28].**

5.14.*Convolvulus scammonia*

A study revealed that the crude alkaloids extracted from the leaves of *Convolvulus scammonia*anticancer activity in mice hepatocarcinoma cell line. It was found that the extract inhibited HCC cell line tumor growth *in vivo*with concentration of 1mg/Kg bw to 97.14% in mice after three weeks treatment compared to untreated control animals**[29].**

5.15. *Cydonia oblonga*

Cydonia oblonga, family Rosaceae, showed a potent cytotoxic effects against human HeLa, A549, and HepG2 cell lines. The study was done on both an aqueous fermented extract (QAFE)and lipophilic quince wax one (QWE) . Both extractsexhibited an effect on the proliferation of the three tested cell lines [30, 31].

5.16.*Citrus volkameriana*

Citrus volkameriana Pasq. Belongs to Family Rutacea.Limonene(68.5%) was found to be the major oil constituent in peel oil of *C. volkameriana.*The oil showed a verystrong cytotoxic effect on the five human tumor cells tested with the highest effect on human hepatoma HepG2cells (IC50 = 0.038mL/mL). D-limonene showed similar cytotoxic effect as the oil, [32].This genus is reported to possessmany bioactive compounds as anticancer agents such as; flavonoids, limonoids, sterols, volatile oils, coumarins and alkaloids [33].

5.17. *Sclerocarya birrea*

*Sclerocarya birrea*is belonging to the Anacardiaceae family [34].A study showed that both acetone and water extracts of *S. birrea* stem bark exhibited anticancer and proapoptotic activities[35].Moreover, the extract exhibited higher ROS-mediated cytotoxic effect in HepG2 cells compared to normal human fibroblasts[34].

5.18.*Phyllanthus emblica* and *Terminalia bellerica*

Phyllanthusemblica L. (Euphorbiaceae) showed a variety of pharmacological activity including anti-mutagenic, anti-carcinogenic, anti-oxidant, anti-pyreticand anti-inflammatory activities. *Terminalia bellerica* (Combretaceae) is known as belleric myrobalan. Both *P.*

emblica and *T. bellerica* extracts showed effect on the proliferation of the liver cancer cell line and causing inhibition of the cell viability in a dose-dependent manner [36].

Table 1: Natural Products against Hepatocellular Carcinoma

No.	Plant Name	Family Name	Active constituents	Mode of action	Reference
1	*Livistona chinensis*	Arecaceae	C-glycoside derivatives of apigenin, luteolin and tricin together with phenolic acids.	Inhibition of tumor growth in HCC xenograft mice and decreased the tumor weight by43%. It also induced cell apoptosis in HCC xenograft mice and HepG2 cells. Moreover, it has induced the loss of the mitochondrion membrane potential in HepG2 cells, leading to apoptosis.0	[16]
2	*Rubus aleaefolious*	Rosaceae	Alkaloids	It affects HCC growth and induces apoptosis in HepG2 cells via mitochondrion-mediated apoptosis by causing the loss of mitochondrion potential and activation of caspases 9 and 3.	[17-20]
3	*Crocus sativus* or saffron	Iridaceae	Picrocrocin, crocin, and safranil	HepG2 cells exposed to 3 mg/mL of crocin had almost a 59% decrease in telomerase activity. In addition, crocin and safranil have shown to increase the cleavage of caspase-3, arrest the cell cycle, and cause DNA damage in HepG2 cells	[1]
4	*Paris polyphylla*	Liliaceae	polyphyllin D, formosanin C, ecdysterone, dioscin, daucosterolheptasaccharide, oligosaccharides, octasaccharide, protogracillin, trigofoenoside A, yunnanosides G-J, padelaoside B, pinnatasterone	Aqueous and ethanol extracts of P. polyphylla showed potential antitumor activity against human liver carcinoma (HepG2) cell line.	[14]
5	*Morus alba*	Moraceae	kuwanol, hydroxymoricin, moranoline, morusin, calystegin, albafuran, albanol. , quercetin, rutin, apigenin	It showed an antiproliferative effect on the HepG2 cell line through the arrest of the cell cycle in G2/M phase.	[21, 22]
6	*Scutellaria barbata*	Lamiaceae	Alkaloids, flavones, steroids and polysaccharides.	Inhibition of HepG2 cells.	[23, 14]
7	*Rabdosiae rubescens*	Lamiaceae	Monoterpenes, sesquiterpene, diterpene, Oridonin, and terpenoids	It has remarkable properties of growth inhibition and the induction of apoptosis in cancer cells.	[24]
8	*Prunus armeniaca*	Rosacea	The fruit contains carotene, flavonoids, organic acids,thiamine, minerals,and oils. The seeds contain plenty of cyanogenic glycosides.	Inhibition of HepG2 cells.	[14]
9	*Perilla frutescens*	Labiatae	Essential oil component "isoegomaketone"	cell proliferation inhibition and upregulation of apoptosis-related gene expression	[25]
10	*Curcuma longa*	Zingiberaceae	Curcumin	Curcumin inhibited HepG2's proliferation in a dose and time dependent fashion, with the most potent inhibition at a concentration of 8 umol/L for 48 h., it leads to HepG2 induced cells apoptosis at high doses.	[1, 14]
11	*Pleiogynium timorense* (DC.) Leenh	Anacardiaceae	Pyrogallol, catechin, gallic acid, kaempferol, quercetin, rutin and quercetrin.	The methanol extract of the bark showed a promising cytotoxic effect against HepG2 cell line more than that of the isolated compounds comparing with doxorubicin.	[26,15]
12	*Clitoria ternatea*	Fabaceae	*C. ternatea* flower extract contains gallic acid and catechin	The treatment with methanol extract decreased tumor volume, packed cell volume and viable count. It also increased the non-viable cell count and mean survival time.	[27]
13	*Cestrum nocturnum*	Solanaceae	Coumarins, β-sitosterol, stigmasterol, protocatechuic acid n-butanol and apigenin	n-butanol extract of the flowers of CN produced an inhibitory effect on the proliferation of human hepatocellular carcinoma.	[28]
14	*Convolvulus scammonia*	Convolvulaceae	crude alkaloids	It is estimated that the extract concentration of 1mg/Kg efficiently inhibited HCC cell line tumor growth *in vivo* to 97.14% in mice after three weeks treatment compared to untreated control.	[29]
15	*Cydonia oblonga*	Rosaceae	lipophilic quince wax extract (QWE) and an aqueous fermented one (QAFE)	The two preparations exerted different effects on the proliferation of the tested cell lines.	[30, 31]
16	*Citrus volkameriana*	Rutacea	Alkaloids , volatile oils , sterols , coumarins,limonoids and flavonoids	The oil showed a very strong cytotoxic effect on the five human tumor cells tested with the highest effect on human hepatoma HepG2 cells (IC_{50} = 0.038mL/mL).	[32, 33]
17	*Sclerocarya birrea*	Anacardiaceae	Phenolic compounds	Phenolic compounds, exert an anticarcinogenic effect, leading to apoptotic effects	[34, 35]

18	*Phyllanthus emblica*	Euphorbiaceae	It was rich in phenolic and flavonoids compounds.	Results showed that the cell line was growth inhibited in a dose-dependent manner after exposure to the plant extracts.	[36]
19	*Terminalia bellerica*	Combretaceae	gallic acid	Inhibition of HCC cell line tumor growth	[36]

6. CONCLUSION

This review highlights the role of natural products in the treatment of hepatocellular carcinomato be used instead of synthetic medications that cause many complications. It showed that medicinal plants play a vital role in the management of hepatocellular carcinoma due to the presence of diversity of phytoconstituents that exert their effect via different mechanisms of action. In addition, more studies are needed to confirm the role of natural product as cytotoxic agent against hepatocellular carcinoma and to be the first choice for the treatment of hepatocellular carcinoma.

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