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Herbal Drugs against Hepatic Cancer: New Possibilities as Alternative Therapy

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Abstract

Hepatic cancer is a severe illness, and the situation is made worse by the lack of specific treatment options. The current treatments for liver diseases are ineffective, and their long-term use is hampered by systemic toxicity. Since the toxicity factor tends to be on the lower side, medicinal plants have been used to treat liver diseases for decades. Several phytochemicals have been discovered to have major hepatoprotective activity while having limited systemic side effects, which can restrict their long-term use. The scenario necessitates comprehensive research that could contribute to the creation of lead molecules for potential hepatoprotective molecules. This review presents the recent advancements concerning herbal medicine and its use in the treatment of hepatic cancer.

Key Words**:** Hepatic Cancer, Medicinal Plants, Herbal Drugs, Toxicity

Introduction

Herbal medicine is described as the use of medicinal herbs, or plant-based preparations, to prevent and treat disease and illness, as well as to encourage health and healing. However, it is important to distinguish between "herbal medicine" and "herbal processing," which is often overlooked [1]. Herbal medicine and herbal cultivation are both plant-based medicines that are used in use, although there is a significant distinction between them. Herbal processing is conventional medicine with definite ingredient(s) and definite pharmacological effects when the "plant drug" is for medicinal use. A separate discipline of herbal medicine that provides a therapeutic understanding of the medicinal use of herbs is divorced from the context of so-called "scientific information" and thus not as thoroughly scientifically validated as the use of herbs in herbal medicine[2].

Hepatic cancer is the fifth most prevalent cancer in the world, with a growing incidence [3]. The three current curative methods are orthotopic liver transplantation (OLT), surgical resection, and local destruction (LD). However, due to the presence and position of the tumor, as well as underlying liver disease such as cirrhosis, only a small number of patients are candidates for "curative therapies [4]." Despite these therapies, the recurrence rate after two years can be as high as 50% [9, 10]. To improve these patients' long-term survival, recurrent hepatic cancer prevention following (or before) successful curative therapeutic procedures must be improved [5]. Many adjuvant therapies have been used, including

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transarterial chemoembolization (TACE), antiviral drugs, and immunotherapy, but their efficacy has never been proven [5], [6]. If there is no curative treatment option, four palliative treatments for hepatic cancer are recommended: transarterial chemoembolization, systemic chemotherapy, interferon, and hormonotherapy. However, since hepatic cancer is highly resistant to systemic therapies, palliative care for hepatic cancer patients remains challenging. Notably, the incidence rate is now about equal to the death rate, and more than 80% of patients have advanced disease [2]. The overall poor results of both curative and palliative therapies in advanced hepatic cancer patients support research into more effective and targeted treatments that could be used alone or in combination with the current care [11-12]. Modern biomolecular science has helped in the comprehension of herbs' various beneficial effects, and some important properties such as antiviral, anti-inflammatory, and anticancer properties have been identified [6–8]. Several "herbal medicines" for the treatment of hepatic cancer are being discovered as more knowledge becomes available. The aim of this review is to present the recent advancements concerning herbal medicine and its use in the treatment of hepatic cancer.

Methodology

Different reputable databases were used to perform the English literature searches. Medline, Embase, Science Citation Index, PubMed databases, and related articles from different integrative and complementary medicine journals including Evidence Based Complementary and Alternative Medicine, were used to compile this list. The quest was undertaken with a time frame of January 2021 in mind. The terms "herb," "lung cancer," "hepatoma," "hepatocellular carcinoma," and "hepatic cancer" were used in the quest. The language of publication was limited, and only English was included. Studies that lacked controls were ruled out. Case reports were not included in the study.

Hepatic cancer-causing factors and their pathological aspects

Impact of non-alcoholic fatty liver diseases

Non-alcoholic fatty liver diseases (NAFLD), also recognized as non-alcoholic steatohepatitis (NASH), is a pathological condition of liver, that is very identical to the damage of fatty liver due to high alcohol intake, but it occurs in non-alcohol exploitation people. NAFLD or NASH is categorized by the accretion of triglycerides inside the liver hepatocytes, which is frequently related with the metabolic conditions and overweightness [13]. The occurrence of NAFLD was recognized through the histologic structures found in approximately 70% of overweight persons effected from steatosis. It was observed that NAFLD was found in the obese persons (approx. 20%) and also in some of the lean persons (approx. 10%) [14].

Apart from this, based on the ultrasound imaging studies it was found that around 25% of non-alcoholic lean persons have been reported to suffer from fatty liver [15,16]. NAFLD has been found to be one of the most effective cause that has led to several chronic liver diseases in both Hong Kong and China [17]. Reports have suggested that the major reason behind this is high fat containing dietary habits of the persons in the modern era lifestyle. Also, NAFLD has been reported to be the one of the major reasons for the increase

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in number of patients suffering from several chronic diseases in various developing as well as developed countries. NAFLD has been found to enhance the risk level of incidence of hepatic cancer alike other pot cirrhotic hepatic diseases. In United States of America, the major of cause of demise of most of the middle-aged men due to obesity-mediated cancer deaths is the last stage of hepatic cancer [18]. It has been observed that the number of cases of hepatic cancer patients has been mostly occurring in non-cirrhotic persons suffering from NAFLD [19].

Other hepatic cancer mediated risk factors might be synergistically included in hepatic cancer progression in addition to NAFLD, including alcoholic liver injuries and chronic hepatitis C infections. Various mechanisms are included in the NAFLD-associated hepatic cancer progression and development [20-21]. Obesity also plays a crucial role in enhancing the risk of the development of hepatic cancer from a low-grade to highly chronic inflammatory effect [22,23].

The growth of adipose tissue triggers the production of the pro-inflammatory cytokines including TNF (tumor necrosis factor) and IL-6 (interleukin-6) [24]. Both, TNF and IL-6 resulting from the adipose tissue have exhibited significant role in the development and progression of hepatic cancer. In one of the studies such effects have been demonstrated through a presumptuous that overweightness augments the development of diethylnitrosamine-triggered malicious liver cancer in mice as animal model [25].

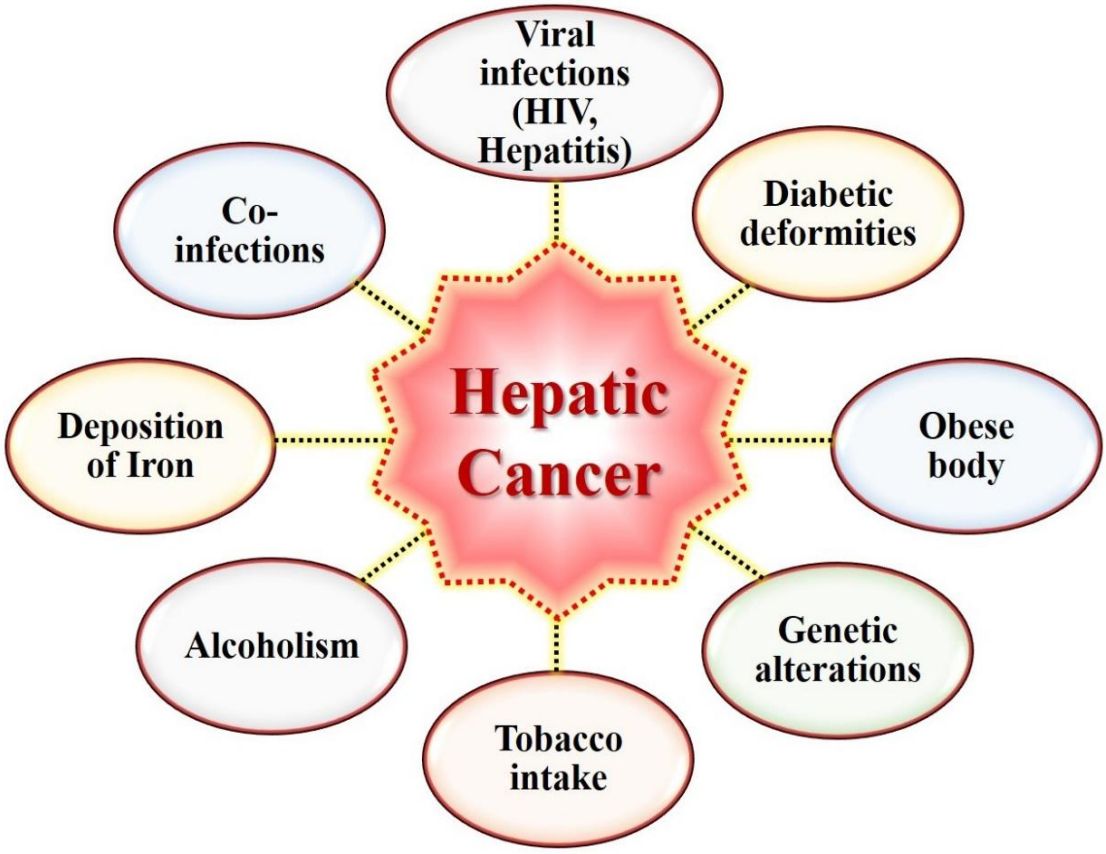

Figure:1 Different etiological factors responsible for hepatic cancer.

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Role of inflammation and anti-inflammatory responses

Generally, inflammation could be described as a state of body which appears as an earlier response in cancer conditions. Inflammation enhances the confrontation to chemotherapy and indorses genes/oncogenes which produces alterations of healthy cells into carcinogenic cells or tumors. The progression and distribution of cancerous cells is also significantly influenced due to inflammation, and the capability of the carcinogenic cells for angiogenesis gets increased. As cancerous condition is considered as inflammation, so the anti-inflammatory drugs could be probably valuable in curing cancers, because the connection amongst cancer progression and inflammation has been valued [26,27].

In case of hepatic cancer, the damage to the liver is either due to acute or chronic inflammations. Various kinds of cells of liver gets activated in response to the type of inflammation. Some of the cell types includes, HSCs (hepatic stellate cells), KCs (Kupffer cells), DCs (dendritic cells) and others, which further releases various types of chemokines, cytokines, and immune intermediaries. Amongst all the types of cytokines, one of the most vital type is IL-6 (interleukin-6) that could potentially hinder both apoptosis as well as inflammation in the tissues [28].

A certain kind of defence mechanism is mediated by the inflammatory responses whenever a microbial infection appears and further the regeneration as well as repairment of tissues takes place. Interestingly, a particular relation amongst the cancer progression and inflammation has been observed because the expansion of dysplasia is stimulated effectively due to chronic inflammations. It has been found that around 20% of cancer types has been severely affected and are related to different types of microbial infection. In immunosuppressant patients, chronic inflammations could usually occur due to the infections caused by hepatitis B and C viruses or human papilloma virus, which ultimately leads to development of hepatic and cervical cancer, respectively [29].

In few cases it has been noticed that hepatic cancers could also get resulted from an unscrupulous infection such as Kaposi's sarcoma, resulted from human herpes virus (HHV)-8 infections. Also, inapt immune responses against the microbes might lead to cancer growth such as gastrointestinal cancers, which might be resulted from the chronic inflammations because of higher level of *Helicobacter pylori* (*H. pylori*) colonization. The long-lasting inflammatory bowel diseases might cause colon or colorectal cancers. Continuous acquaintance to silica, asbestos and smoke, might cause chronic irritations and consequent inflammatory changes within the body which further causes cancer development [30].

The increase in the number of tumor cells is highly dependent on the persistence of the originated cells and their development. Various inflammation mediators such as cytokines, chemokines and eicanosoids, and have shown the capability to trigger the propagation rate of both unchanged cells as well as of the tumor cells [31]. Inflammation have showed significant effects in growth and propagation of the tumour cells through angiogenesis intercession. It has also demonstrated vital role in other prospects of tumour development such as metastasis and tissue incursion. Matrix metalloproteinases (MMPs) and their inhibiting agents have showed significant importance in the remodelling of the extracellular matrixes and angiogenesis, leading to enhanced level of vascular incursion of the propagating cells [32].

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Role of oxidative stress

Oxidative stress usually arises when the body comes in the contact of any harmful endogenous or exogenous stimuli such as per-oxidative based free radicals. Some of the most important and significant per-oxidative based free radicals includes ROS (reactive oxygen species), RNS (reactive nitrogen species) and other types. The free radicals are generally developed during various redox (oxidation-reduction) responses, taking place within the cells. Oxidative stress is typically related with the progress of numerous diseases, some of them including cardiovascular disorders, neuronal diseases, diabetes, and cancer-based disturbances via initiation of oxidative damage of the cellular DNA and irregular protein expressions [33].

Oxidative stress could act as a potential risk factor in case of hepatic cancer and associated disorders, as it assists in enhancing the oxidative damage to the hepatocytic DNA [34]. Moreover, various chronic viral infections might enhance the release of both ROS and RNS by instigating inflammation and mortification of the hepatocytes that convoy immune cell insinuation [35]. The major reason behind the damage of DNA is mutation, which is mostly caused by the augmented level of ROS and failure in DNA repairing leads to increased chances of mutation of the cancer-associated genes, thus leading to severe hepatic cancer [36,37].

Increased level of oxidative stress and DNA damage are mainly responsible for the chances of hepatic cancer associated with the viral infections [38]. The increased levels of TGF-β (transforming growth factor beta) and TNF-α (tumour necrosis factor- α) in the patients with chronic hepatitis C are primarily associated with the oxidative stress. The level of TGF-β is mainly utilized to detect how much tissues are affected and up to which degree they are injured [39].

Oxidative stress also elevates the level of ROS within the cells, that breaks the electron transport chains in the injured mitochondria. The extreme release of TNF-α effects extreme harm to the mitochondrial respiratory chains and damages the cytochrome oxidase. It has been observed that the increased level of ROS significantly effects the normal cell processes, augments the lipid peroxidation and the respiratory electron transport chains get inhibited [40].

ROS significantly alters the metabolic activities of the mitochondria and exhibit significant impacts over the apoptotic pathways, causes variations in the membrane permeability and leads to mitochondrial DNA damage [41]. Oxidative stress also assists in enhancing the telomere shortening which causes an enhanced level of cytoplasmic relocation of the reverse transcriptase telomerase subunits [42]. Various kinds of genes, micro-RNA (miRNA), and expression of various types of immune system mediators gets altered when exposed to oxidative stress. More importantly, dysfunction of miRNA is associated severely with hepatic cancer [43].

Effects of Apoptosis and chemo preventive agents

Apoptosis is referred as the programmed cell death and has immense in the field of oncology [44]. The identification of the individual pathways associated with apoptosis has found to be very crucial in understanding the mechanism behind the development of cancer and in the anticipation and curing of the disease. The normal and healthy tissue homeostasis preserved by maintaining the balance among the cellular proliferation and cellular death.

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Furthermore, the disparity among these two procedures might cause irregulated clonal expansions, the major cause of all kinds of neoplastic diseases, including hepatic cancers [45,46].

The process of apoptosis is one of the major mechanisms that has been utilized by the various cytotoxic agents, used for the therapy of various cancer types, including hepatic cancer. Numerous experimental methods intended to arouse apoptosis that ensues in the development of therapeutic responses. Several herbal products and by-products have exhibited significant role in regulation of cell propagation and distinction. The chemo preventive abilities of various herbal products might be because of their abilities in facilitating diverse pathways involved in the growth and progression of hepatic cancerous cells [47,48]. Also, various physiological changes in the biological system due to hepatic cancer has been illustrated in fig. 2.

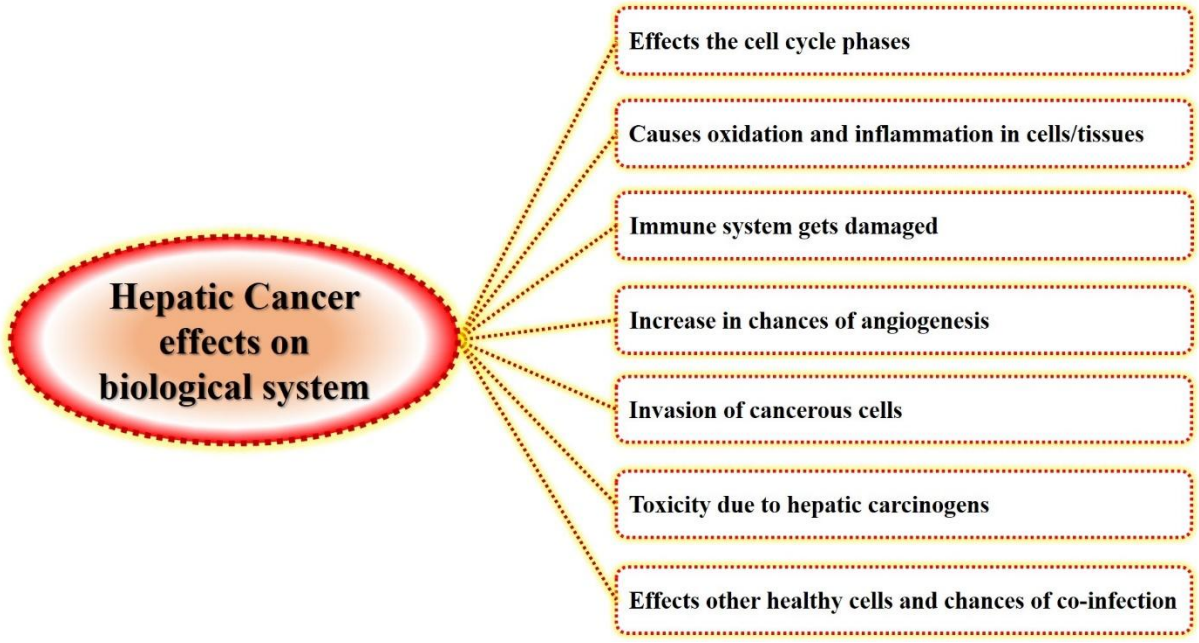

Figure:2 Various physiological changes in the biological system due to hepatic cancer.

Herbal products in hepatic cancer: Abilities and mechanism

Herbal products are usually isolated from the medicinal plants and are profoundly used for the treatment of various kinds of diseases. In ancient times, herbal plants and its products have been used as medicines, even in Mesopotamia. Furthermore, back in 1550 BC, well-preserved records in “Ebers Papyrus” describe the medicinal benefits of more than 700 drugs (49). Similarly, Indian Ayurveda philosophy was followed first millennium BC (50). However, several limitations have been observed for the herbal plants/product-based drug progresses including quality, identification of major bioactive components, complications in the procurement wild samples, and compatibility issues during high-throughput screening (51). Also, it is very hectic and crucial process to identify the exact mechanism of action of the isolated natural products/by-products. Due to these limitations and constrains, the

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pharmaceutical industries and manufacturers have changed their primary importance on newer product progresses towards synthetic constituents (52).

The United States Food and Drug Administration have showed very low approval levels for such plant-based products. Apart of such issues and constrains, researchers have showed credence in developing herbal-products due to their immense potentials in treating diseases. One of the major drug discovery and research including the herbal-based phytoconstituents is for the management and treatment of several kinds of cancer or cancer-mediated deformities (53). These phytoconstituents have found to be very effective and exerts immense potentials as a potential cancer therapy approach. The effectiveness of these phytoconstituents is because they have constrained the initiation, development, and progression of cancerous cells. In additions they have exerted effects over several cellular pathways including cellular division, apoptosis, cellular proliferation, angiogenesis, and cell metastasis (54,55).

Nowadays, huge number of herbal products and phytoconstituents are used for the treatment of various types of cancer, particularly hepatic cancer, or associated disorders. Their usage has enhanced due to budget competence, long-standing valuable actions, and rarer adverse effects. It has been noticed that the phytoconstituents significantly act in hepatic cancers through protecting the hepatic cells by various mechanisms including, virus eradication, obstructing fibrogenesis, inhibiting oxidative injury and suppression of tumour growth and progression process (56,57).

Apart from this, health habits and diet also play crucial role in the prevention and treatment of hepatic cancers. Epidemiological studies have demonstrated that the risk of hepatic cancer could be potentially reduced with the control in daily intake of high-fibre, low-calorie diet complemented by considerable fruits and vegetables (58). Moreover, intake of dietetic natural products could exhibit significant approaches for the management and establishment of novel therapeutic strategies in hepatic cancer therapy. A few anticancer activities of different herbal products and dietary constituents have been reported by the researchers including tumour growth inhibition and metastasis, protective effect against liver carcinogens, immunomodulation and overall improvement in the anticancer drug effects (59). Comparatively, quite a few dietary substances have established discerning inhibitory effects against the cancerous cells (60). This difference is predominantly substantial for the treatment of hepatic cancer, as most of the patients agonize from extremely impaired and hindered liver functions. Figure 1 represents some of the major etiological factors associated with hepatic cancer or associated disorders (61).

Herbal Compounds.

A variety of molecular compounds obtained from herbs have been shown to be beneficial in the treatment of hepatic cancer. Many compounds are active at certain molecular targets, according to recent research [1], [2], [9], which is being used to identify possible newer generation “targeted” biological response modifier drugs. These herbal compounds have been shown to interact with several molecular targets linked to hepatic cancer carcinogenesis and chemoprevention, as determined by laboratory studies and clinical observations. These

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molecular compounds constitute a vast and largely untapped resource for the treatment of hepatic cancer. Table 1 summarizes and discusses some of the herbal compounds.

Herbal compound	Significance in treatment of Liver Cancer	Reference
Curcumin	Inhibits proliferation; induces apoptosis; inhibits p21(ras), PCNA, cyclin E, factor NF-, and elevates mitochondrial membrane potential; reduces ROS, and is very essential for hepatic cancer in human beings	[9], [10]
Resveratrol	Reduces ROS; induces cell-cycle arrest in G1 and G2/M phases; modulates NO/NOS; suppresses ROS-potentiated invasion and is very essential for hepatic cancer	[3], [10]
Silibinin	Allows G1 arrest; inhibits Kip1/p27; lowers cyclin D1, cyclin D3, cyclin E, and is effective for hepatic cancer	[1]
Tanshinone IIA	Downregulates bcl-2; suppresses bcl-2; inhibits DNA synthesis and is very essential for hepatic cancer	[7], [11]

Curcumin

Curcumin is the main curcuminoid found in the common Indian spice turmeric (Curcuma longa L.), which belongs to the ginger family (Zingiberaceae). Turmeric has been used in herbal medicine for the prevention of jaundice and other liver disorders, parasitic infections, ulcers, joint inflammation, and various skin diseases, among other things[9, 10]. Curcuminoids are a group of structurally related phenolic compounds found in turmeric's rhizomes. Curcumin (60–80 percent), demethoxycurcumin (10–20 percent), and bisdemethoxycurcumin (5–10 percent) are the three most common curcuminoids. Curcumin is a diferuloylmethane with a diferulic acid moiety fused to another carbon atom or methylene moiety in terms of chemistry[10]. As a result of hydrogen bonding stabilization, it has a methylene-1, 3-diketo group that exhibits keto-enol tautomerism. Curcumin is often used as a keto-enol rather than a diketo type (Figure 1).

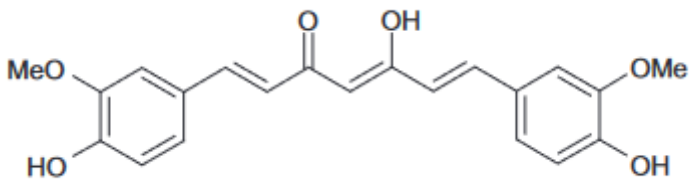

Figure 1. Structure of curcumin

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Resveratrol

Resveratrol is a naturally occurring polyphenol with several health benefits, including antioxidant, anti-inflammatory, anti-aging, cardioprotective, and neuroprotective properties [7]. Plants contain resveratrol, a phytoalexin, when they are attacked by bacteria or fungi. Resveratrol can be found in a variety of plants and fruits, including red grapes, eucalyptus, spruce, blueberries, mulberries, peanuts, and giant knotweed. It's also widely used in red wine. The effect of resveratrol on hepatic cancer has also been extensively studied [1]. Resveratrol has a significant chemo preventive effect on DENA-induced hepatocarcinogenesis by inhibiting cell proliferation and inducing apoptosis [1]. They concluded that the resveratrol-induced apoptogenic signal is mediated by a decrease in Bcl-2 expression and an increase in Bax expression [4]. In an in vitro study, Stervbo et al. discovered that resveratrol inhibits cell proliferation and apoptosis in HepG2 cells. They discovered that resveratrol inhibited DNA synthesis and increased nuclear size and granularity in HepG2 cells during the G1 and S phases [11].

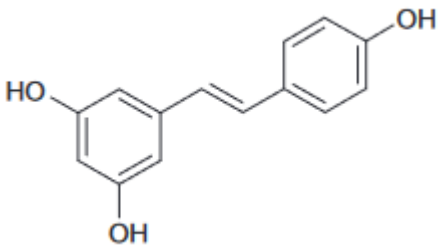

Figure 12. Structure of resveratrol.

Silibinin

The most biologically active compound in milk thistle is silibinin, a polyphenolic flavonoid. Milk thistle is well-known for its health benefits and tolerability, as well as its ability to protect the liver from drug or alcohol-related damage [8], [12]. Silibinin and its crude form, silymarin, are used in both medical and dietary supplements to treat liver toxicity. A randomized controlled multicenter study showed that providing silymarin on a daily basis to patients with alcoholic liver cirrhosis for several years resulted in a significant reduction in mortality [5]. Several cancer cell-lines, like hepatic cancer, have been shown in studies to be inhibited by silibinin. Silibinin was found to have a strong inhibitory effect on both HepG2 and Hep3B cells [1]. According to [2] the impact of silibinin on hepatic cancer cell growth was studied in four human hepatic cancer cell lines: HuH7, HepG2, PLC/PRF/5, and Hep3B cells. After various doses of silibinin were applied to cells, researchers examined their proliferation, apoptosis, cell-cycle progression, histone acetylation, and other related signal transductions. They discovered that silibinin significantly inhibited the growth of HuH7, HepG2, Hep3B, and PLC/PRF/5 human hepatoma cells. They also discovered lower levels of metalloproteinase2 (MMP2) and CD34 in hepatic cancer cell growth cells, implying that silibinin could have anti-angiogenic properties. They also discovered that silibinin increased histone H3 and H4 acetylation (AC-H3 and AC-H4), suggesting that altered histone acetylation can play a role in silibinin's chemoprevention of hepatic cancer cell growth [3].

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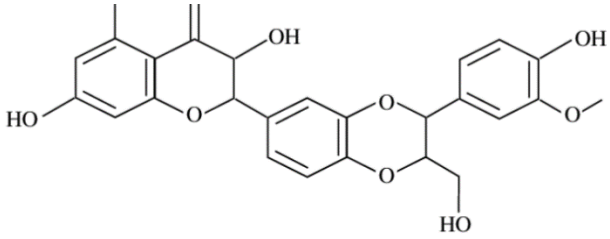

Figure 2: Structure of silibinin

Tanshinone IIA

Tanshinone IIA doubles as one of the most common diterpenes isolated from Salvia miltiorrhiza Bunge (Danshen in Chinese). Tanshinone IIA has antioxidant properties [60] as well as the potential to defend and/or prevent angina pectoris and myocardial infarction [61]. Proliferation inhibition and cytotoxic effects on cell lines derived from various human carcinomas have been observed [12]. Tanshinone II-A therapy clearly inhibited SMMC7721 cell growth and colony formation. The apoptosis index skyrocketed, and the cells joined the G (0)/G (1) cycle. The apoptosis-related genes bcl-2 and c-myc were also downregulated, while fas, bax, and p53 were upregulated [62]. Tanshinone IIA was studied by NavaneethaKrishnan [7] for its effects on HepG2 cell growth and apoptosis. Tanshinone IIA, according to the researchers [61], inhibited cell growth and induced apoptosis in HepG2 cells. Tang et al. examine the impact of tanshinone IIA on the growth and apoptosis of the human HCC cell line BEL-7402. Tanshinone IIA inhibited cell growth and induced apoptosis in BEL-7402 cells [62].

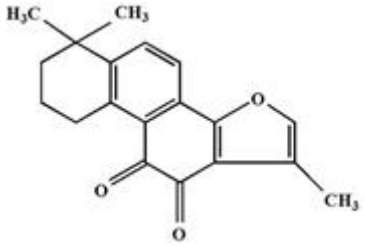

Figure 4: Structure of Tanshinone IIA

Conclusion

Herbal medicines made from plant extracts are increasingly being used or utilised to treat several clinical diseases with lung cancer inclusive. A significant number of patients with liver or hepatic cancer are treated with botanicals. Future attempts will need to make systematic methodological improvements to differentiate between the true therapeutic potential of these agents and the unsubstantiated hopes associated with them. The active molecules must be isolated and tested in well-designed experiments, accompanied by randomized trials, in order to enable fair clinical use of the agents. Several isolated lead molecules have been identified that, if thoroughly investigated, could lead to the development of potential hepatoprotective drugs. Sound and controlled clinical studies with herbals, especially their active ingredients, in chronic liver diseases are crucial in order to discover novel antifibrotic and anti-inflammatory behaviours. The promise of herbal medicines

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requires both experimental and clinical trials, and rigorous scientific research based on evidence-based medicine principles will help herbal medicine become a very justifiable scientific treatment regime.

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