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Exposure, formation, and various available treatments to combat hepatocellular carcinoma: A comprehensive review

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Abstract: Hepatocellular carcinoma (HCC) is a primary liver tumor that develops from chronically damaged tissue that contains large amounts of inflammation and fibrosis, which also promote tumor progression and resistance to therapy. It is the most common cancer with high mortality (>60,000) in low resourced countries, which covers over 5% of the deaths and the sixth most widespread cause of cancer death among cirrhosis patients across the globe. There has been a widespread notion that synthetic agents are the cause of most cancers. There are many other hereditary and environmental factors, which alter the behavior and aggressiveness of HCC, particularly at early stages of disease. This remains a significant public health challenge and is assumed to affect over 1 million people every year by 2025. The present situation reflects that HCC is steadily increasing in developed countries due to poor prognosis. Newer treatments are needed with several being in development, either in pre-clinical or clinical studies. Over the past decade, herbal medicines have been accepted globally as prominent therapeutic agents for prevention and treatment of cancer. This review summarizes several aspects of environmental chemical carcinogenesis and their treatments by using diverse natural bioactive compounds of medicinal plants.

Keywords: anti-cancer; cancer; hepatocellular carcinoma; medicinal plants; herbal treatment

1. Introduction

Liver cancer is endemic in Asia and one of the global deadliest cancers ranked third among the mortality rate caused by all cancers [1]. While hepatocellular carcinoma comprises 70-85% of the initial malignant tumors of the liver and its formation is often linked to chronic inflammation induced by primary infection with HCC or HBV [2]. Across Africa and Asia, some viruses such as the immunodeficiency virus type I (HIV-I), hepatitis C virus (HCV), hepatitis B virus (HBV), and various human papillomaviruses were classified as group 1 carcinogens. Hepatitis B Virus induced cirrhosis and chronic active hepatitis is the major factors that constitute liver carcinogenesis. More than 25% of chronic hepatitis B people are predicted to die of liver disease, with an estimated annual death of over 1 million infected people [3].

The World Health Organization (WHO) evaluates that approximately 170 million's people, or 3% of the global population, are HCV infected and at developing risk of liver cirrhosis or/and liver cancer. The involvements of HCV in HCC genesis are identical to HBV. Where hepatic damage, mediated by chronic immune response, along with tissue reconstruction and inflammation are the critical factors for lesion progression [4].

Emerging scientific evidence also shows the effect of HCC in stable areas of affluent countries is increasing. This lay the door to an expanding incidence of HCV infection and non-alcoholic fatty liver abnormalities linked with obesity [5, 6]. In the USA, HCC mortality rates are increasing rapidly. Since its reappearance chances are high, effective chemotherapeutic drugs are not available at present and the assessment remains unpleasant [7].

2. Free radicals to oxidative stress

Free radicals are ions, atoms, or molecules that are volatile with unpaired electrons through chemical interactions with other compounds. They consist of three elements: sulfur, oxygen, and nitrogen, forming ROS, RNS, and RSS. ROS comprise free radicals such as peroxynitrite, hydroxyl radical, superoxide anion, hydroperoxyl radicals, singlet oxygen, hypochlorous acid (HOCl), nitric oxide (NO), and hydrogen peroxide (H_2O_2). RNS is generated from NO by interacting with peroxynitrite and superoxide anion. The reaction of ROS to thiols easily forms RSS [8]. The

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hydroperoxyl radical diffuses to the superoxide anion at pH 7. They are highly reactive and can interact with several compounds to produce ROS directly or through enzymatic or metallurgical processes. Superoxide ions can be detoxified to H_2O_2 by dismutation reaction with the superoxide dismutase (SOD) and finally passing water by the catalase enzyme (CAT).

If an iron catalyst such as Fe^{2+}, reacts to H_2O_2, the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH–$) can take place to generate a hydroxyl radical $HO^{\cdot}$ [9]. Eventually, RSS emerges from the thiols under oxidative conditions to generate a disulfide that can produce either disulfide-S-dioxide or disulfide-S-monoxide as an intermediate molecule after further oxidation. Therefore, a thiol-reduced reaction may lead to the production of sulfinic acid or sulfenic [10].

Free radicals are generated through various internal factors like phagocytosis, ischemia, peroxisomes, physical exercise, xanthine oxidase, inflammation processes, and arachidonate pathways as potential metabolites within the mitochondria. External factors such as ozone, environmental pollutants, industrial solvents, smoking, pesticides, radiation, and drugs can also boost the generation of free radicals. The balance between antioxidant synthesis and ROS neutralization is particularly sensitive. If the accumulation of ROS increases, cells begin to suffer the impacts of oxidative stress [11]. It is estimated that hydroxyl radicals and other species target a human cell every day and cause oxidative stress an average of 105 times [12].

3. Oxidative stress

An imbalance between the production rate of the oxidizing agent and that of its destruction is oxidative stress. This leads to loss of physiological functions, several types of damages, irregular metabolism, serious illness, and perhaps death which ends in the production of various oxidants. They are generated as a normal aerobic metabolism product and can be produced under several pathophysiological conditions [13]. The four-electron molecular oxygen reduction is performed in mitochondria and at the end of the respiratory chain, it releases water. Most of the time, molecular oxygen is depleted rather than the proteins associated with the respiratory chain and superoxide. Several reactive intermediates are generated which leads to secondary oxidations [14]. If the organism is unable to neutralize them, these oxidizing agents build up and react with a wide range of biomolecules and generate an unfavorable condition [15]. Oxidative stress promotes carcinogenesis through various processes, including damage to DNA, proteins, and lipids changes in intracellular signaling pathways, and alterations in gene expression. These oxidative changes collectively promote the proliferation and carcinogenesis of abnormal cells [16].

4. Reactive oxygen species

ROS can disrupt biological functions and cause cellular damage. Which are generated in various molecular processes and organelles e.g., endoplasmic reticulum (ER), chloroplast, mitochondria, peroxisomes, and mitochondria. ROS-generating enzymes can also be found in the plasma membrane and cytosol [17]. Both chloroplast and peroxisome are considered important origins in the case of ROS creation if there is light. On the contrary, if there is a dark condition, the mitochondrion is the pre-eminent origin of ROS [18].

In many physiological processes, ROS play a role such as cell cycle regulation, signal transmission, and resistance of microorganism [19]. It also stimulates the apoptosis and necrosis of hepatocytes, causing hepatic injuries that initiate the progression of end-stage liver problems. Excessive ROS produced from different oxidative biochemical enzymes interferes with the basic functioning of liver cells and possibly plays a significant role in liver fibrosis pathogenesis. ROS scavenging has been a keystone therapeutic strategy to stop oxidative stress [20]. Several intracellular ROS sources have been recognized mainly for specific enzyme processes. The ROS sources are a potential target for addressing oxidative stress-related disorders, including liver fibrosis since with the evolution of chronic liver disease, they appear to induce excessive ROS.

The rich amount of ROS helps to reduce oxidative stress through the concurrent decline in cellular anti-oxidative stress. This entire proceeding recommends another path in the advancement of this disease. When plant foods are enriched with bioactive compounds such as polyphenols and it becomes a protective source against oxidative stress by showing anti-oxidant activities [21].

5. Domains of ROS

The generation of ROS is located in plants predominantly in peroxisomes, chloroplast, and mitochondria. Secondary locations are also available such as the cell wall, endoplasmic reticulum, apoplast, and cell membrane. ROS is significantly extended at initial levels under favorable circumstances. However, they never lead to any damage they are scavenged by various antioxidant systems [22].

Various types of stress factors such as pathogen infection, heavy metals, salinity, extreme temperatures, high irradiance, drought, and pollution disrupt the delicate equilibrium between ROS production and its scavenging. Several kinds of ROS such as $^1O_2$ (singlet oxygen), $OH^{\bullet}$ (hydroxyl radical), H_2O_2, and $O2^{\bullet-}$ (superoxide radical) are undesirable byproducts [23]. This estimates the generation of ROS results in 1-2 % for consumption of oxygen by the plant tissues or cells. The response of various members of the ROS is shown in Figure 1.

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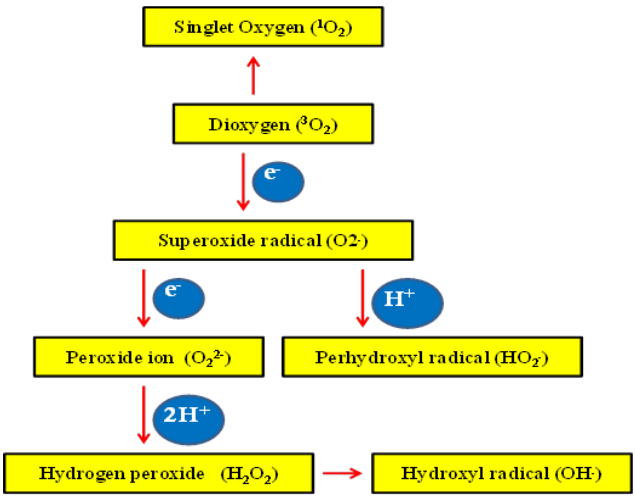

Figure 1. Energy transfer and generation of ROS

6. Production of ROS and mitochondrial antioxidant defense

Mitochondria play a major role in ROS generation [24], which is generated by oxidative phosphorylation. While most of the electrons provided to the mitochondrial respiratory chain (MRC) are migrated to cytochrome c oxidase. In this case, H_2O_2 produces hydroxyl radicals by reacting with iron. In addition, hypochloride radical is produced by active myeloperoxidase [25, 26]. Besides its harmful effects, mitochondrial ROS are also signal transducers, according to intensity, and time of oxidative stress, in functional and pathological conditions.

During oxidative phosphorylation, ATP is produced when the electrons are delivered to O_2 by one electron at a time ($O_2 \rightarrow O_2^{-}\cdot \rightarrow H_2O_2 \rightarrow \cdot OH \rightarrow H_2O$) which forms an electrochemical gradient [27]. In this process, ROS are produced having one unpaired electron and are relatively stable intermediates. Nitric oxide synthase breaks down arginine to citrulline, generating NO as well [28]. NO is a lipophilic uncharged molecule and reacts easily with molecules like oxygen, superoxide radicals, and glutathione, as it contains a single unpaired electron. When NO· reacts readily with O_2 it forms peroxynitrite (O_2^{-} + NO $\rightarrow$ $OONO^{-}$). Peroxynitrite further decomposes to NO_2· and .OH. Among ROS, H_2O_2 as a neutral molecule is the most stable and least reactive molecule in normal body conditions specifically in the absence of metal ions [29].

The most common superoxide ($O_2^{\bullet -}$) is produced most abundantly in mitochondria through the electron transfer chain (ETC). This process occurs through the partial reduction of oxygen. In ETC complex I (NADH: ubiquinone oxido reductase) and complex III (ubiquinol: cytochrome *c* oxido reductase), a small percentage of an oxygen molecule is converted to superoxide anion radical [30]. Complex 2 has FADH2 that donates the electrons directly to the ETC. Complex 4 is Cytochrome c oxidase that delivers electrons to oxygen thereby generating water as well. Complex V of the ETC is an ATP synthase the Fo component of which acts as an ion channel that pumps the proton back into the mitochondrial matrix. Human cytochrome P450s are also important factors in the generation of ROS that play their role in cancer pathogenesis [31]. The role of Cytochrome p450s is dependent on NADPH/O_2 microsomal transport chain system [32, 33]. Increased level of ROS has been rendered responsible for an increase in receptors and the oncogenic activity, and the stimulation of pathways such as growth factor-dependent pathways. As a result, genetic instability is induced by this stimulation.

Whereas nitric oxide synthase (NOS) is distributed intracellularly which is important to regulate all enzymes displayed completely various ROS concentrations, wherever within the cellular contents ROS are present for instance, but especially in some tissue cells (plasma membranes of viscus, epithelial tissue cells, caveolae of the tissue layer, and T tubules) are the best source of eNOS [34].

A recent study in rat hepatocytes suggested that iNOS localize sub-cellularly and showed that a huge amount of the promotors is localized in peroxisomes when infected [35]. Besides this, the molecular reaction between NO· with O_2·- free radicals, formed via a mitochondrial respiratory chain, results in reversible attenuation of the internal respiration through mitochondria by ONOO- free radicals [36, 37]. The process of autophagy allows the degradation and clearance of non-functional cell organelles and misfolded proteins. They can pile up in the nervous and skeletal tissues and cells during the post-mitotic cell division process. In starvation and fasting, autophagy is also induced which helps in the utilization of amino acids by gluconeogenesis which occurs in the liver. ROS molecules are not only generated by mitochondria but they also target mitochondria as well.

Mitophagy is a special form of autophagy in which damaged and non-functional mitochondria are degraded. Important factors like regulation of liver metabolism, prevention of cell death by lowering oxidative stress, and prevention of mitochondrial bioenergetics loss are important hallmarks of mitophagy. Further interruptions in the normal process of mitophagy may cause agglomeration of highly damaged malfunctioned mitochondria initiating the process of necrosis, thus releasing bacterial vestiges retained in mitochondria. This leads to the promotion of liver inflammation and NASH development. ER-mitochondria contacts sites where micro-domains of elevated calcium concentration are present. Where mitochondrial calcium uptake is very carefully regulated. The elevated calcium ion amounts cause many responses leading from stimulation of metabolism and ATP production to PTP opening and the process of apoptosis. All

these mitochondrial changes require alterations in production levels of ROS and its related signaling pathways, changes in the mitophagy process, and alterations in mitochondrial biogenesis. Some of the modifications in cholesterol levels in mitochondria are TNF, lipid peroxidation products, GSH, and FFAs are also required [38].

7. Hallmarks and significant features of cancer

Cancer is prompted by two gene types- tumor suppressor genes and oncogenes. Each plays a significant role in the healthy cells. Hanahan and Weinberg describe six major molecular alterations in cancer cell processes that show their malignant behavior such as maintaining replicative potential, angiogenesis, avoiding cell death, growth factor independence, metastasis, and evading growth suppressors. In 2011, it was subsequently updated by two developing hallmarks (energy metabolism reprogramming and evading immune destruction) and two significant features (instability of genomes and inflammation) [39, 40].

8. Causes and risk factors of liver cancer

The liver is the most complex and largest organ inside our body. The main function of the liver is to remove all types of endogenous and exogenous materials from the blood and are involved in bile production, carbohydrate metabolism, formation of urea, lipid metabolism, and other immune responses. Moreover, as it is the largest internal glandular organ, it fulfills numerous important functions such as the production of vitamins, urea, glycogen, or cholesterol, detoxification, mineral storage, nutrient processing, fat digestion, and blood infiltration [41, 42].

Heavy smoking yields toxins that cause necroinflammation and increases the risk of hepatic lesions associated with HCV or HBV infection [43]. The risk of HCC development among chronic liver disease (CLD) patients with active liver status, is increased by cigarette smoking. Smoking association with HCC has been reported independently of HBV status [44]. Smoking has three main impacts on the liver *i.e.*, toxic effects (direct or indirect), oncogenic, and immunological effects.

Liver cirrhosis is a significant risk of HCC, representing 75-80% of primary liver malignancies, and the third main reason of death due to cancer globally [45]. Whereas, CLD progression relies on many factors such as HBV, HCV, ALD, NAFLD, AIH, and HD, which depend on the geographic area and specific etiology [46, 47].

Smoking enhances pro-inflammatory cytokines production which is involved in the injury of liver cells in the form of excess iron deposition, and apoptosis in the liver. It is the main source of hepatic carcinogen, which is 4-aminobiphenyl [48]. The high amount of hepatic iron increases lipid peroxidation and oxidative stress. Ethanol consumption is another factor that is responsible for cirrhosis incidence and ROS through uncoupling when ethanol is metabolized due to elevated hepatic oxidative stress. It will lead to liver proliferation, cell cycle activation, cell generation, and uncontrolled cell growth associated with the development, dedifferentiation, and hyperplasia, of HCC as shown in Figure 2 [49]. In cases of chronic ethanol consumption CYP2E1 mediated ROS generations result in DNA adducts that have carcinogenic effects in the liver [24]. It can cause various liver abnormalities as ROS produced by it even in substrate absence due to uncoupling reaction [50].

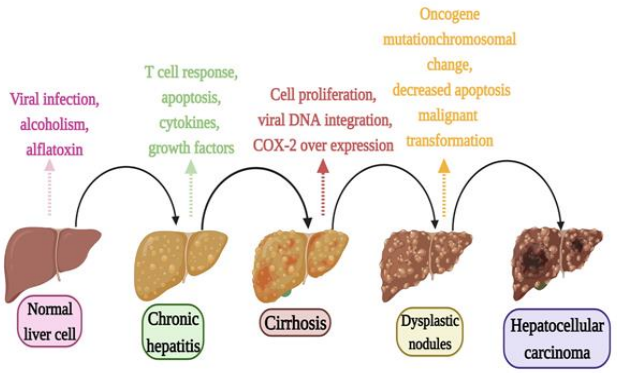

Figure 2. Histological evolution of HCC

Occupational exposure to chemicals is another risk factor for liver cancer which is often classified as an infective and non-infective risk factor. HBV, HCV, and AFB1 are mainly considered infective risk factors. While PVC, TCE, PCE, DDT, PCB, etc. are considered major non-infective risk factors [51]. It is hypothesized that it contributes to liver cancer by developing inflammation. Research evaluating the effects of occupational exposure-induced liver cancer is rare due to numerous considerations including inconsistent case definition and small sample size. Moreover, they also relied on surrogate, exposure-associated measures such as duration and industrial harmful chemical substances [52]. Moreover, cellular components of the microenvironment and molecular mechanisms in the extracellular matrix among stromal (cancer-associated fibroblastic cells, immune cells, and angiogenic cells), inflammatory, and cancer cells create a complex cellular system (as shown in Figure 3) and permissive microenvironment that influence tumor growth and progression [53].

Different factors cause liver cancer. It can be hereditary or environmental. Hereditary factors include abnormal proliferation like inheritance, dysfunction, transplacental, sex-linked, genetic, or metabolic changes, and oncogenes also play a significant role in some early childhood cancers [54]. Environmental factors cause include pro-carcinogens and precursors to carcinogens, such as amines, sodium nitrites, and nitrosamines like N-nitrosodi-ethylamine (DENA) or N-nitrosodimethylamine (NDMA) present in food preservatives, artificial sweeteners, and tobacco [55].

Exposure to specific radiation rays, viral infectious agents (air and water pollutants) viruses, bacteria, and ionizing radiation that forms free radicals. This leads to various kinds of metabolism, DNA damage, mutations, and tumors as shown in Figure 4 [56]. Out of enormous environmental carcinogens, DENA is a potent human carcinogen. Its main sources cover foodstuffs, including milk, soya, salted dry fish, alcoholic drinks, and cured meats [57].

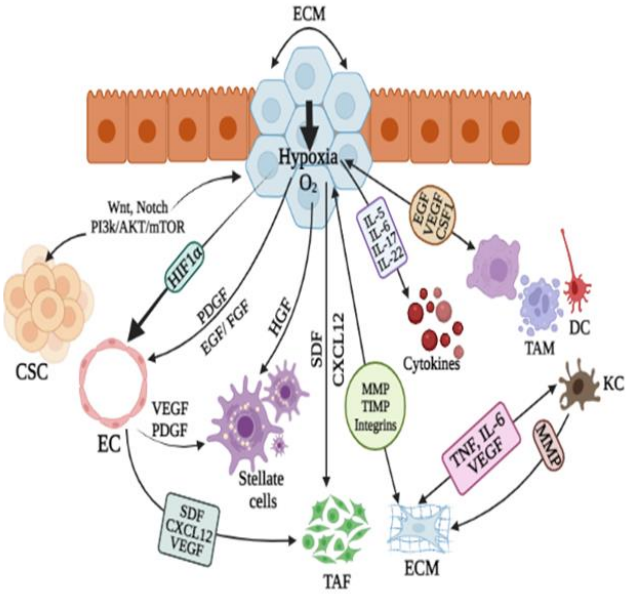

Figure 3. Role of the microenvironment in HCC. ECM: Extracellular matrix; CSC: cancer stem cells; HIF1α: Hypoxia inducible factor 1 α; EC: endothelial cells; VEGF: vascular endothelial growth factor; PDGF: platelet derived growth factor; TNF: tumor necrosis factor; HGF: hepatocyte growth factor; EGF: epidermal growth factor; FGF: fibroblast growth factor; SDF: stromal cell derived factor 1; MMP: metaloproteinases; TIMP: tissue inhibitor of metalloproteinases; DC: dendritic cells; TAM: tumor associated macrophages; KC: kupffer cells

9. Mechanism of action

9.1 Role of carcinogenesis in liver cancer

Carcinogenesis is a result of cirrhosis and chronic hepatitis caused by HBV and viral integration [58]. Normal cells will be transformed into cancer cells for years. The stage of cancer includes three steps i.e., initiation, promotion, and progression as the scheme represented in Figure 5. The first stage is based on the reaction between the carcinogen and the DNA of tissue or cells leading to a permanent gene mutation. The second stage takes place extremely slowly over several months to years causing the formation of a tumor. The third and final stage promotes cancer progression which shows metastasis [59]. It may include many abnormalities such as gene amplifications, modulation of DNA methylation, chromosomal deletions, mutations, re-arrangements, and aneuploidy [60].

Another pro-inflammatory immune mediator tumor necrosis factor-alpha (TNF-α) mainly responsible for

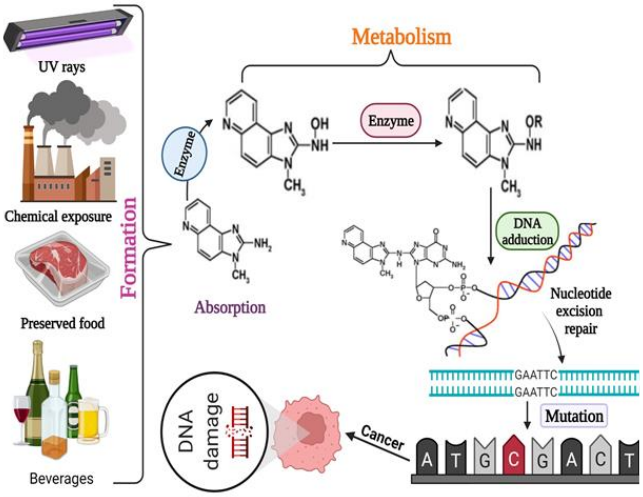

Figure 4. Complex steps involved between carcinogen formation and cancer

inducing tissue damage but it also enhances the process of fibrosis and lastly it accelerates oxidative stress reaction [61]. TNF-α also activates cellular apoptotic and anti-apoptotic pathways. But still, the role of TNF-α is unclear. Elevation of both transforming growth factor-beta (TGF-β) and fibrosis factor TNF-$\alpha$is also associated with oxidative stress injuries in chronic hepatitis patients. Tissue damage and liver fibrosis are mainly associated with TGF-β [62, 63]. The major roles of cytokines are liver inflammation fibrosis and apoptosis but they also regulate various important processes alcoholic steatohepatitis (ASH), nonalcoholic steatohepatitis (NASH), and also regulate some processes like regulation of fever, lipid metabolism, elevates neutrophils, appetite disorders, and insulin resistance [64].

9.2 How oxidative stress causes liver cell injury

Various multiple inflammatory signals and other processes are triggered by oxidative stress affecting different liver cells. How oxidative stress causes liver cancer cell development is summarized in Figure 6. Both acute and chronic types of liver injuries can occur by oxidative stress. More specifically in the case of local inflammation various liver cells such as kupffer cells (KCs), liver sinusoidal endothelial cells (LSECs), and dendritic cells (DCs) are activated. As a result of this activation, they produce different kinds of immune mediator factors such as chemokines and cytokines. For instance, inhibition of tissue inflammation and cellular apoptosis is caused by interleukin-6 [61].

In the human body, many processes receive stimulatory signals from endogenos and exogenos factors, which ultimately lead to oxidative stress. During this process, free radicals including ROS and RNS are elevated. Certain redox reactions in the human body are one of the causes which produce these reactive species [65].

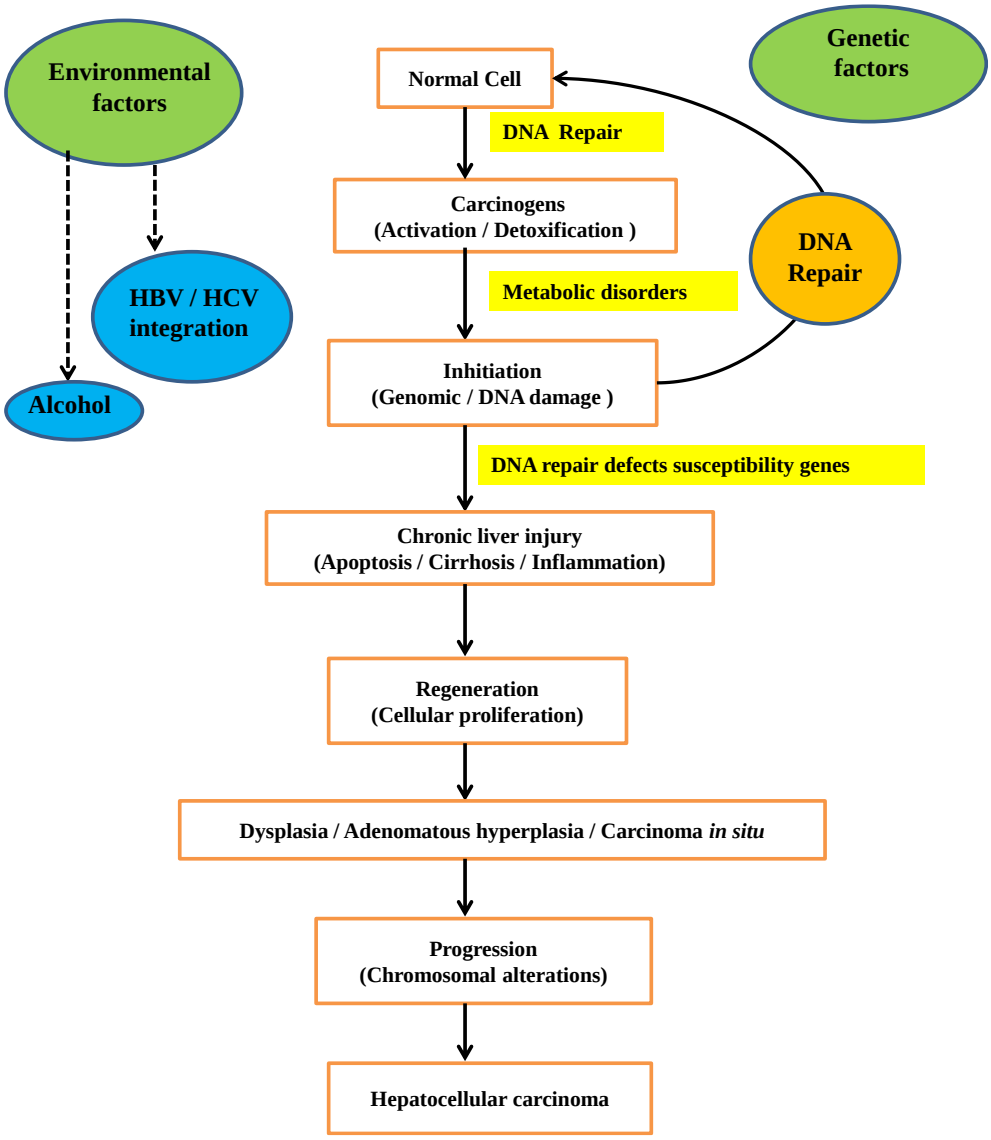

Figure 5. Representation of a formation of hepato-carcinogenesis

10. Treatments available to combat HCC

Currently, there are several treatments available for advanced HCC (Figure 7), and sorafenib is the most promising medical treatment in addition there are 3 types of treatments available to combat HCC, i.e., conventional, alternative, and integrative treatment.

10.1 Conventional treatment

Conventional treatment includes chemotherapy, immunotherapy, surgery, radiotherapy, and the most effective advanced therapies such as gene therapy and nanomedicine are the most prevalent types of cancer treatments available nowadays. German scientist Paul Ehrlich coined the term "chemotherapy", which was interested in alkylating agents and later describe the treatment of various ailments through chemicals. As a result of chemotherapy, several types of toxicities may arise such as myelotoxicity, renal toxicity, cardiotoxicity, and pulmonary toxicity. They show numerous side effects as well which may vary based on the chemotherapy used including acute, delayed, short-term, late/long-term, expected, common, uncommon, rare, and very rare [66-69].

Limitations of conventional treatment

Conventional therapy suffers some limitations as follows [70, 71]:

(i) Lack of aqueous solubility contributes to severe toxicity.
(ii) Lack of selectivity of anticancer drugs which cause damage to the normal cells.
(iii) Multidrug resistance due to increased efflux pumps.

10.2 Alternative treatment: complementary and alternative medicine (CAM)

They are defined as satisfying a demand which does not meet orthodoxy or expanding the medicines conceptual framework [72]. Over the past 15 years, medical, economic, and societal relevance has been gradually increasing in the usage of CAM [73]. In Asia, they make up a high number

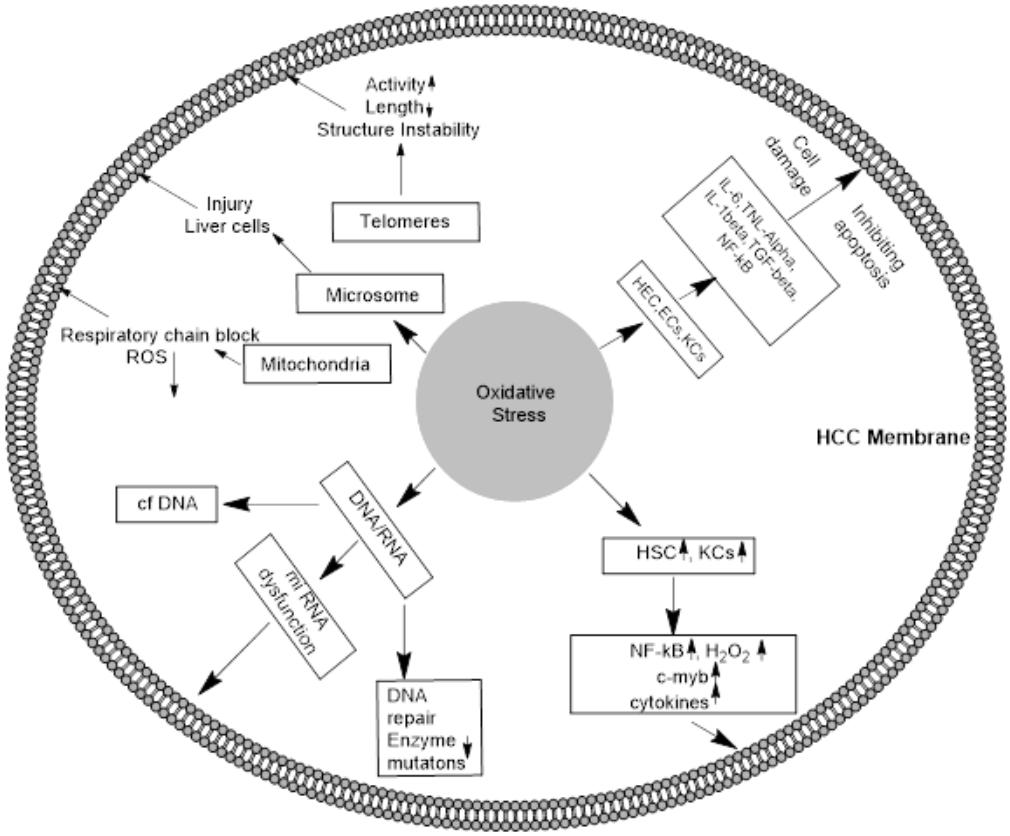

Figure 6. Mechanism of oxidative stress on the regulation of liver cells

of drugs inducing liver injuries [74, 75]. Traditional Chinese medicine (TCM) is also officially formalized and state-supported in China [76].

CAM covers a range of therapies such as homeopathy, dietary treatments, herbal, and hypnotherapy. Non-traditional diets, massage, green tea, and spiritual therapies are also the standard treatments [77-79]. The National Center for Complementary and Alternative Medicine in the USA classifies CAM therapies that are divided into various categories such as:

(i) Alternative medical systems (Ayurveda and TCM)
(ii) Interventions of mind-body
(iii) Biologically based therapies (vitamins or dietary supplements)
(iv) Energy therapies or bioelectromagnetic-based therapies (magnetic fields, Qi Gong, or reiki)

10.3 Integrative treatment through Ayurvedic medication: Tradition to trend

Thousands of years ago, Ayurveda originated in India. Where government recognizes and supports Ayurvedic Medicine (AM) research, practice, and development. It is one of the oldest existing therapeutic systems, focusing on lifestyle habits, self-sustainability, peaceful living, and the co-existence of human life [80-82]. Ayurveda addresses a patient as a whole rather than the disease alone. It gives a wealth of knowledge on the traditional and ethnic folklore treatment approaches [83]. The medicine system underlines the person's individuality in terms of socio-economic status, bio-identity, physiological, and biochemical conditions that might lead to a certain form of disease.

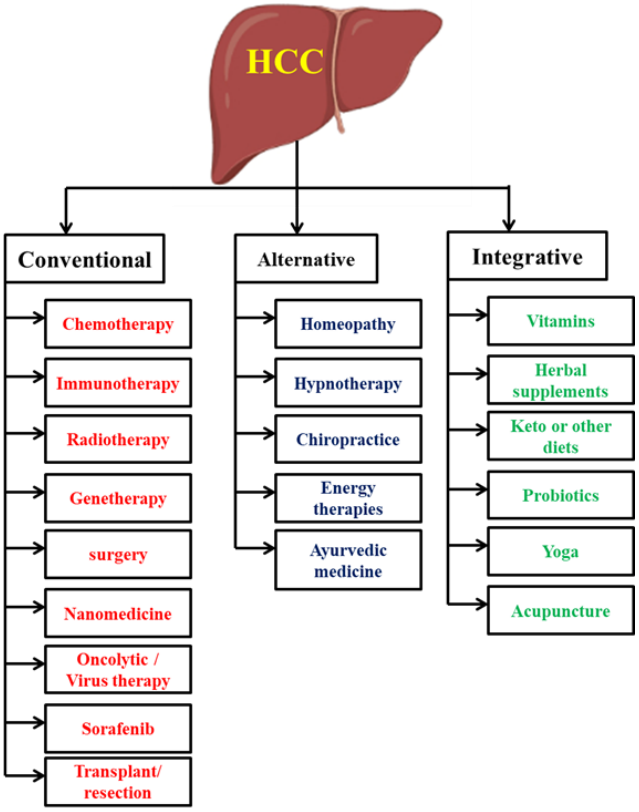

Figure 7. Summary of the available treatments for HCC

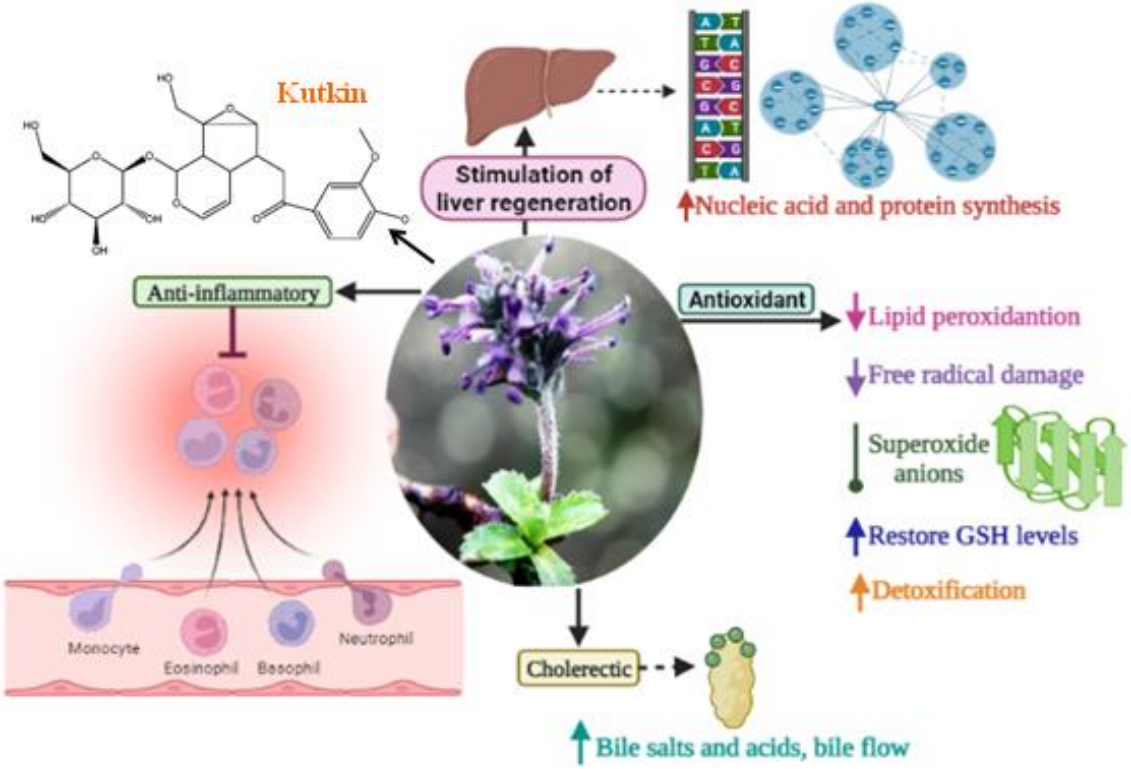

Figure 8. Possible mechanism of action of *Picrorhiza kurroa*

Ayurveda needs further investigation and clarification by using current scientific techniques [84].

Consumer awareness, chemo-profiling, quality control, clinical risk assessment, process validation, standardization, authentication, and post-marketing surveillance are the regulatory aspects to ensure the findings of safety, stability, effectiveness, and quality for the improvement of human health, as they are used crude raw materials for the therapeutic reasons [85].

10.4 Plant-based cancer treatment

A large number of modern medicines from plants have now been developed. The oldest findings of therapeutic plants as mentioned in the texts of Charaka Samhita and Sushruta Samhita around 1000 BC. It was also recorded by Emperor Shen Nung circa in China around 2500 BC. The emergence of effective synthetic chemistry in the early 19th century, help us in transmitting the method of synthesis and isolation of active compounds. The dependency of pharmaceutical

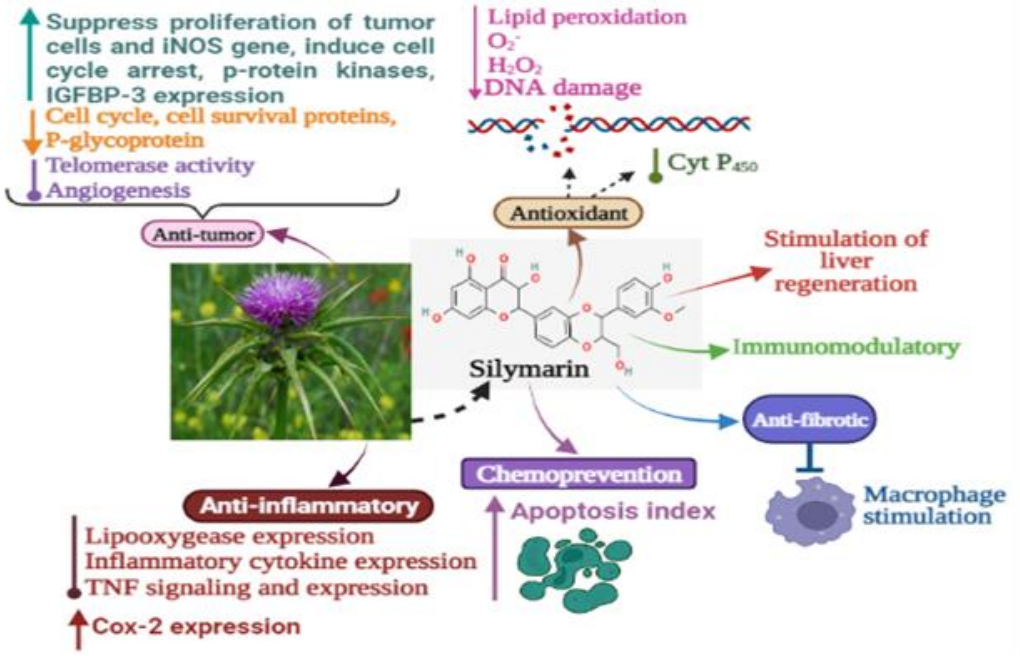

Figure 9. Possible mechanism of action of *Silybum marianum*

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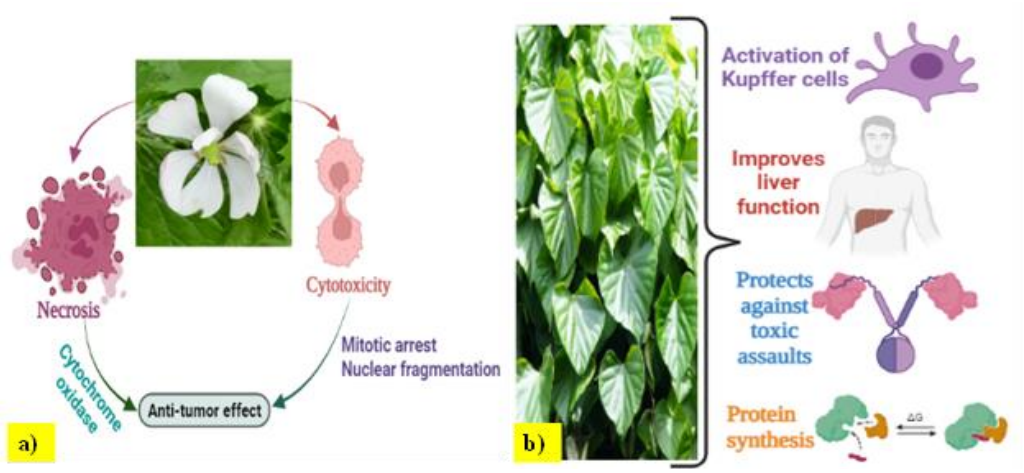

Figure 10. Possible mechanism of action (a) *Podophyllum hexandrum* (b) *Tinospora cordolia*

industries on plant-based compounds led to a considerable change in the focus on drug discovery and development from plant to synthetic chemistry. Any realistic approach to preventing cancer initiation and progression is important. The use of medicinal plants provides an alternative approach to conventional allopathic medicine for the treatment of many ailments [86-88].

Several herbs have been assessed for clinical trials and their tumouricidal properties against cancer are now under investigation. They appear to be producing evidence, which comprises not just cytotoxic treatments but also molecular governance of the physiopathology of cancer. Around 35,000 medicinal plants have been examined by the National Cancer Institute (NCI) for their potential therapeutic anticancer properties. Many plants are still actively investigating the anti-cancerous properties and some have revealed promising outcomes [89].

The extraction and isolation of vinca alkaloids and vinblastine from the *Madagascar periwinkle* and *Catharanthus roseus* G. Don. are one of the main examples of anti-cancer medication [90]. *Gymnosporia senegalensis* is one of them [91]. The objective of such integrative approaches is to regulate the phenotype of cancer, which extends beyond the eradication of the damaged cells, and to characterize the efficacy as chemo-preventive agents of specific extracted components from natural sources. In the Ayurvedic system of medicine, several medicinal plants shown anti-cancerous properties include:

***Picrorrhiza kurroa* (Kutuki):** Its bioactive compound kutkin offers hepatoprotective action based on possible mechanisms of action (Figure 8). It alters the structure of the outer membrane of the hepatocytes to prevent penetration of liver toxins into the interior of cells. It also stimulates the action of nucleolar polymerase. It results in increased ribosomal protein synthesis, regenerative ability of the liver, and formation of new hepatocytes.

***Silybum marianum* (Milk thistle):** Their bioactive compound silymarin shows therapeutic action which involves multiple mechanisms (Figure 9) such as antioxidant, antitumor, immunomodulatory, anti-inflammatory, anti-fibrotic, chemopreventive and by tissue

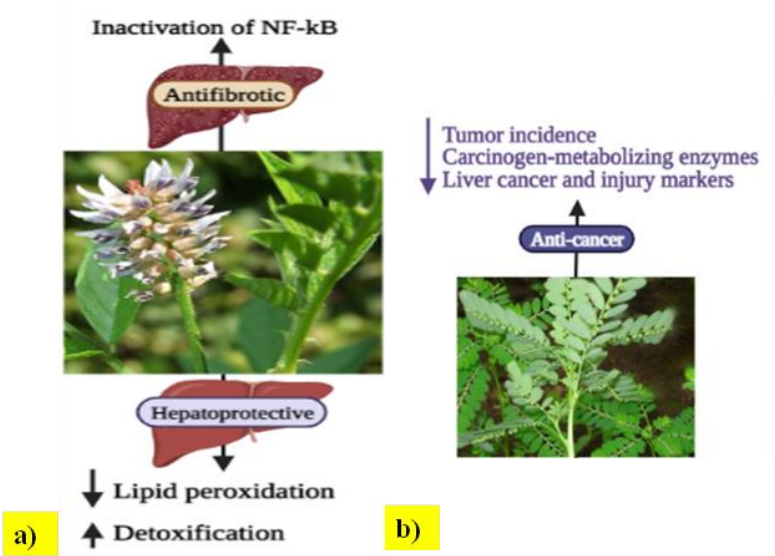

Figure 11. Possible mechanism of action (a) *Glycyrrhiza glabra* (b) *Phyllanthus amarus*

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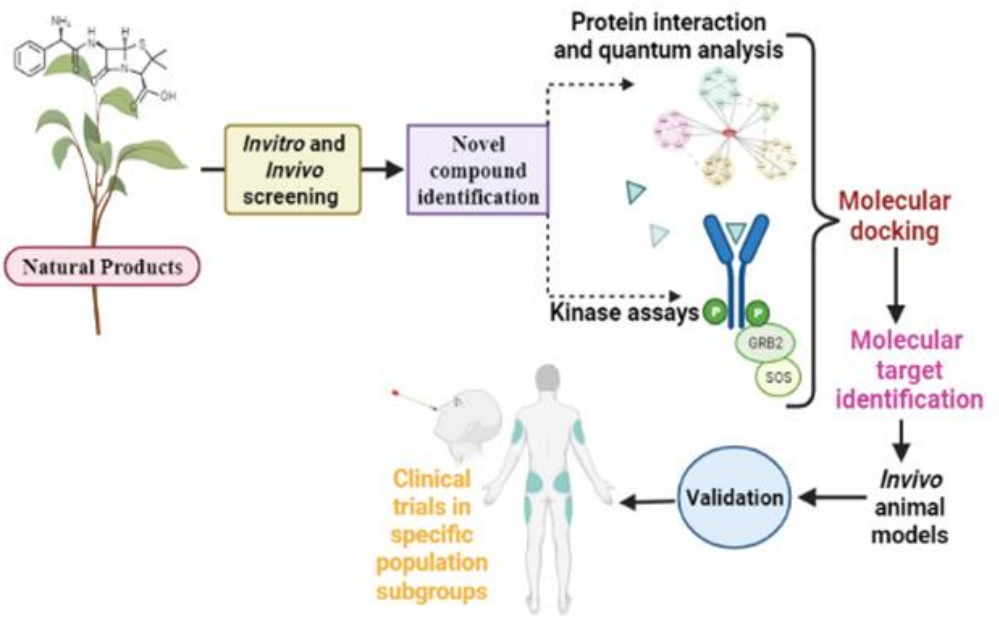

Figure 12. Schematic representation for developing new targeted antitumor compounds from the natural products

regeneration. It is quite effective in treating both acute and chronic hepatitis [92].

***Podophyllum hexandrum* (Indian May apple):** Its bioactive compound podophyllotoxin produces two cytostatic drugs (etoposide and teniposide) which show anti-tumor, anti-mitotic, and anti-viral activities. Their mechanism of action is shown in Figure 10a. It is a potent hepatic stimulant, a blood purifier, and anticancer drug [93].

***Tinospora cordifolia* (Guduchi):** A variety of bioactive compounds have been isolated, which belongs to different classes such as alkaloids, diterpenoid lactones, glycosides, steroids, phenolics, sesquiterpenoid, aliphatic compound, sesquiterpenoid, and polysaccharides. Their possible mechanism of action is illustrated in Figure 10b. It prevents liver fibrosis by stimulating the regeneration of hepatic tissue [94].

***Glycyrrhiza glabra* (Licorice):** The primary bioactive compound glycyrrhizin which offers hepatoprotection. The possible mechanism of action is illustrated in Figure 11a.

***Phyllanthus amarus* (Chanca piedra):** Their two novel compounds phyllanthin and hypophyllanthin possess hepatoprotective activity [95]. The possible mechanism of action is illustrated in Figure 11b.

10.5 Anti-cancer plant-derived drugs

Phytochemicals in the plant-based diet are non-nutritive. The vast structural variety of phytochemicals, cannot define the correlations of structure-activity to derive their basic mechanism of action. A realistic goal is to analyze their impact on signaling pathways associated with cancer. They can reverse or delay the multistep carcinogenesis premalignant stage of initiation and promotion. These are regulated by chemopreventive phytochemicals and include events like DNA repair, angiogenesis and metastasis, differentiation, and apoptosis, functional activation of oncogenes, growth-factor activity, cell proliferation, cell-cycle progression, tumor-suppressor genes expression, and hormonal activities. Many dietary phytochemicals possess chemopreventive potentials such as β-carotene, ascorbic acid, ellagic acid, lupeol, rutin, quercetin, kaempferol, lupenone, gallic acid, riboflavin, phyllantidine, chrysin, naringin, morin, malvidin, fisetin, and daidzein, etc [96, 97].

They are categorized into various classes including topoisomerase inhibitors, antimitotics, ROS inducers, angiogenesis inhibitors, histone deacetylases (HDAC) inhibitors, and mitotic disruptors. Topoisomerase inhibitors consist of podophyllotoxins, taxanes, and vinca alkaloids. Antimitotics consist of Topo I and Topo II [98, 99]. Therefore, it is a combination of different versions of intracellular effects, instead of a single biological reaction. Phytochemicals have shown the potential to be a part or substituent for cancer therapeutic drugs and at the same time, they are pocket friendly with no side effects as shown in Figure 12 [100-105].

11. Conclusion

Scientists concluded that the interaction of various factors leads to cancer. They may be environmental or genetic features of the individual. HCC commonly arises in a damaged organ associated with a poor prognosis by extensive inflammation and fibrosis. It accumulates mutations and other transformations. These findings point out new targets for chemoprevention and possible primary treatment. It is well-accepted for multi-drug resistance and does not respond to current chemotherapeutic drugs. Today, no single or combination chemotherapy is successful yet. Nowadays, natural compounds from plants seem to be

emerging anti-cancer agents because of fewer side effects, cost-effectiveness, and availability. They are potential resources for pharmaceuticals, fine chemicals, and food additives. Hence, better knowledge of the molecular pathways involved in HCC pathogenesis is necessary.

Abbreviations

RNS: reactive nitrogen species; RSS: reactive sulphur species; ROS: reactive oxygen species; ALD: alcohol liver disease; NAFLD: non-alcohol fatty liver disease; AIH: autoimmune hepatitis; HD: hereditary diseases; AFB_1: aflatoxin B_1; PVC: polyvinyl chloride; TCE: trichloroethylene; PCE: perchloroethylene; DDT: dichlorodiphenyltrichloroethane; PCB: polychlorinated biphenyl

Declarations

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