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Berberine verses Sorafenib for the treatment of Hepatocellular carcinoma

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Abstract

Traditional Chinese medicine as Complimentary Alternative Medicine (CAM) is useful in the treatment of chronic diseases including Cancer. Studies have shown components in plants responsible for their synergic effect and, analysis has revealed multiple components of plants that work synergistically to produce useful toxic effect against hepatocellular carcinoma of which a single conventional drug cannot produce. Different types of medicines have been discovered for HCC, but, a compiled quantitative analysis of these compounds will influence clinicians and researchers decisions about their use, research methodology to yield new drugs and most importantly, it can reduce research cost and time. 80% of the general population in the world are using plants to treat several illnesses and about 25% of the drugs prescribed worldwide come from plants. Sorafenib has been the drug of choice for over 10 years for the treatment of Hepatocellular Carcinoma patients of which Berberine a Traditional Chinese Medicine has also shown to be effective. This review in campuses articles obtained from western and Chinese journal data base. In conclusion, TCM has a vast number of components that can be used as alternative novel compounds in cancer treatment. Alkaloid Berberine has components that can be utilized to circumvent Hepatocellular Carcinoma when used in combination.

Keywords: Berberine; Sorafenib; Traditional Chinese Medicine; Hepatocellular Carcinoma

Introduction

Hepatocellular carcinoma is the second leading cause of cancer-related mortality worldwide; it was reported as the fifth most common cancer in men and the ninth in women its incidence is especially high in Asia, with the sum of 50% occurs in China [1-3]. Hepatocellular carcinoma is the 6th most common cancer globally. Chronic viral hepatitis B and C infection and aflatoxin B 1 exposure are the major risk factors as well as a nonalcoholic fatty liver disease [4]. Nonalcoholic fatty liver disease (NAFLD) is a common chronic condition of which Diabetic fatty liver accounts for a large proportion, with 50 to 75% of the subjects demonstrating fat in the liver on Ultrasound. In Western Europe and North America, nonalcoholic steatohepatitis as a major contributor to hepatocellular carcinoma. [5]. The arterial ketone bodies represent the liver function. There is a relationship between venous ketone bodies and hepatocellular carcinoma. The changes in the venous ketone body were associated with muscle status. Ketone bodies are composed of three molecules, 3-hydroxybutyrate (3-OHB), acetoacetate (AcAc), and acetone, which are produced from fatty acids in the liver [6]. Other biomarkers highlighted for diagnosis, prognosis and drug target regulation points

includes Alpha-1 fetoprotein (AFP), Des-gamma Carboxy-Prothrombin (DCP), Interleukin-2, Urinary tumor growth factor-ß1 MAGE-4 protein receptors, small nucleolar RNA ACA11 group for cyclinD1 and EMT, lysosome-associated protein transmembrane-4 β gene (LAPTM4B) and Rapamycin (mTOR) [7-9]. Different countries set up a staging and classification system for hepatocellular carcinoma, on which recommendations for treatment are based. Examples of this staging systems: American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) system, Barcelona Clinic Liver Cancer (BCLC) systems and the Cancer of the Liver Italian Program (CLIP), Chinese University Prognostic System (CUPI), and Okuda [10].

Treatment of hepatoma cellular carcinoma

Various chemical and therapy are discovered and utilized as treatment of Hepatocellular carcinoma, options include surgical therapies; liver resection, liver transplantation, nonsurgical, radiofrequency ablation, percutaneous ethanol injection, trans arterial chemoembolization, and systemic medical therapies, but no one gives total cure till now. Blames level on late diagnosis and development of drug-resistant cancer cells from the existing less potent chemicals [3, 11-13]. Generally, multidrug resistance (MDR) cancer cells making cancer systemic treatment often fails. The cause for MDR is overexpression of P-glycoprotein (P-gp) and drug efflux; the MDR1 gene product extrudes antitumor agents out of the cells, thereby reducing the amount [14]. Major side effect from systemic chemotherapy is tumor lysis syndrome is associated with aggressive hematologic malignancies [15]. Another limitation of systemic chemotherapy is the defects in apoptosis regulators invariably accompany tumorigenesis and the sustenance of malignant progression. The chemotherapeutics disruption during tumor evolution can promote intrinsic drug resistance and result in therapy failure as noticed in the cancer cells of Glioblastoma Multiforme (GBM). The cancer cells have resistance to every chemotherapeutic agent and encourage deregulated tumor genome containing opportunistic deletions of tumor suppressor genes as well as amplification or mutational hyper activation of receptor tyrosine kinase receptors. The GBM is associated with dismal prognoses [18]. A call for combined treatment is needed in hepatocellular carcinoma due to the presence of soluble programmed cell death-ligand 1 (sPD-L1) biomarker in hepatocellular carcinoma (HCC). The level of sPD-L1 is associated with tumor aggressiveness and outcomes. The increases in sPD-L1 after RT suggests that combined treatment with RT and immune checkpoint inhibitors may be a promising therapeutic strategy in HCC [2].

Natural medicine contains more than one component. The exploration in the hub rich of traditional medication especially TCM to cure hepatocellular carcinoma is necessary. TCM has long clinical history and wider choice for the novel compound. As shown in the above medicinal, TCM and Berberine like herbs are a good inhibitor to serve as anticancer against hepatocellular carcinoma cells and were found to be significant in devising new drugs and providing unique ideas for the war against this cancer type. The western medicine; Sorafenib can prolong the survival time of the patient for about three months for the advanced HCC, however, it is accompanied with severe adverse effects and is costly [27].

Traditional Chinese medicine for hepatocellular carcinoma

Plants are a natural source of novel compounds in drug discovery. Most natural medicines were used several years ago and even presented as treatment regimen in traditional medica text and pharmacopeia like Traditional Chinese Medicine (TCM) Pharmacopeia, People Republic of China. Traditional medicine is not only limited to plants but also in insect, yeast and bacteria that are utilized in microbiology to produce anticancer and antibiotics [15,16]. Importantly, over 80% of the general population in the world use plants to treat several illnesses and about 25% of the drugs prescribed worldwide come from plants [17]. Over the years there has been an urgent need for medication to cure chronic diseases such as cancer and researches are in the doors of forest and gardens of medicinal plants for the novel compounds. The plants Amaryllidaceae family have been investigated and found to produce a large variety of alkaloids and non-basic secondary metabolites. The crinine-type alkaloids based on the 5,10b-ethanophenanthridine ring system possess effective anti-proliferation against both normal cancer cells and the resistant type with dismal prognoses refractory to current chemotherapy, such as glioma, melanoma, non-small-cell lung, esophageal, head and neck cancers, among others. The compounds exhibited single-digit micromolar activities and retained this activity in a variety of drug-resistant cancer cell cultures [18]. Cordyceps militaris (CM) from the class ascomycetes extracts have pharmacological activities including anticancer, antivirus, an anti-inflammatory and immunomodulatory [19]. Fructus Schizandrae (FS), tonic TCM, have been found to significantly improve liver dysfunction in chronic hepatitis patients, as well as possesses reversal effect on MDR in cancer cells by

inhibition of function and expression of Pgp and total PKC [20]. Curcumin, a secondary metabolite, from the turmeric of Curcuma longa L. has biological activities for MDR modulation in various cancer cell models. It is a significant P-gp inhibitor due to its ability to inhibit both P-gp function and expression [21] (**Figure 1**). Ginsenoside (Rg3), a red ginseng saponin, can inhibit [3H] vinblastine efflux and reversed MDR to doxorubicin, COL, VCR, and VP-16 in KBV20C cells by repression of MDR1 gene expression. It can compete with the anticancer drug for binding to Pgp thereby blocking drug efflux [22-36]. The family of Triterpenoids, cucurbitane-type are P-glycoprotein modulators. Members of this family possessed strong MDR reversing activity in a dose-dependent mode with multi-fold activity when compared with verapamil when used as positive control. Both the tetracyclic nucleus and the side chain play an important role in ATP binding cassette subfamily B member 1 (ABCB1) reversal activity [23].

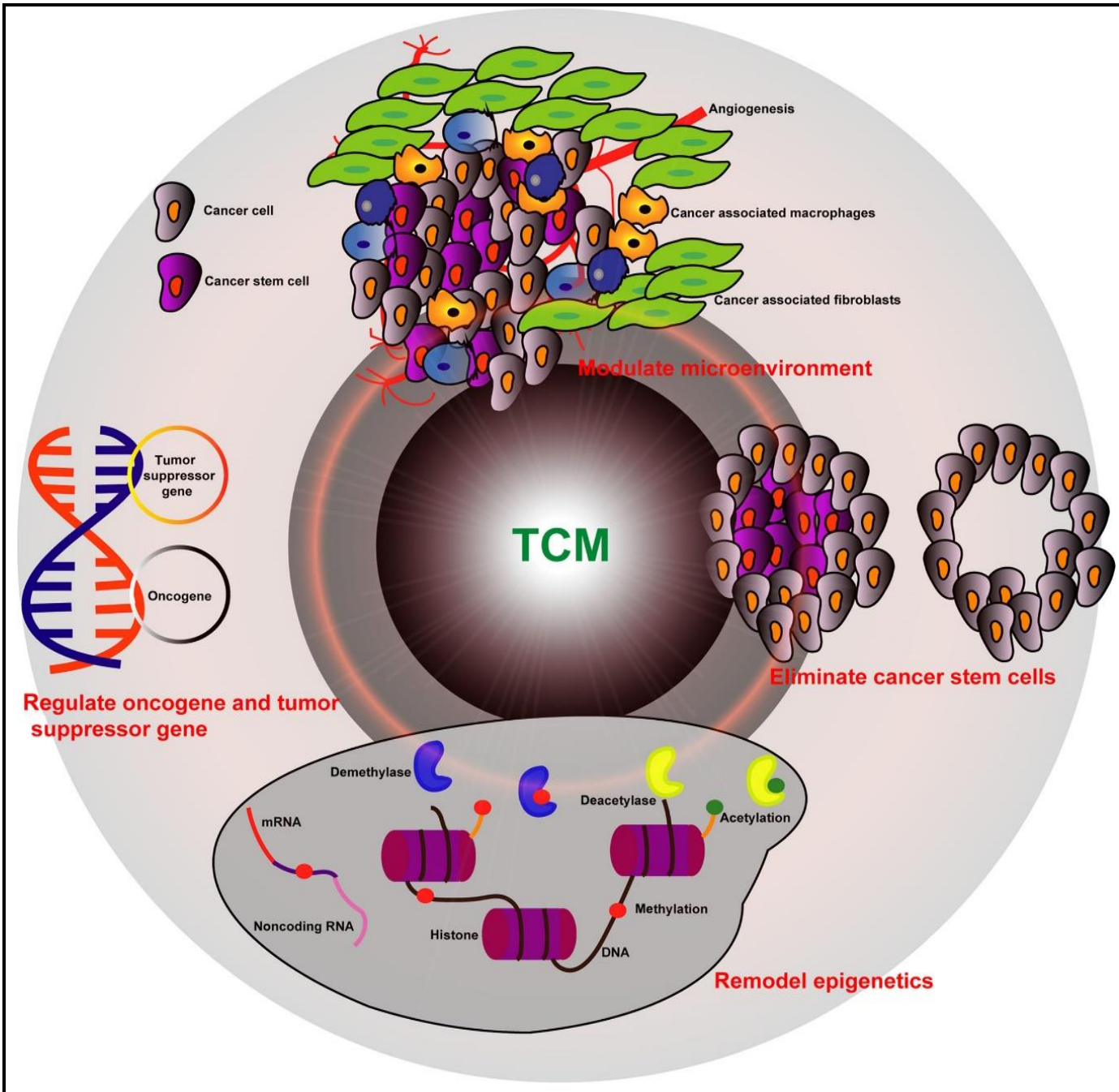

Figure 1: Summary of roles of traditional Chinese medicine in cancer treatment [46].

Records emerge that showed plants working side by side with chemical medications as maintenance therapy for cancer in order to decrease its global incidence. In the cancer type Hepatocellular carcinoma, several treatment protocols are used in the treatment and are associated with diverse side effects. Natural medicine have limited side effect as compare to western medication, they inhibit the liver cancer development and progression in several ways such as; protecting against liver carcinogens, enhancing effects of chemotherapeutic drugs, inhibiting tumor cell growth and metastasis, and suppression of oxidative stress and chronic inflammation [24]. Nevertheless, no matter how minor a toxicity is, it can still lead to ultimate death, precaution been said about the use of TCM and all other Traditional medica for adverse reactions, especially from excess doses, interaction with conventional drug, from undesired and undetected components which making the rounds present toxicity and quality control laboratories around the world. A call for updated research on knowledge about medicinal plants and their potential quality analysis is highly encouraged by many official medical and scientific organizations [16,26]. Celastrol and tripterine, from the Chinese herb Tripterygium wilfordii Hook F. (namely Thunder of God vine), have atomic orbital energy responsible for ianti-tumor activity against a broad spectrum of tumors, both in vitro and in vivo from the carbons C_2 on A-ring and C_6 on B-ring that exhibited a high susceptibility toward a nucleophilic attack. Quercetin, bioactive plant flavonoid in onions, grapes, and beverages has antihypertensive, anti-inflammatory, and antitumor effects. It is considered as a prototype for naturally occurring chemopreventive agents for almost all stages of carcinogenesis from initiation to invasion and metastasis. Tanshinone II-A obtained from the root of the Chinese herb Salvia miltiotthiza Bge. (Danshen), have pharmacological activities such as anti-inflammatory, anti-oxidative, anticancer, clinically utilized in angina pectoris and myocardial infarction and found to inhibit the proliferation of various human carcinomas including hepatocellular carcinoma. Curcumin, a diketones compound mainly extracted from the radix of Curcuma longa L. (turmeric), has a lot of medicinal benefits includes to alleviate pain, antitumor, anti-inflammatory, antivirus, ant oxidation, and anti-HIV activities. Its anticancer property is based on its antioxidant, apoptotic and anti-inflammatory effects against HCC, curcumin is emerging as a promising agent in the treatment of HCC [27].

Sorafenib hepatocarcinoma medication

Sorafenib was initially approved by the FDA for treatment of metastatic renal cell carcinoma, and later it was approved for management of HCC and meta-static differentiated thyroid carcinoma [28, 48-51]. Sorafenib was rapidly approved by the Food and Drug Administration (FDA), irrespective of the degree of cirrhosis [52-55]. Sorafenib (**Figure 2**) is an oral multi-kinase inhibitor that inhibits cell proliferation through a strong inhibition of the serine/threonine kinase RAF. Moreover, it was shown to inhibit pro-angiogenic VEGF and platelet-derived growth factor receptor [56].

Sorafenib inhibits the action of tyrosine kinase Raf and other factors involved in vasculogenesis (vascular endothelial growth factor receptor and platelet-derived growth factor receptor), which in turn inhibits activation of other downstream multikinases that are normally essential for cell growth, angiogenesis, proliferation and metastasis of HCC cells [39] (**Figure 3**).

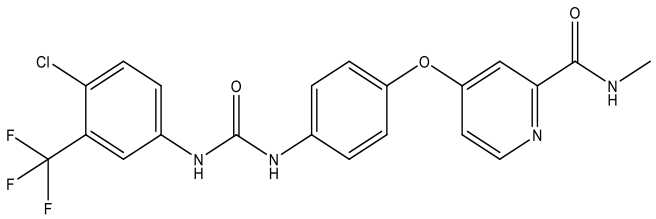

Figure 2: Sorafenib

Like Doxorubicin, gemcitabine, 5-FU, cisplatin, capecitabine, interferon alpha-2b, fluorouracil, tamoxifen, megestrol, octreotide, Bevacizumab, Brivanib, erlotinib, and lanreotide the first line Sorafenib have failed to meet the primary endpoint in either phase I, II and III [30]. Most recently, combinational medication is emerging; Gemcitabine-Oxaliplatin, Oxaliplatin-Capecitabine, added to the call for second-line treatments; Axitinib [29]. The cytokine-induced killer (CIK) cell infusions combined with conventional treatments have been assessed to significantly prolong recurrence-free and overall survival. The recommendation also has claimed to be immunotherapy for hepatocellular carcinoma patients [31, 38-41]. In general, limited benefit and high toxicity notices from all classes of existing systemic chemotherapeutics, responsible for the low response rates recorded about them, however, the disease status and differences in ethnic populations also contribute to these distinct outcomes. The novel Sorafenib is not recommended outside clinical trial [3].

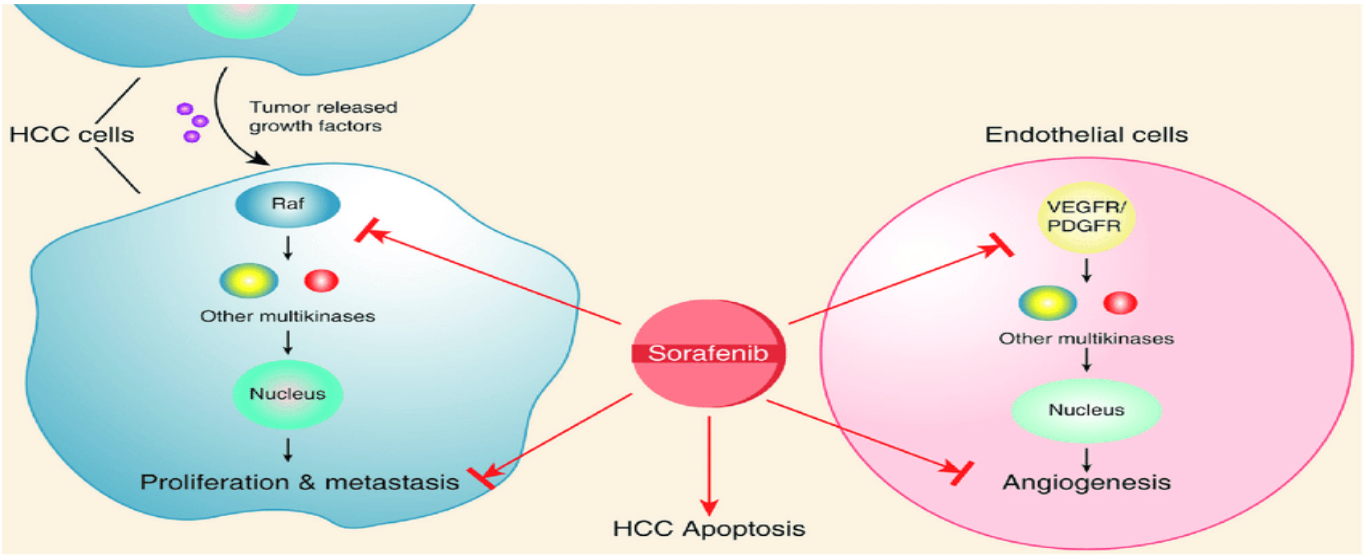

Figure 3: Sorafenib mechanism of action.

Berberine a TCM in hepatocellular carcinoma treatment

Berberine isolated from Chinese medica; Huanglian and Huang Bo (the isolation technique briefly discussed below) is an active herb with biological and pharmacological activities recommended for alternative treatment in many diseases including hepatocellular carcinoma [42] (**Figure 4**).

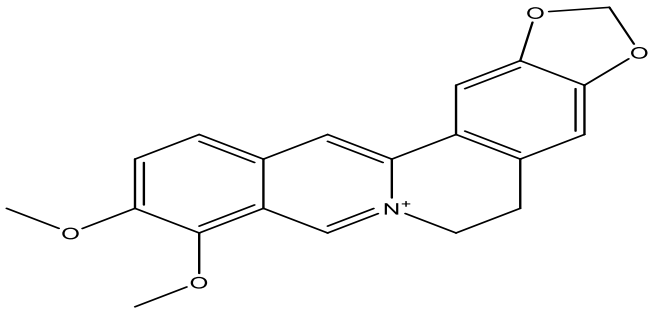

Figure 4: Berberine

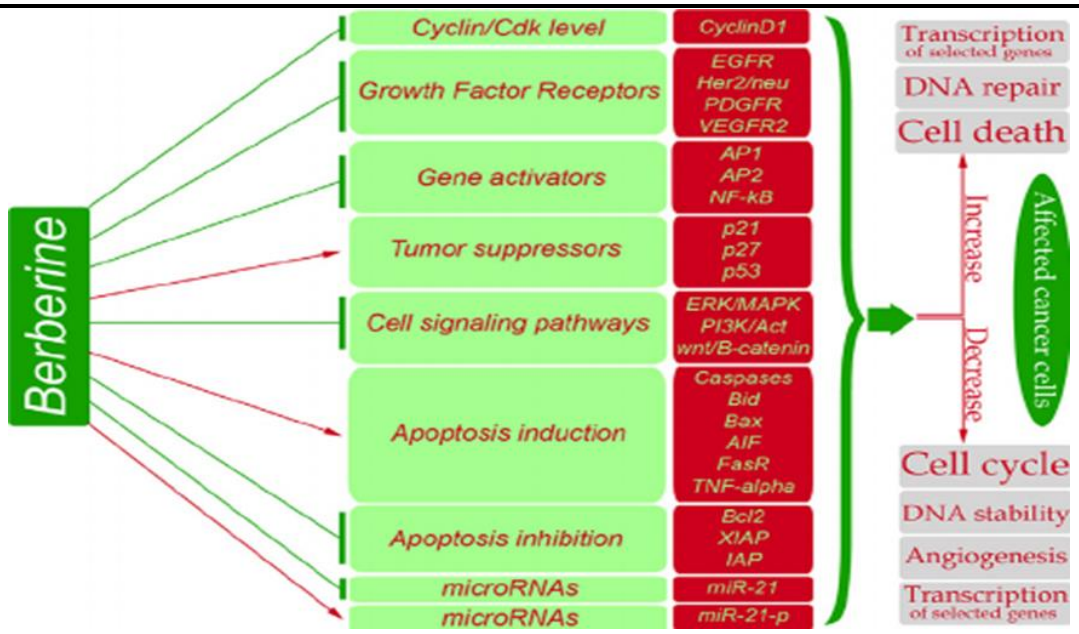

Figure 5: An overall summary of the molecular effects of Berberine and anti-cancer outcomes [47].

So far Yangyang Hu et al 2013 compiled partially the antineoplastic activity of Berberine towards hepatocytes and its biomarkers from reports made before 2013 and summarized that; the antineoplastic activity of Berberine can bring induction of apoptosis and cell circle arrest, as well as inhibition of cell migration and invasion through regulation of multiple pathways [27, 44-46]. Reports the cytotoxicity in hepatoma HepG2 cells with negligible toxicity to normal human Chang liver cells, mediation in mitochondria-dependent pathway the activation of caspases and decrease expression of Bcl-2, Bcl-XL and Bid, expressed a glycosylated immunoglobulin superfamily transmembrane protein CD147 and the overexpression of CD147 is highly associated with tumor invasion, metastasis, cell apoptosis, anoikis and also tumor angiogenesis included the antiangiogenic prevention of the secretion of VEGF [28,47].

Berberine treatment could significantly inhibit HepG2 and SMMC7721 cell viability in a dose- and time-dependent manner via downregulation of CD147, trigger autophagic cell death in both HepG2 and MHCC97-L cells which may be diminished by cell death inhibitor 3-methyladenine through beclin-1 and mammalian target of rapamycin (mTOR) signaling pathway inhibition, alternative change in expression against invasive hepatoma cells through PI3K-AKT and ERK pathway-dependent downregulation of MMP-9 [31,57,58]. In combination with another TCM such as Evodiamine, the inhibition rate on SMMC-7721 cells could be higher, 50.00% than independent compound over 48 h and in the present of gamma-radiation the anti-HCC effects through the p38 MAPK pathway and ROS generation are enhanced [37]. However, until now the molecular bases of Berberine on cancer cells still remain to be defined, and the poor bioavailability further makes it less likely to be an independent anti-tumor agent [27] (**Figure 5**).

Analytical instruments for purification and isolation of medicinal herbs

Chromatography is suitable to detect the compound (s) in samples, and it is essential to yield out by isolation techniques of novel components from herbs. Mostly, chromatography is coupled with mass spectrometer and other ultraviolet light. A great example is the ultimate HPLC-DAD (high-performance liquid chromatography-diode array detector) [32]. The HPLC analysis of the herb; Huang Bo (Cortex Phellodendron Chinensis) showed it contains Berberine, Phellodendron, Jatrorrhizine, and Palmatine as main constituents [33] and the Huang Lian, Rhizoma Coptidis, HPLC analysis records that it contains Berberine, Palmatine, Jatrorrhizine, Worenine, Coptisine, Epiberberine, Groenlandicine, Berberastine, Columbamine [34]. Before this isolation, screening techniques are essential for sustainable structures and concentration. Though lots of screening/extraction techniques are available, the commonly used methods are the conventional liquid-liquid or solid-liquid extraction and the advanced include pressurized-liquid extraction, subcritical and supercritical extractions, and microwave- and ultrasound-assisted extractions [35].

Methodology

Thoroughly, we did a systematical search in the English and Chinese database; PubMed, Scopus, Web of Science, Medline, and CNKI database using the keywords in our topic and keyword section to scrutinize and download 100s of related literature that made up the reference.

Discussion and Conclusion

In analyzing the present situation in the search and design of curative medicine for difficult hepatocellular carcinoma, hindrances from existing chemotherapeutics are; toxicity, single medication less potent to elucidate the action, and present chemotherapy results in MDR. Sorafenib is useful systemic chemotherapeutic than the others [51-53]. Though TCM has records of toxicity, they contained multiple components that can contribute to the fight against hepatocellular carcinoma. Evidence from above, the combined compound approach is the present option at hand for effective treatment options to overcome cancer and the MDR phenomena. However, purification and isolation of essential herbal product are prudent in there manufacturing processes to reduce their toxicity. Combinations of different herbs especially those with Berberine are useful in increasing potency [58,59]. In recent years, as stated by Lahlou et al. the development of new technologies has revolutionized the screening of natural products in the discovering process of new drugs. Applying these technologies compensates for the inherent limitations of natural products and offers a unique opportunity to re-establish natural products as a major source for drug discovery [59]. Cancer is multiple diseases, the most records showed that is cell generating disease from protein that is damaged or works in other ways different from their original way. The changes can be blocked and the bad cells killed or the protein can be set to reverse its action and lead to the cure of the disease [54]. Components in herbs including Berberine and some herbs have been investigated and found to have moderate-high strength to treat Hepatocellular Carcinoma. Our suggestion is to combine the herb, remove the less useful components. Chromatography technique is the most suitable for

Isolation and separation of compounds for quality quantification. Harvey et al. leveled that from high put screening database in combinatorial chemistry, only Sorafenib reached the market, but the chemical diversity of natural products is a better match to that of successful drugs, notably, an only small fraction of plants have been extensively screened for bioactivity [60]. This review will serve as vital in drug clinical decision and discovery process and is a comprehensive summary of what is to be known by researchers in this domain.

Conflict of interest

The authors declare no potential conflict of interest.

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