Biomedicine & Pharmacotherapy 107 (2018) 1246–1258

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Herbal management of hepatocellular carcinoma through cutting the pathways of the common risk factors

Nabil M. Abdel-Hamid[a,*], Shimaa A. Abass[a], Ahmed A. Mohamed[b], Daniah Muneam Hamid[c]

[a] Biochemistry Department, Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, 33516, Egypt
[b] Biochemistry Department, Faculty of Pharmacy, Mansura University, Mansura, Egypt
[c] Biotechnology Department, Technical Medical Institute Al-Mansour, Middle Technological University, Baghdad, Iraq

ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Non-alcoholic fatty liver
Inflammation
Oxidative stress
Hepatitis
Cytotoxic agents
Herbal therapy

ABSTRACT

Hepatocellular carcinoma (HCC) is considered the most frequent tumor that associated with high mortality rate. Several risk factors contribute to the pathogenesis of HCC, such as chronic persistent infection with hepatitis C virus or hepatitis B virus, chronic untreated inflammation of liver with different etiology, oxidative stress and fatty liver disease. Several treatment protocols are used in the treatment of HCC but they also associated with diverse side effects. Many natural products are helpful in the co-treatment and prevention of HCC. Several mechanisms are involved in the action of these herbal products and their bioactive compounds in the prevention and co-treatment of HCC. They can inhibit the liver cancer development and progression in several ways as protecting against liver carcinogens, enhancing effects of chemotherapeutic drugs, inhibiting tumor cell growth and metastasis, and suppression of oxidative stress and chronic inflammation. In this review, we will discuss the utility of diverse natural products in the prevention and co-treatment of HCC, through its capturing of the common risk factors known to lead to HCC and shed the light on their possible mechanisms of action. Our theory assumes that shutting down the risk factor to cancer development pathways is a critical strategy in cancer prevention and management. We recommend the use of these plants side by side to recent chemical medications and after stopping these chemicals, as a maintenance therapy to avoid HCC progression and decrease its global incidence.

1. Introduction

The mortality rate due to hepatocellular carcinoma (HCC) increased rapidly during the past decade. Unluckily, the clinically satisfactory and successful treatment for HCC patient is still absent [1]. Several risk factors are involved in hepatocarcinogenesis like non-alcoholic fatty liver disease (NAFLD), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcoholism, obesity, aflatoxin B1, iron accumulation and diabetes [2]. There are several protocols used in the treatment of HCC, including, surgical resection, ablation, chemotherapy and embolization. The use of these methods is limited due to their side effects and the development of resistance to the available chemotherapy and their complexities. Due to the limited treatment options to HCC, other than surgery and the poor prognosis of the disease, there is a critical need for additional therapies to enhance the survival or the quality of life. Complementary and alternative medicine (CAM) is considered as one way that may improve the anticancer drug efficacy and reduce their toxic effects [3]. The use of herbal medicines can be traced back to more than 4000 years ago in ancient China and Egypt. Over recent decades, an increasing number of herbal products, including medicinal herbs and phytochemicals, have been used for treating chronic liver diseases worldwide due to cost effectiveness, higher safety margins, long-lasting curative effects and few adverse effects. According to the previous studies, medicinal herbs and phytochemicals could protect the liver by several mechanisms such as eliminating the virus, blocking fibrogenesis, inhibiting oxidative injury and suppressing tumorigenesis [4].

In this review, we discuss several factors that lead to HCC development, focusing on the role of different herbal medicines that used in the treatment of HCC by alleviating these risk factors.

2. Non-alcoholic fatty liver disease (NAFLD) AND treatment to prevent HCC development

Non-alcoholic fatty liver disease (NAFLD), or alternatively, non-alcoholic steatohepatitis (NASH), is a condition of liver pathology, which

* Corresponding author at: Faculty of Pharmacy, Kafrelsheikh University, Kafrelsheikh, 33516, Egypt.
E-mail address: nabilmohie@yahoo.com (N.M. Abdel-Hamid).

https://doi.org/10.1016/j.biopha.2018.08.104
Received 24 June 2018; Received in revised form 11 August 2018; Accepted 15 August 2018

is similar to the fatty liver damage that caused by alcoholism, but, it happens in non-alcohol abuse people. NAFLD is characterized by the accumulation of triglycerides within hepatocytes, which is usually associated with metabolic syndrome and obesity [5]. The prevalence of NAFLD was established by the histological features found in ~70% of obese individuals suffering from steatosis, while steatosis was present in ~ 35% of lean individuals. NAFLD was also present in about18.5% of obese individuals and in about 2.7% of leans [6]. Fatty liver is also found in about 13–22% of lean non-alcoholic individuals through several studies based on ultrasound imaging [7,8]. NAFLD is present in 20–35% of adult individuals and 5–17% of children in the Western world [9]. NAFLD is considered as one of the important reasons leading to chronic liver diseases in Hong Kong (~27.3%) [10] and China (~15%) [11]. This is because of the high-fat content in the modern diet and individual's lifestyle. NAFLD is considered as one of the most important reasons that cause chronic liver disease in developing and developed countries. NAFLD increases the risk of hepatocarcinogenesis similar to other pot cirrhotic liver diseases. HCC is now the end stage as a leading cause of obesity-related cancer deaths in middle-aged men in the USA [12]. An increasing number of case reports showed that HCC arises in non-cirrhotic individuals suffering from NAFLD [13].

Other HCC risk factors may be synergistically involved in HCC development besides NAFLD, such as alcoholic liver injury and chronic hepatitis C. Several mechanisms are involved in NAFLD-related HCC development (Fig. 1) [14–16]. Obesity participates in increasing the risk of cancer development through a low-grade, chronic inflammatory impact [17,18]. The expansion of adipose tissue stimulates the generation of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) [19]. TNF and IL-6 derived from adipose tissue play an important role in HCC development. This role has been supported in an experimental model, assuming that obesity enhances the growth of diethylnitrosamine-induced malignant liver tumor in mice [20]. The prevalence of HCC due to NAFLD is increasing around the world [21], where, 4–22% of HCC patients in Western countries are attributable to NAFLD [22]. In Asia, viral hepatitis remains endemic, so that, 1–2% of HCC patients are attributed to NAFLD [23,24].

2.1. Herbals with anti NAFLD activity used in HCC treatment

2.1.1. Lycii fructus (wolfberry)

Wolfberry, a famous traditional Chinese supplement or drug, is the fruit part of Lycium barbarum plant, family Solanaceae. It has valuable benfits in both eyes and liver [26]. The most important part of wolfberry is the Lycium polysaccharide portion(LPP), which has a numerous biological actions, like immunoregulation, antioxidant effect, neuroprotection, control of glucose metabolism and anti-tumor activities. The lymphocyte number, interleukin-2 and immunoglobulin G level, were found to be increased upon the intake of polysaccharide juice in human beings in one of the clinical trials. It was reported also that it increases the levels of serum antioxidants and decreases the lipid peroxide level [27,28].

In the liver, LPP was found to inhibit hepatocyte proliferation and induce apoptosis of hepatoma cells, which indicate its possible application as anti-tumor [29,30]. Another study demonstrated that LPP causes a restoration of the activities of antioxidant enzymes and reduction of oxidative stress products caused by high-fat diet induced liver injury [31]. The co-treatment of LPP with ethanol administration markedly enhanced the liver injury in an alcohol-induced liver injury rat model by decreasing the oxidative stress and the accumulation of lipid in the liver [32]. In acute liver injury, LPP was found to keep the normal hepatic histology, decrease the hepatic inflammation/chemoattraction, stimulate the partial regeneration of the liver through the nuclear factor kappa B (NF-κB)–dependent pathway, and reduce the oxidative stress when used prior CCl_4 intoxication in mice [33].

LPP is helpful in NAFLD due to its useful properties in decreasing the inflammation and the oxidative stress. The co-treatment with LPP, orally, in NAFLD in rats, showed a significant improvement in the hepatic histology, reduction in the fibrosis, oxidative stress, inflammation, accumulation of fats and apoptosis, through modulating the transcriptional factors NF-κB and activator protein-1 (AP-1). Furthermore, the

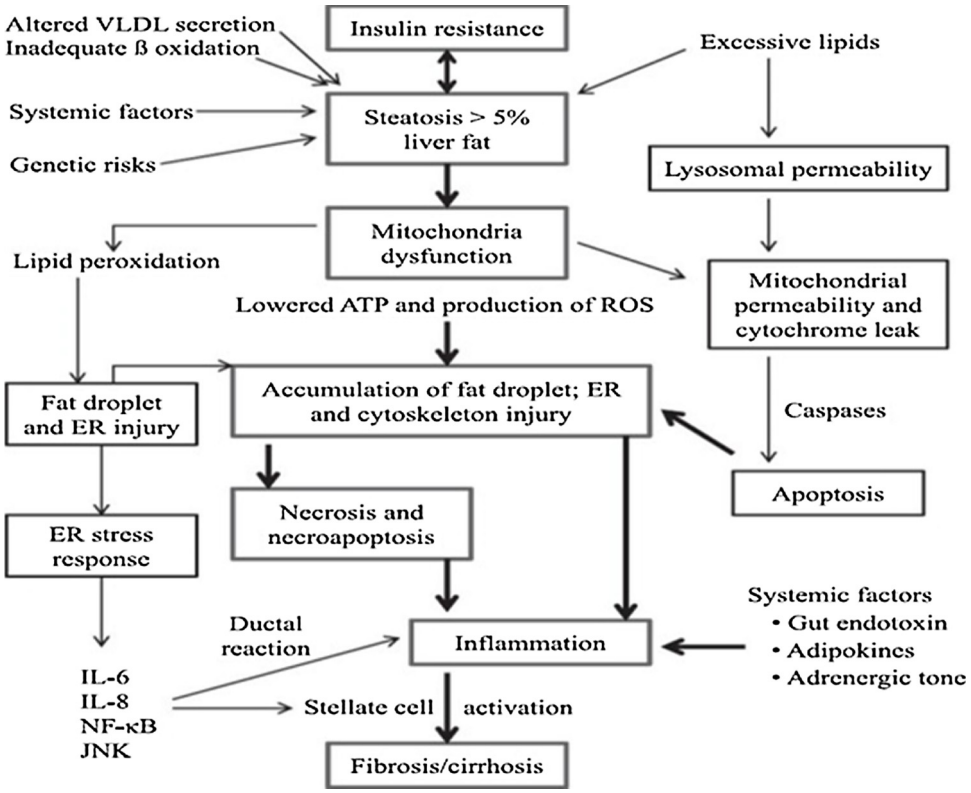

Fig. 1. Molecular mechanisms of NAFLD [25].