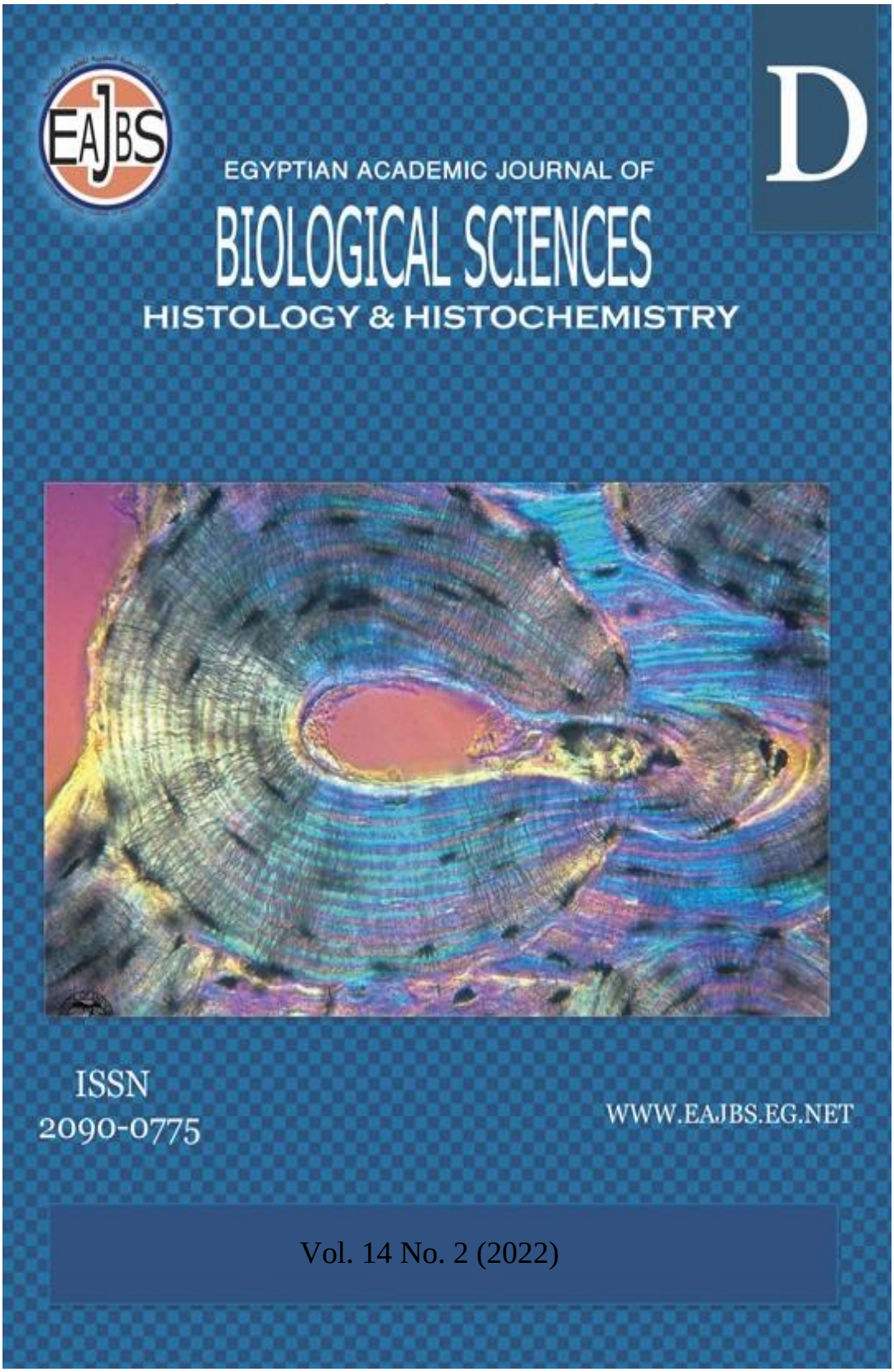

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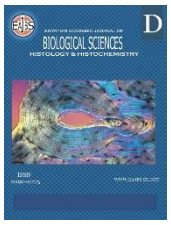

The Rationale Behind the Therapeutic Potential of Drugs Containing Hydroxycinnamic Acid on Hepatocellular Cancer Induced by 4-Dimethylaminoazobenzene: Technique-Related Implications

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common cause of cancer-related death. Although there are several therapeutic options, including surgery, chemotherapy, and radiation that are helpful in the early stages of HCC, and sorafenib is an effective systemic therapy in the advanced stages of HCC, not all HCC cases are susceptible to sorafenib. This is a significant issue that the treatment of hepatocellular carcinoma faces globally. Recently, new methods for the prevention and therapy of HCC have been developed using phytochemicals. One phytochemical substance that many researchers are particularly interested in is hydroxycinnamic acid. According to mounting evidence, oxidative stress contributes to the growth of hepatocellular carcinoma by damaging DNA and altering the expression of genes relevant to inflammation and apoptosis. Hydroxycinnamic acid compounds have a powerful antioxidant, anti-inflammatory, and anti-microbial activity. Thus, many recent studies investigate the potential role of hydroxycinnamic acid compounds in the prevention and treatment of numerous diseases related to oxidative stress such as cancer. In this study, we hypothesize that compounds containing hydroxycinnamic acid may have a potential therapeutic role in HCC caused by 4-dimethylaminoazobenzene. Evaluating the data and methodological findings that support our hypothesis may aid in identifying a new compound and techniques for developing an anticancer drug or strengthening the resistance of currently used therapy.

INTRODUCTION

Hepatocellular Carcinoma, Etiology, and Biomarkers:

The most typical primary liver cancer is called hepatocellular carcinoma (HCC). It is the sixth most common cancer and is the second most common cause of cancer mortality (Holvoet *et al.*, 2015). The World Health Organization suspected that about 1.3 million individuals suffering from liver cancer will die in 2040 (Cao *et al.*, 2021).

Over the past 20 years, the prevalence of HCC has increased, and there will soon be more than one million cases worldwide each year (Bray *et al.*, 2018). Although HCC incidence and mortality are rising in various parts of Europe and the USA, East Asia and Africa still have the highest rates of HCC (McGlynn *et al.*, 2015). The main causes of chronic liver inflammation, which results in fibrosis or cirrhosis, and ended with HCC development, are viral chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated food, chronic alcohol consumption, and metabolic disorders (Llovet *et al.*, 2016). Other less common risk factors for HCC include primary biliary cholangitis, hemochromatosis, and 1-antitrypsin deficiency (Fracanzani *et al.*, 2001).

Alpha-fetoprotein (AFP) has been used as a biomarker for HCC diagnosis, and many reports revealed that AFP is not a precise marker due to its limited specificity (Morimoto *et al.*, 2012). Therefore, a biomarker with improved diagnostic precision and reliability is required. Many tumor biomarkers for HCC have been found, including the Golgi 73 proteins (GP73), Glypican-3 (GPC3), and microRNAs (Ba *et al.*, 2012; Feng and Ho, 2014).

Oxidative Stress and Hepatocellular Carcinoma Development:

The primary cause of oxidative stress is the mitochondria's oxidative metabolism of aerobic respiration (Sosa *et al.*, 2013). Reactive oxygen species (ROS) can encourage the growth and spread of tumors. There are two main pathways controlled by ROS including, the phosphatidylinositol 3-kinase/protein kinase-B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, and the mitogen-activated protein kinase (MAPK) pathway (Son *et al.*, 2011; Koundouros and Poulogiannis, 2018). On the other hand, the reactive oxygen and nitrogen species (ROS and RNS) with aldehydes can interact with DNA bases to generate pro- mutagenic DNA adducts and DNA damage (Bartsch and Nair, 2006). ROS can cause permeabilization of the mitochondrial membrane and lead to the release of apoptosis initiating factors (AIF) including, cytochrome c, Smac/DIABLO., and induce activation of caspases-9 and -3, which will lead to apoptosis (Clifford, 2000).

Dimethylaminoazobenzene and Animal Model for Hepatocellular Carcinoma:

The animal model has played a vital role in cancer studies. In which the rodent animal models, particularly mice, have an important role in HCC research because of their short lifespan and reproduction capacity (Heindryckx *et al.*, 2009). The epidemiological studies revealed that exposure to the genotoxic and cytotoxic chemicals that are present in the environment such as nitroso compounds and azo dyes are potential carcinogens and induce HCC (Loeb and Harris, 2008).

Dimethylaminoazobenzene (DAB) (C14H15N3) is known as 4 dimethylaminoazobenzene, para-dimethylamino-azobenzene, N, N-dimethyl-4- aminoazobezene, N, N-di-methyl-4-(phenylazo) - benzenamine, N, N-dimethyl-p-phenylazoaniline, benzeneazodimethylaniline, butter yellow or methyl yellow, and it is an azo amine dye that presents at room temperature in yellow crystals as leaf shape crystals. It is soluble in alcohol, benzene, chloroform, ether, petroleum ether, mineral acids, oils, and pyridine but insoluble in water (Program, 2011). The International Agency for Research on Cancer classifies dimethylaminoazobenzene (DAB) as a group-2B carcinogen because it has the potential to cause liver cancer in both humans and rats (Althouse *et al.*, 1979). Its carcinogenicity in rat liver due to the fluorine atom in the DAB structure and its tight connection with the carbon atom, which leads to inhibition of DNA

repair and enhances tumor formation and tumor development (Thomas *et al.*, 2016). Many previous studies reported that DAB has a potent carcinogenic effect on rodent models and is aimed at different organs depending on the time of DAB exposure in which DAB can cause the development of HCC in albino rats of different strains, and continuous DAB feeding resulted in changes in the kidneys and stomach papilloma (Kinosita, 1940).

Another study explains the pathophysiology pathway of DAB to induce HCC in rats, in which DAB can be converted to N-hydroxy-N-methyl-4-aminoazobenzene (oxidative pathway) or catabolized by cytochrome P450 (reductive pathway) in the liver of rats. These pathways result in the production of reactive electrophiles and free radicals, which then produce reactive oxygen species (ROS), which are crucial for the development of cancer (Thomas *et al.*, 2016) as shown in Figure 1. Many studies have documented that, using other chemicals such as phenobarbital (PB) with DAB is important for acceleration of the development of HCC in which DAB act as an initiator and PB act as a promoter for the development of HCC foci (Biswas and Khuda-Bukhsh, 2002).

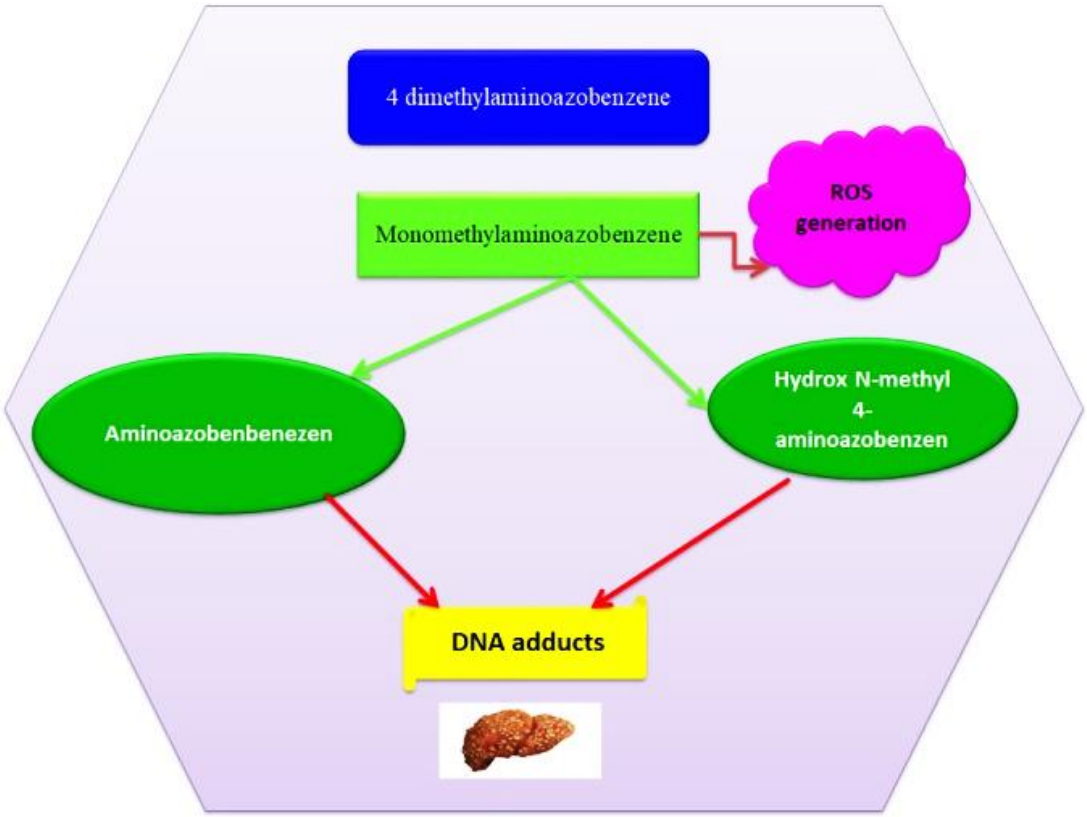

Fig. 1. Metabolism of4 dimethylaminoazobenzene in rat liver and development of HCC

The molecular pathway of DAB exposure has been shown to activate nuclear factor (NF) -κB which is a crucial regulator of inflammation and cell proliferation through IKK-dependent phosphorylation and degradation of the NF-κB inhibitor (IκB) proteins. NF-κB upregulates the expression of proliferation and angiogenesis markers like vascular endothelial growth factor (VEGF), VEGF receptor 1, and matrix metalloproteinase (MMP) -9 and -2, and upregulates the expression of anti-apoptotic proteins such as Bcl-2, and Bcl-XL, on the other hand, it downregulates the expression of pro-apoptotic proteins like Bax, caspase-9, and -3.(Murugan *et al.*, 2009; Murugan *et al.*, 2010).

The Prevention and Treatment of Hepatocellular Carcinoma*:*

There are two types of HCC prevention. Primary prevention is intended to stop the development of HCC in patients with chronic liver illnesses of various etiologies, Secondary prevention is intended to stop the formation of new HCC lesions following successful surgical or non-surgical HCC therapy (Lok, 2004). The effective treatment of HCC is based on the cancer stage and the time of diagnosis (Forner *et al.*2012). Whereas a late diagnosis renders chemotherapy less effective, and an early diagnosis results in successful treatment (Liu *et al.*, 2015). About 50% of HCC patients have been diagnosed at an advanced stage, and 70% of patients relapse within the first five years of receiving the first treatment (Llovet *et al.*, 2016).

In the last 10 years, Sorafenib was the first-line systemic therapy in advanced HCC, with local treatment, including external irradiation, transarterial chemoembolization, and ablation (Li and Wang, 2016; Forner *et al.*, 2018). It is a multiple kinase inhibitor (TKI) that inhibits angiogenesis and proliferation (Llovet *et al.*, 2008). Sorafenib is capable to reduce the proliferation of tumor cells by blocking Raf-1, B-Raf, and kinase activity in the Ras/Raf/MEK/ERK, as well as it can target the platelet-derived growth factor receptor (PDGFR-), the vascular endothelial growth factor receptor (VEGFR) 2, the hepatocyte factor receptor (c-KIT, and is an activator of AMP-activated protein kinase (AMPK) (Wilhelm *et al.*, 2004). Many studies have revealed that only 40% of HCC patients benefit from Sorafenib and others show resistance to it (Labeur *et al.*, 2018). Furthermore, HCC patient who initially responds well to Sorafenib usually changes their response within 6 months (Spinzi and Paggi, 2008; Zhu *et al.*, 2017), thus Sorafenib resistance is a big problem facing its use.

The actual mechanism of the Sorafenib resistance development is still unknown. Although recent studies have documented the possible reason may be due to gene polymorphism that can affect the Sorafenib function. In which the polymorphism of ATP binding cassette subfamily B member 1 (ABCB1), subfamily G member 2 (ABCG2), the solute carrier family 15 members 2 (SLC15A2), and endothelial nitric oxide synthase (eNOS) were associated with the Sorafenib effect (Lee *et al.*, 2015; Tandia *et al.*, 2017). Therefore, nowadays numerous researchers have been searching for, finding new phytochemicals to improve Sorafenib effectiveness or can be used as a new therapeutic agent for HCC treatment.

Hydroxycinnamic Acids (HCAs) and Its Derivatives:

There are several healthy, beneficial components in natural plants; among them are Polyphenols and phenolic compounds that have the main function to protect plants from pathogen invasion or ultraviolet radiation (Manach *et al.*, 2004; Sova and Saso, 2020), and phenolic acids are hydroxycinnamic acids (HCAs) that are found in ester form with quinic, shikimic, or tartaric acid, saccharides, flavonoids, or plant structural components (i.e., cellulose, lignin, and proteins) (Clifford, 2000; Shahidi *et al.*, 2019).

Structurally, HCAs have a C6–C3 skeleton, all of them have the same basic structure of HCA (known as p-coumaric acid) as well as caffeic, ferulic, and sinapic acids (Adom and Liu, 2002). The primary hydroxycinnamic acid present in food is caffeic acid (CA), which is primarily found as chlorogenic acid (CGA), which is formed by the esterification of one to four molecules of hydroxycinnamic acids with (-)-quinic acid (Clifford, 2000). The esters of this acid are formed preferably on carbon 5, and may carbon 3 and 4, and less on carbon 1 of quinic

acid (Farah and Donangelo, 2006). HCAs can be found in a variety of foods and beverages that we consume every day, including fruits (such as apples, berries, plums, cherries, peaches, and some citrus fruits), vegetables (such as carrots, salad, cabbage, and artichokes), cereals, and drinks (such as tea and coffee), grapes, and wine (Bento-Silva *et al.*, 2020). HCAs are regarded as important dietary components of our diet since they enhance the flavor, color, nutritional content, and health benefits (Bento-Silva *et al.*, 2020). HCAs and their derivatives have powerful antioxidants (Razzaghi-Asl *et al.*, 2013), anti-inflammatory (Nagasaka *et al.*, 2007), and antimicrobial activities (Taofiq *et al.*, 2017), Thus HCAs and their derivatives consider promising therapeutic agents for treating the chronic disease related to oxidative stress, including cancer.

The Hypothesis's Implications and Discussion:

Despite the massive amount of research and rapid advancements that have occurred in the last ten years, cancer is already the leading cause of death in many high-income nations and is predicted to become a major source of morbidity and mortality in the coming decades in every part of the world. Therefore chemoprevention has received a lot of interest as a different strategy for cancer control (Kang *et al.*, 2011). Numerous research investigated the potential therapeutic effect of hydroxycinnamic acids in different cancer cell lines (Rocha *et al.*, 2012). HCAs derivatives including Caffeic acid phenyl ester (CAPE) inhibited MMP-9, and -2 expression in Hep3B cells by blocking NF-κB activity, and showed anti-invasive activity in rat ascites hepatoma cell line (AH109A) (Weng and Yen, 2012). Another investigation revealed that Cinnamic acid (CA) and CAPE both induced a dose-dependent inhibition of HepG2 cell growth. In which the treatment with CAPE at a low dose of 20 g/mL, and CA treatment at a dose of 200 μg/mL can reduce the viability of HepG2 cells to 72 % and 61 % respectively when compared to control by suppress the MMP-9 expression by blocking NF-κB activity (Jaganathan and Mandal, 2009). As a result, hydroxycinnamic acids have been discovered to have a direct impact by reducing tumor cell development as revealed in Figure 2. However, there is a lack of data obtained from studies employing human and animal models.

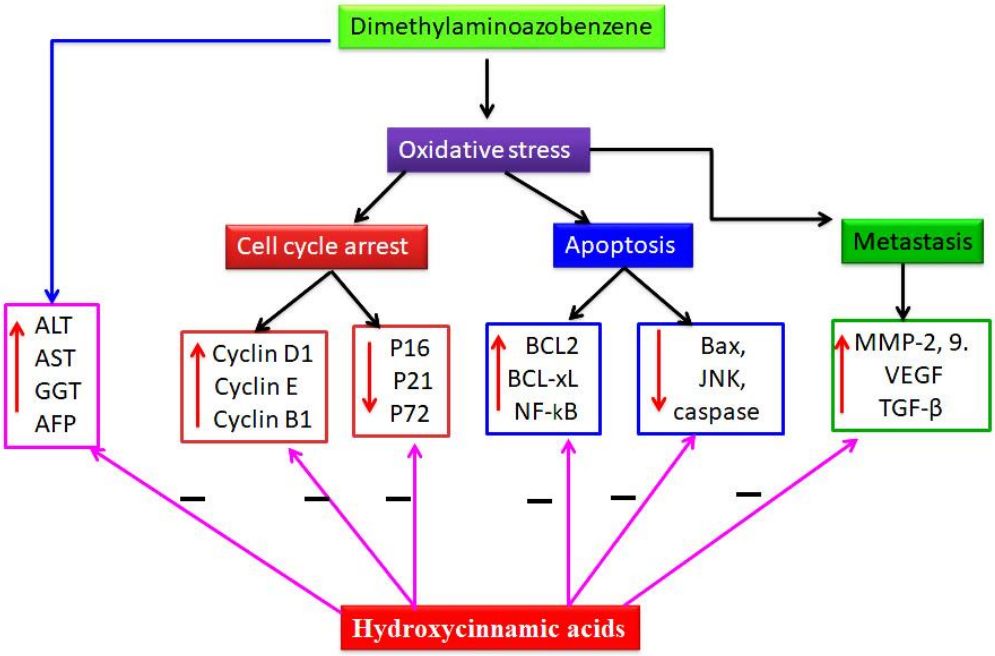

Fig. 2. Hydroxycinnamic acids ameliorate oxidative stress and gene expression in HCC induced by dimethylaminoazobenzene.

The present study rationale was conducted on 80 male mice and divided into 8 groups, each group contains 10 mice, at the end of the experiment, the blood sample was obtained for biochemical analysis such as (liver markers, and assessment of oxidative and antioxidant status). Furthermore, the hepatic tissue was excised for histopathology study and gene expression analysis. The rationale revealed that hydroxycinnamic acids (HCAs) may affect the alterations in the liver function and gene expression induced by dimethylaminoazobenzene and phenobarbital in an animal model through changing transcription factor binding sequences or influencing alternative mRNA splicing.

HCC is a highly vascular tumor in which angiogenesis is crucial to the development and progression of the tumor (Moawad *et al.,* 2020). The high expression of angiogenesis factors, including Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), angiopoietins (Ang), and platelet-derived growth factors are noticed in solid tumors (Papetti and Herman, 2002). The most popular angiogenic factor is VEGF(Risau, 1997), it is weakly expressed in the human body in a normal state, and it is highly expressed in tumors in which, more than 91% of advanced HCC patients show high expression of VEGF (Dent *et al.*, 2009). In addition, fibroblast growth factors (FGF) are growth factors that interact with tyrosine kinase receptors (Chae *et al.*, 2017). Furthermore, FGF and its receptors are responsible for the differentiation and maintenance of neovascularization initiated by VEGF and stimulate the invasion of endothelial cells to induce metastasis (Compagni *et al.*, 2000). in which, anti-angiogenic therapy was created on the theory that these medications cause the improperly shaped blood vessels to be destroyed, causing tumor hypoxia and shrinking (Folkman, 1971). As well as, oxidative stress encourages the overexpression of MMPs, which results in angiogenesis and invasiveness (Ma-On *et al.*, 2017).

The molecular pathway of ROS-induced HCC cell migration and invasion is still not fully known. However, it is known that epithelial-mesenchymal transition (EMT) plays a crucial role in the HCC progression (Jayachandran *et al.*, 2016), the EMT induction in HCC cells via PI3K/AKT pathway activation (Zhang *et al.*, 2016). Furthermore, the hypoxia and inflammation upregulated the TGF that induces EMT (Jing *et al.*, 2011). Our rationale HCAs and their derivatives inhibit cancer growth through apoptosis of cancer cells and inhibited cancer metastasis by inhibiting the expression of matrix metalloproteinase, and angiogenesis-related gene

Conclusion

Hydroxycinnamic acids (HCAs) are one of the most significant classes of natural phenolic compound, and are abundant in a variety of foods, including fruits, vegetables, cereals, and beverages (tea and coffee), and has a high healthy, beneficial effect due to its high antioxidant and anti-inflammatory, and antimicrobial activity. Recently, many researchers have investigated the potential impact of reported hydroxycinnamic acids and their derivatives on various cancer lines (*in vitro*) and revealed that, their potential impact on the treatment of cancer disease. However, the data from *in vivo* investigations using human and animal models is still sparse and inconsistent. Thus, more clinical research is required to show the positive health effects of HCAs and clarify their underlying mechanisms of action. The rationale of our study design will investigate the potential therapeutic impact of hydroxycinnamic acids on hepatocellular carcinoma induced by dimethylaminoazobenzene in animal models. This methodological finding supports our hypothesis and could result

in the conception of novel anticancer drug development strategies.

Conflict of Interest.

There are no conflicting interests have been disclosed by the authors

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