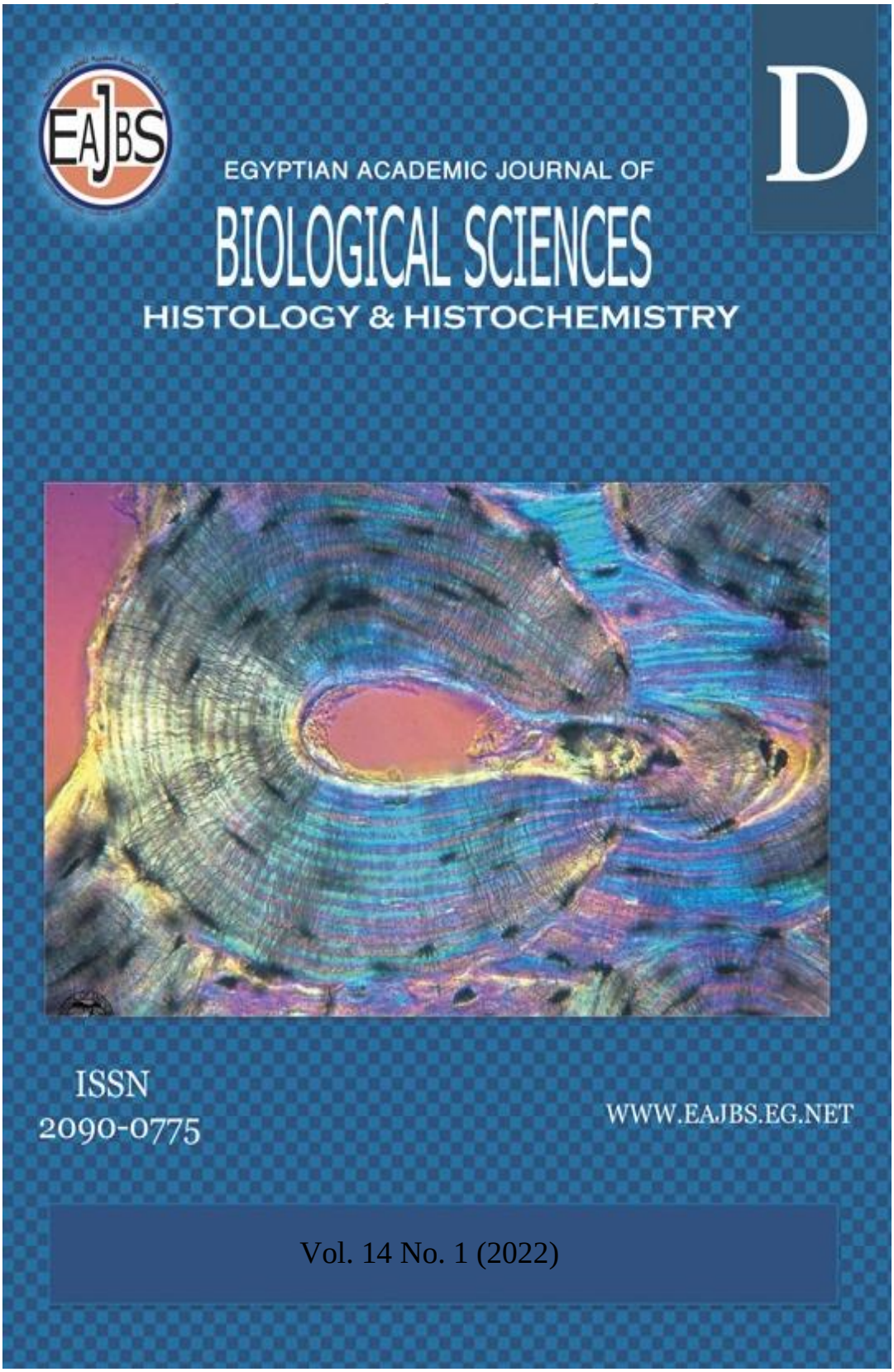

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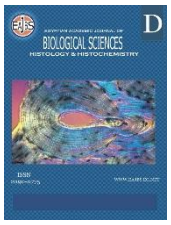

The Rationale of Diarylheptanoid in Ameliorating Dimethylaminoazobenzene-Induced Hepatocellular Carcinoma: Methodical Implication

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ABSTRACT

Hepatocellular carcinoma (HCC) is the world's fifth leading cause of cancer and a major health problem in Egypt. At best, liver transplantation and surgical excision are the only therapy choices. As a result, there is a pressing need to research and assess different chemopreventive and therapeutic techniques that could be useful in the treatment of liver cancer. The most common environment in which HCC originates and advances is one of oxidative stress and inflammation. Phytochemicals, such as diarylheptanoids, which have powerful antioxidant and anti-inflammatory activities, are a viable alternative in the treatment of HCC. Anti-inflammatory, antioxidant, and anti-cancer effects are all present in it. Its effects can be inconsistent in some cases, with unknown consequences for human treatment. While additional research is needed to fully explain these inconsistencies, diarylheptanoid has the potential to be a disease-modifying and chemopreventive drug. As our study design rationale, we evaluate the data for diarylheptanoid's therapeutic potential in animal models. This methodological conclusion that verifies our hypothesis could lead to the identification of novel anticancer drug development methodologies.

INTRODUCTION

Hepatocellular Carcinoma (HCC):

Cancer is the leading cause of morbidity and mortality worldwide, affecting nearly every organ in the human body (Sung *et al.*, 2021),(Elmetwalli *et al.*, 2019). HCC is the fourth and second leading cause of cancer mortality in men and women, respectively (Zhu *et al.*, 2016). Antioxidant, antiproliferative, anti-invasive, apoptotic, antimutagenic, anticarcinogenic, antitumor, and cytotoxic activity, are all strategies to suppress liver cancer (Roleira *et al.*, 2015).

Diarylheptanoids and Cytotoxicity and Anti-Carcinogenic Activity:

Natural medicine and chemicals produced from plants, animals, oceans, and bacteria are abundant in nature.

Plants, for example, provide many novel anticancer compounds (Cragg and Newman 2005), such as alkaloids, flavonoids, glycosides, saponins, tannins (Dembitsky, Gloriozova, and Poroikov 2005), hydroxyphenylalkanes, and diarylheptanoids (Sun *et al.,* 2020), which are found in a plant and have antioxidant and anticancer properties in a variety of cancer cell lines, particularly liver cancer. Diarylheptanoids, natural products with the basic skeleton 1,7-diphenylheptane, are categorized into three major groups: linear diarylheptanoids (LDHs), cyclic biphenylheptanoids ([7.0]-metacyclophanes) (CDHs), and cyclic diphenyl ethers (14-oxa-[7.1]-metaparacyclophanes) (Motiur Rahman *et al.,* 2018). Diarylheptanoids have the potential to be therapeutic in a variety of pathophysiological disorders, including cancer (Sferrazza *et al.,* 2020). Diarylheptanoids had higher antioxidant activities as measured by the diphenyl-1-picrylhydrazyl (DPPH) test and improved the CCl4-induced disruption of intracellular GSH/GSSG balance (Telysheva *et al.,* 2011).

Diarylheptanoids extracted from sea grass *Cymodocea nodosa* was shown to be cytotoxic. Cymodienol had a stronger impact, but cymodiene had a mild effect (Kontiza *et al.,* 2005). Rubanol from *M. rubra* was shown to be cytotoxic to the Lun-06, Neu-04, and Bre-04 cell lines (Sun *et al.,* 2013). Blepharocalyxins D and E extracted from *A. blepharocalyx* seeds displayed anti-proliferative action against murine colon 26-L5 cancer and human HT-1080 fibrosarcoma cells, with ED50 values of 3.61 and 9.02 M, respectively (Ganapathy *et al.,* 2019). *T. chantrieri* rhizome diarylheptanoid compounds displayed more cytotoxic activity against HSC-2 human oral squamous cancer cells than against normal human gingival fibroblasts (Ganapathy *et al.,* 2019).

Therapeutic Challenges and the Importance of Experimental Models:

Numerous cellular mechanisms, such as cell cycle and apoptosis dysregulation, molecular pathways related to inflammation, and fibrogenesis processes, are involved in the development of liver cancer; all of these, in turn, represent important molecular targets for the development of novel drug therapies (Galicia-Moreno *et al.,* 2021). Sorafenib, a multikinase inhibitor approved for the treatment of liver cancer, is the first-line therapy for advanced HCC (Dawkins and Webster 2019); this drug has been shown to provide a significant improvement in overall survival but is unable to counteract disease progression due to the development of resistance to antiproliferative therapies (Nasser *et al.,* 2021). As a result, it is critical to design novel compounds with pharmacological efficacy and safety.

Animal models have played an essential role in biomedical research and are a useful tool for studying and understanding the etiology of numerous liver illnesses, including cancer (Attia et al. 2022), (Elmalla et al. 2021); they also aid in assessing the pharmacological effectiveness and safety of novel medications (Elmalla *et al.,* 2021). There are several experimental liver cancer models available, each with its own set of restrictions and scopes; which one to choose relies on the goals that have been specified. An ideal animal model should replicate the natural history, physiopathology, and biochemistry of human liver cancer (Ali *et al.,* 2021).

Experimental Models of Dimethylaminoazobenzene (DAB) for HCC Research*:*

Dimethylaminoazobenzene ($C_{14}H_{15}N_3$) (DAB) is also known as 4-dimethylaminoazobenzene, It is an azo amine dye that exists as yellow leaf-shaped crystals at room temperature (Thomas, George, and Namasivayam 2016). It is insoluble in water but soluble

in alcohol, benzene, chloroform, ether, petroleum ether, mineral acids, oils, and pyridine. The International Agency for Research on Cancer (IARC) classified DAB as a group-2B carcinogen, potentially harmful to humans (Chen et al. 2022). The fluorine atom in the DAB structure, as well as the tight link with the carbon atom, causes carcinogenesis in the rat liver. DAB has demonstrated a significant promotional effort in addition to functioning as an initiator (Ali *et al.*, 2018).

The study of DAB-induced hepatocarcinogenesis in animal models aided in understanding the histological, biochemical, and molecular processes of DAB carcinogenesis, as well as the severity of DAB exposure in humans (Chavan 2015). It has been demonstrated in animal models that the procarcinogen DAB is mostly metabolised by cytochrome P450 enzymes, resulting in the generation of toxic electrophiles and reactive oxygen species (ROS), which then form DNA adducts and contribute to the development of hepatic tumours (Thomas *et al.,* 2016). A recent study reveals that dietary phytochemicals and plant polyphenols are prospective agents for reducing the incidence of DAB-induced hepatocarcinogenesis by decreasing the production of harmful electrophiles and ROS, hence lowering the development of DNA adducts (Biswas *et al.,* 2021).

DAB is mostly administered orally through dietary methods by combining 0.06 % DAB (the highest effective dosage) with the meal (Yang *et al.,* 2017). The meal composition administered to animals has a considerable influence on tumour incidence through DAB. The alternative approach is through intraperitoneal injection (1 mg/kg diluted in 3% dimethylsulfoxide) or subcutaneous injection (5 mg in olive oil or 7.5 mg in Arachis oil), which results in a rapid and simultaneous response to DAB-induced carcinogenesis in the mouse (Pathak *et al.,* 2006).

The Hypothesis's Ramifications and Discussion:

The current study rationale was conducted in 8 groups, each consisting of 6 female mice, by then the biochemical parameters and the expressed genes were assessed. The rationale revealed that the diarylheptanoids may affect liver function and expression via changing transcription factor binding sequences or influencing alternative mRNA splicing. As a result, diarylheptanoid has been found to have a direct effect by decreasing tumor cell growth as well as an indirect action by inhibiting angiogenesis, as illustrated in Figure 1.

Extrinsic and intrinsic mechanisms can both initiate apoptosis or programmed cell death. Internal cues such as DNA abnormalities, ischemia, viral infection, cellular distress, and so on activate the intrinsic route. Extracellular messenger proteins, such as TNF, activate the extrinsic (receptor-mediated) route (Ivanisenko and Lavrik 2019).

In our rationale, the family of proteins regulates the intrinsic route, which includes pro-apoptotic members that induce apoptosis and anti-apoptotic members that protect cells against apoptosis, such as Bcl-2 and P53.

HCC is characterized by active neovascularization, which promotes tumor development. Angiogenesis begins when tumor cells transmit signals to neighboring normal host tissue, causing the production of signaling molecules that initiate and enhance angiogenesis (Attia *et al.,* 2022), (Ivanisenko and Lavrik 2019). This angiogenesis offers oxygen and nutrition to tumor cells as well as a pathway for them to reach the general circulation. HCC cells release angiogenesis activators such as VEGF, platelet-derived growth factor, and TGF. VEGF is the most important antigenic factor among them (Poon *et al.,* 2001). Cancer cells develop in hypoxic environments, which causes the expression of many hypoxia response genes implicated in

metabolic dysregulation (Brahimi-Horn, Chiche, and Pouysségur 2007). ROS produced in cells as a result of oxidative stress promotes the upregulation of MMPs, which leads to angiogenesis and invasiveness (Ma-On *et al.*, 2017). Mandlik et al. (Mandlik and Mandlik 2021) revealed that the treatment with diarylheptanoid decreased cell proliferation and induced apoptosis in cancer cells. in also our rationale the diarylheptanoids also inhibited cancer metastasis by inhibiting the release of MMP-9 (Mahomoodally *et al.*, 2021).

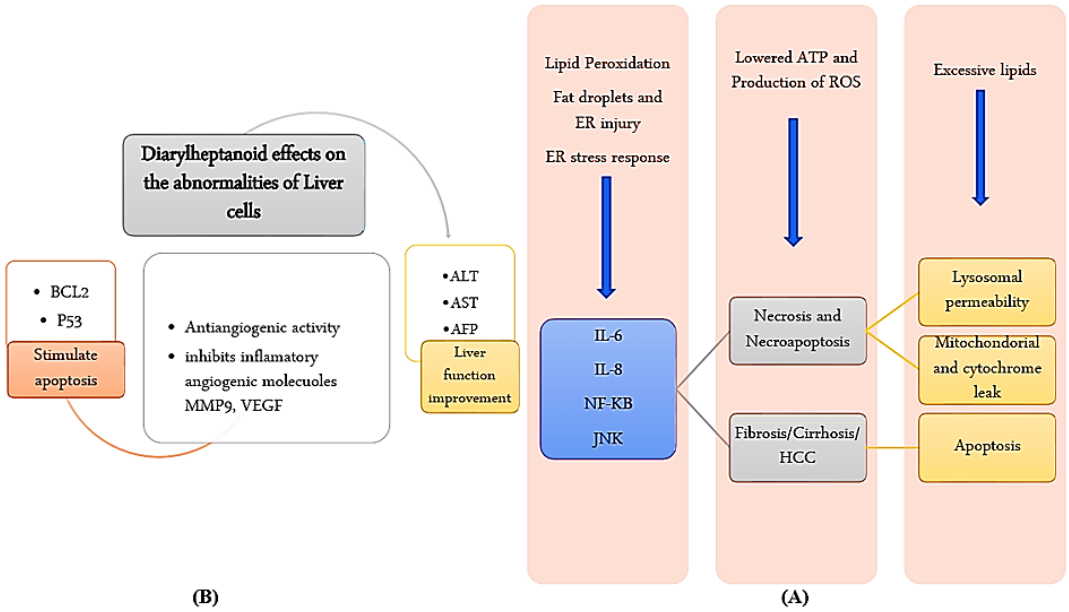

Fig. 1: (A); Flow chart depicting the mechanism of what happened after implementation of EAC cells in mice; **(B)** Various anti-cancer properties after treatment with Diarylheptanoids. **AFP**; alpha-fetoprotein; **ALT**: alanine aminotransferase; **AST**: aspartate aminotransferase **HCC**: hepatocellular carcinoma; **IL-6**: interleukin-6; **IL-8**: interleukin-8; JNK: c-Jun N-terminal kinase; **NF-κB**: nuclear factor-kappa; **VEGF**: vascular endothelial growth factor; **MMP9**: matrix metalloproteinase-9.

CONCLUSION

In this respect, diarylheptanoid has anti-inflammatory, antioxidant, and anti-cancer properties. In other situations, its effects might be inconsistent, with unknown repercussions for human therapy. While further study is needed to completely understand these discrepancies, diarylheptanoid has the potential to be a disease-modifying and chemopreventive medication. We assess the evidence on diarylheptanoid's therapeutic potential in animal models as our study design rationale. This methodological finding, which validates our hypothesis, might lead to the discovery of innovative anticancer drug development strategies.

Conflict of Interest: There are no competing interests declared by the authors.

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