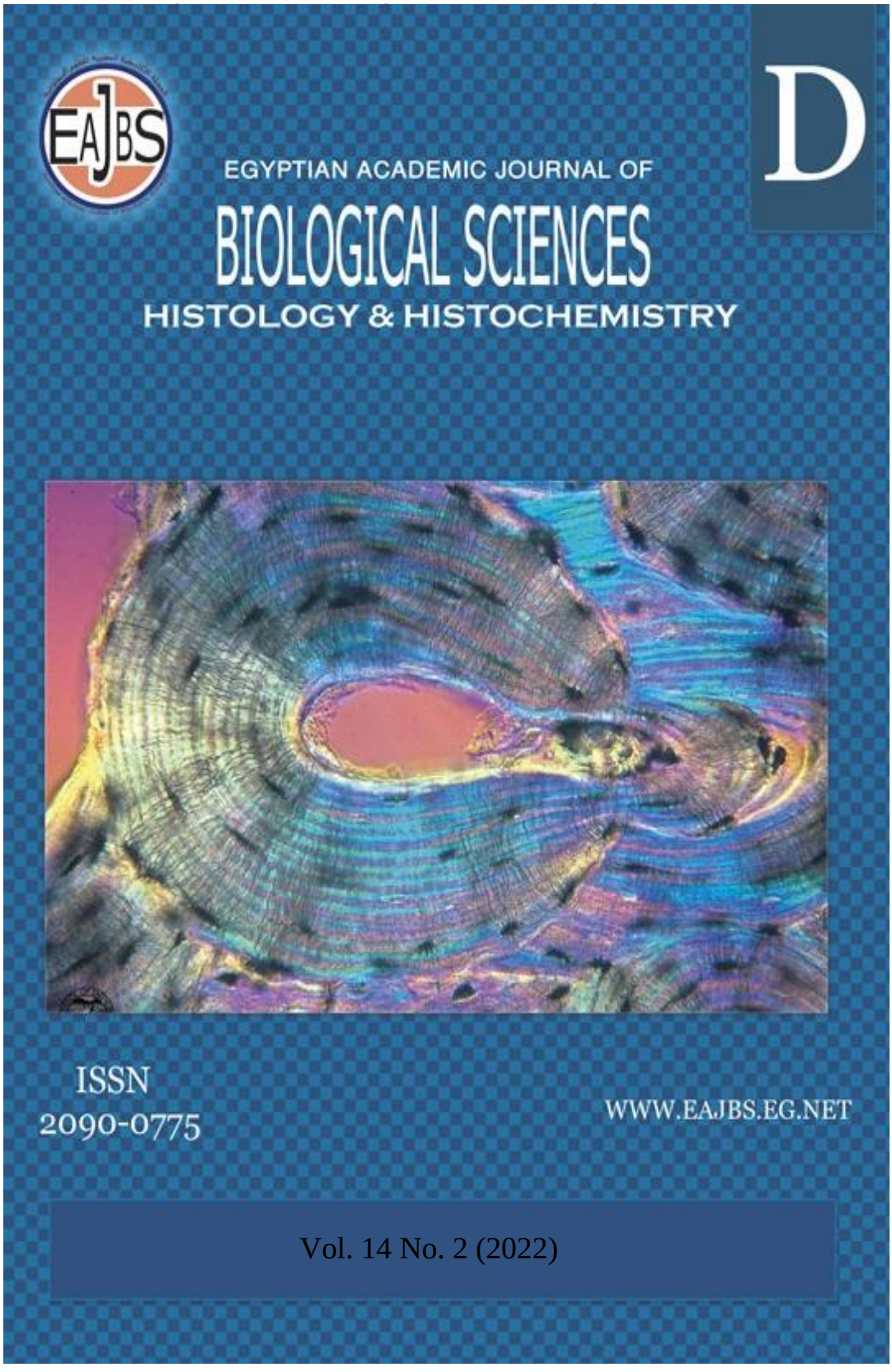

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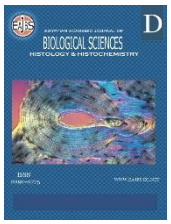

The Rationale of Gingerol as a Main Phenolic Compound of Zingiber in Improving Hepatocellular Carcinoma Induced by Dimethylaminoazobenzene: Scientific Implication

Esraa Ali Anbar[1], Sabry Ali El-Naggar[2] and Afrah Fatthi Salama[1*]

1. Division of Biochemistry, Department of Chemistry, Faculty of Science, Tanta University, Egypt.
2. Physiology Department, Faculty of Science, Tanta University, Tanta, Egypt.

E.Mail*: afrahsalama@science.tanta.edu.eg -afrahsalama@yahoo.com

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ABSTRACT

Among different types of cancers, hepatocellular carcinoma (HCC) is widely distributed and considered to be the fifth leading cause of death around the world. Although the presence of different treatment choices with liver transplantation and liver excision is at the top of the list, there is a high need for more investigations to be done to figure out variant options with higher efficacy and lower cost. Inflammation and oxidative stress are very common factors in cancer biology that play a substantial role in cancer development and progression. These deep understandings resulted in exploring the branch of phytochemistry to help find effective natural products and their derivatives. Among hundreds of phytochemical choices, gingerol is known for its powerful antioxidant and anti-inflammatory activities positioning it to be a very promising compound added to the list of cancer treatment options. Besides these activities, gingerol was documented to have anti-cancer effects as it arrests the cell cycle as well as induces apoptosis. In our study design, the therapeutic potential of gingerol was evaluated in an animal model. The conclusion that confirms our hypothesis is hoped to have a distinct role in developing cancer therapies.

INTRODUCTION

Hepatocellular Carcinoma (HCC):

Cancer, with its ability to develop in different organs within the body, is considered a main leading cause of death around the world (Sung *et al.*, 2021). The presence, of hepatocellular carcinoma, is one of these malignancies with a high incidence rate and mortality (Yang *et al.*, 2019). Great efforts were intensified in the research field to find different therapeutic strategies (Lurje *et al.*, 2019).

Gingerol Cytotoxicity and Anti-tumor Activity:

The herbal medicine includes natural products produced from plants and used in medicine according to their therapeutic effects (Wachtel-Galor & Benzie, 2011). These natural products are also known as phytochemicals which include flavonoids, glycosides, and others such as gingerol which is famous for its anticancer activities (Johnson, 2007). Gingerol, a phenolic compound found in ginger, is used for medicinal purposes due to its antioxidant, anti-tumor, anti-invasive and anti-inflammatory properties (Bode & Dong, 2011). With different constituents, [6]- gingerol has been reported to be more frequent rather than others including [4]-, [8]-, [10]- and [12]-gingerols which are present in lower amounts in ginger (Jiang, *et al.*, 2005).

Gingerol was found to have cytotoxicity according to the experiment applied to the HCT-116 cell line and it was not cytotoxic to normal cells (El-Naggar *et al.,* 2017). The mechanism of gingerol by which it acts to inhibit proliferation and induce cancer worked to classify it to have an anti-tumor activity (Habib *et al.,* 2008). *In vitro* study on gastrointestinal cancer treated with [6]- gingerol showed a high increase of caspase-3/7 activation and down-regulation of cytosolic inhibitor of apoptosis (cIAP)-1 (Prasad & Tyagi, 2015). Other studies on glioblastoma showed the role of [6]- gingerol in increasing death receptors, apoptotic proteins such as Bax, as well as down-regulating anti-apoptotic proteins like Survivin and Bcl-*2 (*Lee, e*t al.,* 2008). In liver cancer, there was a report for down-regulating NF-κB in the animal model, while in the HepG2 cell line, cathepsin D was detected followed by an increase in ROS production (Yang *et al.,* 2012).

Therapeutic Challenges and the Value of Experimentation:

Several molecular mechanisms were shown to be involved in HCC development including disrupted cell cycle or programmed cell death pathway, so deep research investigations on the molecular level can help improve available cancer treatments (Calderaro *et al.,* 2019). Sorafenib is considered one of the most prominent drugs prescribed for HCC patients. It is a multikinase inhibitor that extends lifetime and retard cancer progression (Keating & Santoro, 2009). More research was investigated due to the inability of Sorafenib to prevent tumor progression and a high need has been raised for discovering new pharmacological compounds (Galmich *et al.,* 2014).

Along with research history, animal models proved to be a powerful tool that played the main role in understanding different diseases including cancer. Additionally, they supported evaluations of the pharmacological efficiency of different drugs (Derakhshanfar, 2020). With several experimental liver cancer models, each with its own limitations, the choice depends on the objectives that have been set. An ideal animal model would mimic that of human liver cancer (He *et al.,* 2015).

Dimethylaminoazobenzene (DAB) Experimental Models for HCC Research:

Dimethylaminoazobenzene (C14H15N3) also abbreviated as (DAB) is an azo amine dye that crystallizes at room temperature into yellow leaves. It is soluble in alcohol, mineral acids, oils, benzene, and other alcoholic derivatives but insoluble in water (Thoma *et al.,* 2016). DAB has been categorized as a group-2B carcinogen by the International Agency for Research on Cancer (IARC), meaning that it is very dangerous to human health. According to its chemical structure, the presence of the fluorine atom as well as the strong bond of carbon made DAB an excellent cancer initiator compound (Suzuki *et al.,* 2006).

Animal models for studying the effect of DAB in hepatocarcinogenesis added great value in understanding how DAB can initiate liver cancer on biochemical and molecular bases (Köhle *et al.,* 2008). Due to metabolizing DAB by cytochrome P450 enzymes, a large number of electrophiles and reactive oxygen species (ROS) are produced which react with DNA and form adducts leading to tumor formation (Mirbahai *et al.,* 2011). A recent study showed that the formation of DNA adducts can be decreased significantly by lowering the percentage of produced ROS and electrophiles. This can be achieved by dietary phytochemicals (Biswas *et al.,* 2021).

DAB is usually mixed with food and its highest effective dose is 0.06% (Biswas & Khuda-Bukhsh, 2002). Other methods of DAB

administration include intraperitoneal or subcutaneous injection with different dosages (1 mg/kg diluted in 3% dimethylsulfoxide and 5 mg in olive oil respectively). The last method was approved to have a faster stimulation and formation of DNA adducts (Patha *et al.*, 2006).

Impacts of the Assumption and Discussion:

The basis of our study was applied in 8 groups each containing 10 male mice. Biochemical parameters in addition to expressed genes were evaluated. As a result, gingerol was shown to have a direct effect on cancer progression through down-regulating inhibitors of apoptosis as well as activation of apoptotic proteins as shown in Figure 1.

There are different mechanisms that can start apoptosis. Intrinsic mechanisms can be initiated through ischemia, DNA mutations, or viral infections. The extrinsic mechanism can be activated by extracellular proteins (Feng & Anderson, 2017).

In our study, protein family members were detected that regulate the intrinsic pathway. This includes proteins responsible for activation of apoptosis and others responsible for preventing cells from death such as Bax and Bcl-2.

Angiogenesis is a remarkable feature of HCC allowing tumor cells to develop. On the molecular level, cancer cells send signals to normal surrounded cells that act to enhance the vascularization to develop (Morse *et al.*, 2019). As a result, more blood supply is received for tumor cells containing oxygen and enough nutrition so that cancer can be progressed and even be transmitted to different parts of the body. Studies showed the ability of gingerol to inhibit angiogenesis through down-regulating VEGF.

The presence of oxidative stress in cancer cells can result in increased ROS production. PAT-induced intracellular ROS was shown to be suppressed by gingerol (Yang *et al.*, 2011). Gingerol's role as an anti-inflammatory compound was discovered by decreasing cytokines related to inflammation as tumor necrosis factor (TNF-α) and interleukin (IL)-1β and inducing Mitogen-activated protein kinase phosphatase-5 (MKP5) *(*Liang *et al.*, 2018).

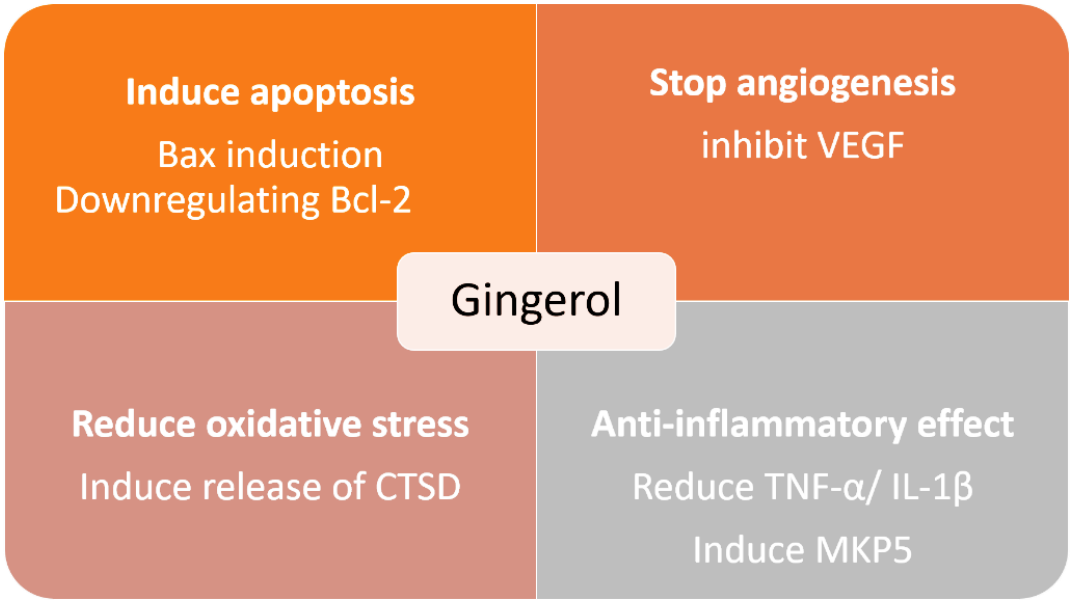

Fig. 1: Role of gingerol in cancer cells at a molecular level. Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; VEGF: Vascular endothelial growth factor; CTSD: cathepsin D; TNF-α: Tumor necrosis factor alpha; IL-1β: Interleukin-1β; MKP5: MAP kinase phosphatase-5.

Conclusion

According to this aspect, gingerol has antitumor properties as well as antioxidant and anti-inflammatory effects. In other cases, it might conflict with different unknown impacts leading to adverse results on health. As a consequence, more research needs to be initiated to better understand these conflicts. Even so, there is no doubt that gingerol has a significant role as a disease-modifying and chemopreventive medication. As justification for our study design, we evaluate the data on gingerol's therapeutic potential in animal models. These findings which support our hypothesis can guide us to develop new drug strategies for cancers.

Conflict of Interest: No competing interests were pronounced by the authors.

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