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Potential Prophylactic Effects of Curcumin and Fish Oil on Diethylnitrosamine-Induced Hepatocellular Carcinoma in Experimental Rats

Sara I. I. Mousa[1], Eman E. Abd Elhady[1], Hanan S.E. Eldamaty[1] and Mohamed Elzallat[2]

[1.] *Nutrition and Food Science Department, Faculty of Home Economics, Al-Azhar University, Egypt.*
[2.] *Immunology Department, Theodor Bilharz Research Institute (TBRI), Giza, Egypt.*

Abstract

Diethylnitrosamine (DEN) is a highly potent substance that causes severe damage to the liver and contributes to the development of liver toxicity and liver cancer. This study assessed the potential protective effects of curcumin and fish oil on biological and biochemical parameters in rats suffering from DEN-induced carcinoma. Twenty-eight mature rats were divided into four groups: The normal-control group, the positive-control group, the 3rd group (curcumin group): rats received a daily dose of curcumin (100mg/kg) for 28 days, along with a single intraperitoneal injection of DEN on day 21, and the 4th group (fish oil group): rats received a day after day dose of fish oil (300 mg/kg) for 28 days, along with a single intraperitoneal injection of DEN on day 21. Administration of curcumin and fish oil protected against DEN-induced hepatocellular carcinoma (HCC). This protection resulted in decreased liver enzyme levels and elevated total protein, albumin, and globulin levels. Additionally, curcumin and fish oil protected against DEN-induced decreases in antioxidant enzyme activities and increases in tumor necrosis factor-alpha (TNF-α), interleukin-1beta (IL-1β), and alpha-fetoprotein (AFP) in the sera of rats. Furthermore, they protected against dysregulation of Wnt pathway genes (cyclin D1, β-catenin, and PCNA). This suggests that curcumin and fish oil may have potential prophylactic effects against DEN-induced HCC.

Keywords: Hepatocellular carcinoma, Diethylnitrosamine, Curcumin, Fish oil, Wnt pathway.

Introduction

Nitrosamines encompass a range of environmental carcinogens present in nitrite-cured meats, tobacco smoke, and smoked pickled fish [1]. Diethylnitrosamine (DEN) is a highly potent substance that causes severe damage to the liver and is a known cause of liver cancer. Amines undergo activation through a reaction with nitrate, resulting in the formation of N-nitrosamines under the effect of acidity in the stomach [2-3]

Liver cancer remains a major health issue, with its occurrence increasing on a global scale. By 2025, the number of patients suffering from liver cancer each year is projected to exceed 1 million. Hepatocellular carcinoma (HCC) is the predominant type of liver cancer, representing 90% of all occurrences [4].

The induction of hepatocyte damage, characterized by increased cell proliferation and hepatocellular necrosis, is a widely recognized mechanism for the development of hepatocellular carcinoma (HCC) using DEN [5-6].

Although there have been notable improvements in cancer treatment, the rates of cancer occurrence and death are still elevated. Hence, pursuing of more effective and less harmful cancer prevention methods continue to be a primary focus of ongoing scientific investigation.

Curcumin, a bioactive compound derived from the *Curcuma longa* plant, has garnered significant interest in the last 20 years because of its potent anticancer effect. [7]. Furthermore, it exhibits a range of pharmacological functions, such as anti-inflammatory, antiproliferative, antioxidant, and antiangiogenic activities [8].

Fish oil has also garnered significant interest in the last 20 years because of its ω3 polyunsaturated fatty acids content. It has been reported that it may reduce cell proliferation and cause apoptosis [9].

*Corresponding authors: Mohamed Elzallat, E-mail: zallatzallat@gmail.com, Tel.: +201002654529
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Research has demonstrated that consuming fish oil can provide protection against some chronic degenerative diseases, including autoimmune disorders, rheumatoid arthritis, cardiovascular disease, type 2 diabetes, and cancer [10].

Fish oil ω3 also provides protection against liver damage by counteracting free radicals, enhancing antioxidant enzyme functions, and decreasing the synthesis of inflammatory cytokines [11].

Therefore, we studied the potential preventive properties of curcumin and fish oil against the early stage of chemically induced HCC.

Material and Methods

Experimental design

Twenty-eight mature male albino rats from the *Sprague-Dawley* strain, weighing 150±10g, were housed in clean, well-ventilated cages. They were provided with a basal diet, as described by Reeves et al. [12]. The rats were randomly divided into four equitably sized groups (7/group) and categorized as follows:

1. The normal-control group consisted of rats that were given a basic diet and administered 0.5% carboxyl methylcellulose (CMC) daily through a stomach tube at a volume of 0.5 ml per rat.

2. The positive-control group consisted of rats that were given a basic diet and administered a single toxic dosage of Diethylnitrosamine (DEN) (200 mg/kg, Intraperitoneally) (Sigma-Aldrich, USA) on day 21 of the trial, as described by Tessitore et al. and Bansal et al. [13-14].

3. administered a daily dose of curcumin (100mg/kg) dissolved in 0.5% CMC [15] by a tube into their stomachs for 28 days. On day 21, they received a single injection of DEN (200 mg/kg, intraperitoneally).

4. The fish oil group: rats were given a standard diet and orally administered fish oil (300 mg/kg) day after day for 28 days, along with a single dose of DEN (200 mg/kg, intraperitoneally) on day 21. This information is based on studies conducted by Raghu et al. and Aljadani et al. [16-17]. Following the completion of the experiment, which lasted for a duration of 28 days, the rats underwent an overnight fasting period before being euthanized. Serum and liver samples were collected.

Nutritional related parameters

Relative liver weight, body weight gain percent (BWG%), Feed intake (FI), and feed efficiency ratio (FER) were calculated in accordance with Chapman et al. [18].

Biochemical analysis of serum

The determination of liver enzymes levels was conducted using the methodology described by Bergmeyer et al. [19]. Quantification of albumin was conducted following the methodology outlined by Drupt [20]. The quantification of total protein was conducted following the methodology described by Sonnenwirth and Jaret [21], whereas the calculation of serum globulin was performed using the procedure described by Chary and Sharma [22]. The levels of Malondialdehyde (MDA) and superoxide dismutase (SOD) were measured in liver tissue using the protocols established by Paoletti and Mocali, and Satoh [23-24], respectively.

In addition, the levels of inflammatory markers, specifically tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), were measured using the enzyme-linked immune sorbent assay (ELISA) technique. The IL-1β levels were assessed using the ELISA kit from Hycult Biotech in the Netherlands, while the TNF-α levels were examined using the ELISA kit from RayBio in the USA. Measurements were conducted following the instructions provided by the respective manufacturers. Nuclear factor-erythroid 2-related factor 2 (Nrf2) and the cancer marker alpha-fetoprotein (AFP) were evaluated using ELISA kits from Kamiya Biomedical (USA) and Cusabio (China), respectively, following the instructions provided by the manufacturer Sell & Beckar [25].

Histopathological examination

The liver was preserved in a 10% neutral buffered formaldehyde solution with a pH of 7.5, treated with xylol to remove impurities, and then enclosed in paraffin for further analysis. A segment with a thickness of 4-5 μm was produced and treated with Hematoxylin and Eosin (H&E) stain for further examination, following the method of Bancroft and Gamble [26].

Gene expression analysis

Following the homogenization of the liver samples, RNA was extracted and subsequently reverse-transcribed according to the provided manufacturer's instructions (Qiagen, USA).

Gene expression was performed using real-time PCR as per the manufacturer's instructions. Ready-made primers for Cyclin D1, β-catenin, and proliferating cell nuclear antigen (PCNA) were obtained from Thermo Scientific, USA. The reference gene used was β-actin.

Statistical analysis

The sample size was determined following the method outlined by Arifin and Zahiruddin [27].

Statistical analysis was performed using SPSS version 11. The data were analyzed using one-way classification and analysis of variance (ANOVA). A Duncan test, with a significance level set at $p<0.05$, was employed to evaluate the significance of mean differences. The findings were reported as mean ± SD.

Ethical approval

This study was revised and approved by the Medical Research Ethical Committee (Approval No. 008092023), National Research Center, Giza, Egypt.

Results

Nutritional related parameters

Table (1) indicated that there were no significant alterations in the total feed intake (FI) among the experimental groups. The data from the same table showed that the positive-control group had a notable reduction in both body weight gain percent (BWG%) and feed efficiency ratio (FER) compared with the normal-control group. The values for the positive-control group were 37.860±3.024% and 0.041±0.004 for BWG% and FER, respectively, whereas the values for the normal-control group were 52.140±1.574% and 0.053±0.005.

Rats that consumed curcumin and fish oil via oral gavage experienced a considerable increase in BWG% and FER. The average values were (69.710±2.563%, 81.290±2.138%) and (0.074±0.008, 0.084±0.008) respectively. The curcumin group achieved the most favorable outcome, closely resembling the normal-control group.

While the data given in Table (2) demonstrated the impact of curcumin and fish oil on the liver's relative weight in rats. The mean values of relative liver weight did not show any significant differences among the normal-control, curcumin, and fish oil groups, with values of 3.371±0.756%, 3.771±0.725%, and 3.228±0.325%, respectively. On the other hand, the positive-control group exhibited a substantial rise (4.914±0.614%) compared to the normal-control group.

Biochemical analysis of serum

Liver functions

The impact of curcumin and fish oil on alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels is summarized in Table (3). The levels of ALT and AST in the positive-control group showed a significant increase, with values of 88.640±1.312 U/L and 114.780±2.168 U/L, respectively, compared to the normal-control group, which had values of 21.912±1.298 U/L and 35.288±1.873 U/L, respectively. Rats that received curcumin and fish oil exhibited a notable reduction ($p<0.05$) in the same parameters compared to the positive-control group. The group that received curcumin achieved the most favorable outcome, with values closely resembling those observed in the normal-control group.

Serum Total protein, Globulin and Albumin

The data in Table (4) shows the impact of curcumin and fish oil on the levels of total protein (T.P), globulin (GLOB), and albumin (ALB) in the blood serum of rats. The positive-control group showed a significant decrease in total protein, albumin, and globulin levels (4.150±0.111 g/dL, 1.900±0.406 g/dL, and 2.250±0.320 g/dL, respectively) compared to the normal-control group (6.394±0.267 g/dL, 2.160±0.114 g/dL, and 4.234±0.169 g/dL, respectively). Rats administered with curcumin and fish oil demonstrated noticeable improvements in all the mentioned criteria, with no significant difference compared to the normal control group.

Oxidant and antioxidant parameters

The study was conducted to examine the effects of curcumin and fish oil on superoxide dismutase (SOD), an antioxidant enzyme, and malondialdehyde (MDA), an oxidative parameter, in the sera of rats (Table 5). The results of the SOD analysis showed a significant decrease in the positive-control group (503.600±2.292 U/L) compared to the normal-control group (1032.800±1.923 U/L). Oral administration of curcumin and fish oil resulted in a statistically significant increase ($p<0.05$) when compared to the positive-control group. The group administered with curcumin showed the most favorable outcome, with values similar to those observed in the normal-control group.

The MDA analysis revealed a substantial increase in the positive-control group (402.900±1.779 mmol/L) compared to the normal control group (87.290±1.947 mmol/L). Rats administered with curcumin and fish oil exhibited a significant reduction ($p<0.05$) compared to the positive-control group. Once again, the group administered with curcumin showed the most favorable outcome, with values closely resembling those of the normal control group.

Immunological parameters

Table (6) displays the impact of curcumin and fish oil on tumor necrosis factor-alpha (TNF-α), Interleukin-1beta (IL-1β), nuclear factor erythroid 2–related-factor 2 (Nrf2) and alpha-fetoprotein (AFP) levels in rat's blood. The positive-control group showed a substantial increase in IL-1β, TNF-α, and AFP levels compared to the normal-control group. Specifically, IL-1β increased to 8.932±0.567 ng/ug, TNF-α increased to 175.740±1.728 U/mL, and AFP increased to 10.832±1.699 ng/mL in the positive-control group. In contrast, the normal-control group had IL-1β levels of 4.752±0.423 ng/ug, TNF-α levels of 58.600±2.302 U/mL, and AFP levels of

1.716±0.617 ng/mL. Rats administered curcumin or fish oil exhibited a statistically significant reduction ($p<0.05$) in the aforementioned measures when compared to the positive-control group. The group treated with curcumin achieved the most favorable outcomes in terms of IL-1β and AFP levels, which closely approached those of the normal-control group. The fish oil group achieved the most favorable outcome in terms of TNF-α, with a value closest to that of the normal-control group. The results of the study on Nrf2 showed a substantial drop in the positive-control group (2.750 ±0.129 pg/mL) compared to the normal-control group (4.330 ±0.2016 pg/mL). The curcumin group achieved the most favorable outcome for Nrf2, exhibiting no notable disparity compared to the normal-control group.

Histopathological examination of liver tissue

The livers of the normal-control group had typical hepatocytes organized in cords around a central vein (Fig. 1a). In contrast, the positive-control group showed significant neoplastic characteristics in the hepatocytes, along with noticeable periportal and intralobular oval cell proliferation (Fig. 1b).

The livers of the group treated with curcumin exhibited a significant reduction in neoplastic features within the liver cells and an increase in apoptosis (cell death) within the liver cells (Fig. 1c). Meanwhile, the livers of the group that received fish oil showed a significant reduction in neoplastic features within the liver cells, including decreased variation in shape and cytoplasmic basophilia (Fig. 1d).

Gene expression analysis

The data reported in Table (7) demonstrate the impact of curcumin and fish oil on B-catenin, PNCA, and Cyclin D in the livers of rats. A notable increase in their expression was observed in the positive-control group (3.088±0.250), (3.006±0.331), and (2.072±0.297), respectively, compared to the normal-control group (1.303±0.126), (1.068±0.113), and (1.010±0.162), respectively. The rats that were administered curcumin or fish oil exhibited a notable decrease in expression ($p<0.05$) when compared to the positive-control group. The best result for B-catenin was recorded by the curcumin group, which was the closest value to the normal-control group. The best result for PNCA was recorded by the curcumin group, which was the closest value to the normal-control group. The curcumin group recorded the best result for Cyclin D, which was the nearest value to that of the normal-control group.

Discussion

The current study showed that curcumin and fish oil have possible prophylactic effects against DEN-induced HCC. This could be attributed to their anti-inflammatory and antioxidant effects as well as to their anti-cancer effects through suppression of the Wnt signaling pathway.

The prevalence of HCC is expected to increase because of the growing incidence of alcohol-related liver disease and metabolic dysfunction-associated steatotic liver disease. The therapeutic landscape is changing and necessitates a multidisciplinary approach that frequently incorporates multi-modal treatments such as surgical removal, transplantation, local regional therapy, and systemic treatments [28]

Despite significant advancements in cancer treatment, the incidence and mortality rates of cancer remain high. Therefore, the ongoing scientific inquiry focuses on developing more efficient and less harmful cancer prevention strategies.

Curcumin, a dietary supplement originating from the turmeric family, is anticipated to selectively prevent the progression of HCC. Curcumin has demonstrated favorable therapeutic effects across the entire course of nonalcoholic fatty liver disease and liver fibrosis. The progression was hindered by mechanisms that affected numerous pathways, including antioxidant, anti-inflammatory, and apoptotic regulation [29]

Omega-3 fatty acids regulate the formation of eicosanoids, which are inflammatory signaling molecules that control the inflammatory response and cell proliferation. Studies and meta-analysis have also investigated the potential impact of ω-3 fatty acid supplementation on different types of cancer [30]. Several studies have indicated that consuming ω-3 fatty acids may protect against cancer risk. Nevertheless, the actual connection between ω-3 fatty acid intake and cancer risk remains a subject of debate [31]

The aim of this research was to explore the potential protective effect of curcumin and fish oil against liver cancer in DEN-induced rats.

The data presented earlier showed that the positive-control group experienced a significant decrease in both body weight gain percent (BWG%) and feed efficiency ratio (FER) compared to the normal-control group. On the other hand, the consumption of curcumin and fish oil resulted in a notable increase in BWG% and FER. Metwally et al. [32] found that the group injected with DEN experienced a significant reduction in BWG% compared with the control group. Sreepriya and Bali [33] explained that the decrease in body weight observed in mice treated with DEN may be attributed to the loss of adipose tissue and skeletal muscle. Curcumin possesses digestive characteristics, thus enhancing growth performance [34]. Hixson [35] found that curcumin improves the digestion and the use of nutrients by reducing the number of excreted nutrients. According to Manal [36], the inclusion of curcumin in the diet of Nile tilapia, *O. niloticus*, at

doses of 5, 10, and 20 g/kg resulted in enhanced feed efficiency ratio (FER) and growth. Ismail & El Meligy [37] also noticed that rats who received curcumin experienced a considerable increase in their final body weight. Pérez-Martínez et al. and Atakisi et al. [38-39] demonstrated that the administration of fish oil along with DEN injection resulted in enhanced body weight growth compared to the group that received only DEN injection. Including omega 3 in the diet led to a significant increase in both BWG% and FI compared with the positive control group, as reported by Rabeh et al. [40].

The liver weight relative to body weight in the DEN group was considerably greater than that in the control group, likely because of the formation of liver tumors in the DEN group [41]. Uehara et al. [42] also observed a notable rise in the proportionate liver weight in rats that were administered DEN. Oral administration of curcumin in rats significantly decreased relative liver weights [43]. In contrast, Uehara et al. [42] found no statistically significant variations in the liver's relative weight among rats fed a diet containing a mixture of fish oil and virgin olive oil, with or without the injection of DEN, compared to the control group.

Sivaramakrishnan et al. [44] corroborated the findings of our investigation, which indicated that DEN administration led to a notable elevation in ALT levels. They further established that this increase in ALT levels caused by DEN may be attributed to the process of lipid peroxidation in the membranes of hepatocytes. Al-Rejaie et al., Sayed-Ahmed et al., and Altindag et al. [45- 47] similarly observed that treatment with DEN resulted in a significant increase in AST and ALT levels compared to the control group. The current study further demonstrated that regular ingestion of curcumin reduces ALT and AST levels. Consistent with these findings, Hussein et al. [48] reported that the use of curcumin in rats with liver toxicity resulted in a notable reduction in ALT and AST levels. This reduction was attributed to the curcumin's ability to inhibit peroxidation, inflammation, and oxidative stress, while also improving the antioxidant status of the liver tissues. The current finding was also corroborated by Li et al. [49], who observed that curcumin led to a decrease in the levels of ALT and AST. Conversely, the group that consumed fish oil demonstrated a noteworthy reduction in ALT and AST levels. Administration of fish oil at concentrations of 5% and 10% for a duration of 25 days effectively improved DEN-induced alterations in biochemical parameters and protected against hepatocellular cancer [32]. A study conducted by Moghadamnia et al. [11] found that fish oil omega-3 supplements have a protective effect against thioacetamide-induced hepatic dysfunction in rats. The hepatic protective action of fish oil can be described by its ability to enhance antioxidant capacity, hence inhibiting the reactive oxygen species (ROS) formation induced by the synthetic pesticide fipronil in female rats [50].

Similar to our results, the injection of nanoparticulate curcumin leads to an increase in total protein and albumin levels because of its strong anti-inflammatory, anti-carcinogenic, antioxidant, and anti-angiogenic properties. In addition, it significantly suppresses the development of liver cancer produced by DEN Mohammed et al., [51]. Metwally et al. [32] found that administering fish oil to rats injected with DEN resulted in an enhancement of total protein levels. The study conducted by Rabeh et al. [40] found that rats with Crohn's disease showed an increase in blood albumin content when they were given omega 3.

Our study also observed a notable reduction in SOD levels in the positive-control group compared to the normal-control group, as well as a considerable elevation in MDA levels in the positive-control group compared to the normal-control group. Consistent with these findings, Mohammed et al. [51] elucidated those mice treated with DEN exhibited a notable decrease in the activities of SOD. Furthermore, there was a notable rise in MDA levels, suggesting an intensified production of free radicals because of DEN injection. This injection affects the protective mechanisms against oxidative stress, elevating ROS levels and the peroxidation of membrane lipids. Amer et al. [52] assessed the effects of dietary curcumin on the growth, antioxidant activity, histomorphology of specific organs, production of proinflammatory cytokines, and immune status of *Oreochromis niloticus*. The results showed that the addition of curcumin to the diet increased the activity of serum SOD and decreased the level of MDA. Metwally et al. [32] showed that administering fish oil to the experimental group resulted in a substantial and statistically significant decrease in MDA levels compared to the group treated with DEN. The administration of fish oil resulted in a substantial elevation in SOD levels compared to the positive-control group. Consistent with these findings, Lee and Kyung [53] demonstrated that Omega-3 influenced oxidative stress indicators, specifically reducing MDA levels and increasing SOD activity. Omega-3-supplemented diets led to a notable reduction in MDA levels because of their antioxidant properties, as reported by Rabeh et al. [40].

The current results demonstrated elevated levels of IL-1β, TNF-α, and AFP in the positive-control group compared with the normal-control group. This conclusion aligns with the study conducted by Mansour et al. [54], which also observed an upregulation of oxidative stress and inflammation biomarkers as well as AFP in response to DEN induction. Simultaneously, DEN reduced Nrf2 levels

in the liver. Sun et al. [55] demonstrated notable elevations in the levels of TNF-α, IL-1β, and IL-6 in the DEN group compared to the control group. Curcumin exhibited a notable reduction in the concentration of AFP in the bloodstream, which was attributed to its anticarcinogenic and antioxidant characteristics [56]. According to Shahcheraghi et al. [57], curcumin activated the antioxidant pathways Nrf2 HO-1 and Nrf2-Keap1 and increased the expression of the modifier subunit of glutamate-cysteine ligase, which is involved in the synthesis of the intracellular antioxidant glutathione. Curcumin was found to dramatically reduce TNF-α and IL-6 levels compared to the positive group, as assessed by Hatipoglu and Keskin [58]. The administration of Omega-3 reduced the generation of TNF-α when the body was exposed to cyclophosphamide. Furthermore, omega-3 supplementation reduced the levels of nuclear factor-κB, TNF-α, interferon-γ, and interleukin-8 in peripheral blood mononuclear cells [59]. Administration of fish oil alone in female rats resulted in a reduction in the expression levels of IL-1β and TNF-α, which were comparable to those observed in the control group of female rats. The hepatoprotective action of fish oil can be ascribed to its ability to enhance antioxidant capacity, hence inhibiting the production of ROS generated by the synthetic pesticide fipronil in female rats [51], Saleh et al. [60] proposed that ω-3FA has demonstrated a significant stimulation of the Nrf2/HO-1 signaling pathway in response to Doxorubicin-induced liver damage.

Our histopathological findings were consistent with those of Al-Aameli et al. [61]. Shahcheraghi et al. [57] demonstrated that curcumin effectively protected liver cells exposed to AFB1 from hepatic damage, and this protection exhibited a pattern that depended on the dosage of curcumin. Conversely, the livers of the group that received fish oil exhibited a significant reduction in neoplastic features within the liver cells, such as decreased variation in shape and cytoplasmic basophilia (Fig. 1d), which is consistent with the findings of Chen et al. [62]. Joana et al. [63] found that the DeRitis index showed a small but statistically significant decrease in hypercholesterolemic rats treated with fish oil (G3) compared to hypercholesterolemic control rats (G2).

Additionally, the administration of curcumin or fish oil exhibited a notable decrease in expression ($p<0.05$) of the Wnt/ β-catenin signaling pathway genes. The preceding findings aligned with the studies conducted by Dou et al., Chang et al. and Vallée et al. [64-66]. These studies concluded that curcumin and fish oil can hinder the advancement of hepatocellular carcinoma by decreasing the Wnt/β-catenin pathway expression.

Conclusion

In conclusion, the results of the present study suggest that curcumin and fish oil have protective effects against DEN-induced hepatocarcinogenesis in albino rats. They help protect the liver from pathological changes and elevated levels of liver enzymes, as well as stimulate the hepatic antioxidant system and inhibit the production of proinflammatory cytokines. It is believed that curcumin and fish oil exert their protective effects by inhibiting the Wnt/β-catenin pathway. Incorporating significant amounts of curcumin and fish oil into one's daily routine, either through diet or as dietary supplements, can effectively prevent and treat liver illnesses, particularly hepatocellular carcinoma. Further *in vitro* and preclinical investigations are recommended to determine the precise bioavailability, bioefficacy, and cellular transduction signaling mechanisms of curcumin and fish oil for treating liver disorders associated with oxidative stress.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

This study was revised and approved by the Medical Research Ethical Committee (Approval No. 008092023), National Research Center, Giza, Egypt.

TABLE 1. The impact of curcumin and fish oil on the consumption of food (feed intake (FI)), the percentage of weight growth (BWG%), and the efficiency of converting feed into body weight (feed efficiency ratio (FER)) in rats.

Groups	FI (g/28 day)	BWG%	FER
Normal-control-group	985.710±29.500[a]	52.140±1.574[c]	0.053±0.005[c]
Positive-control-group	977.570±62.60a	37.860±3.024[d]	0.041±0.004[d]
Curcumin group	954.710±79.233[a]	69.710±2.563[b]	0.074±0.008[b]
Fish oil group	996.000±100.457[a]	81.290±2.138[a]	0.084±0.008[a]

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 2.The impact of curcumin and fish oil on relative liver weight in rats

Groups	Relative liver weight (%)
Normal-control-group	3.371±0.756b
Positive-control-group	4.914±0.614a
Curcumin group	3.771±0.725b
Fish oil group	3.228±0.325b

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 3. impact of curcumin and fish oil on aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in blood of rats

Groups	ALT (U/L)	AST (U/L)
Normal-control-group	21.912±1.298[d]	35.288±1.873[d]
Positive-control-group	88.640±1.312[a]	114.780±2.168[a]
Curcumin group	32.000±3.082[c]	39.022±1.987[c]
Fish oil group	57.114±1.363[b]	74.798±1.517[b]

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 4. Impact of curcumin and fish oil on Total protein (T.P), Globulin (GLOB), and Albumin (ALB) in sera of rats

Groups	T.P (g/dL)	GLOB (g/dL)	ALB (g/dL)
Normal-control-group	6.394±0.267[a]	2.160±0.114[a]	4.234±0.169[a]
Positive-control-group	4.150±0.111[b]	1.900±0.406[b]	2.250±0.320[b]
Curcumin group	6.900±0.070[a]	2.960±0.230[a]	3.940±0.250[a]
Fish oil group	6.880±0.083[a]	2.980±0.258[a]	3.900±0.187[a]

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 5. Impact of curcumin and fish oil on superoxide dismutase (SOD) and malondialdehyde (MDA) in sera of rats

Groups	SOD (U/L)	MDA (mmol/L)
Normal-control-group	1032.800±1.923[a]	87.290±1.947[d]
Positive-control-group	503.600±2.292[d]	402.900±1.779[a]
Curcumin group	964.680±1.557[b]	106.020±0.736[c]
Fish oil group	852.400±1.097[c]	153.760±2.667[b]

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 6. Impact of curcumin and fish oil on Tumor necrosis factor alpha (TNF-α), Interleukin-1beta (IL-1β), alpha fetoprotein (AFP), and nuclear factor erythroid 2–related factor 2 (Nrf2) in sera of rats.

Groups	TNF (U/mL)	IL-1β (ng/ug)	AFP (ng/mL)	Nrf2 (pg/mL)
Normal-control-group	58.600±2.302^{d}	4.752±0.423^{d}	1.716±0.617^{d}	4.300±0.216^{b}
Positive-control-group	175.740±1.728^{a}	8.932±0.567^{a}	10.832±1.699^{a}	2.750±0.129^{c}
Curcumin group	75.080±3.825^{b}	5.810±0.431^{c}	4.000±0.524^{c}	4.050±0.602^{b}
Fish oil group	68.560±1.960^{c}	7.350±0.510^{b}	6.076±0.539^{b}	5.950±0.506^{a}

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

TABLE 7. Impact of curcumin and fish oil on hepatic B-catenin, PNCA, and Cyclin D gene expression

Groups	B-catenin	PNCA	Cyclin D
Normal-control-group	1.303±0.126^{b}	1.068±0.113^{c}	1.010±0.162^{d}
Positive-control-group	3.088±0.250^{a}	3.006±0.331^{a}	2.072±0.297^{a}
Curcumin group	1.215±0.254^{c}	1.177±0.121^{c}	1.316±0.143^{b}
Fish oil group	1.553±0.212^{b}	1.596±0.245^{b}	1.438±0.110^{b}

- Values are represented as the average value plus or minus the standard deviation.
- Significance is indicated at a significance level of $p<0.05$.
- Values that have distinct letters in each column exhibit significant differences, but those that share similar letters exhibit insignificant differences

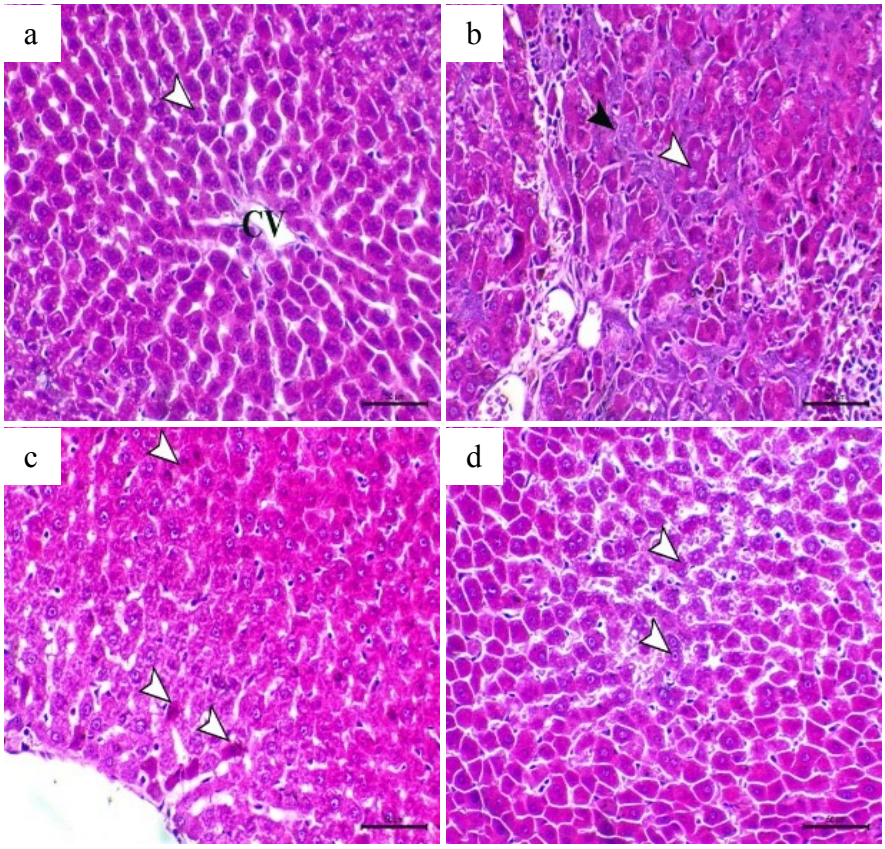

Fig.1. Livers of (a) the normal-control-group showed normal hepatocytes arranged in cords around a central vein (CV indicates central vein and arrowhead indicates normal hepatocytes), (b) the positive-control-group showed marked neoplastic features within the hepatocytes (white arrowhead), and marked periportal and intralobular oval cells proliferation(black arrowhead), (c) the curcumin group showed marked decrease neoplastic features within the hepatocytes and increased the apoptosis within the hepatic cells (white arrowheads), (d) the fish oil group showing marked decrease neoplastic features within the hepatocytes associated with decrease pleomorphism and cytoplasmic basophilia (white arrowheads), (H&E stain), X200, bar= 50 µm.

References

1. Huang, S., Fu, W., Fang, Q., Ni, L., Zheng, R., Yong, L. and Dai, R. Occurrence and carcinogenic risk assessment of N-nitrosamines in some dried aquatic products in China. *Food Control*, **152**(7),109845 (2023).

2. Cai, H., Qian, H. L., Xue, Z. Y., Pei, S. F., Zhang, Y. and Shen, C. Y., Distribution and health risk assessment of nitrosamines in drinking water in Shanghai. *Journal of Environmental and Occupational Medicine*, **39**(7), 752-757 (2022).

3. Mansour, D. F., Abdallah, H. M., Ibrahim, B. M., Hegazy, R. R., Esmail, R. S. and Abdel-Salam, L. O., The carcinogenic agent diethylnitrosamine induces early oxidative stress, inflammation and proliferation in rat liver, stomach and colon: protective effect of ginger extract. *Asian Pacific Journal of Cancer Prevention*: *APJCP,* **20**(8), 2551(2019).

3. Janani, P., Sivakumari, K., Geetha, A., Ravisankar, B. and Parthasarathy, C., Chemopreventive effect of bacoside A on N-nitrosodiethylamine-induced hepatocarcinogenesis in rats. *Journal of Cancer Research and Clinical Oncology,* **136**,759-770(2010).

4. Villanueva, A., Schwartz, M. E. and Llovet, J. M., Liver cancer. Mount Sinai Expert Guides: *Oncology*, 89-100(2019).

5. Glauert, H. P., Calfee-Mason, K., Stemm, D. N., Tharappel, J. C. and Spear, B. T., Dietary antioxidants in the prevention of hepatocarcinogenesis: a review. *Molecular Nutrition & Food Research*, **54**(7), 875-896 (2010).

6. Qiu, W., Wang, X., Leibowitz, B., Yang, W., Zhang, L. and Yu, J., PUMA–mediated apoptosis drives chemical hepatocarcinogenesis in mice. *Hepatology,* **54**(4), 1249-1258(2011).

7. Tomeh, M. A., Hadianamrei, R. and Zhao, X. A review of curcumin and its derivatives as anticancer agents. *International Journal of Molecular Sciences*, **20**(5), 1033 (2019).

8. Nair, A., Gupta, S., Choudhury, H., Jacob, S., Dhanawat, M. and Munjal, K., Pharmacokinetic and tissue distribution study of hydrazinocurcumin in rats. *Pharmacological Reports*, **73**(6),1734-1743 (2021).

9. Lee, K. H., Seong, H. J., Kim, G., Jeong, G. H., Kim, J. Y., Park, H. and Gamerith, G. Consumption of fish and ω-3 fatty acids and cancer risk: an umbrella review of meta-analyses of observational studies. *Advances in Nutrition*, **11**(5), 1134-1149 (2020).

10. Manzi, L., Costantini, L., Molinari, R. and Merendino, N., Effect of dietary ω-3 polyunsaturated fatty acid DHA on glycolytic enzymes and warburg phenotypes in cancer. *BioMed Research International*, **2015**(2), 137097 (2015).

11. Moghadamnia, D., Mokhtari, M. and Khatamsaz, S., Protective Effects of Fish Oil Omega-3 Supplement on Thioacetamide Induced Liver Dysfunction in Male Rats. *Biosciences Biotechnology Research Asia*, **13**(2), 1253-1258 (2016).

12. Reeves, P. G., Nielsen, F. H. and Fahmy, G. C. Reported Of American Institute Of Nutrition Adhoc Writing Committee On The Reformulation Of Ain-76a Rodent Diet. *Journal of Nutrition*, **123**, 1939-1951 (1993).

13. Tessitore, L. Hepatocellular carcinoma is induced by a subnecrogenic dose of diethylnitrosamine in previously fasted-refed rats. *Nutr Cancer*, **32**, 49-54 (1998).

14. Bansal, A. K., Bansal, M., Soni, G. and Bhatnagar, D., Protective role of Vitamin E pre-treatment on N-nitrosodiethylamine induced oxidative stress in rat liver. *Chemico-biological Interactions*, **156**(2-3) 101-111 (2005).

15. Guo, J., Cao, X., Hu, X., Li, S. and Wang, J., The anti-apoptotic, antioxidant and anti-inflammatory effects of curcumin on acrylamide-induced neurotoxicity in rats. *BMC Pharmacology and Toxicology*, **21**(1), 1-10 (2020).

16. Raghu N., R., Fan, C. M., Su, Y. W., Howe, P. R. and Xian, C. J., Fish oil in comparison to folinic acid for protection against adverse effects of methotrexate chemotherapy on bone. *Journal of Orthopaedic Research*, **32**(4), 587-596 (2014).

17. Aljadani, N. A., Elnaggar, M. H. and Assaggaff, A. I., The role of fish oil and evening primrose oil against the toxicity of fenitrothion pesticide in male rats. *Int J Pharm. Re.s Allied Sci.,* **9**(2), 108-122 (2020).

18. Chapman, D. G., Castillo, R. and Campbell, J. A., Evaluation of protein in foods: 1. A method for the determination of protein efficiency ratios. *Canadian Journal of Biochemistry and Physiology*, **37**(5), 679-686 (1959).

19. Bergmeyer, H. U., Horder, M. and Rey, J., Approved Recommendation On Ifcc Methods For The Measurement Of Catalytic Enzymes. Part 2: IFCC method for aspartate aminotransferase". *J. Clin. Chem. Clin. Biochem.*, 497–510 (1986).

20. Drupt, F. Colorimetric method for determination of albumin. *Pharm. Biol*., **9**, 777-779 (1974).

21. Gradwohl, R. B., Sonnenwirth, A. C. and Jarett, L., Gradwohl's Clinical laboratory methods and diagnosis. *Mosby*, Edition:8 ed View all formats and editions, Publisher: C.V. Mosby, Saint Louis, 1980, Show more information (1980).

22. Chary, T. M. and Hariom S., Practical biochemistry for medical and dental students. *Jaypee Brothers Publishers*, (2004).

23. Paoletti, F. and Mocali, A. Determination of superoxide dismutase activity by purely chemical system based on NAD (P) H oxidation. *Methods in Enzymology,* **186**, 209–220 (1990).

24. Satoh, K. Estimation of lipid peroxides by thiobarbituric acid reactive substances (TBARS). *Clin. Chim. Acta*, **90**, 37–43 (1978).

25. Sell, S. and Beckar, F.F. Alpha Fetoprotein. *Natl Cancer Inst*., **60**(1), 19-26(1978).

26. Bancroft, J. D. and Gamble, M. Theory and practice of histological techniques, [Book], 6 Edition,. *Elsevier Health Sciences*, (2008).

27. Arifin, W. N. and Zahiruddin, W. M. Sample Size Calculation in Animal Studies Using Resource Equation Approach. *The Malaysian Journal of Medical Sciences*, **24**(5), 101–105 (2017).

28. Kinsey, E. and Lee, H. M. Management of Hepatocellular Carcinoma in 2024: The Multidisciplinary paradigm in an Evolving Treatment Landscape. *Cancers,* **16**(3), 666 (2024).

29. Li,Y., Deng, X., Li, Q., Yu, Z., Wu, W. and Wang, X. Protective role of curcumin in disease progression from non- alcoholic fatty liver disease to hepatocellular carcinoma: a meta- analysis. *Frontiers in Pharmacology*, **15**, 1343193 (2024).

30. Manson, J. E., Cook, N. R., Lee, I. M., Christen W., Bassuk, S.S. Mora, S., Gibson, H., Albert, C.M., Gordon, D. and Copeland, T. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N. Engl. J. Med.,* **380**(1), 23-32 (2019).

31. Lee, K. H., Seong, H. J., Kim, G., Jeong, G.H., Kim, J. Y., park, H. and Gamerith, G. Consumption pf fish and ω-3 fatty acids and cancer risk: an a umbrella review of meta- analysis of observational studies. *Advances in Nutrition*, **11**(5), 1134-1149(2020).

32. Metwally, N. S., Kholeif, T. E., Ghanem, K. Z., Farrag, A. R., Ammar, N. M. and Abdel-Hamid, A. H., The protective effects of fish oil and artichoke on hepatocellular carcinoma in rats. *Eur. Rev. Med. Pharmacol. Sci.*, **15**(12), 1429-1444(2011).

33. Sreepriya, M. and Bali, G. Chemo-preventive effects of embelin and curcumin against N-nitrosodiethylamine/phenobarbital-induced hepatocarcinogenesis in Wistar rats. *Fitoterapia,* **76**(6), 549-555(2005).

34. Wen, Z. P., Zhou, X. Q., Feng, L., Jiang, J. and Liu, Y. Effect of dietary pantothenic acid supplement on growth, body composition and intestinal enzyme activities of juvenile Jian carp (Cyprinus carpio var. Jian). *Aquaculture Nutrition*, **15**(5), 470-476(2009).

35. Hixson, S. M. Fish nutrition and current issues in aquaculture: the balance in providing safe and nutritious seafood, in an environmentally sustainable manner. *Journal of Aquaculture Research and Development*, **5**(3), 1000234 (2014).

36. Manal, I. Impact of garlic and curcumin on the hepatic histology and cytochrome P450 gene expression of aflatoxicosis Oreochromis Niloticus using RT-PCR. *Turkish Journal of Fisheries and Aquatic Sciences,* **18**(3), 405-415(2018).

37. Ismail, O. I. and El-Meligy, M. M. Curcumin ameliorated low dose-Bisphenol A induced gastric toxicity in adult albino rats. *Scientific Reports*, **12**(1), 10201(2022).

38. Perez-Martinez, P., Garcia-Rios, A., Delgado-Lista, J., Perez-Jimenez, F. and Lopez-Miranda, J. Mediterranean diet rich in olive oil and obesity, metabolic syndrome and diabetes mellitus. *Current Pharmaceutical Design,* **17**(8), 769-777 (2011).

39. Atakisi, O., Atakisi, E., Ozcan, A. Y. L. A., Karapehlivan, M. and Kart, A. Protective effect of omega-3 fatty acids on diethylnitrosamine toxicity in rats. *European Review for Medical & Pharmacological Sciences,* **17**(4), 467-471 (2013).

40. Rabeh, N. M., Hoda S. I. and Fatma N. A. Efficacy of diet supplementation with Vvitamin D And Omega-3 on rats with induced Crohn's disease. *Egypt. J. of Appl. Sci.,* **37**(5-6), 1-16 (2022).

41. Abe, R., Okano, J. I., Imamoto, R., Fujise, Y. and Murawaki, Y. Sequential analysis of diethylnitrosamine induced hepatocarcinogenesis in rats. *Experimental and Therapeutic Medicine*, **3**(3), 371-378 (2012).

42. Uehara, T., Ainslie, G. R., Kutanzi, K., Pogribny, I. P., Muskhelishvili, L., Izawa, T. and Rusyn, I. Molecular mechanisms of fibrosis-associated promotion of liver carcinogenesis. *Toxicological Sciences,* **132**(1), 53-63 (2013).

43. Gangarapu, V., Gujjala, S., Korivi, R. and Pala, I. Combined effect of curcumin and vitamin E against CCl4 induced liver injury in rats. *Am. J. Life Sci.,* **1**(3), 117-124 (2013).

44. Sivaramakrishnan, V., Shilpa, P. N. M., Kumar, V. R. P. and Devaraj, S. N. Attenuation of N-nitrosodiethylamine-induced hepatocellular carcinogenesis by a novel flavonol—Morin. *Chemico-Biological Interactions,* **171**(1), 79-88 (2008).

45. Al-Rejaie, S. S., Aleisa, A. M., Al-Yahya, A. A., Bakheet, S. A., Alsheikh, A., Fatani, A. G. and Sayed-Ahmed, M. M. Progression of diethylnitrosamine-induced hepatic carcinogenesis in carnitine-depleted rats. *World Journal of Gastroenterology: WJG.*, **15**(11), 1373 (2009).

46. Sayed-Ahmed, M. M., Aleisa, A. M., Al-Rejaie, S. S., Al-Yahya, A. A., Al-Shabanah, O. A., Hafez, M. M. and Nagi, M. N., Thymoquinone attenuates diethylnitrosamine induction of hepatic carcinogenesis through antioxidant signaling. *Oxidative Medicine and Cellular Longevity,* **3**, 254-261 (2010)

47. Altındağ, F., Boğokşayan, S. and Bayram, S., Eumelanin protects the liver against diethylnitrosamine-induced liver injury. *Toxicology,* **480**, 153311 (2022).

48. Hussein, S. A., Elhadary, A. E. and Elgzar, Y. M., Biochemical study on the protective effect of curcumin on thioacetamide induced hepatotoxicity in rats. *BVMJ,* **27**(1), 175-185 (2014).

49. Li, W., Jiang, L., Lu, X., Liu, X. and Ling, M. Curcumin protects radiation-induced liver damage in rats through the NF-κB signaling pathway. *BMC Complementary Medicine and Therapies,* **21**(1), 1-10 (2021).

50. Refaie, A. A., Ramadan, A., Sabry, N. M., Khalil, W. K. and Mossa, A. T. H. Synthetic insecticide fipronil induced over gene expression, DNA and liver damage

in female rats: the protective role of fish oil. *Egyptian Journal of Chemistry*, **64**(5), 2325-2336 (2021).

51. Mohammad, H. F., Mahdi, Z., Fatemeh, P., Fardous, F. E., Ilias, M., Ericsson C., Rozita N., Seyed, M. N., Roja, R. and Mohammad, A. Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. *Nutrients,* **10**, 855 (2021).

52. Amer, S. A., El-Araby, D. A., Tartor, H., Farahat, M., Goda, N. I., Farag, M. F. and Osman, A., Long-term feeding with curcumin affects the growth, antioxidant capacity, immune status, tissue histoarchitecture, immune expression of proinflammatory cytokines, and apoptosis indicators in Nile tilapia, Oreochromis niloticus. *Antioxidants,* **11**(5), 937 (2022).

53. Lee, S. I. and Kang, K. S., Omega-3 fatty acids modulate cyclophosphamide induced markers of immunosuppression and oxidative stress in pigs. *Scientific Reports,* **9**(1), 26-84 (2019).

54. Mansour, D. F., Abdallah, H. M., Ibrahim, B. M., Hegazy, R. R., Esmail, R. S. and Abdel-Salam, L. O. The carcinogenic agent diethylnitrosamine induces early oxidative stress, inflammation and proliferation in rat liver, stomach and colon: protective effect of ginger extract. *Asian Pacific journal of cancer prevention: APJCP.,* **20**(8), 2551 (2019).

55. Sun, Z., Sun, L. and Li, W. Effect of ganoderic acid on diethylnitrosamine-induced liver cancer in mice. *Tropical Journal of Pharmaceutical Research*, **19**(12), 2639-2644 (2020).

56. Abdelmageed, A. D., Badawi, A. M. and Eid, A. A. Effect of cetyltrimethylammonium bromide surfactant coated Curcumin copper nanocomposite on hepatocellular carcinoma in rats. *Benha Veterinary Medical Journal*, **38**(1), 79-81 (2020).

57. Shahcheraghi, S. H., Salemi, F., Peirovi, N., Ayatollahi, J., Alam, W., Khan, H. and Saso, L. Nrf2 regulation by curcumin: Molecular aspects for therapeutic prospects. *Molecules,* **27**(1), 167 (2021).

58. Hatipoglu, D. and Keskin, E., The effect of curcumin on some cytokines, antioxidants and liver function tests in rats induced by Aflatoxin B1. *Heliyon*, **8**(7), e09890 (2022).

59. Lee, S. I. and Kang, K. S. Omega-3 fatty acids modulate cyclophosphamide induced markers of immunosuppression and oxidative stress in pigs. *Scientific Reports*, **9**(1), 2684 (2019).

60. Saleh, D. O., Mahmoud, S. S., Hassan, A. and Sanad, E. F. Doxorubicin-induced hepatic toxicity in rats: Mechanistic protective role of Omega-3 fatty acids through Nrf2/HO-1 activation and PI3K/Akt/GSK-3β axis modulation. *Saudi Journal of Biological Sciences,* **29**(7), 103-308 (2022).

61. Al-Aameli, M. H., Al-Taee, R. A. M. and Kadhim, K. S. Histological and Physiological Effect of Turmeric (Curcuma Longa) on Liver, Pancreas and Kidney. Medico-Legal Update, **20**(4),726-731 (2020).

62. Chen, X., Wang, Q., Guo, Z., Zhao, Y., Gao, Y., Yu, T. and Wang, G. Effects of dietary oxidized fish oil on growth performance and antioxidant defense mechanism of juvenile Rhynchocypris lagowski Dybowski. *Aquaculture,* **512**, 43-68 (2019).

63. Joana, É. L., Rocha, M. M., Furtado, R. S. and Mello, N. Effects of Fish Oil Supplementation on Oxidative Stress Biomarkers and Liver Damage in Hypercholesterolemic Rats. *Nutrients,* **14**(3), 426 (2022).

64. Dou, H., Shen, R., Tao, J., Huang, L., Shi, H., Chen, H. and Wang, T. Curcumin suppresses the colon cancer proliferation by inhibiting Wnt/β-catenin pathways via miR-130a. *Frontiers in Pharmacology*, **8**, 877 (2017).

65. Chang, F. Z., Wang, Q., Zhang, Q., Chang, L. L. and Li, W. Omega-3 polyunsaturated fatty acid inhibits the malignant progression of hepatocarcinoma by inhibiting the Wnt/β-catenin pathway. *European Review for Medical & Pharmacological Sciences,* **22**(14), 4500-4508 (2018).

66. Vallée, A., Lecarpentier, Y. and Vallée, J. N. Curcumin: a therapeutic strategy in cancers by inhibiting the canonical WNT/β-catenin pathway. *Journal of Experimental & Clinical Cancer Research,* **38**(1), 1-16 (2019).

التأثير الوقائي المحتمل للكركمين وزيت السمك على سرطان الخلايا الكبدية الناجم عن ثنائي إيثيل نيتروز أمين في فئران التجارب

سارة ابراهيم ابراهيم موسي[1] ، ايمان السيد عبد الهادي[1] ، حنان صلاح الدين الدماطي [1] و محمد الزلاط [2]

[1] قسم التغذية وعلوم الأطعمة - كلية الاقتصاد المنزلي- جامعة الأزهر - مصر.

[2] قسم المناعة – معهد تيودور بلهارس للأبحاث - الجيزة - مصر.

الملخص

يعد ثنائي إيثيل نيتروزأمين (DEN) واحدًا من أهم المواد السامة والمسببة لسرطان الخلايا الكبدية. أجريت هذه الدراسة لتقييم التأثير الوقائي المحتمل للكركمين وزيت السمك على التقييم البيولوجي والمؤشرات البيوكيميائية لذكور الجرذان البيضاء التي تعاني من سرطان الخلايا الكبدية الناتج عنDEN . تم تقسيم الفئران إلى أربع مجموعات متساوية تحتوي كل مجموعة على 7 فئران. المجموعة الأولى (المجموعة الضابطة السالبة)، المجموعة الثانية (المجموعة الضابطة الموجبة)، المجموعة الثالثة (مجموعة الكركمين):تلقت الفئران الكركمين (100 ملجم/كجم من وزن الجسم) يومياً عن طريق الأنبوب المعدي لمدة 28 يوماً + جرعة واحدة من DEN (200 ملجم / كجم من وزن الجسم) في اليوم 21. بينما المجموعة الرابعة (مجموعة زيت السمك): وفيه تلقت الفئران زيت السمك (300 ملجم/كجم من وزن الجسم) يومًا بعد يوم عن طريق الفم لمدة 28 يومًا + جرعة واحدة من DEN (200 ملجم / كجم من وزن الجسم) في اليوم 21. أشارت النتائج إلى أن استخدام مادة ال DEN أدى إلى زيادة مستوى إنزيمات الكبد مثل الانين ترانس امينار (ALT) أسبارتات ترانس امينار .(AST)في المقابل، تسبب في انخفاض مستويات البروتين الكلي والألبومين والجلوبيولين. كما أدى لانخفاض نشاط الإنزيم المضاد للأكسدة سوبر أوكسيد ديسميوتيز (SOD) وزيادة معامل الأكسدة المالون داي الديهايد (MDA) في مصل الدم. كما أدى إلى زيادة إنترلوكين 1 بيتا(IL-1β) ، وعامل نخر الورم ألفا (TNF-α) وبروتين ألفا فيتو بروتين (AFP) في مصل الجرذان. في حين انخفض العامل النووي لكريات الدم الحمراء2 (NRF2) . من ناحية أخرى، أدى تناول الكركمين وزيت السمك إلى تحسين جميع العوامل المذكورة أعلاه وتحسن حالة سرطان الخلايا الكبدية وقد يكون هذا بسبب محتواهم من مضادات الأكسدة وغيرها من المواد الفعالة. أكد الفحص النسيجي والتعبير الجيني للكبد تلك النتائج. أثبتت النتائج أن تناول كلا من الكركمين و زيت السمك له تأثير وقائي ضد سرطان الخلايا الكبدية المحدث بمادة ثنائي إيثيل نيتروزأمين ، إلا أنه كان للكركمين أفضلية عن زيت السمك في تحسين كل المعاملات المختبرة.

الكلمات الدالة: سرطان الخلايا الكبدية، ثنائي إيثيل نيتروزامين، الكركمين، زيت السمك، انزيمات وظائف الكبد.

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