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Research Article

THE PROTECTIVE EFFECT OF TURMERIC RHIZOMES EXTRACT FROM HEPATOTOXICITY AND NEPHROTOXICITY INDUCED BY INDOMETHACIN

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ABSTRACT

Objective: This study was conducted to investigate the effect of the ethanolic extract of turmeric rhizomes (*Curcuma longa*)on reducing hepatotoxicity and nephrotoxicity induced by Indomethacin in male white mice (the Balb-c strain), and to examine its potential in mitigating the side effects of this drug.

Methods: Mice were randomly divided into four groups (10 mice/group). The first group (G1) was dosed with dimethyl sulfoxide (DMSO) 10%. The second group (G2) was given only turmeric rhizome extract dissolved in DMSO 10%. The third group (G3) was dosed with one dosage (166 mg/kg) of Indomethacin drug for 6 h. The fourth group (G4) was dosed with a dosage (300 mg/kg) of turmeric rhizome extract for 30 days then was dosed a dosage (166 mg/kg) of Indomethacin after 6 h. Serum levels of creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) were measured, and a histological study of the livers and kidneys was performed.

Results: Results showed a significant increase in liver enzymes (AST and ALT), LDH, and creatinine in G3 (477 U/L, 942 U/L, 5323 U/L, and 1.37 mg/dl, respectively), compared to G1 (41, 48, 455, and 0.63, respectively), while observed reduction in those biochemical parameters in G4 (63, 102, 1625, and 0.82, respectively). Results also showed the ability of turmeric rhizome extract (300 mg/kg) to decrease the pathological changes induced by indomethacin in the liver and kidney, as severe degenerative changes, Necrotic single cells, and vascular congestion.

Conclusion: This study showed the important role of the ethanolic extract of turmeric rhizome in keeping the tissue structure of each liver and kidney safe from oxidative stress established by Indomethacin.

Keywords: Hepatotoxicity, Nephrotoxicity, Indomethacin, Turmeric.

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INTRODUCTION

The Industrial Revolution was closely linked to a significant revolution in the pharmaceutical industry. It produced chemical drugs with speed, offering effective treatment compared to the effectiveness of long-term natural botanical treatment.

However, side effects of chemical drugs might be life-threatening, such as drug-induced liver injury, which is considered the most common and most dangerous cause of liver diseases that lead to death [1]. Furthermore, pharmaceutical nephrotoxicity is categorized as one of the common dangerous injuries that form 60% of renal insufficiency in hospitals [2], and it is categorized as one of the major causes of acute kidney injury [3].

Non-steroidal anti-inflammatory drugs are one of these drugs with hepatotoxic and nephrotoxic effects, and they are classified as the most used pharmaceutical groups that cause oxidative stress, and as a result, they cause histological injuries [4]. Indomethacin is one of the non-steroidal anti-inflammatory drugs that have a high therapeutic effectiveness, which is due to its strong effect and short half-life in the human body [5]. However, these advantages of this drug, in addition to the dosage amount, are responsible for its dangerous toxic effects on different body organs when it is used randomly to treat both chronic and severe pains [5]. These dangers led to the necessity of looking for an alternative natural botanical treatment with relative effectiveness without side effects.

Within this framework, the biological and pharmaceutical effectiveness of around 20% world's plants were tested by many researchers, and a large number of new active substances were determined and used in the pharmaceutical industries by a number of methods. The most important method is botanical extract, which allows estimating the preventive and remedial effectiveness and efficiency of these new active substances for a number of physiological diseases and disturbances. Medical plants have a great importance due to their richness in anti-oxidative substances that have a significant role in disease treatment [6], and their richness in secondary metabolites, which have a significant pharmacological importance [7]. One of these medical plants is the turmeric plant *Curcuma longa,* which has several healthy effects, such as: Anti-bacterial and anti-parasitical effects [8,9]; anti-diabetic [10]; Alzheimer's treatment [11]; anti-inflammatory [12]; anti-oxidation [13]; anti-cancer [14]; anti-gastric ulcer [15]. Due to there being a few studies on the effects of Indomethacin Hepatotoxicity and Nephrotoxicity in comparison to studies on other non-steroidal anti-inflammatories, this research will shed light on estimating injury caused by high dosages of Indomethacin from one side, and the potential preventive effectiveness of ethanol turmeric rhizomes extract in reducing the severity of histological injury.

METHODS

Experimental animals

Albino male Mice of the species *Mus musculus* and the Balb-c strain were used in this study (26–33.2 g). They were brought from the Scientific Research Center in Damascus at the age of 4–5 weeks; they were left in the laboratory for 8–12 weeks to adapt to experimental conditions.

They were put in special plastic cages with sawdust-furnished floor in the Central Laboratory of Scientific Research, Faculty of Medicine,

Latakia University, under room temperature, good ventilation, and a lighting period of 12 h light and 12 h darkness. During the experiment period, the whole wheat and the required water were introduced to the mice regularly.

All experimental procedures involving animals were reviewed and approved by the Scientific Committee of the Department of Animal Biology, Faculty of Science, Latakia University, and conducted in accordance with institutional and national ethical guidelines. Protocols adhered to the 8th Edition of the Guide for the Care and Use of Laboratory Animals (Institute for Laboratory Animal Research, USA) and complied with ARRIVE guidelines.

Plant material

Taxonomic classification of turmeric plant (C. longa)

Kingdom: Plantae; Phylum: Spermatophyta; Class: Liliopsida; Order: Zingiberales; Family: Zingiberaceae; Genus: *Curcuma*; Species: *Curcuma longa* (Erdtman, 1960) [16].

Turmeric rhizomes were collected from the local market in Latakia Governorate (imported from India). Plant authentication is done by Dr. Afifah Eissa (Associate Professor, Department of Botany, Faculty of Science, Latakia University). Rhizomes were ground in a private grinder to get the powder, which is saved in the freezer at a temperature of (−20°C) for later usage.

Preparation of ethanol extract of turmeric rhizomes

The extract was prepared according to the method of Wang and Waller [17] using the powder obtained above. The amount of 250g of the powder was soaked in 2.5 L of ethanol (95%) at room temperature for 10 days. The extract was filtered using Whatman filter paper No. 1, and then the filtrate was evaporated using a rotary evaporator to remove the solvent at a temperature of 40°C. The floating material was saved at a temperature of 4°C for later usage. The extract was dissolved in dimethyl sulfoxide (DMSO) 10% before utilization [9].

Experimental induction of hepatorenal toxicity

Male mice were orally dosed with Indomethacin 100% (raw active material from Asia Company) using a feeding tube size 4 to establish the toxicity. Indomethacin was dissolved in dimethyl sulfoxide to become a suspension of solution, which should be shaken before using in one dose of 166 mg/kg [18] and left for 6 h. Mice were prevented from food for 18 h while water was provided to them, and then they were dosed with one dosage of indomethacin. The study was performed during April and May 2024.

Design of the experiment

Albino male mice were randomly divided into four groups. Their weights ranged from 26–33.2 g (10 individuals in each group) as follows:

- The first group (G1): (Physiological control) individuals were dosed with 0.2ml of dimethyl sulfoxide 10% during the experiment
- The second group (G2) was treated with 300 mg/kg turmeric rhizome extract dissolved in 10% DMSO during the experiment
- The third group (G3) was treated with one dose of indomethacin 166mg/kg to induce hepatotoxicity and nephrotoxicity, then blood drawing and livers and kidneys were collected for later tissue study after 6 h
- The fourth group (G4) was treated with ethanol extract of turmeric rhizomes 300mg/kg [19] for 30 days, then they were dosed with indomethacin, 1 day after. Mice were dissected after 6 h then the livers and kidneys were collected for later tissue study.

Blood sample collection and biochemical analysis

At the end of the experiment, mice were anesthetized using chloroform then blood samples were collected directly from the heart. Serum was separated by centrifuge at 3000 rpm for 15 min, and kept in the refrigerator at a temperature of −20°C. Serum levels of creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) were determined using kits from Human company and a spectrophotometer (COBAS Mira plus).

Statistical analysis

All data are presented as mean ± standard deviation. We evaluated group differences with one-way analysis of variance followed by *post hoc* test (least significant difference [LSD]) to determine the accuracy of the variance in case of obtaining a significant difference between the means of the vital indicators between the experimental groups using the Statistical Package for the Social Sciences. A $p<0.01$ was considered significant.

Histological study

Mice's bodies were dissected, and their livers and kidneys were collected and preserved in 10% formalin. The specimens were then prepared for tissue sections by passing them through routine preparation stages, which included processing with commercial ethanol, absolute ethanol, and finally xylene. The specimens were subsequently embedded in paraffin molds. Tissue sections were made using a tissue microtome of Meditome A550 with a thickness of 5 microns. Sections were processed in solutions of ethanol and xylene before coloring them with hematoxylin and eosin stain according to the method of Bagheri *et al*. [20]. Tissue microscopic slides were studied using an optical microscope equipped with a digital camera.

RESULTS

Experimental induction of hepatorenal toxicity

Biochemical analysis

The results of the statistical analysis of the control group and the experimental groups, which were treated with *C. longa* extract only (dissolved in DMSO 10%), showed the presence of significant differences in the mean differences in ALT, AST, LDH, and creatinine values between the studied groups. To infer the locations of these differences, the LSD test was used (Table 1).

The results of the statistical analysis showed that no significant differences ($p>0.01$) in ALT, AST, LDH, and creatinine levels, when male mice were treated with the extract compared to the physiological control group.

The results of the statistical analysis for the difference in biochemical parameters between the physiological group and the pathological which were treated with indomethacin, showed the presence of significant differences in the values of ALT, AST, LDH, and creatinine between the studied groups (Table 2).

A negative difference sign (−) indicates that the mean of the compared group (physiological control) is lower than the mean of the standard studied in the experimental group (Pathological group).

Table 1: Physiological effect of *Curcuma longa* extract (dissolved in DMSO 10%) only on kidney and liver functions

The studied group compared with the physiological control	Means± Standard error	P-VALUE	Result
Treat with turmeric extract only (AST)	30.591±3.9990	0.897	Non-significant
Treat with turmeric extract only (ALT)	18.923±2.000	0.916	Non-significant
Treat with turmeric extract only (LDH)	358.298±10.000	0.978	Non-significant
Treat with turmeric extract only (creatinine)	0.6695±0.02300	0.732	Non-significant

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, DMSO: Dimethyl sulfoxide

The mean ALT, AST, LDH, and creatinine levels were significantly increased ($p<0.01$) when treated with indomethacin compared to the physiological control group (Figs. 1-3).

The results of the statistical analysis for the difference in biochemical parameters between the pathological group and the experimental groups, which were treated with *C. longa* extract before the induction of toxicity, showed significant differences in the values of ALT, AST, LDH, and creatinine between the studied groups (Table 3).

The mean ALT, AST, LDH, and creatinine levels were significantly decreased ($p<0.01$) when treated with *C. longa* extract before toxicity was induced, compared to the pathological control group.

Histological study

Livers and kidneys of male mice (G1) dosed with DMSO 10% all the time during the experiment showed a perfect normal tissue structure (Fig. 4).

Livers and kidneys of male mice (G2) dosed with turmeric rhizome extract dissolved in 10% DMSO during the experiment. Showed a perfect normal tissue structure (Fig. 5).

Mice livers of (G3) showed severe degenerative changes, unique necrotic cells, and vascular congestion. However, it was noticed that a renal tissue injury resulted from the effect of indomethacin dosed to male mice. This injury appeared through glomerulus degeneration, vascular congestion, and degenerative changes in the near tubules (Fig. 6).

Livers of (G4) dosed with ethanol extract of turmeric rhizomes for 30 days, then were dosed with Indomethacin for 6 h in a row, showed a reduction in lymphatic infiltration in portal spaces and around the central vein in addition to congestion in the central vein (Fig. 7).

Kidneys of (G4) dosed with ethanol extract of turmeric rhizomes for 30 days, then were dosed with Indomethacin for 6 h in a row,

Table 2: The effects of indomethacin only on kidney and liver functions

Pathological group compared with the physiological control	Means±Standard error	p-value	Result
AST	−435.800±30.591	0.000	Significant
ALT	−894.100±18.923	0.000	Significant
LDH	−4868.600±358.298	0.000	Significant
Creatinine	−0.7370±0.6695	0.000	Significant

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase

Table 3: The protective effect of *C. longa* extracts only on kidney and liver functions in hepatorenal toxic mice

The studied group compared with the pathological control	Means± Standard error	p-value	Result
C. longa then indomethacin (ALT)	839.60±18.923	0.000	Significant
C. longa then indomethacin (AST)	413.50±30.591	0.000	Significant
C. longa then indomethacin (LDH)	3698.40±358.298	0.000	Significant
C. longa then indomethacin (creatinine)	0.4860±0.6695	0.000	Significant

C. longa: *Curcuma longa*, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase

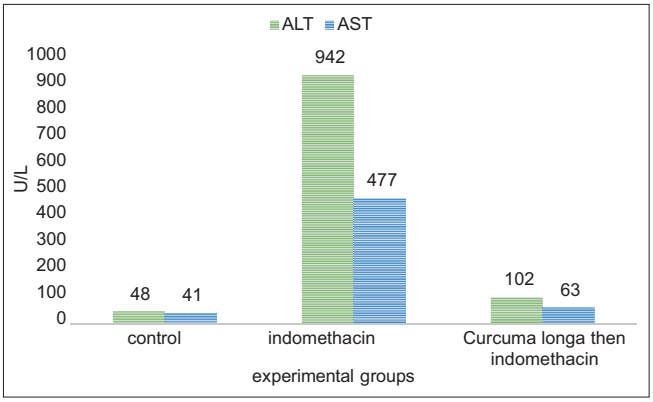

Fig. 1: The protective effects of turmeric extract on levels of ALT, AST. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

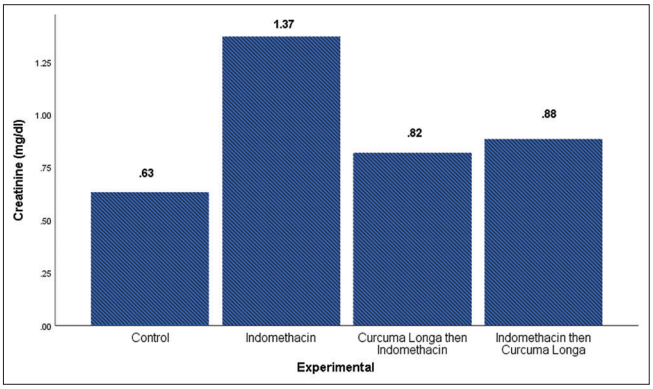

Fig. 2: The protective effects of turmeric extract on levels of creatinine

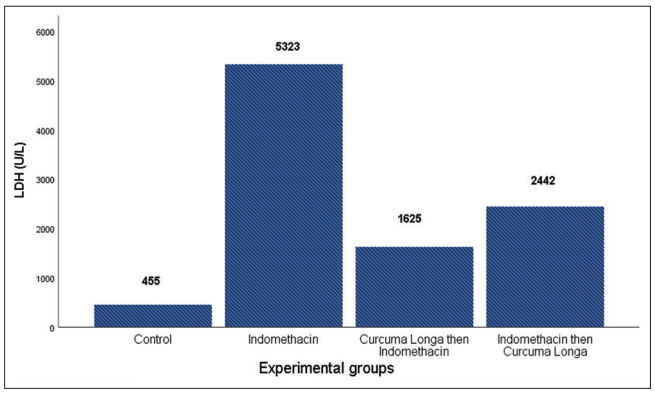

Fig. 3: The protective effects of turmeric extract on levels of lactate dehydrogenase

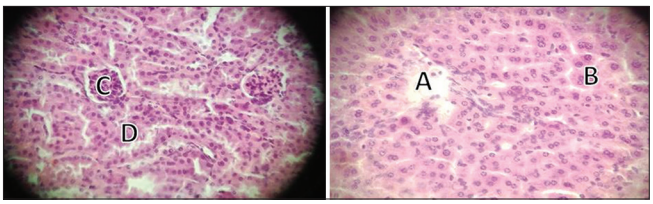

Fig. 4: Livers and kidneys of mice (physiological control group) dosed with dimethyl sulfoxide for 30 days (40×). A: The central vein; B: Normal hepatocytes. C: Normal renal glomeruli; D: Normal renal tubules

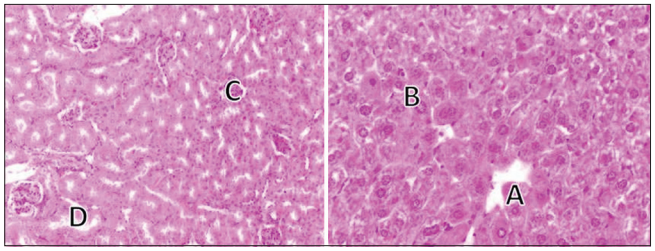

Fig. 5: Livers and kidneys of mice dosed with turmeric rhizome extract dissolved in 10% dimethyl sulfoxide for 30 days (40×). A: The central vein; B: Normal hepatocytes. C: Normal renal glomeruli; D: Normal renal tubules

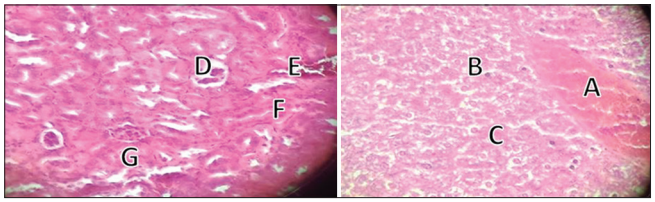

Fig. 6: Effect of Indomethacin on liver and kidneys dosed with one dosage (166 mg/kg) for 6 h in a row (40×). A: Severe central vascular congestion; B: Necrotic hepatocytes; C: Severe cytoplasmic necrosis. D: A necrotic glomerulus; E: Vascular congestion; F: Degenerative changes in the near tubules; G: Tubular cells sloughing off

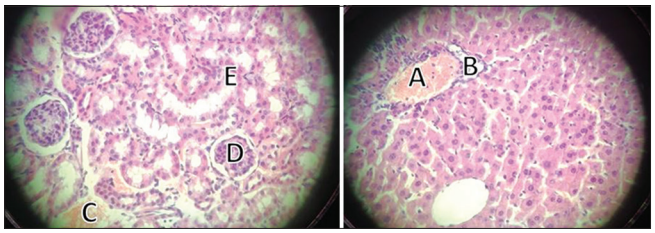

Fig. 7: Protective effect of ethanol extract of turmeric rhizomes from toxicity established by indomethacin (40×). A: Congestion in the central vein; B: A reduction in lymphatic infiltration in portal spaces and around the central vein. C: Vascular congestion; D: Normal glomeruli; E: Normal renal tubules

showed only occurrence of vascular congestion without occurrence of inflammatory infiltrations (Fig.7).

DISCUSSION

Drugs are metabolized in the liver, gut, and kidneys in different levels and mechanisms [21]. However, the liver is the most targeted organs with chemically established infections because it is the main organ of biological metabolism processes, as detoxification enzymes CYP P450 concentrate mainly within it [22]. Some drugs cause an increase in oxidative stress, which is associated with tissue injury in many organs, such as the liver and kidneys, in addition to decreasing activity of most anti-oxidative enzymes [23,24].

This study showed the hepatic and renal tissue injury caused by indomethacin in the male white mice, which included central vein congestion; severe cytoplasmic degeneration, and focal necrosis in some hepatocytes. In addition to renal tissue injury appeared in glomerulus degeneration and generation appeared near the tubules, with inhomogeneous limits between them. Furthermore, there was a vascular congestion due to the used drug, which induced oxidative stress and led to hepatotoxicity [25-27]. Our results agree with several studies regarding the hepatotoxic effects of indomethacin [28-31], and its nephrotoxic effects [31-34].

The mechanism by which indomethacin causes hepatotoxicity in overdose is still not sufficiently clear. Many hypotheses have been proposed to explain its toxic effect; Indomethacin increases generating ROS [35] because it is a strong pro-oxidant initiator [36]. However, when their generation exceeds the normal rate, they may cause damage to essential cellular components due to their increased lipid peroxidation, such as damage to hepatic DNA and protein oxidation, causing hepatic necrosis [26].

Another hypothesis suggests that indomethacin impairs the effectiveness of detoxification enzymes in all their forms, due to its inhibition of nitric oxide synthesis, or occurs through inflammatory mediators released from Kupffer cells and hepatocytes [31]. Due to its pivotal role in detoxification, hepatocytes are exposed to severe stress, which in turn causes an increase in the secretion of inflammatory cytokines. Consequently, these cells become more susceptible to apoptotic agents such as tumor necrosis factor [37]. Furthermore, indomethacin disrupts mitochondrial function, so when the mitochondrial membrane is damaged, the cell's ATP content will be depleted, and cellular necrosis will occur [26,38]. Elevated ALT and AST levels reflect cellular damage through cell membrane disruption, cell rupture, and subsequent leakage of enzymes from damaged hepatocytes into the bloodstream, proving the hepatotoxic effect of indomethacin in causing cellular necrosis. A significant increase in Lactate dehydrogenase levels was recorded after toxicity induction, indicating tissue damage. LDH is a cytoplasmic enzyme whose elevation indicates acute hepatocellular necrosis [39].

Kidneys play a prominent role in synthesizing prostaglandins and eliminating toxins from the body. Consequently, they are responsible for eliminating large amounts of free radicals, which can lead to an imbalance between oxidants and antioxidants, ultimately causing kidney damage [33]. Oxidative stress, causing kidney damage, involves an increase in inflammatory cytokine [40]. Monitoring creatinine levels is one of the most common laboratory markers used to monitor kidney function. Elevated creatinine levels reflect a low glomerular filtration rate [41].

Several mechanisms have been proposed to explain the renal toxicity of indomethacin, including increased free radicals generated by neutrophil activation 01and, consequently, oxidative stress [34]. In addition to causing disturbance in the function of proximal tubule mitochondria [42]. Inhibits prostaglandin activity [43] and the synthesis of endothelial nitric oxide [44], which leads to a decrease in blood flow and thus kidney damage. Confirming the above, Stephanie et al. [31] emphasized the hepatotoxic and nephrotoxic effects of indomethacin (hepatorenal) by causing an increase in caspase-3, proving that indomethacin induces apoptosis, a programmed cell death that leads to liver and kidney cell damage.

Several researchers concentrated most of their efforts to investigate the preventive effect of plant species on different human body organs, and as an example, is the turmeric species, which has an important effectiveness in liver protection [8,45], and kidney protection [46-48]. Turmeric is rich in secondary metabolites with important medical effects categorized into two essential groups: Non-volatile phenolic compounds such as curcuminoids, and volatile terpenoid compounds such as essential oils [49,50]. Essential turmeric oils enhance the bioavailability of Curcumin, which is low oral absorption [9,51]. Recent studies indicate that its other active compositions have a strong remedial effectiveness as potent as, or even superior to, Curcumin's effectiveness. It was noticed a significant preventive effect of ethanol extract of turmeric rhizomes from hepatotoxicity and nephrotoxicity effects of Indomethacin; the Histological effects are limited to low lymphatic infiltrates within portal distances and congestion in hepatic central vein while there no important renal changes except a vascular congestion, in addition to significant decrease in the averages ALT, AST, LDH, creatinine Compared with the pathological control.

This protective effect of *C. longa* extract is due to the presence of natural antioxidants within it, such as terpenes, which belong to essential oils. Hassan *et al*. [30] refer to the presence of many compounds within the ethanol extract of turmeric rhizomes, essential oils such as Tumerone, Curlone, α-Curcumene, phenolics like 2-vinylpheno-4 Methoxy, terpenes like Beta-Myrcene, 1,3,8-p-Menthatriene, Dehydrolinalool, and Tridecanoic acid as a fatty acid. Tumerone, Curlone, 2-vinylpheno-4-methoxy, 1,3,8-p-Menthatriene, Tridecanoic acid have anti-oxidative and ant-inflammatory effects [52,53]. The extract also has a supportive and regulating activity on detoxification enzymes [54], like Beta-Myrcene is considered a strong enhancer to detoxification enzymes that lead to protection from oxidative damage [55]. In addition to the presence of anti-inflammatories in the extract as Tumerone, Curlone, 2-vinylpheno-4-methoxy, 1,3,8-p-Menthatriene, and Tridecanoic acid. Results of the histological study in this research proved the effective protection for the liver and kidney from degenerative effects resulting from the drug by dosing male mice with the extract before giving the drug.

We emphasize, in light of these research results, the interpreting hypothesis of the effectiveness of turmeric rhizome extract resulting from the outcome of synergistic work of different effective substances, as it was mentioned before, and it does not relate to a certain compound. Ethanol extract of turmeric rhizomes is added to the list of extracts inhibiting ROS resulting from oxidative stress induced by indomethacin, such as strawberry extract [30], seed extract of *Plantago ovata* [20]. Both of these extracts kept the healthy tissue structure of the liver, except for noticing lymphatic leaks in the portal spaces. However, there was no noticeable renal inflammatory infiltration in the results of our research. Sarfraz *et al*. [56] emphasized the hepatoprotective and renal activity of turmeric rhizome extract, confirming and agreeing with our results.

This research proved the effectiveness of turmeric rhizome extract in protecting the hepatic and renal from degenerative effects resultant from the indomethacin by dosing male mice with the extract before giving the drug.

CONCLUSION

Research results refer to the significant protective effectiveness of the ethanol extract of turmeric rhizomes in reducing the effects of oxidative stress induced by indomethacin. This effect is due to its richness in natural anti-oxidative and anti-inflammatory secured a significant protection that reduced the significant generation of free radical effects of the drug.

AUTHORS' CONTRIBUTIONS

Hassan G. conceived the work, designed and performed the work, and wrote the paper. Nahla Ibrahim was a major contributor in writing the manuscript, reviewing & editing the paper. Akil Hajjouz reviewed and edited the paper. All author(s) read and approved the final manuscript.

CONFLICTS OF INTEREST STATEMENT

Authors indicate that no conflicts are present.

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