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Evaluation of Gastric and Hepatic Protective Effects of Kiwifruit Extract on Toxicity of Indomethacin in Swiss Albino Mice Using Histological Studies

M. Ahmad Amer[1], J. Ibrahim Eid[2], S. Ramadan Hamad[3]

[1]Professor of cell Biology, Department of Zoology, Faculty of Science, Cairo University, Egypt

[2]Lecturer of Genetics; Department of Zoology, Faculty of Science, Cairo University, Egypt

[3]Assisstant Researcher, National Organization for Drug Control and Research, Dokki – Giza, Egypt

Abstract: ***Consumption of fruits plays a special role in prevention and treatment of various diseases. Fruits have several compounds with antioxidant properties. Kiwifruit is one of the most popular fruits worldwide and is cultivated in many countries. It is a rich source of several compounds with antioxidant properties such as polyphenols, flavonoids and vitamins. The aim of this study is to evaluate the gastric- and hepatic protective effects of kiwifruit extract (KFE) against toxicity of indomethacin (Indo) in mice. 36 Swiss albino mice (25–30 g) were randomly divided into six groups. The first group served as control and was injected intraperitonieal (i.p.) with distilled water (1ml DW/ once), animals of the second group were injected with vehicle of Indo (1 ml of 4% sodium bicarbonate, once, i.p.) and served as vehicle -Indo group and those of the third group was injected with Indo (40 mg/ kg.b.w./i.p./ once). One hour before Indo injection (40 mg/ kg.b.w./i.p./ once), fourth group was injected with pantoprazole (10 mg/kg.b.w./i.p./ once), and animals of the fifth and sixth group were injected with KFE (500 mg /kg bw/i.p./once) and (750 mg /kg bw/i.p./once), respectively. Kiwi fruit extract was found to be safe up to 4000 mg/kg when kiwi fruit administrated i.p. in Swiss albino mice. Indo treatment induced histological lesions in both gastric and hepatic tissue as revealed by light microscope. Gastric sections showed ulcerated and erosion of mucosal layers with congested dilated blood vessels in submucosal layer and liver sectios showed marked vacuolated hepatocyte, congested dilated vascular channels, and dense aggregation of inflammatory cells. Pretreatment with KFE prior Indo administration resulted in marked ameliorations of the gastric and hepatic lesions induced by Indo. We can conclude that kiwi fruit extract is useful in combating tissue injury caused by indomethacin toxicity and protect gastric and hepatic tissues from toxicity of indomethacin. Further studies on both gene and DNA level are recommended.***

Keywords: NSAIDS, indomethacin, gastric, liver, histological, fruit, kiwi fruit and mice

1. Introduction

Indomethacin, an non-steroidal anti-inflammatory drug (NSAID) (methylated indole derivative), was introduced in 1963 for the treatment of inflammatory diseases as rheumatoid arthritis, degenerative joint diseases, ankylosing spondilitis, gout, and acute musculoskeletal disorders**[1 and 2]**.It is readily absorbed from the gastrointestinal tract almost completely after oral ingestion and is metabolized by the liver and converted to active metabolites. Some of these metabolites undergo entero-hepatic cycling and are eliminated through bile **[3, 4 and 5].**The clinical use of indomethacin is associated with potentially life-threatening deleterious effects as gastrointestinal ulceration, bleeding **[6 and 7],** renal toxicity **[8]**, hepatic injury **[4, 9,10],** intestinal damage, anemia and the loss of protein **[11 and,12]**. In addition to, administration of indomethacin results in serious adverse effects in cardiovascular system **[13, 14].** These injurious effects have been attributed to multiple mechanisms **[15]** including production of reactive oxygen species **[16 and 17]**, initiation of lipid peroxidation **[17]**, elevation of oxidative stress **[18]**, infiltration of inflammatory cells **[19, 20]**, and depletion of endogenous prostaglandins via inhibition of the enzyme cyclooxygenase **[21]**

The commercially available synthetic anti-ulcer-drugs like histamine H2 receptor antagonists, anti-acids and proton pump inhibitors are often expensive, have many side effects, and do not prevent ulcer recurrence **[22].** Pantoprazole as proton pump inhibitors -induced **[23]**, sub-acute cutaneous lupus Erythematous **[24]** and hepatitis **[25, 26]** in human. Hence, **in recent years, there has been growing** interest in alternative therapies and the use of natural products, especially those derived from plants **[27, 28]**.

Consumption of fruits plays a special role in prevention and treatment of various diseases such as cardiovascular diseases and gastric ulcerations and cancer **[29 and 30].**Kiwifruit (*Actinidia deliciosa*) is one of the most popular fruits worldwide and is cultivated in many countries, such as New Zealand, Italy, Japan, Greece and France **[31]**.There are many Kiwi fruit cultivars and the most known is 'Hayward' , which is known for good taste **[32]**.Kiwi fruit contains high level of vitamin C and strong antioxidant compounds such as carotenoids, lutein, phenolics, flavonoids and chlorophyll **[33 and 34]**. It is commonly reported to be also a, good, rich source of vitamin E fructose, galactose, minerals and polysaccharides **[35 and 36].** Recent studies have shown that kiwi fruit has antioxidant activity in vivo **[37 and 38]** and vitro **[39, 40, and 41]** with immune stimulatory activity **[40 and 42]**. Consumption of kiwi fruit attenuates the severity of oxidative colonic damage and lipids profile in rats **[43]** and inhibits platelet aggregation in humens **[38 and 44]**. Extracts of kiwi fruit inhibit cancer cell growth **[45]** and provided protection effect on hepatotoxicity induced both by carbon tetra chloride **[46]** and potassium bromate in rats **[47].** The current study is aimed to evaluate the protective

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effect of KFE on gastric and hepatic toxicity of Indo in Swiss albino mice, using histological examination.

2. Materials and Methods

2.1. Animals

Swiss albino mice (25–30 g) were used after 1 week for proper acclimatization to the animal house conditions (12-hour lighting cycle and 25 ± 2° C temperatures) with free access to standard rodent chow and water. The animals were obtained from animal house of National Organization for Drug Control and Research **(NODCAR)**, Egypt. The mice were deprived of food for 24 h prior to the experiment in mesh bottomed cages to minimize coprophagia but allowed free access to water except for the last hour before the experiment. All experimental procedures were conducted in accordance with the ethical standards approved by the Institutional Animal Care and Use Committee (IACUC) at Zoology Department, faculty of science, Cairo University (approval no. CUFS/S/Mol.Biol. 20/14).

2.2. Chemicals and drugs

Indomethacin was purchased in the form of white powder at 100% concentration from El-kahira Pharmacy & chemistry industry CO., Cairo- Egypt, and was dissolved with 4 % sodium bicarbonate in water **(sadayoshionodera*et al.*, 1999),** just before use to obtain the administration dose of indomethacin which is 40 mg/k.g. bw., according to **[49]** . Pantazole was obtained in the form of 40 mg vial lyophilized powder (40mg pantaprazole) from Sigma-Tec pharmaceutical CO., Giza, Egypt, and was dissolved with suspended in sterile deionized water just before use to obtain the administration dose, which is 10 mg/k.g. bodyweight according to **[50]**. All other chemicals were of analytical grade and were obtained from commercial sources. All drugs and reagents were prepared immediately before use.

2.3. Preparation of aqueous kiwifruit extract

For this study, we selected Hayward green kiwi-fruits (*Actinidia deliciosa*), the most common commercially available breed of kiwi. Fresh Kiwifruit was purchased from the local market in Cairo, Egypt. The plant material was identified in the Department of tropical fruits research, Cairo University, Egypt. The KFE was prepared according to the method described by **[37 and 40]** but with some modification. The flesh was weighed, cut into appropriate sizes, and mixed using a mixer for two min. The resulting homogenate was centrifuged at 3000 rpm for 10 min, and then the resulting supernatant was filtered using Whatman No. one filter paper. Then, the resulting extract was left to dry at 40°C in hot air oven for evaporation of water. The extract yield was 0.104 g dry weight per 1 g fresh kiwifruit/ 1ml. The crude extract was kept at -80°C and re-dissolved in distilled water before used for the subsequent assays.

2.4. Acute Toxicity Studies

The acute toxic study was used to determine a safe dose for kiwi fruit extract. Experimental animals were injected i.p. with a single dose of kiwifruit extract at different dose levels (5000 mg/kg body weight; 4000 mg/kg; 3000mg/kg; 2000 mg/kg; and1000 mg/kg), (5 mice in each dose) and observed for mortality, body weight effects, and the clinical signs for 72 h after the administration **[51].** The safe dose was found to be ≤ 4000 mg/kg body weight. For the study two doses were selected, 750 mg /kg body weight (TP: 16.9 mg/kg bw andTF: 0.175 mg/kg. bw) and 500 mg/kg body weight (TP: 11.26mg/kg. bw and TF:0.117mg/kg.bw).

2.5. Determination of Total Phenolic Compounds:

Total phenolic compounds were determined spectrophotometrically using a modified Folin-Ciocalteu method **[52]**. The standard gallic acid solutions were prepared with different concentrations (ranged between 0.025mg/ml to 0.4 mg/ml of distilled water) whereas the plant extract was prepared in 4 to 50 mg/ml distilled water. Briefly, 1 ml of aliquot of the extract or standard was mixed with 5ml of Folin-Ciocalteau reagent (previously diluted ten-fold with distilled water). Then, 4 ml of 0.7M sodium bicarbonate solution was added and the samples were allowed to stand at room temperature for 2 hrs, before measuring the absorbance at 725 nm. The data was calculated as mg of gallic acid equivalents (GAE) from the calibration curve of gallic acid standard and expressed as mg GAE/g dry weight (DW) of the plant material.

2.6. Determination of Total Flavonoid Compounds:

The total flavonoid content of the plant extracts was determined by using a procedure described by **[53],** with some modifications. An aliquot (1ml) of extracts (prepared from 4 to 50 mg/ml distilled water) or standard solutions of quercetin (0.01-0.1 mg/ml) was mixed with 5ml 2% aluminum chloride (w/v). The content was incubated for 30 min at room temperature and absorbance was measured at 415 nm. The total flavonoid content was expressed as mg quercetin equivalents (QE).

2.7. Experimental design

Pantoprazole, a proton pump inhibitor, at a dose of 10 mg/kg of body weight used as positive control for comparison. The mice were randomly divided into six groups, each group consisting of six animals as following: 1st group (Negative control group): animals in this group were injected i.p. with distilled water (1ml D.W. / once); 2nd group (Vehicle-Indo group): each animal in this group was injected i.p. with vehicle of indomethacin (1ml 4% sodium bicarbonate /once); 3rd group (Indo-group): animals were injected i.p. with single dose of indomethacin (40 mg/ kg.b.wt.) and 4th group (Positive control group): each animal in this group was injected i.p. with pantoprazole (10mg/kg.bw) one hour before indomethacin administration (40 mg/ kg.b.wt.) .5th (500KFE +Indo group) and 6th group (750KFE+Indo group): animals in this group were injected i.p. with KFE at 500 mg /kg, *i.p.*/ once, and 750 mg /kg, *i.p.*/ once, respectively, one hour before indomethacin administration (40 mg/ kg.b.wt.). The animals were sacrificed 24 hr after indomethacin administration and liver and stomach tissues of all mice were then sampled for histological examination.

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2.8 Histological Examination

For histology examination, stomach and liver of all animals groups were collected and fixed in neutral buffered of formalin. After 24 hours, the specimens were washed, dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin wax. Five micron thick paraffin sections were prepared, mounted on clean slides , stained with Ehrlich's haematoxylin-eosin **[54]**and examined under an Olympus microscope (BX41, Hamburg, Germany).

3. Results and Observations

3.1. Total phenolic and flavonoid contents of kiwi fruit extract:

Total phenolic content were expressed as milligrams of gallic acid equivalents per gram of dry weight of extract of plant (DW) (mg GAE/g DW) in extract, While, the flavonoid contents was expressed as milligrams of quercetin equivalents per gram of dry weight of extract of plant (DW) (mg QE /g DW) in extract. Kiwi fruit extract had 2251mg/ 100 gram DW total phenolic content and 23.403 mg/100gram DW of total flavonoid contents.

3.2. Histological examination of gastric tissues

Figure (1and 2) showed that histological examination of stomach sections from Swiss albino mice in control group and vehicle-Indo group revealed normal histological structure of the gastric mucosa and sub-mucosal layers. **On other hand,** histological examination of stomach sections from animals treated with Indo alone showed large area of ulceration and erosion in mucosa with dense aggregation of inflammatory cell in base of mucosal layers **(fig. 3a)**. Disruption and degeneration in cells were observed in other areas of mucosa layer associated with scattered dilated congested blood vessels and mild aggregation of inflammatory cells together with edema in submucosal layer compared to negative control group **(fig. 3b).** Section of stomach from mice pretreated with pantoprazole in positive group revealed normal appearance of gastric mucosa and sub-mucosal layers with mild inflammatory cell infiltration in the base of mucosa layer compared to Indo group (fig 4).

Histological examination of stomach section in mice pretreated with KFE revealed amelioration in gastric lesions according to dose of treatment and compared to Indo group. Group pretreated with 500 mg/kg bw KFE revealed marked appearance of gastric mucosa and sub-mucosal with moderate aggregation of inflammatory cell infiltration in infiltration in large area of base of mucosa layer (fig 5a) compared to Indo group. However, some areas still showed mild erosion in mucosa layers (fig 5b). Animals pretreated with 750 mg/kg bw KFE showed no histological alterations in mucosa and sub-mucosal compared to control group and positive group (fig 6).

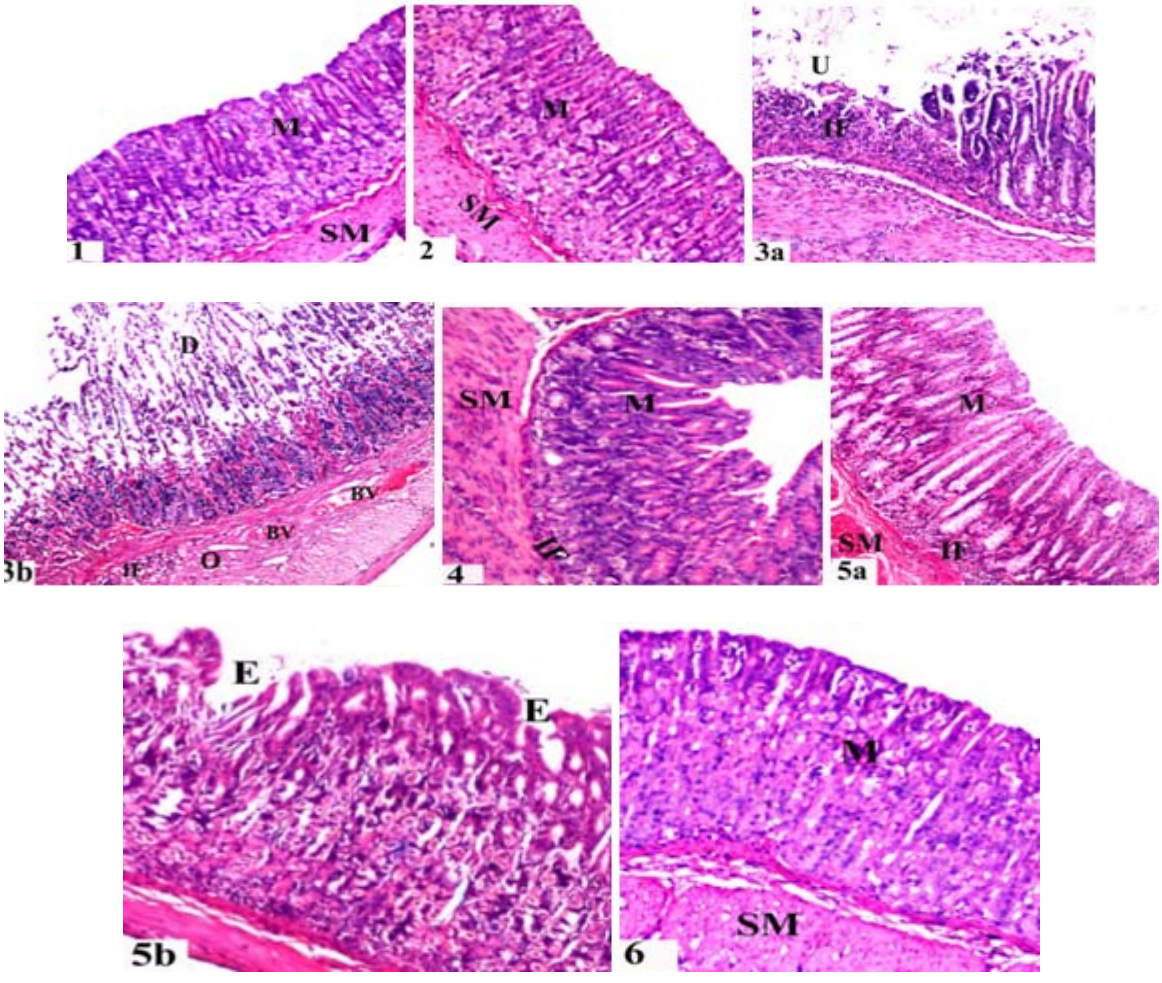

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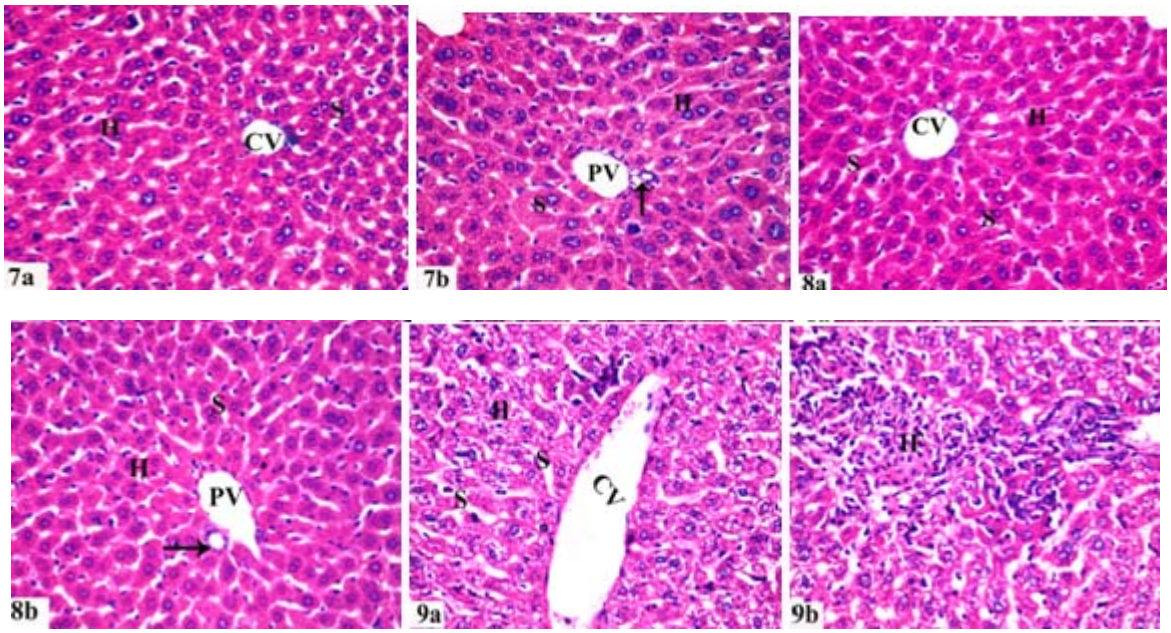
Figure 1 & 2: A photomicrograph of stomach sections from control and vehicle -Indo group showing normal histological structure of the gastric mucosa (M) and sub-mucosal layers (SM) **(H & E. X 200)**. **Figure 3**: A photomicrograph of stomach sections taken from mice treated with Indo: (a) showing large area of ulceration and erosion in mucosa layer (U) with dense aggregation of inflammatory cell in base of mucosal layers (IF); **(b):** showing disruption and degeneration in cells of mucosa layers (D) associated with dilated congested blood vessels (BV) and mild aggregation of inflammatory cells (IF) together with edema (O) in submucosal layer. **Figure 4:** A photomicrograph of stomach sections taken from mice pretreated with pantoprazole prior Indo showing normal appearance of gastric mucosa (M) and sub-mucosal layers (SM) with mild inflammatory cell infiltration in the base of mucosa layer (IF). (H & E. X 200). **Figure 5**: A photomicrograph of stomach sections taken from mice pretreated with 500 mg / kg KFE prior Indo showing marked appearance of gastric mucosa (M) and sub-mucosal (SM) with moderate aggregation of inflammatory cell infiltration in large area of base of mucosa layer (IF)**. (H & E. X 200) ;(b):** showing scattered focally areas of mild erosion in mucosal layers (E). **(H & E. X 200). Figure 6:** A photomicrograph of stomach sections taken from mice pretreated with pantoprazole prior Indo showing no histological alterations in mucosa (M) and sub-mucosal layers (SM)**. (H & E. X 200)**

3.3. Histological examination of hepatic tissues

The histological examination of the liver sections from control groups showed normal hepatic architecture. The normal liver consists of a number of hepatic lobules. Each hepatic lobule built up of cords of hepatic cells radiating from the central vein to periphery of the lobule. The cell cords are separated by narrow blood sinusoids lined by Kupffer cells and endothelial cells. The hepatic cells (hepatocytes) are polygonal in shape with acidophilic cytoplasm and darkly stained nuclei. Each cell has one or two vesicular round nuclei with fine chromatin network. At the angles of the lobules, the portal canals are found (portal vein, bile duct) (fig 7 a and b). Liver sections from Swiss albino mice treated with vehicle - Indo revealed normal appearing of hepatocyte, central vein, sinusoid, portal vein and bile duct (fig 8 a and b).

Histological examination of liver tissues in Swiss albino mice treated with Indo alone revealed marked hepatic alteration as marked vacuolated hepatocyte, marked dilated central vein and mild dilated sinusoid compared to control group (fig. 9a,). Dense aggregation of inflammatory cells infiltrations in hepatic tissues were noticed more prominent compared to control group (fig.9b). In other areas, an-nucleated hepatocyte associated with marked dilated congested portal vein and moderate dilated bile ducts were seen (fig.9c). Hemorrhage and scattered mild aggregation of inflammatory cells infiltration in hepatic tissues compared to control group were observed (fig.9d,).Also, , histological examination of Liver sections from animals pretreated with pantoprazole prior Indo showed severe histological hepatic lesions , as severe cytoplasmic vacuolization of hepatocyte, and dilated, congested central vein (fig. 10a). Severe dilated, congested portal vein and moderate dilated bile duct with dense inflammatory cells infiltration in the portal area were noticed prominent (fig. 10b). In some areas, shrinking hepatocyte with dens aggregations of inflammatory cells in hepatic tissue and around central vein were also seen Other areas, showed, shrinking of hepatocyte, dilated sinusoids infiltrated with inflammatory cells together with (fig. 10e). On the other hand, pretreatment with KFE prior Indo ameliorated the hepatic histological lesions induced by Indo alone accordance to dose. Sections of the liver from animals pretreated with 500mg /kg bw kiwifruit extract revealed normal appearance of hepatocyte, central vein and sinusoid (fig. 11a). However still some marked congested portal vein and mild dilated bile duct with focally aggregation of inflammatory cells in hepatic tissue were noticed (fig. 11b). liver sections of animals pretreated with kiwifruit extract at 750mg /kg bw showed normal histology of hepatocyte, central vein, (fig. 12 a) and portal vein and bile duct. Rarely mild inflammatory cells infiltration in sinusoid was seen (fig. 12 b).



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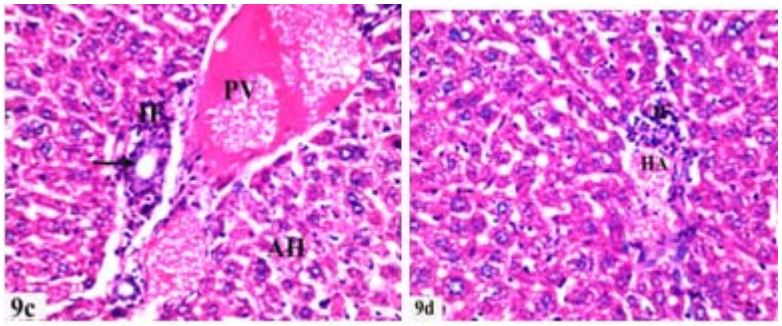

Figure 7a & 7b: A photomicrograph of liver sections from control and vehicle -Indo group showing normal hepatic architectures with normal appearance of hepatocyte (H) radiated from vascular channels (central vein (CV) and portal vein (PV)) to gather with normal sinusoid (S) and bile duct(arrow). **(H & E. X 400). Figure 8a&b:** A photomicrograph of liver sections from control and vehicle - Indo group showing normal hepatic histology in form of normal hepatocyte (H) radiated from vascular channels (central vein (CV) and portal vein (PV)) to gather with normal sinusoid (S) and bile duct(arrow). **(H & E. X 400). Figure 9:** A photomicrograph of liver sections taken from mice treated with Indo: (a): showing marked vacuolated hepatocyte (H), marked dilated central vein (CV) and mild dilated sinusoids (S)**.; (b) :** showing dense aggregation of inflammatory cells infiltration (IF) in hepatic tissues (H & E. X 400). **(c) :** showing some annucleated hepatocyte (AH) together with marked dilated congested portal vein (PV). Mild inflammatory cells infiltration (IF) in the portal area was also seen. (H & E. X 400). **(d) :** showing hemorrhage (HA) and mild aggregation of inflammatory cells (IF) in hepatic tissues..(H & E. X 400).

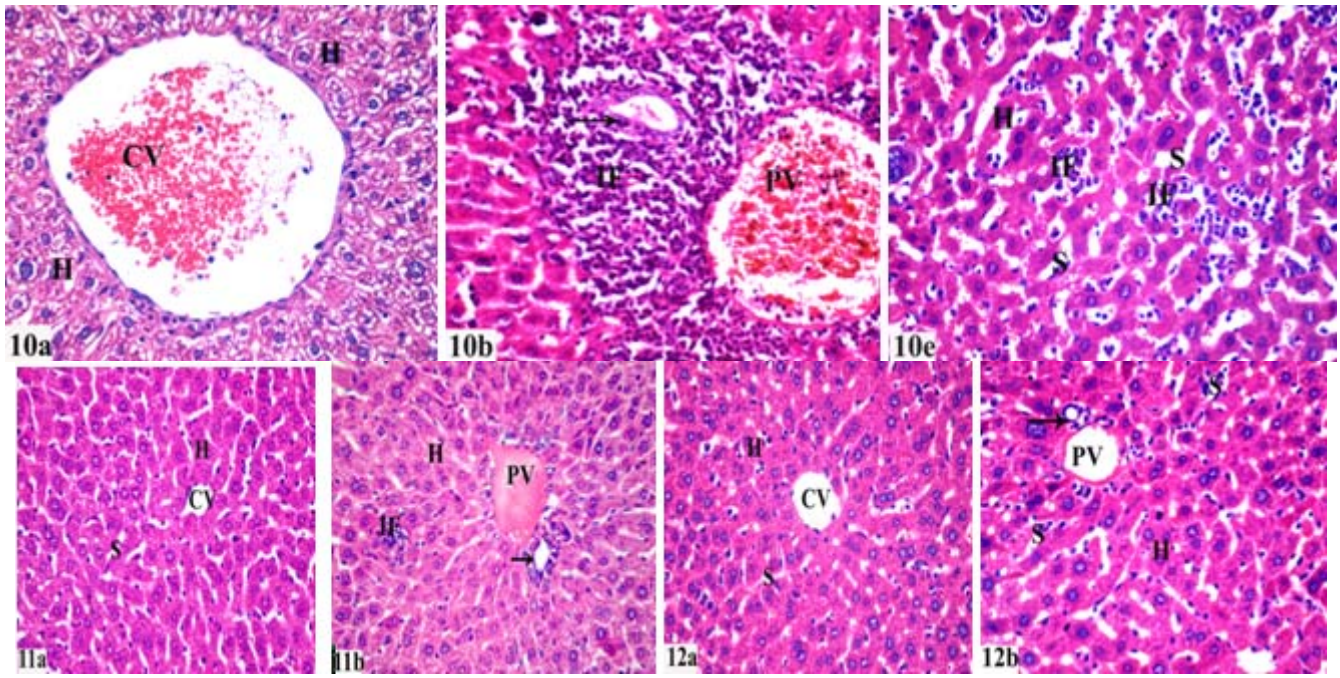

Figure 10: A photomicrograph of liver sections taken from mice pretreated with pantoprazole prior Indo : (a) showing sever vacuolated hepatocyte (H) and severe dilated, congested central vein (CV). **(b) :** showing severe dilated, congested portal vein (PV) with moderate dilated bile duct (arrow) with dense inflammatory cells infiltration (IF) in the portal area **(e):** showing dilated sinusoid (S) infiltrated with mild aggregation of inflammatory cells (IF). **(H & E. X 400). Figure 11:** A photomicrograph of liver sections taken from mice pretreated with 500 mg KFE prior Indo: (a): showing normal hepatic structures; hepatocyte (H), central vein (CV) and sinusoid (S). **(b):** showing marked congested portal vein (PV), mild dilated bile duct (arrow) with mild aggregation of inflammatory cells (IF) in hepatic tissue. **(H & E. X 400). Figure 12:** A photomicrograph of liver sections taken from mice pretreated with 750 mg KFE prior Indo : (a): showing normal hepatocyte, central vein and sinusoid. **(b) :** showing normal portal vein (PV) and bile duct (arrow). Mild inflammatory cells infiltration in sinusoid was occasionally seen **(H & E. X 400).**

4. Discussion

Our study, evaluated the gastric and hepatic protective effect of KFE on toxicity of indomethacin in mice using histological examination. The choice of the indomethacin model for use in the present study was based on the fact that non-steroidal anti-inflammatory drugs are widely used worldwide [**55]** because they exert excellent efficacy in the management of pain, fever and inflammation [21 and 56] but

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use of NSAIDs were accompanied with serious adverse effects not only in upper gastrointestinal tract but in the small intestine , cardiovascular system **[57]** and liver [**58 and 59].** Recently, administration of indomethacin induced inhibition of DNA synthesis, and development oxidative stress in vivo **[60]**. Our study also, showed that administration of indomethacin at 40 mg / kg bw., once induced histological lesions in mucosal and submucosal as revealed by histological examinations compared to control group. These was in agreement with other previously studies **[7, 19, 49, 60, 61, 62, 63, 64 and 65].** The mechanisms of gastric toxicity of indomethacin is widely believed to inhibited production of prostaglandins and their therapeutic actions through inhibition of cyclooxygenase (COX) enzymes [63, 64 and 66) and activation of inflammatory cells **[65 and 67].** Suppression of prostaglandin synthesis is associated with reduction of gastric mucosal blood flow, disturbance of microcirculation, decrease in mucus secretion, lipid peroxidation and neutrophil activation, which are involved in the pathogenesis of gastrointestinal mucosal disorders **[68]**. Further, it was also reported that indomethacin induce gastric damage through apoptosis of gastric mucosa cells **[69],** depletion of nitric oxide [61 and 65], and gastric mucosal blood flow **[70].**It is known that nitric oxide modulate acid levels, and plays a role in stimulating mucus secretion and improves blood flow in gastric tissues which is believed to constitute one of the primary levels of mucosal defense **[71].**

There is a growing interest and needs to find non-toxic, safe, and inexpensive natural antioxidants especially those derived from plants. Natural antioxidants are usually considered safe by most consumers **[72].** Consumption of fruits plays a special role in prevention and treatment of various diseases [29, 30 and **73]**.Kiwifruit is rich in bioactive compounds especially in polyphenols **[74] ,** many flavonoids , vitamins (vitamin A, C, folate, B2, and vitamin E) and minerals (potassium, phosphorus, magnesium, calcium, and copper) [75,76 and 77]. In particular, they contain a high amount of vitamin C (more than oranges), as much potassium as bananas and a good amount of beta-carotene [77]**.** It has stronger anti-oxidative effects than other fruits **[40].** The body absorbs the antioxidants found in kiwi fruit more effectively than other antioxidant-rich fruits **[**36 and **39].**

Our results revealed that pretreatment with KFE prior Indo ameliorated gastric lesions induced by indomethacin in dose dependent manners, that was evident by normal appearing of mucosal and submucosal layers. Pantoprazole, strong proton pump inhibitors, also ameliorated histological lesions induced by Indo. For this reason we used pantoprazole as appositive control group in this study and compared the effectiveness of KFE with pantoprazole. 500 mg/kg KFE was less effective than pantoprazole in improving gastric lesions and 750 mg/kg of KFE was more effective than pantoprazole.

The gastric ulcer-healing property of KFE in current study could be attributed to its antioxidant , anti-inflammatory properties and ability to scavenge free radicals as recorded by [**78, 79, 80 and 81].**

Kiwifruit contains higher source of potentially antioxidant polyphenol content than in other fruits [82]**.** It also contains isoflavones and flavonoids which have an important function as anti-carcinogenic, neuro-protective and cardio-protective activity [83]. **Total phenolic, flavonoid contents**, reducing power, **radical-scavenging activity** of kiwi fruit extract increased with the increase of its concentration **[41]**.The potential antioxidant property of kiwi fruit is most often attributed to their potential to remove free radicals through their phenolics which can donate electrons to H2O2, thus neutralizing it to water [84], while their potential anti-inflammatory property attributed to inhibition of inducible nitric oxide synthase,expressions of cyclooxygenase 2 enzyme **[78 and 79]**, and increasing the mucosal prostaglandin content through their flavonoid content. **[85].** Prostaglandins have cytoprotective effects on gastric mucosa. **[86]**. Consumption of kiwi fruit ameliorated histology change of colon induced chemically and attenuates the severity of oxidative colonic damage and lipids profile and elevation antioxidant enzymes levels in rats [43].Observed anti-ulcerated activity of pantaprazole could be attributed to suppre gastric acid secretion effectively, by irreversible inhibition of H+/K+-ATPase, which is responsible for gastric acid secretion in parietal cells of the stomach**.** It also induces the expression of heme oxygenase-1 (HO-1) by activated Nrf2 through inactivation of Keap1 [**50 and87]**

Our study also revealed that treatment with Indo resulted in obvious changes in hepatic tissues as marked vacuolated hepatocyte, dilated congested vascular channels, these were confirmed with the previous workers **[59, 88 and 89].** Observed hepatotoxicity of indomethacin, could be attributed to active metabolites of indomethacin **[5]** and activation of inflammatory cells **[20]** with increased synthesis of fibrinogen **[90]** through stimulatory action of interleukins TNF-α, IL-1 and IL-6, released by the inflammatory process and fibrinogen degradation products (FDP) **[91].** The FDP cause metabolic changes in the liver **[92].**Indomethacin is metabolized by the liver to active metabolites **[5],** which undergoes enterohepatic circulation with repeated conjugation in the liver then excretes in bile as conjugates **[93]**. Protective action of the bile component, phosphatidylcholine (PC) was reduced by indomethacin. Biliary PC plays an important physiological role in protecting hepatic tissue from the cytotoxic actions of bile salts **[94].**Another mechanism for hepatotoxicity of indomethacin is elevation of free radical / reactive oxygen species and oxidative stress with initiation of lipid peroxidation [7, **9, 16, 18 and 64, 65,** 95]**.** Oxidative stress and production of free radicals such as reactive oxygen species (ROS) have been implicated in the pathophysiology of various disease including; heart failure [96]**,** hepatic injury [97]**,** and chronic renal failure [98]**.**

On another hand, pretreatment with KFE abated the hepatic lesions produced by Indo as evidenced by normal hepatic hepatocyte, and vascular channels according to dose compared to control and positive groups**.** These results were in agreement with the findings of [**46 and 47].** The amelioration effects of KFE on hepatic toxicity of indomethacin may be attributed to the combination of several different mechanisms included: antioxidant activity**;**

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anti- inflammatory properties, and direct scavenge of free radicals **with reduction oxidative stress and lipid peroxidation [**36, **41, 43, 46 and 99]**. It also inhibited lipid peroxidation by metal chelating activity [41 and 100].

Micronutrients such as vitamins C and E, as well as carotenoid and phenolic compounds of kiwi fruit are able to scavenge free radicals and can delay or inhibit the oxidation of both lipids and other molecules by suppressing the initiation/ propagation steps of oxidative chain reactions [99]. Vitamin C and E are protect body from free radicals, dramatically improving the health of individuals [36]**.** Administration of kiwi fruit juice to mice induced increasing in cytokine production and marked inhibition in urinary oxidative stress markers and exerting antioxidant effects dose dependent **[37].** Abundant vitamins, polyphenols, and lipophilic constituents in kiwi fruits are also used for the treatment of many different types of cancers like stomach, lung and liver cancer **[39and 101]** and lowering the formation of atherosclerotic lesions **[80]**.

However, pretreatment with pantoprazole as positive group induced hepatic injury which was in agreement with [25, 26 and 102] **.**This is evidence by severe vacuolated hepatocyte marked dilated congested vascular channels, and dense aggregation of inflammatory cells and may be attributed to inhibit or induce of cytochrome P450 [103 and 104] ,drug-drug interaction [105 and 106]. It also induced idiosyncratic hepatocellular damage [26] and systematically compromised immunity as a result of inhibition of the lysosome enzymes [107]. Cytochrome P450 (CYP450) enzymes are necessary for the detoxification of foreign chemicals and the metabolism of drugs [108 and109]. The hepatic CYPs are also involved in the pathogenesis of several liver diseases. Enhanced Cytochrome P450 enzymes activity increased lipid peroxidation [110] ; oxidative stress and inflammation in lung and liver [111], while a CYP450 inhibitor is combined with a poor metabolizer of drug [112].In conclusions, kiwifruit extract decreased; in the present work pathological lesions in the gastric and hepatic tissue as manifested by the light microscopic examination.

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