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## ABSTRACT

Diclofenac (DIC) (Voltaren) belongs to the non-steroidal anti-inflammatory drug family. It is one of the compounds derived from phenylacetic acid; liver toxicity is one of the main concerns for this drug. The present study investigated the effect of ethanolic extract of *ficus sycomorus* leaves and fruits against diclofenac-induced oxidative stress and hepatotoxicity in rats. Forty-two male albino rats weighing (150±10 g) were divided into seven equal groups. The first group (6 rats) was fed on a basal diet and served as a negative control. The second group (36 rats) received a single intraperitoneal dose of DIC (150 mg/kg b.w.) at the end of the experimental period. It was divided into six subgroups: Group 1 was fed on a basal diet only and served as a positive control (+v), Group 2 was fed on a basal diet, and silymarin (100 mg/kg b.w., orally). Groups (3&4) were orally fed on a basal diet and ethanolic extract of sycamore fruits (200 and 400 mg/kg b.w.) for 28 days, respectively. Groups (5&6) were fed on a basal diet and sycamore leaves ethanolic extract orally (200 and 400 mg/kg b.w.), respectively. Biological data were calculated at the end of the experiment, and blood samples were taken for biochemical analysis. In addition, liver tissues were analyzed for antioxidant markers, malondialdehyde (MDA), and histological examination was also examined. The results revealed that the diclofenac group caused an increase in liver weight, serum liver enzymes, liver MDA and NO, and a decrease in serum liver $GP_X$, SOD, and CAT. All treated groups with fruits and leaves extracts showed improvement in all previous parameters compared with the (+ve) control group. In conclusion, consuming the ethanolic extract of *ficus sycomorus* leaves and fruits can lower the side effects of the diclofenac toxicant**.**

**Keywords:** diclofenac, *ficus sycomorus*, silymarin, hepatotoxicity

## INTRODUCTION

The liver helps detoxify drugs, exogenous toxins, and therapeutic agents; it also helps with the bio-regulation of amino acids, proteins, carbohydrates, fats, blood coagulation, and immunomodulation **(Juza and Pauli, 2014)**.

Drug-induced liver toxicity is one of the main worries for the pharmaceutical industry and physicians **(Labbe *et al.*, 2008)** Non-steroidal anti-inflammatory drugs have anti-inflammatory and analgesic

properties that are widely prescribed, and some of them cause liver toxicity **(Boelsterli, 2013).**

Diclofenac (DIC) belongs to the Non-steroidal anti-inflammatory drug family, one of the compounds derived from phenylacetic acid. Still, liver toxicity is one of the main concerns for this drug. The mechanism of liver toxicity induced by DIC has been partly associated with mitochondrial damage **(Adeyemi and Olayaki, 2018)**, disruption of the antioxidant defense system, changes in the integrity of covalent protein by reactive metabolites **(Galati *et al.*,2002)**, and the mechanisms mediated by the immune system **(Lim *et al.*, 2006)**.

Reports from previous studies have demonstrated that DIC metabolites (40, 5- hydroxy diclofenac) are capable of causing neutrophil infiltration in hepatic cells and hepatocyte necrosis. These effects were associated with forming of reactive oxygen species (ROS) **(Alabi *et al.*, 2017)**. **Shehata *et al.*, (2020)** found that marjoram oil and propolis effectively improved oxidative stress and reduced inflammation and damage induced by Diclofenac sodium in rats. **Esmaeilzadeh *et al.*, (2020)** demonstrated that the liver levels of the GSH, GPx, SOD, and CAT significantly reduced and the levels of the serum protein carbonyl, AST, ALP, ALT, total bilirubin, MDA, serum IL-1b, and the liver IL-1b gene expression were remarkably increased in DIC group compared to control group.

Many hepatoprotective herbal preparations have been recommended in alternative medicine for treating liver diseases. Medicinal herbs protect the body from hazardous chemical substances by restoring the antioxidant status and inhibiting oxidative stress via ROS scavenging **(Iwu *et al.*, 1990).**

Silymarin is a flavonoid complex derivate from the seeds of *Silybum marianum*. Silymarin creates a hepatoprotective effect because of its radical scavenger effects (**Wellington and Jarvis 2001).** Because silymarin is an antioxidant, it stabilizes cell membranes, regulates the intracellular content of reduced glutathione, and chelates metal ions (iron and copper) **(Borsari *et al.*, 2001; Taleb *et al.*, 2018).** Silymarin has been used worldwide for many years as a complementary alternative medicine because of the beneficial effects associated with treating hepatic diseases (**Abenavoli *et al.*, 2010). Heidarian and Nouri, (2019)** who confirmed that silymarin has a protective effect on DIC-induced liver toxicity and oxidative stress in male rats.

*Ficus sycomorus*, also called sycamore fig or the fig Mulbern belongs to the mulberry family, *Moraceae*, consisting of about four genera and over one thousand four hundred species of trees **(Zerega *et al.*, 2005)**. The plant is indigenous to Africa and grows South of the Sahel and North of the tropic of Capricorn **(Dale, 2007)**. *F. sycomorus* stem

bark has been reported to have an effect against tuberculosis, and this plant's sedation and anti-convulsion properties have also been reported **(Sandabe *et al.*, 2003)**.

The plant extracts of *F. sycomorus* were screened for their phytochemical composition. Alkaloids, flavonoids, saponins, tannins, oxalates, and hydrogen cyanide were detected in all the samples (leaves, stems, roots, seeds, and fruits) with significantly high vitamin C in the fruit extract. Flavonoids are most predominant in the leaves, alkaloids in the stems, and saponins and tannins in the roots. Also, flavonoids have been reported to possess antioxidant, antimicrobial, anticancer, anti-allergic, and anti-inflammatory activity **(Prochazkova, 2011).**

**Refaat et al., (2020)** found that the rats fed with mixture fig and sycamore as powder improving the kidney functions, liver functions and lipid profile. **Sayyad *et al.*, (2015)** concluded that wood and leaf extracts possess significant hepatoprotective activity against Nitroso diethylamine and $CCl_4$-induced hepatic-carcinogenesis in rats. **Ojo *et al.*, (2017)** found that the *F. asperifolia* (Miq) leaf extract had a hepatoprotective effect against carbon tetrachloride-induced hepatic damage in male Wistar rats. So, the present study investigated the protective effect of Sycamore fruits, and its leaves extract against diclofenac-induced liver toxicity in male rats.

## MATERIALS AND METHODS

### Materials

1 - sycamore (*Ficus sycamorus*) fruits and leaves were obtained from Nawag farm in Tanta, Egypt. The plant was identified by Agricultural Research Center.

2 - Corn oil and starch were purchased from the local market. Casein, cellulose, vitamins, minerals, dextrin, L-cysteine, and choline chloride were obtained from the Cairo Company for Chemical Trading, Cairo, Egypt.

3 - Voltaren (Diclofenac sodium) was purchased from Novartis Pharma Co, Egypt.

4-Silymarin was purchased from Sigma Chemical Co., St. Louis, USA.

5– Forty-two male albino rats (*Sprague Dawley* strain) were obtained from the Laboratory Animal Colony, Helwan, Cairo – Egypt, weighing approximately 150± 10g.

6- Kits were purchased from Egyptian American Company for Laboratory Service and Supplied by Alkan Company.

### Methods

### Plant material and preparation

sycamore fruits and leaves were washed thoroughly under running tap water and dried in an oven at 45°C for 12 hours. The dried samples were

milled using an electric stainless still mill (Braun, Model 537, Germany) to give a homogenous sample and kept in polyethylene bags at -20°C until use. The air-dried powdered leaves (1.0 kg) and fresh fruit (1.5 kg) of F. sycomorus (FS) were separately extracted with 70% ethanol by maceration at room temperature. Each extract was concentrated using a rotary evaporator at 40°C obtain crude extract weights of 60 g and 50 g, respectively**(Alqasoumi, 2012)**.

**Experimental design**

Forty-two adult male albino rats *Sprague Dawley* strain weighting (150± 10g) were housed in well-aerated cages under a hygienic condition and fed on a basal diet according to **Reeves *et al*., (1993)** for one week for adaptation. After this week, the rats were divided into two main groups: The first group (6 rats) was fed on a basal diet as a negative control group. The second main group received a single intraperitoneal dose of DIC (150 mg/kg b.w.) at the end of the experimental period according to **Alaaeldin, (2007)** and divided into six subgroups as follows: Group 1 was fed on basal diet only (and serve as positive control). Group 2 was fed orally on a basal diet and silymarin at (100 mg/kg b.w.). Groups (3 &4) were fed on basal diet and ethanolic extract of ethanolic extract sycamore fruits 200 and 400 mg/kg b.w.) orally for 28 days, according to **El-Sayyad *et al*.,(2015).** Groups (5&6) were fed on a basal diet, and sycamore leaves ethanolic extract orally at (200 and 400 mg/kg b.w.) according to **Sakpa and Wilson, (2019).** for 28 days, respectively. At the end of the experiment (28) days, the animals fasted overnight before sacrifice. Blood samples were taken in dry centrifuge tubes from the hepatic portal vein. Serum was separated at 4000 runs per minute "RPM" for 10 minutes and kept in plastic vials at -20 until analysis. The liver was removed, cleaned in saline solution, and dried with filter paper at 4 C°. The first liver sample was kept in formalin saline 10% for histopathological examination. The second sample was kept at -20°C to prepare tissue homogenate to determine antioxidant parameters. The homogenate was centrifuged at 10,000 rpm for 20 min. The supernatant was used for the assay of some laboratory analyses.

**Nutritional and Biological parameters**

At the end of the experiment, feed intake, weight gain, liver weight to body weight, and feed efficiency ratio were calculated according to **Chapman *et al*., (1959).**

**Biochemical analysis of serum**

Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were determined according to **Bergmeyer *et al*., (1986)**, and Alkaline phosphatase (ALP) was performed according to the method of **Roy, (1970)**. γ glutamyl transferase (GGT) was determined according to

**Shaw *et al.*, (1983).** Serum total bilirubin and direct bilirubin were estimated by **Walters, and Gerard, (1970).** Total protein was determined according to **Sonnenwirth and Jaret, (1980)**. Albumin was estimated according to **Drupt, (1974)**, and serum globulin was calculated according to **Chary and Sharma, (2004)**.

**Assessment of Oxidant/Antioxidant Activity in liver tissue**

Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and nitric oxide (No) were determined according to the methods of **(Ohkawa *et al.*, 1979**; **Nishikimi *et al.*, 1972**; **Aebi, 1984** and **Montgomery and Dymock, 1961)**.

**Histopathological examination**

The liver of each sacrificed rat was removed and fixed in a 10% neutral buffering formaldehyde solution at a pH of 7.5, then cleaned in xylol before being fixed in paraffin. For histological analysis, a 4-5 µm thick piece was cut and spotted with Hematoxylin and Eosin (H&E) (**Bancroft and Gamble, 2008).**

**Statistical analysis**

All the obtained data were statistically analyzed by SPSS computer software. The calculation used analysis of variance ANOVA and follow-up test LSD by SPSS ver.11 according to **Armitage and Berry (1987)**.

**RESULTS AND DISCUSSION**

**-Biological evaluation**

Results of feed intake (FI), body weight gain (BWG) %, feed efficiency ratio (FER), and liver weight % are shown in (Table 1). There are significant decreases in these parameters in positive control compared to normal control. On the other hand, there were significant increases in the other groups when compared with the positive control. The best results were recorded for high doses of sycamore leaf extracts (400 mg). Liver weight values significantly increased in the positive control group compared to the negative control group. All treated groups showed a significant decrease ($p<0.05$) compared to the positive control group. The best result is recorded by the silymarin group and leaves 400 (which is the nearest value to the (-ve) group. These results agree with **Gupta *et al* (2021),** who reported that daily administration of DIC for 21 continuous days led to an 18.5 % decrease in body weight**.** Significant rise (4.3 %) in relative liver weight, signifying the adverse effect of DIC intoxication in rats. It has been reported that DIC causes gastric ulceration, which makes it difficult for the animals to have food, resulting in malnutrition. **Alabi *et al.*, (2020)** found that diclofenac treatment significantly decreased the body weight of rats.

The decrease in the body weight of rats treated with DIC alone could be correlated with the incidence of diarrhea in the treated rats. **Guo**

***et al.*, (2016)** showed that taking silymarin reduces total body weight while not affecting lean body weight when eating fat-rich food. **Dawod *et al* ., (2022)** stated that *F. sycomorus*-treated group showed a non-significant increase in the covariate final body weight, body gain, and feed intake, as well as a significant decrease in the feed conversion rate compared with the positive control group. This could be attributed to the positive effect of F. sycomorus extract in reducing oocyst shedding, anti-oxidant, and anti-inflammatory effects. The non-significant decrease in body weight in the extract-treated rabbits could be due to the anti-nutritional effect of the *F. sycomorus* tannins, as the *F. sycomorus* stem bark is rich in condensed tannins (procyanidin type). These tannins could bind to the intake proteins and change their physicochemical nature. In addition, it has an astringent nature that may adversely affect food palatability, food intake, and growth performance **(Konai *et al.*, 2017). Krishna *et al., (*2007)** reported that, a possible mechanism of leaf extract of *F. carica Linn*. on rats with liver damage might be due to its anti-oxidant effect or inhibition of cytochrome

P450s. Flavonoids, coumarins, tannins, steroids/triterpenoids, and their glycosides have been reported as constituents of this genus. **El-Sayed *et al.*, (2010)** mentioned that these constituents are free radical scavengers and have hepatoprotective activity; it may be speculated that these constituents of *F. sycomorus L*. are responsible for the observed protective effects. Plants with flavonoids impact arachidonic acid metabolism and are thought to have anti-inflammatory effects, subsequently enhancing liver weight **(Qureshi *et al.*, 2019)**.

**Table1: The protective effect of ethanolic extract of ficus sycomorus fruits and leaves on changes in feed intake, body weight gain %, feed efficiency ratio, and liver weight % for rats with hepatotoxicity induced by diclofenac**

| Parameters / Groups | FI (g/28 day) | FER | BWG (%) | liver weight (%) |
|---|---|---|---|---|
| (-Ve) Control | 623 ± 43$^{a}$ | 0.07 ± 0.006$^{a}$ | 30 ± 1$^{a}$ | 2.9 ± 0.25$^{e}$ |
| (+Ve) Control | 418 ± 23$^{d}$ | 0.04 ± 0.008$^{c}$ | 10 ± 2$^{e}$ | 4.4 ± 0.22$^{a}$ |
| Silymarin | 554 ± 20$^{b}$ | 0.06 ± 0.007$^{ab}$ | 23 ± 3$^{b}$ | 3.1 ± 0.19$^{ed}$ |
| Fruits 200 | 493 ± 28$^{c}$ | 0.05 ± 0.005$^{b}$ | 17 ± 1$^{d}$ | 3.6 ± 0.30$^{bc}$ |
| Fruits 400 | 476 ± 42$^{c}$ | 0.06 ± 0.006$^{ab}$ | 19 ± 1$^{dc}$ | 3.3 ± 0.22$^{dc}$ |
| Leaves 200 | 503 ± 23$^{c}$ | 0.06 ± 0.012$^{ab}$ | 22 ± 3$^{bc}$ | 3.7 ± 0.25$^{b}$ |
| Leaves 400 | 543 ± 28$^{b}$ | 0.06 ± 0.009$^{ab}$ | 22 ± 3$^{bc}$ | 3.1 ± 0.17$^{de}$ |

Means in the same column with completely different letters are significantly different at $p<0.05$.

**- Liver functions**

Effects of sycamore fruits and leaves extract in serum and liver enzymes of rats were illustrated in Table 3. It was found that the positive control recorded a significant increase in the activities of all studied liver enzymes, namely alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ glutamyl transferase (GGT), and alkaline phosphatase (ALP) compared with the normal control group and treated groups. The results found that high doses of sycamore fruits and leaves extracts groups led to significant decreases in ALT, AST, GGT, and ALP activities compared with the positive control group and were so close to the activity of its normal control values as shown in Table 2. The high levels of ALT, AST, and ALP content in the DIC group agree with results from previous studies **(Alabi *et al*. 2017, Giridharan and Sabina 2017, Adeyemi and Olayaki 2018)**. **El-Hadary *et al* ., ( 2019)** found that DcNa elevated serum ALT, AST, ALP, and GGT, indicating chronic hepatotoxicity with a hazardous injury to hepatic cell membranes and liberation of enzymes into circulation. Increases in cytosolic enzymes in blood are requisites for markers of liver damage. Although the

breakdown of the antioxidant system could precipitate pro-inflammatory responses, it could also be the underlying factor responsible for the recorded significant increases in AST, ALT, and ALP activities and the significant elevation in the plasma level TB **(Adeyemi *et al* ., 2018 ).**

On the other hand, treatment with silymarin reversed DIC-induced alteration in the systemic levels of AST and ALT. Silymarin preserved the structural integrity of hepatocyte membranes and prevented these enzymes' leakage into the plasma **(Heidarian and Nouri, 2021). Heidarian and Nouri, (2021**) noted that the reduction in ALP activity in silymarin-administered groups was related to its antioxidant and anti-inflammatory properties. **Pilapil et *al., (*2017)** found that *F. sycomorus L* leaves have antitumor, anti-inflammatory, antioxidant, and cytotoxic activities, which could negate the harmful effect of liver damage. According to **Sirisha *et al*., (2010),** Ficus species are rich in polyphenolic compounds and flavonoids, responsible for their antioxidant properties that help prevent and treat oxidative stress related to hepatic diseases. *F. benjamina* contains naringenin, quercetin, and caffeic acid, both antioxidants and anti-inflammatory agents **(Sirisha *et al*., 2010).**

**Table2**: **The protective effect of silymarin, fruits 200 & 400, and leaves 200 & 400 ethanolic extract on changes in ALT, AST, ALP, and GGT for rats with hepatotoxicity induced by diclofenac**

| Parameters / Groups | ALT (U/L) | AST (U/L) | GGT (U/L) | ALP (U/L) |
|---|---|---|---|---|
| **(-Ve) Control** | 37.83 ± 4.44$^{f}$ | 113.33 ±6.47$^{f}$ | 9.00 ±3.40$^{f}$ | 312 ± 12.03$^{f}$ |
| **(+Ve) Control** | 79.00 ± 4.04$^{a}$ | 284.66 ±10.93$^{a}$ | 40.16 ±3.97$^{a}$ | 566 ± 19.23$^{a}$ |
| **silymarin** | 49.66 ± 4.80$^{d}$ | 126.50 ±7.66$^{e}$ | 13.83 ±2.48$^{e}$ | 353 ± 28.84$^{e}$ |
| **Fruits 200** | 62.66 ± 2.87$^{b}$ | 231.00 ±8.29$^{b}$ | 30.00 ±2.28$^{b}$ | 487 ± 19.41$^{b}$ |
| **Fruits 400** | 5.00 ± 1.78$^{d}$ | 143.83 ±6.73$^{d}$ | 19.16 ±2.13$^{d}$ | 376 ± 10.05$^{c}$ |
| **Leaves 200** | 56.66 ± 5.64$^{c}$ | 185.13 ±13.01$^{c}$ | 23.83 ±2.85$^{c}$ | 416 ± 16.46$^{c}$ |
| **Leaves 400** | 43.66 ±2.06$^{e}$ | 125.66 ±13.96$^{e}$ | 15.50 ±2.73$^{e}$ | 354 ± 17.37$^{e}$ |

Means in the same column with completely different letters are significantly different at $p<0.05$.

Table 3 shows that the positive control group recorded significant increases in the activities of total bilirubin (T.BIL), Direct bilirubin (D.BIL), and indirect bilirubin compared with a normal control group and other groups. The results found that high doses of sycamore fruits and leaf extract significantly decreased these parameters. Sycamore fruits and leaf extract (400) recorded the best result compared to the positive control group and other groups. This study agrees with **El-Hadary *et al* ., ( 2019),** who found that DIC elevated total bilirubin and direct bilirubin indicating chronic hepatotoxicity with a hazardous injury to hepatic cell membranes and liberation of enzymes into circulation. Increases in cytosolic enzymes in blood are requisites for markers of liver damage. Although the breakdown of the antioxidant system could precipitate pro-inflammatory responses, it could also be the underlying factor responsible for the recorded significant elevation in the plasma level of TB (**Adeyemi *et al* ., 2018 ).**

**Heidarian and Nouri, (2021)** found that reduced total bilirubin activities in silymarin-administered groups were related to its antioxidant and anti-inflammatory properties. On the other hand, **Mandal *et al* ., (2000)** stated that the extract of *ficus rasemosa* exhibited a significant protective effect by lowering bilirubin. **Kurniawan and Wardany,( 2021)** mentioned that leaves contain high flavonoid compounds that can act as hepatoprotective agents, inhibiting the process of liver damage. The extract of *F. asperifolia* reduces the total bilirubin level in the serum of intoxicated rats, suggesting its potential hepatoprotective effect. These could be due to phytochemicals such as saponins, alkaloids, and phenols **( Ojo *et al* ., 2014).**

This study agrees with **Abd El Raheim *et a*l ., (2013)** noted that The ability of the ethanol extract of *F. ingens* (200 and 400 mg/kg) to reduce the level of TB in the serum of intoxicated rats suggests its potential hepatoprotective effect. Administration of the ethanol extract of *F. ingens* in doses of 200 and 400 mg/kg remarkably reduction of TP in serum. This assures the hepatoprotective activity of this extract against liver damage.

**Table3: The protective effect of silymarin, fruits 200 & 400, and leaves 200 &400 ethanolic extract on changes in T.bilirubin, direct and indirect bilirubin ) for rats with hepatotoxicity induced by diclofenac**

| Parameters / Groups | T.bilrubin (mg/dl) | Direct bilrubin (mg/dl) | In direct bilirubin (mg/dl) |
|---|---|---|---|
| **(-Ve) Control** | $0.22 \pm 0.02^{e}$ | $0.05 \pm 0.02^{f}$ | $0.18 \pm 0.01^{c}$ |
| **(+Ve) Control** | $0.75 \pm 0.07^{a}$ | $0.46 \pm 0.02^{a}$ | $0.53 \pm 0.04^{a}$ |
| **Silymarin** | $0.29 \pm 0.06^{ed}$ | $0.10 \pm 0.02^{ed}$ | $0.20 \pm 0.04^{c}$ |
| **Fruit 200** | $0.50 \pm 0.03^{b}$ | $0.18 \pm 0.01^{b}$ | $0.30 \pm 0.03^{b}$ |
| **Fruit 400** | $0.39 \pm 0.03^{c}$ | $0.16 \pm 0.07^{bc}$ | $0.26 \pm 0.03^{b}$ |
| **Leaves 200** | $0.45 \pm 0.08^{bc}$ | $0.14 \pm 0.03^{cd}$ | $0.31 \pm 0.05^{b}$ |
| **Leaves 400** | $0.30 \pm 0.03^{d}$ | $0.09 \pm 0.01^{e}$ | $0.20 \pm 0.02^{c}$ |

Means in the same column with completely different letters are significantly different at $p<0.05$.

**-Serum Total protein, Albumin, and Globulin**

Table (4) represents the mean values of total protein, albumin, and globulin of the negative control group, positive control group, and treated groups with silymarin, leaves 200 & 400, and fruits 200 &400 ethanolic extract. The positive control group decreased the activity of the total protein (T.P), albumin (ALB), and globulin (GLB) compared to the normal control. Conversely, Sycamore fruits and leaf extract (400) increased significantly compared to the positive and other groups. **Adeyemi *et al.*, (2018)** noted that the breakdown of the antioxidant system caused precipitate pro-inflammatory responses; it could also be the underlying factor responsible for the recorded significant increases in the activities of ALP by diclofenac. The decrease in protein, albumin, and globulin caused by the toxicity of DIC leads to alteration in mitochondrial function and inhibiting protein synthesis, all of which are due to liver damage through the induction of lipid peroxidation **( El-Hadary*et al.*, 2019).**

(**Famurewa *et al.*, 2019)** reported the beneficial health impact of natural product polyphenols in scavenging and preventing free radicals that cause membrane impairment and damage to intracellular proteins and structures, increasing albumin and total protein that represent the synthetic liver function. **(Khan *et al.*, 2011)** showed that the decrease in total protein and albumin in rats treated with diclofenac was significantly

recovered by chemicals such as flavonoids, terpenoids, tannins, and other chemicals. The results increase in total protein and albumin revealed that the hepatoprotective effect of the extract of *Ficus hispida* might be due to its ability to block the bioactivation of toxicant and its potent antioxidants activity or by scavenging the free radicals and inhibit lipid peroxidation **(senthilkumar, 2012).**

**Table4: The protective effect of silymarin, fruits 200 & 400, and leaves 200 &400 ethanolic extract on total protein, albumin, and globulin for rats with hepatotoxicity induced by diclofenac**

| Parameters / Groups | TP (g/dl) | ALB (g/dl) | GLB (g/dl) |
|---|---|---|---|
| **(-Ve) Control** | $8.00 \pm 0.18^{a}$ | $4.70 \pm 0.14^{a}$ | $3.30 \pm 0.04^{a}$ |
| **(+Ve) Control** | $5.84 \pm 0.14^{e}$ | $3.17 \pm 0.16^{d}$ | $2.63 \pm 0.05^{e}$ |
| **Silymarin** | $7.64 \pm 0.27^{b}$ | $4.52 \pm 0.27^{ab}$ | $3.12 \pm 0.05^{bc}$ |
| **Fruit 200** | $6.53 \pm 0.25^{d}$ | $3.67 \pm 0.16^{c}$ | $2.84 \pm 0.09^{d}$ |
| **Fruit 400** | $7.42 \pm 0.36^{b}$ | $4.25 \pm 0.28^{b}$ | $3.10 \pm 0.07^{bc}$ |
| **Leaves 200** | $6.92 \pm 0.64^{c}$ | $3.39 \pm 0.31^{c}$ | $3.00 \pm .017^{c}$ |
| **Leaves 400** | $7.62 \pm 0.26^{b}$ | $4.41 \pm 0.26^{b}$ | $3.21 \pm 0.14^{ab}$ |

Means in the same column with completely different letters are significantly different at $p<0.05$.

**- Antioxidant enzymes and lipid peroxidation indicators in liver tissues**

Table 5 represents the mean values of CAT, SOD, NO, and MDA for the negative control group, positive control group, and treated groups with silymarin, leaves 200 & 400, and fruits 200 &400 ethanolic extract. The catalase (CAT) and superoxide dismutase (SOD) activities significantly declined in the control+ve group compared with the control (–ve). All other treated groups recorded a significant increasement compared to the control +ve group. The best finding was the effect of Sycamore fruits and leaf extract (400) extract. The table also shows a highly significant increase in malondialdehyde (MDA), and nitric oxide (NO), in the positive group compared to normal control and other groups.

Administration of Sycamore fruits and leaf extract revealed a significant decrease in MDA and NO compared to the positive groups. **Alabi *et al*., (2020)** showed that the significant increases in the level of lipid peroxidation marker MDA and hydrogen peroxide (H2O2)by DIC were an indication of the reduction in the body's antioxidant system and decreased body defense mechanism to scavenging the free radicals **( Galati *et al* ., 2002). Ramezannezhad *et al*., (2019) stated** that **DIC**-induced liver toxicity led to a noticeable elevation in the content of MDA in serum and hepatic tissue relative to the control animals. **Heidarian and Nouri ., (2021)** showed that DIC-induced liver toxicity caused a significant increase in the level of MDA in liver tissues and serum compared to the control group, which is in agreement with the other reported studies **(Ahmad *et al*., 2013., Adeyemi and Olayaki, 2018).** The results align with the reports, showing that nitric oxide plays a critical role in DIC hepatotoxicity and nephrotoxicity **(Guan *et al*., 2014., Safari *et al*., 2017).** A remarkable reduction of nitrite content in silymarin-treated groups suggested that this antioxidant offered hepatoprotection in DIC-exposed animals by lowering NO content and nitrosative stress. **(Heidarian and Nouri, 2021). Heidarian and Nouri,( 2021)** noted that an increase in SOD and CAT activities in silymarin-treated animals could be due to the restoration of SOD and CAT towards normal levels, as silymarin reduced oxidative stress, which is evident by reduced LPO and nitrite contents. Treatment with *F. asperifolia* significantly ($p < 0.05$) decreased the levels of MDA, suggesting that it has antioxidant activity, as reported by Ojo ***et al*., (2014). Abd El Raheim *et al*., (2013)** noted that the possible mechanism of the antihepatotoxic effect of *F. ingens* extract may be partly attributed to its antioxidant activity. This effect was evidenced by the ability of *F. ingens* to return the reduced activities of SOD, GPx, CAT, and GSH levels in the liver homogenate to their control levels, preventing the toxic effects by restoring the increased MDA level in the liver homogenate toward the level of control animals. The protective effect of *F. ingens* extract against toxic may be attributed to the presence of phytoconstituents such as flavonoids.

**Table5: The protective effect of silymarin, fruits 200 & 400, and leaves 200 &400 ethanolic on antioxidants (CAT & SOD) and oxidant (NO and MDA) parameters for rats with hepatotoxicity induced by diclofenac**

| Parameters / Groups | SOD (U/g.t.) | CAT (U/gg.t.) | NO (µmol/g.t.) | MDA (nmol/g.t.) |
|---|---|---|---|---|
| **(-Ve) Control** | $137.33 \pm 7.76^{a}$ | $8.84 \pm 0.42^{a}$ | $0.86 \pm 0.03^{d}$ | $9.66 \pm 1.63^{e}$ |
| **(+Ve) Control** | $67.66 \pm 2.16^{e}$ | $3.58 \pm 0.42^{f}$ | $2.05 \pm 0.10^{a}$ | $40.50 \pm 3.61^{a}$ |
| **Silymarin** | $125.50 \pm 4.32^{b}$ | $8.08 \pm 0.40^{ab}$ | $0.72 \pm 0.06^{d}$ | $11.33 \pm 2.58^{de}$ |
| **Fruit 200** | $85.16 \pm 4.07^{d}$ | $5.40 \pm 0.37^{e}$ | $1.28 \pm 0.11^{b}$ | $27.50 \pm 3.08^{b}$ |
| **Fruit 400** | $123.16 \pm 6.79^{b}$ | $7.16 \pm 0.77^{c}$ | $0.78 \pm 0.13^{d}$ | $14.83 \pm 5.03^{d}$ |
| **Leaves 200** | $98.50 \pm 3.61^{c}$ | $6.16 \pm 0.45^{d}$ | $1.09 \pm 0.13^{c}$ | $23.00 \pm 2.82^{c}$ |
| **Leaves 400** | $133.00 \pm 5.17^{a}$ | $7.81 \pm 0.46^{b}$ | $0.71 \pm 0.09^{d}$ | $12.66 \pm 3.26^{de}$ |

Means in the same column with completely different letters are significantly different at $p<0.05$.

**-Histological Results**

Histopathological sections of rat liver stained with hematoxylin and eosin. Photomicrograph of centrolobular area of liver of control group (A) showing polyhedral-shaped hepatocytes arranged in a cord-like pattern (HC) radiating from an intact central vein (CV) and separated by blood sinusoids (S): stain, H&E. photomicrograph of the portal area of liver of Voltaren treated group(B) showing inflammatory cellular infiltration (asterisk), vacuolar degeneration and nuclear pyknosis (white arrows) of hepatocytes besides proliferation of bile duct (black arrows), congestion and hemolysis of portal vein (black arrowhead) in addition to fibrosis of portal area (white arrowheads): stain, H&E. photomicrograph of the portal area of liver of voltaren+silymarin treated group(C) showing congestion and hemolysis of portal vein (white arrow), a mild proliferation of bile duct (black arrows) in addition to a mild degree of fibrosis of portal area (arrowhead): stain, H&E. photomicrograph of portal area of liver of voltaren+fruits 200 treated group (D) showing inflammatory cellular infiltration (black arrow), vacuolar degeneration (arrow heads) and necrosis (white arrows) of hepatocytes: stain, H&E. photomicrograph of portal area of liver of voltaren+fruits 400 treated group (E) showing significant amelioration of liver parenchyma with mild vacuolar degeneration of hepatocytes (arrow heads) and mild bile duct proliferation (black arrows): stain, H&E. photomicrograph of portal

area of liver of voltaren+leaves 200 treated group (F) showing mild fibrosis (arrow head) and moderate congestion of portal vein (black arrows). Stain, H&E. photomicrograph of the portal area of liver of voltaren+leaves 400 treated group(G) showing a normal architecture of liver tissue with the intact portal artery (PA), bile duct (BD), and hepatocytes arranged in the cord-like pattern with mild vacuolar degeneration of hepatocytes (arrow heads). Stain, H&E. These results agree with **Heidarian and Nouri, (2019)** who found that administration of DIC-only in group 2 demonstrated mononuclear cells filtration and histological changes compared to the control group that reflected liver toxicity. **Alabi and Akomolafem, (2020)** Found that the liver of DF treated rats showed dilated central vein, mild paracentral, hepatocyte cellloss, prominent cell degeneration, and inflammation in the centrilobular areas. **Esmaeilzadeh *et al* ., (2020)** showed that Injection of DIC in the DIC-alone treated group led to the infiltration of lymphocyte cells in comparison with the control group. Also, DIC-injected rats supplemented with silymarin showed decreased inflammatory cell infiltration relative to the DIC-alone treated group. **Abd El Raheim *et al*., (2013)** reported that rats treated with the ethanol extract of *F. ingens* in a dose of 400 mg/kg showed normal hepatic cords and absence of severe congestion and pyknosis indicating pronounced protection of hepatocytes. **Parameswari *et al*., (2013)** showed that the rats treated with methanolic extract of *Ficus religiosa* showed a good sign of protection against the toxicant to considerable extent as it was evident from the formation of normal hepatic cords and absence of necrosis and vacuoles. **Pilapil *et al*., (2017)** noted that A mild distortion of liver parenchymal architecture was observed in *F. benjamina* extract-treated mice while a moderate distortion of liver parenchymal architecture was observed in untreated mice.

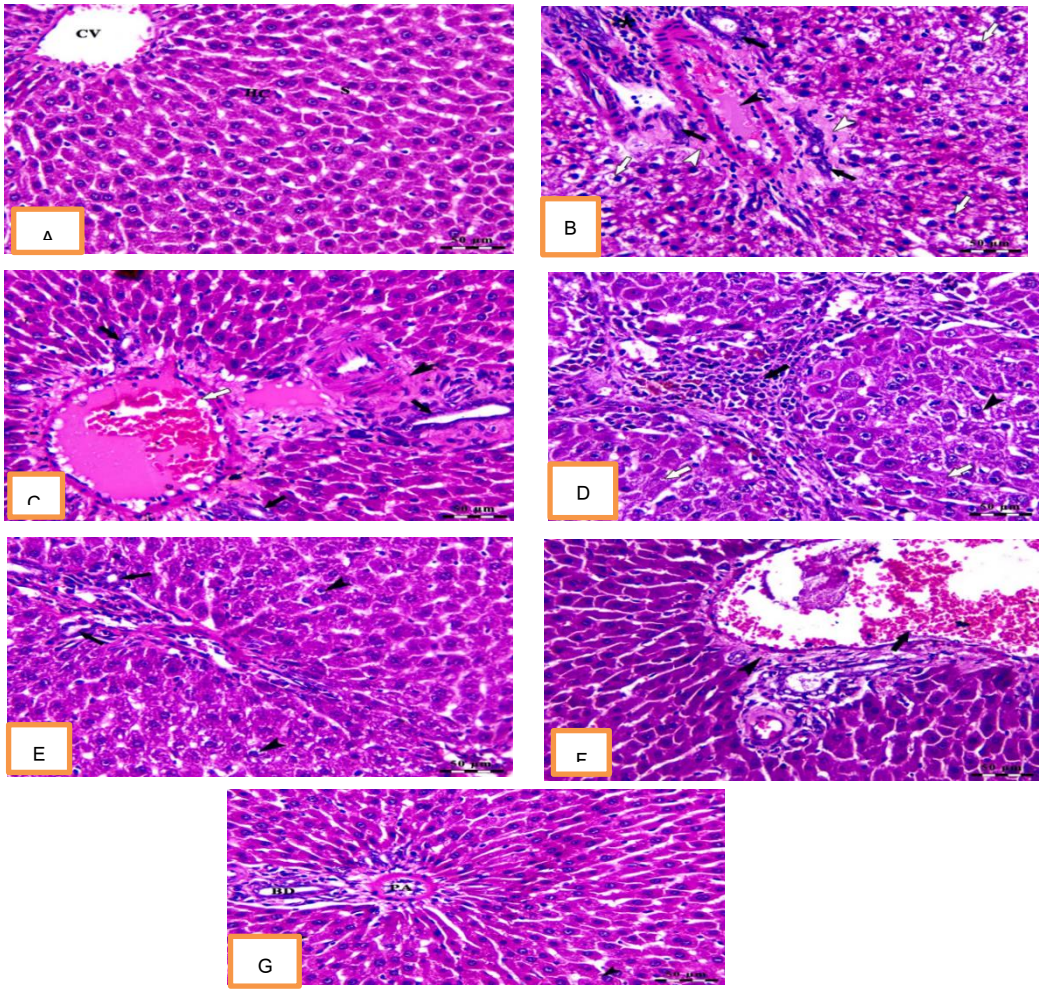


**Fig 1**: Histopathological sections of rat liver stained with hematoxylin and eosin. (A) is the control group. (B) is the positive group, (C) is voltaren+silymarin treated group. (D) is voltaren+fruits 200 treated group. (E) voltaren+fruits 400 treated group. (F) is voltaren+leaves 200 treated group. (G) is voltaren+leaves 400 treated group.

## Conclusion

Voltaren has toxic side effects on liver tissue proved by biochemical and histological results. Sycamore fruits and leaf extract may have beneficial effects on liver toxicity due to their antioxidant compounds, fibers, and polysaccharides.

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**الملخص العربى:**

ينتمي الديكلوفيناك (DIC) (الفولتارين) إلى عائلة الأدوية غير الستيرويدية المضادة للالتهابات، وهو أحد المركبات المشتقة من حمض فينيل أسيتيك؛ سمية الكبد هي واحدة من المخاوف الرئيسية لهذا الدواء. قامت الدراسة الحالية بدراسة تأثير المستخلص الإيثانولي لثمار الجميز وأوراقه ضد الإجهاد التأكسدي الناجم عن الديكلوفيناك والسمية الكبدية في الفئران. تم تقسيم اثنين وأربعين ذكور جرذان ألبينو وزنها (١٥٠ ± ١٠ جم) إلى سبع مجموعات متساوية. المجموعة الأولى (٦ فئران) كانت تتغذى على الغذاء الأساسي وهي المجموعة السالبة. تلقت المجموعة الثانية (٣٦ جرذاً) جرعة واحدة فى تجويف البطن بالفولتارين بتركيز (١٥٠ملليجرام /كجم من وزن الجسم) في نهاية التجربة. وتم تقسيمها إلى ست مجموعات فرعية: المجموعة ١ تم تغذيتها على الغذاء الأساسي فقط وهي المجموعة الضابطة الموجبة (+ v)، المجموعة الثانية الفرعية تغذت على الغذاء الأساسي وسيليمارين (١٠٠ مجم / كجم من وزن الجسم، عن طريق الفم). تم تغذية المجموعتين (٣ و٤) عن طريق الفم على الغذاء الأساسي ومستخلص إيثانولي من ثمار الجميز بتركيز (٢٠٠ و٤٠٠ مجم / كجم من وزن الجسم) لمدة ٢٨ يومًا على التوالي. تم تغذية المجموعتين (٥ و٦) على الغذاء الاساسي، والمستخلص الإيثانولي لأوراق الجميز عن طريق الفم بتركيز (٢٠٠ و٤٠٠ مجم / كجم من وزن الجسم) على التوالي. تم حساب التقديرات البيولوجية في نهاية التجربة، وأخذت عينات الدم للتحليل البيوكيميائي. بالإضافة إلى ذلك، تم تحليل أنسجة الكبد بحثًا عن مضادات الأكسدة، ومالون الدهيد كما تم عمل الفحص النسيجي. أظهرت النتائج أن مجموعة الديكلوفيناك تسبب زيادة في وزن الكبد، إنزيمات الكبد في الدم، المالونالدهيد واكسيد النيتريك فى الكبد، وانخفاض في مصل الكبد والجلوتاثيون بيروكسيديز والسوبر اوكسيد ديسميوتيز والكتاليز، أظهرت جميع المجموعات المعاملة بمستخلصات الفاكهة والأوراق تحسناً في جميع التحاليل السابقة مقارنة بالمجموعةالمصابة. في الختام، فإن استهلاك المستخلص الإيثانولي لثمار وأوراق الجميز يمكن أن يقلل من الآثار الجانبية لمادة الديكلوفيناك السامة.

**الكلمات المفتاحية:** ديكلوفيناك، فيكس سكومورس، سيليمارين ، سمية كبدية