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ABSTRACT

Diclofenac (DIC), also known as Voltaren, is a member of the group of drugs that don't contain steroids that fight inflammation. Liver toxicity is one of the primary concerns regarding this medication, which is one of the substances that come from phenylacetic acid. This study examined the impact of a ficus sycomorus leaf and fruit ethanolic extract on oxidative stress and hepatotoxicity caused by diclofenac in rats. There were forty-two male albino rats, each weighing about 150 grammes (±10 g). They were divided into seven equal groups. The first group of six rats was given a basic diet as a negative control. At the conclusion of the trial, the second group (36 rats) was given a single dose of DIC (150 mg/kg b.w.) given through the abdomen. Six subgroups were created from it: As a positive control (+v), Group 1 was given only a basal diet. Group 2 was given silymarin (100 mg/kg b.w., orally) along with a basal diet. For 28 days, groups 3 and 4 were given a basal diet and an ethanolic sycamore fruit extract (200 and 400 mg/kg b.w.), in that order. A basal diet and an oral ethanolic extract of sycamore leaves (200 and 400 mg/kg b.w.) were administered to groups 5 and 6, respectively. Blood samples were collected for biochemical analysis, and biological data were computed at the conclusion of the experiment. Malondialdehyde (MDA), antioxidant markers, and histological analysis were also performed on liver tissues. According to the findings, the diclofenac group decreased serum liver GPX, SOD, and CAT while increasing liver weight, serum liver enzymes, liver MDA, and liver NO. When you look at the (+ve) control group, every group that received fruit and leaf extracts demonstrated improvement in every prior metric. To sum up, eating the ficus sycomorus leaf ethanolic extract and fruits can lessen the negative effects of the toxicant diclofenac.

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

INTRODUCTION

In addition to aiding in the bioregulation of amino acids, proteins, carbohydrates, fats, blood coagulation, and immunomodulation, the liver aids in the getting rid of drugs, outside toxins, and therapeutic agents **(Juza and Pauli, 2014)**.

Drug-induced liver toxicity is one of the main issues facing physicians and the pharmaceutical industry **(Labbe *et al.*, 2008)**. Non-

steroidal anti-inflammatory medications are commonly prescribed due to their analgesic and anti-inflammatory qualities., but some of them can be harmful to the liver **(Boelsterli, 2013)**.

Diclofenac (DIC), a substance derived from phenylacetic acid, is a member of the family of non-steroidal anti-inflammatory medications. However, one of the primary issues with this medication is liver toxicity. Mitochondrial damage has been partially linked to DIC's mechanism of liver toxicity **(Adeyemi and Olayaki, 2018)**, disturbance of the antioxidant defence system, alterations in the covalent protein's integrity caused by metabolites that react (**Galati *et al.*, 2002**), and mechanisms mediated by the immune system **(Lim *et al.*, 2006)**.

According to reports from earlier research, DIC metabolites (40, 5-hydroxy diclofenac) can induce hepatocyte necrosis and neutrophil infiltration in hepatic cells. Reactive oxygen species (ROS) formation was linked to these effects **(Alabi *et al.*, 2017)**. **Shehata *et al.* (2020)** discovered that propolis and marjoram oil successfully mitigated oxidative stress and reduced rat inflammation and damage caused by diclofenac sodium. According to **Esmaeilzadeh *et al.* (2020)**, the while the DIC group's serum protein carbonyl, AST, ALP, ALT, total bilirubin, MDA, serum IL-1b, and liver IL-1b gene expression were significantly higher than the control group's, the DIC group's liver levels of GSH, GPx, SOD, and CAT were significantly lower.

Alternative medicine has suggested a number of hepatoprotective remedies made from herbs to treat liver problems. Remedies made from herbs to treat liver problems. By re-establishing antioxidant status and preventing oxidative stress through ROS scavenging, medicinal herbs shield the body from dangerous chemicals **(Iwu *et al.*, 1990).**

A flavonoid complex derived from *Silybum marianum* seeds is called silymarin. Because silymarin scavenges radicals, it has a hepatoprotective effect **(Wellington and Jarvis, 2001)**. As an antioxidant, silymarin chelates iron and copper metal ions, stabilises cell membranes and regulates the amount of reduced glutathione inside cells. **(Borsari *et al.*, 2001; Taleb *et al.*, 2018)**. Because of its beneficial effects on hepatic disorders, silymarin has been used as a complementary and alternative medicine for many years throughout the world (**Abenavoli *et al.*, 2010**). **Heidarian and Nouri (2019)** who verified that silymarin protects male rats from oxidative stress and liver damage brought on by DIC.

Ficus sycomorus, commonly known as the fig or sycamore fig Mulbern is a member of the *Moraceae* family, which includes over 1,400 tree species and roughly four genera **(Zerega *et al.*, 2005)**. Native to Africa, the plant grows north of the tropic of Capricorn and south of the

Sahel **(Dale, 2007)**. In addition to its sedative and anti-convulsive qualities, *F. sycomorus* stem bark has been shown to have an impact against tuberculosis **(Sandabe *et al.*, 2003)**.

The phytochemical makeup of the *F. sycomorus* plant extracts was screened. All of the samples (leaves, stems, roots, seeds, and fruits) contained alkaloids, flavonoids, saponins, tannins, oxalates, and hydrogen cyanide, while the fruit extract had a noticeably elevated vitamin C content. The leaves contain the most flavonoids, the stems contain the most alkaloids, and the roots contain the most saponins and tannins. Additionally, flavonoids have been shown to have anti-inflammatory, anti-allergic, anti-cancer, antimicrobial, and antioxidant properties **(Prochazkova, 2011)**.

Refaat *et al.* (2020) discovered that the rats' kidney, liver, and lipid profiles improved when they were fed a mixture of fig and sycamore powder. **Sayyad *et al.*, (2015)** determined that wood and leaf extracts have strong hepatoprotective effects against CCl_4-induced hepatic carcinogenesis in rats and Nitroso diethylamine. **Ojo *et al.* (2017)** discovered that the leaf extract from *F. asperifolia* (Miq) protected male Wistar rats' livers from hepatic damage caused by carbon tetrachloride. Therefore, the current study examined how well sycamore fruits and leaf extract protected male rats' livers from diclofenac-induced toxicity.

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. We bought starch and maize oil from the neighbourhood market. The casein, cellulose, vitamins, minerals, dextrin, L-cysteine, and choline chloride were supplied by the Cairo Company for Chemical Trading, Cairo, Egypt.
3. Voltaren (Diclofenac sodium) was purchased from Novartis Pharma Co, Egypt.
4. Sigma Chemical Co., located in St. Louis, USA, was the supplier of silymarin.
5. Forty-two male albino rats (*Sprague Dawley* strain) weighing roughly 150±10g were acquired from the Laboratory Animal Colony, Helwan, Cairo, Egypt.
6. Alkan Company supplied the kits, which were purchased for laboratory services from an American company based in Egypt.

Methods

Plant material and preparation

Sycamore fruits and leaves were washed thoroughly under running tap water and dried for 12 hours at 45°C in an oven. To create a homogenous sample, the samples that had dried were ground in an electric stainless still mill (Braun, Model 537, Germany) and kept at -20°C in polyethylene bags until they were needed. The fresh fruit (1.5 kg) and air-dried powdered leaves (1.0 kg) of *F. sycomorus* (FS) were macerated at room temperature and extracted separately using 70% ethanol. A rotary evaporator was used to concentrate each extract at 40°C, yielding crude extract weights of 60 g and 50 g, respectively **(Alqasoumi, 2012)**.

Experimental design

In order to adapt, for a week, 42 adult male albino rats of the *Sprague Dawley* strain, weighing (150± 10g), were housed in hygienic, well-ventilated cages and fed a basal diet as outlined by **Reeves *et al.* (1993)**. The rats were divided into two main groups after this week: The initial six rats were fed a basal diet as a negative control group. As stated by **Alaael din (2007)**, the second main group was split up into six subgroups and given 150 mg/kg b.w. a single intraperitoneal dose of DIC at the conclusion of the experimental period. Group 1 served as a positive control and received only a basal diet. Group 2 was given a basal diet and silymarin (100 mg/kg b.w.) orally. As stated by **El-Sayyad *et al.* (2015)**, groups 3 and 4 were given a basal diet and an oral ethanolic extract of sycamore fruits (200 and 400 mg/kg b.w.) for 28 days. According to **Sakpa and Wilson (2019)**, groups 5 and 6 were given a basal diet and an oral ethanolic extract of sycamore leaves at (200 and 400 mg/kg b.w.) for 28 days, respectively.

The animals fasted overnight before being sacrificed at the conclusion of the 28-day experiment. Dry centrifuge tubes were used to collect blood samples from the hepatic portal vein. Prior to analysis, the serum was kept at -20 degrees in plastic vials. after being separated at 4000 runs per minute, or "RPM," for 10 minutes. After being taken out, the liver was cleaned in saline solution and dried at 4 C° using filter paper. For histopathological analysis, the initial liver sample was preserved in 10% formalin saline. In order to prepare tissue homogenate and measure antioxidant parameters, the second sample was stored at -20°C. For 20 minutes, the homogenate was centrifuged at 10,000 rpm. Some laboratory analyses were assayed using the supernatant.

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 using **(Chapman *et al*., 1959).**

Biochemical analysis of serum

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured using **Bergmeyer *et al*. (1986**), and Alkaline Phosphatase (ALP) was carried out using the technique of **(Roy, 1970)**. GGT (γ glutamyl transferase) was measured using **(Shaw *et al*., 1983). Walters and Gerard (1970)** estimated serum total bilirubin and direct bilirubin. In accordance with **Sonnenwirth and Jaret (1980)**, total protein was calculated. Serum globulin was computed using **Chary and Sharma (2004)**, and albumin was estimated using **(Drupt, 1974).**

Evaluation of Liver Tissue Oxidant/Antioxidant Activity

Nitric oxide (No), catalase (CAT), superoxide dismutase (SOD), and malondialdehyde (MDA) were measured using methods developed by **Ohkawa *et al.* (1979), Nishikimi *et al.* (1972), Aebi (1984),** and **Montgomery and Dymock (1961).**

Histopathological examination

The liver of each rat was removed and preserved in a 10% neutral buffering formaldehyde solution (pH 7.5). After that, it was preserved in paraffin and cleaned in xylol. A 4-5 µm thick piece was selected for histological analysis using haematoxylin and eosin (H&E) **(Bancroft and Gamble, 2008).**

Statistical analysis

SPSS software was used to statistically analyse all of the collected data. According to **Armitage and Berry (1987)**, the computation made use of SPSS version 11's follow-up test (LSD) and analysis of variance (ANOVA).

RESULTS AND DISCUSSION

-Biological evaluation

Table 1 shows the results for feed intake (FI), body weight gain (BWG) percentage, feed efficiency ratio (FER), and liver weight percentage. When compared to normal control, these parameters significantly decline in positive control. Comparing the other groups to the positive control, however, revealed notable increases. High dosages of sycamore leaf extracts (400 mg) produced the best outcomes. In comparison to the negative control group, the positive control group's liver weight values increased significantly. All treated groups showed a noteworthy decline ($p<0.05$) when compared to the positive control group. The silymarin group achieves the best result, leaving 400, the value closest to the (-ve) group. These results align with those of **Gupta**

***et al.* (2021)**, Who discovered that administering DIC daily for 21 straight days resulted in an 18.5% reduction in body weight. Rats' relative liver weight increased significantly (4.3%), indicating the negative effects of DIC intoxication. According to reports, DIC results in gastric ulceration, which makes it difficult for the animals to eat and leads to malnutrition. Rats treated with diclofenac showed a notable decrease in body weight, as reported by **(Alabi *et al.*, 2020)**.

The decrease in rats' body weight after being given 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. According to **Dawod *et al.* (2022)**, The *F. sycomorus*-treated group exhibited a significant decrease in the feed conversion rate group and a non-significant increase in the covariate final body weight, body gain, and feed intake when compared to the positive control. This may be explained by *F. sycomorus* extract's beneficial anti-oxidant, anti-inflammatory, and oocyst shedding-reducing properties. Considering the high concentration of procyanidin-type condensed tannins in *F. sycomorus* stem bark, the extract-treated rabbits' non-significant drop in body weight may have resulted from the tannins' anti-nutritional effect. These tannins have the potential to alter the physicochemical makeup of the proteins they bind to. Furthermore, it has an astringent quality that could negatively impact growth performance, food intake, and food palatability **(Konai *et al.*, 2017)**. According to **Krishna *et al.* (2007)**, *F. carica Linn* leaf extract might have antioxidant properties. effect or inhibit cytochrome P450s in rats with liver damage. This genus has been reported to contain flavonoids, coumarins, tannins, steroids/triterpenoids, and their glycosides.

It is possible that these components of *F. sycomorus L.* are in charge of the observed protective effects because **El-Sayed *et al.* (2010)** noted that they have hepatoprotective activity and are free radical scavengers. Plant-based flavonoids are thought to have anti-inflammatory and arachidonic acid metabolism-influencing effects, which raise liver weight **(Qureshi *et al.*, 2019)**.

Table1: Rats with diclofenac-induced hepatotoxicity demonstrated defence against variations in liver weight, feed efficiency ratio, body weight gain percentage, and feed intake percentage when given an ethanolic extract of ficus sycomorus fruits and leaves.

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}
Fruit 200	493 ± 28^{c}	0.05 ± 0.005^{b}	17 ± 1^{d}	3.6 ± 0.30^{bc}
Fruit 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}

At $p<0.05$, there is a significant difference between indicates using completely different letters in the same column.

- Liver functions

Table 2 shows the effects of sycamore fruit and leaf extract on the serum and liver enzymes of rats. When compared to the normal control group and treated groups, it was discovered that the positive control group had significantly higher levels of all the liver enzymes under investigation, including alanine aminotransferase (ALT), Alkaline phosphatase (ALP), γ glutamyl transferase (GGT), and aspartate aminotransferase (AST). According to Table 2, the results showed that groups receiving high doses of sycamore fruit and leaf extracts significantly reduced their ALT, AST, GGT, and ALP activities when in contrast to the positive control group. Additionally, these activities closely matched the typical control values. The DIC group's elevated ALT, AST, and ALP content levels are consistent with findings from earlier research **(Alabi *et al.*, 2017; Giridharan and Sabina, 2017; Adeyemi and Olayaki, 2018)**. According to **El-Hadary *et al.* (2019)**, serum levels of ALT, AST, ALP, and GGT rose in response to DcNa, suggesting chronic hepatotoxicity with potentially harmful hepatic cell membrane damage and the release of enzymes into the blood. For indicators of liver damage, blood cytosolic enzyme levels must rise. The notable rise in the plasma level and the noted notable increases in AST, ALT, and ALP activities of tuberculosis could be caused by the breakdown of the antioxidant system, which may also trigger pro-inflammatory reactions **(Adeyemi *et al.*, 2018)**.

However, silymarin treatment undid the change in systemic AST and ALT levels brought on by DIC. Silymarin stopped these enzymes from seeping into the plasma and maintained the structural integrity of hepatocyte membranes **(Heidarian and Nouri, 2021)**. According to

Heidarian and Nouri (2021), silymarin's anti-inflammatory and antioxidant qualities were linked to the decrease in ALP activity in groups that received it. According to **Pilapil *et al.* (2017)**, the leaves of *F. sycomorus L.* exhibit cytotoxic, antioxidant, antitumor, and anti-inflammatory properties that may counteract the negative effects of liver damage. Ficus species are abundant in flavonoids and polyphenolic substances, which aid in their antioxidant properties and help prevent and treat oxidative stress associated with hepatic disorders **(Sirisha *et al.*, 2010)**. Naringenin, quercetin, and caffeic acid are antioxidants and anti-inflammatory substances found in *F. benjamina* **(Sirisha *et al.*, 2010)**.

Table 2: **ALT, AST, ALP, and GGT changes in rats with diclofenac-induced hepatotoxicity and the protective effect of silymarin, fruits 200 and 400, and leaves 200 and 400 ethanolic extract**

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}
Fruit 200	62.66 ± 2.87^{b}	231.00 ±8.29^{b}	30.00 ±2.28^{b}	487 ± 19.41^{b}
Fruit 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}

At $p<0.05$, there is a significant difference between indicates using completely different letters in the same column.

Compared to other groups and a typical control group, **Table 3** demonstrates that total bilirubin (T.BIL), direct bilirubin (D.BIL), and indirect bilirubin activities all significantly increased in the positive control group. According to the findings, these parameters were considerably lowered by high dosages of sycamore fruit and leaf extract. When compared to the positive control group and other groups, sycamore fruits and leaf extract (400) produced the best results. This study supports the findings of **El-Hadary *et al.* (2019)**, who discovered that DIC increased both total and direct bilirubin, indicating chronic hepatotoxicity with enzyme release into the bloodstream and dangerous hepatic cell membrane damage. For indicators of liver damage, blood cytosolic enzyme levels must rise. While the degeneration of the antioxidant system may trigger pro-inflammatory reactions, it may also be the fundamental cause of the observed notable increase in the TB plasma level **(Adeyemi *et al.*, 2018)**.

According to **Heidarian and Nouri (2021)**, silymarin's anti-inflammatory and antioxidant qualities were linked to lower levels of total bilirubin in groups that received it. However, by reducing bilirubin, the ficus rasemosa extract demonstrated a noteworthy protective effect,

according to **(Mandal *et al.*, 2000)**. According to **Kurniawan and Wardany (2021)**, leaves are rich in flavonoid compounds that can function as hepatoprotective agents, preventing the progression of liver damage. The extract of *F. asperifolia* may have a hepatoprotective effect because it causes drunk rats' serum levels of total bilirubin to drop. Phytochemicals like phenols, alkaloids, and saponins may be the cause of these **(Ojo *et al.*, 2014)**.

This study supports the findings of **Abd El Raheim *et al.* (2013)**, who observed that the amount of TB in the serum of intoxicated rats was reduced by the ethanol extract of *F. ingens* (200 and 400 mg/kg), indicating that it might have a hepatoprotective effect. Serum TP significantly decreased after 200 and 400 mg/kg doses of *F. ingens* ethanol extract were administered. This guarantees that this extract has hepatoprotective properties against liver damage.

Table 3: 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 ± 0.02^{e}	0.05 ± 0.02^{f}	0.18 ± 0.01^{c}
(+Ve) Control	0.75 ± 0.07^{a}	0.46 ± 0.02^{a}	0.53 ± 0.04^{a}
Silymarin	0.29 ± 0.06^{ed}	0.10 ± 0.02^{ed}	0.20 ± 0.04^{c}
Fruit 200	0.50 ± 0.03^{b}	0.18 ± 0.01^{b}	0.30 ± 0.03^{b}
Fruit 400	0.39 ± 0.03^{c}	0.16 ± 0.07^{bc}	0.26 ± 0.03^{b}
Leaves 200	0.45 ± 0.08^{bc}	0.14 ± 0.03^{cd}	0.31 ± 0.05^{b}
Leaves 400	0.30 ± 0.03^{d}	0.09 ± 0.01^{e}	0.20 ± 0.02^{c}

At $p<0.05$, there is a significant difference between indicates using completely different letters in the same column.

- Albumin, Globulin, and Serum Total Protein

The average levels of albumin, globulin, and total protein for the silymarin-treated, positive, and negative control groups, leaves 200 and 400, and fruits 200 and 400 ethanolic extract are shown in **Table 4**. The positive control group exhibited reduced levels of total protein (T.P.), albumin (ALB), and globulin (GLB) activity in comparison to the normal control group. On the other hand, when compared to the positive and other groups, sycamore fruits and leaf extract (400) increased significantly. According to **Adeyemi *et al.* (2018)**, the antioxidant system's breakdown precipitated pro-inflammatory responses; this could also be the underlying cause of the notable increases in ALP activities that diclofenac was shown to cause. Through the induction of lipid peroxidation, protein, albumin, and globulin levels decline as a result of

DIC toxicity, which in turn alters mitochondrial function and inhibits protein synthesis **(El-Hadary *et al.*, 2019)**.

According to **Famurewa *et al.* (2019)**, natural product polyphenols have a positive health impact by scavenging and blocking free radicals that harm intracellular proteins and structures and interfere with membrane function. Albumin and total protein, markers of synthetic liver function, rise as a result. **Khan *et al.* (2011)** demonstrated that chemicals like flavonoids, terpenoids, tannins, and others significantly restored the decline in albumin and total protein in rats treated with diclofenac. The extract's hepatoprotective properties *Ficus hispida* may be due to its strong antioxidant activity and capacity to prevent the bioactivation of toxicants, or it might be because of its ability to prevent lipid peroxidation and scavenge free radicals, as indicated by the increase in total protein and albumin **(Senthilkumar, 2012)**.

Table 4: Rats with diclofenac-induced hepatotoxicity showed protection from total protein, albumin, and globulin when silymarin, fruits 200 and 400, and leaves 200 and 400 ethanolic extract were administered.

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

At $p<0.05$, there is a significant difference between indicates using completely different letters in the same column.

- Antioxidant enzymes and lipid peroxidation indicators in liver tissues

The mean CAT, SOD, NO, and MDA values for the negative and positive control groups, as well as the groups that received 200 and 400 ethanolic extracts of leaves, 200 and 400 ethanolic extracts of fruits, and silymarin, are shown in **Table 5**. The catalase (CAT) and superoxide dismutase (SOD) activities in the control (+ve) group were significantly lower than those in the control (-ve) group. All other treated groups exhibited a significant increase in comparison to the control (+ve) group. The best finding was the effect of Sycamore fruits and leaf extract (400) extract. The table also shows malondialdehyde (MDA) and nitric oxide (NO) levels in the positive group were significantly higher than those in the normal control and other groups. When Sycamore fruits and leaf extract were administered, MDA and NO levels significantly dropped in

comparison to the positive groups. **Alabi *et al.* (2020)** demonstrated that the notable rises in hydrogen peroxide (H_2O_2) and the lipid peroxidation marker MDA caused by DIC were a sign of a collapse in the body's antioxidant system and defence mechanism against free radical scavenging **(Galati *et al.*, 2002)**.

According to **Ramezannezhad *et al.* (2019)**, the amount of MDA in serum and hepatic tissue was significantly higher in DIC-induced liver toxicity than in control animals. Consistent with previous research findings **(Ahmad *et al.*, 2013; Adeyemi and Olayaki, 2018; Heidarian and Nouri (2021)** demonstrated that DIC-induced liver toxicity resulted in a significant increase in the level of MDA in liver tissues and serum when compared to the control group. According to the findings, nitric oxide is essential for DIC hepatotoxicity and nephrotoxicity **(Guan *et al.*, 2014; Safari *et al.*, 2017)**.

The antioxidant silymarin provided hepatoprotection in animals exposed to DIC by lowering nitrosative stress and NO content, as shown by the silymarin-treated groups' appreciable drop in nitrite content **(Nouri and Heidarian, 2021)**. Since silymarin decreased oxidative stress, as shown by lower LPO and nitrite contents, **Heidarian and Nouri (2021)** noted that silymarin-treated animals showed increased SOD and CAT activities, which could be the result of SOD and CAT levels returning to normal. According to **Ojo *et al.* (2014)**, treatment with *F. asperifolia* significantly ($p<0.05$) reduced MDA levels, indicating that it has antioxidant activity. **Abd El Raheim *et al.* (2013)** pointed out that the antioxidant activity of *F. ingens* extract may be a contributing factor in the potential mechanism of its antihepatotoxic effect. *F. ingens* prevented the toxic effects and restored the decreased activities of SOD, GPx, CAT, and GSH levels to their control levels in the liver homogenate by restoring the elevated MDA level in the liver homogenate to that of control animals. Because *F. ingens* extract contains phytoconstituents like flavonoids, it may have a protective effect against toxins.

Table 5: The protective effect of silymarin, fruits 200 and 400, and leaves 200 and 400 ethanolic on oxidant (NO and MDA) and antioxidant (CAT & SOD) parameters in rats with diclofenac-induced hepatotoxicity

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

At $p<0.05$, there is a significant difference between indicates using completely different letters in the same column.

-Histological Results

Haematoxylin and eosin-stained histopathological sections of rat liver. A photomicrograph of the control group's liver's centrolobular region (A) reveals polyhedral hepatocytes grouped in a cord-like pattern (HC) that radiate from an intact central vein (CV) and are divided by blood sinusoids (S): stain, H&E. A photomicrograph of the liver's portal region in the Voltaren-treated group (B) reveals fibrosis of the portal area (white arrowheads), bile duct proliferation (black arrows), inflammatory cellular infiltration (asterisk), vacuolar degeneration, and nuclear pyknosis (white arrows) of hepatocytes. Photomicrograph of the liver's portal area of the voltaren+silymarin treated group (C) reveals congestion and haemolysis of the portal vein (white arrow), a mild proliferation of the bile duct (black arrows), and a mild degree of fibrosis of the portal area (arrowhead): photomicrograph of the liver's portal area of the voltaren+fruits 200 treated group (D) reveals inflammatory cellular infiltration (black arrow), vacuolar degeneration (arrow heads), and necrosis (white arrows) of hepatocytes: stain, H&E. stain, H&E. photomicrograph of the liver's portal region in the voltaren+leaves 200 treated group (F) displaying moderate portal vein congestion (black arrows) and mild fibrosis (arrow head). A photomicrograph of the liver's portal region of the voltaren+leaves 400 treated group (G) using stain and H&E reveals a normal liver tissue architecture, with the bile duct (BD), portal artery (PA), and hepatocytes arranged in a cord-like pattern. However, there is mild vacuolar degeneration of the hepatocytes (arrow heads). Stain, H&E.

These findings concur with those of **Heidarian and Nouri (2019)**, who discovered that group 2's administration of DIC-only resulted in histological alterations and mononuclear cell filtration, which indicated

liver toxicity, when compared to the control group. **Alabi and Akomolafem (2020)** discovered that the liver of rats given DF exhibited inflammation in the centrilobular regions, hepatocyte cell loss, a dilated central vein, and mild paracentral. In contrast to the control group, **Esmaeilzadeh *et al.* (2020)** demonstrated that the DIC-alone treated group experienced lymphocyte cell infiltration as a result of DIC injection. Furthermore, rats given silymarin in addition to DIC demonstrated less inflammatory cell infiltration than the group given DIC alone. **Abd El Raheim *et al*. (2013)** revealed that rats given 400 mg/kg of *F. ingens* ethanol extract had normal hepatic cords and no signs of severe congestion or pyknosis, suggesting that the hepatocytes were significantly protected.

Parameswari *et al*. (2013) demonstrated that the development of normal hepatic cords and the absence of vacuoles and necrosis demonstrated the rats' good level of protection against the toxin after being administered *Ficus religiosa* methanolic extract. According to **Pilapil *et al.* (2017)**, mice given extract from *F. benjamina* exhibited a slight deformation of the liver parenchyma. whereas mice that were not treated showed a moderate distortion of liver parenchymal architecture.

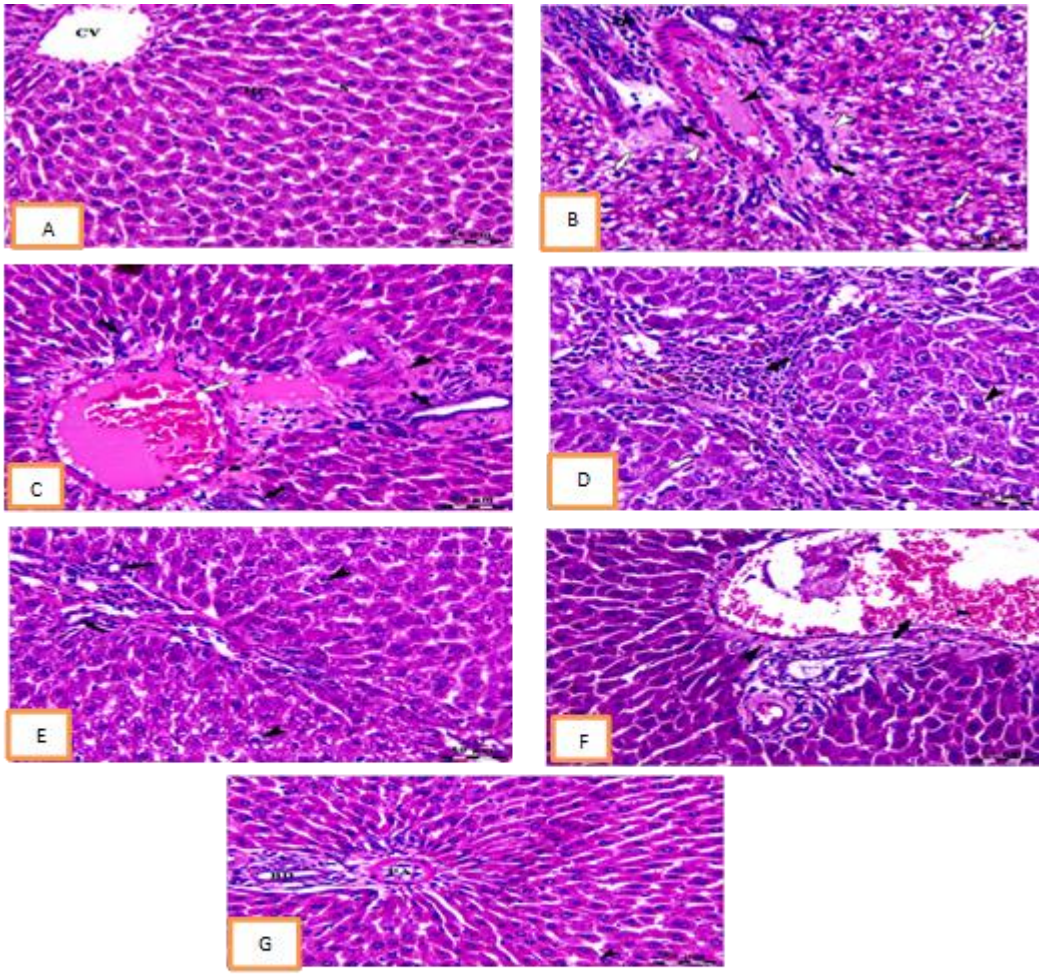

Fig 1: Haematoxylin and eosin-stained rat liver histopathological sections. (A) is the control group. The positive group is (B), and the group treated with voltaren and silymarin is (C). The voltaren+fruits 200 treated group is shown in (D). (E) group treated with 400 voltaren+fruits. The voltaren+leaves 200 treated group is (F). The voltaren+leaves 400 treated group is denoted by (G).

Conclusion

Histological and biochemical findings demonstrate that voltaren has harmful side effects on liver tissue. 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 ديكلوفيناك (DIC)، المعروف أيضًا باسم فولتارين، الي فئة الأدوية المضادة للالتهابات غير الستيرويدية. تُعد سمية الكبد أحد المخاوف الرئيسية المتعلقة بهذا الدواء، وهو أحد المركبات المشتقة من حمض فينيل أسيتيك. بحثت هذه الدراسة تأثير مستخلص إيثانولي من أوراق وثمار الجميز على الإجهاد التأكسدي والسمية الكبدية التي يسببها ديكلوفيناك في الفئران. تم تقسيم اثنين وأربعين من ذكور الجرذان البيضاء (ألبينو) يزن كل منها (١٥٠ ± ١٠ جم) إلى سبع مجموعات متساوية. كمجموعة تحكم سالبة، أعطيت المجموعة الأولى المكونة من ستة جرذان نظامًا غذائيًا أساسيًا. في نهاية التجربة، أعطيت المجموعة الثانية (٣٦ جرذًا) جرعة واحدة من الفولتارين داخل تجويف البطن بتركيز (١٥٠ملليجرام مجم / كجم من وزن الجسم). تم تقسيم ست مجموعات فرعية منها: كمجموعة تحكم إيجابية (+ ٧)، أعطيت المجموعة ١ نظامًا غذائيًا أساسيًا فقط. أعطيت المجموعة ٢ السليمارين (١٠٠ ملجم/كجم من وزن الجسم، عن طريق الفم) مع نظام غذائي أساسي. لمدة ٢٨ يومًا، أعطيت المجموعتان ٣ و٤ نظامًا غذائيًا أساسيًا ومستخلصًا إيثانوليًا لثمار الجميز عن طريق الفم (٢٠٠ و٤٠٠ ملجم/كجم من وزن الجسم) على التوالي. كما تم إعطاء نظام غذائي أساسي ومستخلصًا إيثانوليًا لأوراق الجميز وذلك عن طريق الفم (٢٠٠ و٤٠٠ ملجم/كجم من وزن الجسم) للمجموعتين ٥ و٦ على التوالي. في نهاية التجربة تم أخذ عينات الدم للتحليل البيوكيميائي، وتم حساب التقديرات البيولوجية. كما تم إجراء تحليل المالونديالدهيد (MDA) وعلامات مضادات الأكسدة والتحليل النسيجي على أنسجة الكبد. ووفقًا للنتائج، خفضت مجموعة الديكلوفيناك كلا من الجلوتاثيون بيروكسيديز والسوبر اوكسيد ديسميوتيز والكتاليز في مصل الكبد مع زيادة وزن الكبد وإنزيمات الكبد في الدم والمالونالدهيد في الكبد واوكسيد النيتريك في الكبد. بالمقارنة مع مجموعة التحكم (الموجبة)، أظهرت كل مجموعة تلقت مستخلصات ثمار الجميز والأوراق تحسنًا في جميع التحاليل السابقة. باختصار، يمكن أن يُخفف تناول المستخلص الإيثانولي لأوراق وثمار الجميز من الآثار السلبية لمادة الديكلوفيناك السامة.

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