Hepatoprotective Effect of *Typhonium Flagelliforme* Against Thioacetamide Produced Liver Cirrhosis in Rats

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***Abstract*—*Typhonium flagelliforme* (*T. flagelliforme*) was utilized in outdated medication for handling numerous syndromes. This study aimed to investigate hepatoprotection effects of *T. flagelliforme* against thioacetamide (TAA) hepatotoxicity in rodents.**

Thirty rodents arbitrarily separated five clusters. Collection 1 was intraperitoneally injected distilled water thrice /week and fed (p.o) daily with 10% Tween 20 to eight weeks. Collection 2-5 i.p. injected with 200 mg/kg TAA three times thrice per week for 8 weeks and fed 10% Tween 20, 50 mg/kg silymarin, 250 and 500 mg/kg of *T. flagelliforme* extract daily for 8 weeks, respectively. Hepatotoxic assembly showed suggestively rise hepatic biochemistry markers together with a considerable lessening of proteins and albumin compared to normal assemblage. The hepatotoxic group displayed decreased catalase and superoxide dismutase activities and increase lipid peroxidation. Macroscopy of hepatotoxic liver exhibited irregular, rough surface with micro and macro nodules, and histopathology-stained Hematoxylin and Eosin, and Masson's Trichome exhibited inflammation infiltration of lymphocytes, focal necrosis, fibrosis, and bile duct propagation. *T. flagelliforme* fed clusters have expressively reduced TAA toxicity in gross and histology as designated by fewer disturbances of hepatic tissue, slight fibrosis, and low-grade cells infiltration. Thus, our results showed that the hepatoprotective effect of this plant might be due to reduce toxicity, inhibition of hepatocytes proliferation, decrease enzyme markers, increase protein and albumin, increased endogenous enzymes, and reduced lipid peroxidation level.

***Index Terms*— *T. flagelliforme,* liver cirrhosis, TAA, histology, liver function tests**

I. INTRODUCTION

T. flagelliforme curative herb which fits Araceae. This herb is widely utilized in *vitro* [1-3], and in *vivo* [4] due to its medicinal treatment properties for many diseases such as cancer, edema, injuries, coughs, pulmonary ailments, and bleeding [5]. Also, this plant widely utilizes South East Asia as a traditional remedy for many diseases [6]. *T. flagelliforme* has biological active chemicals such as alkaloids, saponins, steroids, and glycosides [2]. Rodent tuber has potential components of anticancer and antiviral [7], anti-inflammatory, analgesic, and antihepatotoxic [8, 9].

Although the liver is a highly important organ for cleansing, diseases of the liver can be the greatest dangerous healthiness complications [10]. The most common liver diseases are cirrhosis hepatocellular carcinoma, viral hepatitis, and alcoholic hepatitis, which remain predominant disorders Worldwide, and are strongly linked with jaundice [11]. In scientific literature, several studies have the well-known helpful influence of uncountable medicinal plants defending the liver from hepatotoxic damage of TAA in laboratory animals [10, 12]. The most common hepatoprotection agent is silymarin, which is an herbal substance that has been cleansed from seeds of the *Silybum marinum* plant [13]. The latter is used broadly as a therapeutic supplement aimed at liver illnesses like hepatitis, fatty acid infiltration, and cirrhosis resulting from toxic chemical and alcohol effects [11]. Numerous training several academics utilized silymarin ordinary medicine hepatoprotective contrary to the hepatotoxicity of thioacetamide [14-16].

Thioacetamide (TAA) causes an increase in oxidative stress, attractive free radical–facilitated injury to proteins, lipids, and DNA [17]. TAA makes hepatic cells impairment subsequent its breakdown to thioacetamide sulphene and sulphone, by dangerous trail comprises CYP4502E1-intermediated bio-transformation [10]. Abundant studies by different co-researchers evidenced TAA has been used at the beginning of liver fibrosis [3, 18, 19].

The effectiveness of rodent tuber herb since traditional right necessity verified to aid progress novel medicines functioning in contradiction of liver syndromes. However, no work was started on the hepatoprotective achievement of this plant. The existing training is designed to assess hepato-protection action *Typhonium flagelliforme* on TAA-persuaded hepatic injuries in rodents.

II. MATERIALS AND METHODS

A. Ethics Announcement

The current experiment was authorized through conscience team rodents' examination, Faculty Sciences Cihan University-Erbil, Ethical Number PM/07/05/2020/MMA. All animals for the duration of trials, obtained human attention by principles set forth "Director Maintenance Utilize research" organized nationwide School Science has issued nation-wide Institution healthiness.

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B. Thioacetamide

TAA purchased Sigma-Aldrich, liquefied 10% Tween 20 also mixed whole liquified. Then, 200 mg/kg body mass inserted rodent 3 periods weekly 8 weeks. TAA produced vicissitudes together with biology besides morphology structures similar to humanoid hepatic fibrosis [20].

C. Silymarin

Silymarin is a reference drug (International Laboratory, USA), which is used in normal medication in testing. Silymarin melted in double glass-distilled water, then gavage rodents in amount 50mg/kg [21, 22].

D. Plant preparations and extraction

T. flagelliforme fresh plants received from (Ethno Resources Sdn Bhd), detected when compared with the Voucher sample placed at Herbarium Garden, institute of Science Biology. Dried plants are processed to powder using Electrical Blender. One thousand millilitres of 95% ethanol were used to dissolve 300 grams of *T. flagelliforme* powder for 72 hours. After this period, the plant residue was cleared via clean muslin fabric, then the mixture was filtered using mesh paper. Resulted suspension evaporated at a low-pressure lab rotary evaporator. Dried extract soaked in 10% Tween 20 then rats administrated a dosage of 250 and 500 mg/kg (5 ml/kg) [23].

E. Experimental animals and hepatoprotective activity

Rats weight approximately 180 - 200 grams were housed individually via wide-mesh wire bottoms to avoid coprophagy throughout the experimental time, at 25˚± 2˚C temperature, approximate moisture 55-65% and 12 hours exposure light/dark rotation. All the rats were fed on tape water and a standard pellet. The experimental designed and authorized through Ethics Committee for Animal Research. Human care for whole experimental animals was applied and followed Maintenance usage Animal which produced Nationwide College Knowledge issued through countrywide Institute of healthiness.

Thirty healthy adults' Sprague Dawley rodents were arbitrarily alienated into five clusters with six rats respectively. Rats clusters divisions besides treatment protocol were determined following the method of [22, 24] with a few modifications; Group 1 (normal), which was treated by normal saline (5 mL/kg). injection for 3 weeks, and 10% Tween 20 via oral administration every day for 2 months. Group 2 (hepatotoxic) inoculated (i.p) (200 mg/kg) of TAA 3 periods weekly every day administrated orally by 10% Tween 20 for two months. Assembly 3 (reference drug) assumed 3 times weekly of TAA inoculation then daily administered Silymarin (50 mg/kg) for 8 weeks. Collection 4 and 5 were conventional TAA injections thrice/weekly for 2 months, daily oral administration of *T. flagelliforme* extract, respectively.

After the last treatment at the end of experimental time (two months), all animals fated 24 hours and then processed for general anesthesia using ketamine xylazine [25]. Blood is collected from intracardial puncture and stored in a gel-activated tube for liver functions test [26].

F. Biochemical parameters (liver function test)

Blood in clot-activator tubes was separated via centrifuge 10 minutes 2500 rpm. Spectrophotometer used for evaluation alanine aminotransferase aspartate aminotransferase, alkaline phosphatase, total bilirubin, total protein besides albumin. Biochemical parameters evaluated by Medicine Center [25].

G. Macroscopic appearance of liver

The liver assessment was done by opening the rat's abdominal and thoracic cavities. The livers showed significant macroscopic proof of pathological changes. Also, other organs showed pathological gross lesions but were excluded from the current study. All livers were separately washed in cold saline [27].

H. Histopathology of liver tissue

H & E stain & Masson Trichrome stain

Liver samples were washed in cold saline, cut 2 cm cubic, fixed in 10% phosphate-buffered formalin. Leica, Germany tissue processor machine was used to process the specimens. Five µm slices are routinely stained by H&E (hematoxylin and eosin) [25] in addition Masson trichrome stain [25]. Nikon microscope (Y-THS, Japan) was used to evaluate the liver slides.

I. Hepatic homogenate endogenic (CAT, SOD) oxidative Stress

Neutral ice-cold phosphate buffer saline 10% (w/v) was used to wash rats' livers. Teflon homogenizer was used to homogenize liver samples (all steps done on ice), then centrifugation was detached. Clear supernatant collected verify antioxidant activity via SOD, CAT analyzes kits. Also, Oxidative stress, Malondialdehyde (MDA), assess kits were utilized to govern thiobarbituric acid reactive substance (TBARS, Caymical Compony) [28].

J. Statistic examination of information

Information analysis was showed mean ± SEM, One-Way ANOVA using Tukey post hoc assessment, SPSS software, version 24. The *p* values statistical meaning at $p<0.05$.

III. RESULTS

A. Hepatic biochemical markers

The hepatotoxic effect of TAA was meaningfully augmented ($P<0.001$, mean ± SE) levels of ALT, ALP, total bilirubin AST, referred to as liver damage (**Table 1**). Moreover, the TAA cluster exhibited substantial decreases ($P<0.001$, mean ± SE) total protein albumin compared with the normal collection, demonstrating hepatocellular injury. *T. flagelliforme* and silymarin treated groups are significantly dropped ($P<0.001$, mean ± SE) enzyme ALT, ALP, total bilirubin AST. In addition, total protein total albumin values were elevated ($P<0.001$, mean ± SE) in *T. flagelliforme* and silymarin treatments in comparison with the TAA control group. Hence, *T. flagelliforme* revoked the hepatotoxic effect of TAA via reinstating typical liver activities. *T. flagelliforme* effectively prevented TAA-induced hepatotoxicity at a dosage of 250 mg/kg, whereas slightly affected at a dosage of 500 mg/kg.

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Table 1: *Influence T. flagelliforme liver biochemistry markers TAA-produced hepatotoxic rats*

Clusters	ALP IU/L	ALT IU/L	AST IU/L	T. Bilirubin (µM/L)	T. Protein g/L	T. Albumin g/L
Normal	70.3±0.6	30.4±0.6	63.9±0.7	1.2±0.01	73.2±0.7	32.9±0.5
TAA + NS	193±1.1*	130.3±0.5*	172.5±0.5*	5.1±0.07*	45.8±0.6*	13.2±0.2*
Silymarin + TAA (50mg/kg)	62.4±0.6#	28.1±0.9#	62.5±0.6#	1.4±0.01#	68.1±0.7#	29.4±0.6#
LD + TAA (250mg/kg)	58.2±0.8#	22.3±0.6#	55.4±0.5#	1.9±0.03#	60±0.8#	22.1±0.6#
HD + TAA (500mg/kg)	54.3±0.5 #	25±0.4#	58.7±0.7#	1.7±0.05#	64.8±0.4#	25.6±0.6#

Effects of *T. flagelliforme* or silymarin on ALT, AST, ALP actions, on level of total bilirubin, albumin, protein. Values stated mean ± SEM. Important alteration normal collection *p < 0.001, Substantial variance TAA control assembly

Gross appearance of liver

The morphological changes of liver in all groups (Fig. 1 (GA)) were evaluated and showed that normal control group liver was contained smooth surface with regular lobs (Fig. 1, GA (a). TAA-induced hepatotoxic group liver was demonstrated unregular surface with several macro and micronodules (Fig. 1, GA (b)). TAA + silymarin treated group was presented smooth surface closed to normal group (Fig. 1, GA (c)). TAA + *T. flagelliforme* 250 mg/kg TAA+ *T. flagelliforme* 500 mg/kg assemblages were exhibited liver with even superficial closely maintain hepatic usual architectural structure and form (Fig. 1, GA (d, e)).

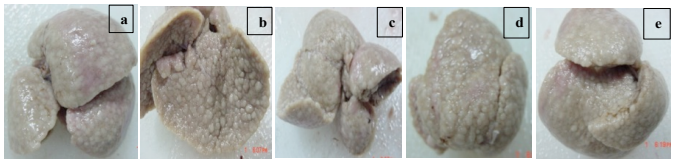

Fig. 1: Macroscopical displays influences T. flagelliforme TAA-produced hepatic injury rodents. (a) Normal cluster expressions are even superficial. (b) Rodents injected TAA demonstration several micro-nodules and macro-nodules in the hepatic parenchyma. (c) Rats inoculated TAA + silymarin viewing usual flat external. (d) Rats inserted TAA + T. flagelliforme 250 mg/kg and (e) Rodents injected TAA + T. flagelliforme 500 mg/kg. T. flagelliforme ordinary even exterior and closely reserve hepatic ordinary anatomy outline advent.

Histopathological examination of hepatocyte sections

A histopathological change of liver sections stained with hematoxylin and eosin is shown in Fig. 2 (H&E). Liver slides of the normal group are demonstrated typical hepatocytes construction, preserved cytoplasm, distinguished nucleus and nucleolus with distinct regular plates of liver cells which are divided via sinusoidal capillaries and central vein (Fig. 2, H&E (a)). Liver sections from the TAA group were showed irregular hepatocyte architecture resulting from the existence of reforming nodes. Moreover, the hepatic section is separated via a rubbery septum stretching the chief vein to the portal area. Hepatocytes presented severe damage, necrosis and extensive propagation of the bile duct, congested central vein, fatty changes, and granulocytes and monocytes which are presented surround the central vein due to the inflammation (Fig. 2, H & E stain (b)). Silymarin+TAA, low and high dose of *T. flagelliforme* + TAA groups were illustrated relative protection from hepatocyte-disruptions induced by TAA. The hepatic cellular compositions showed a reduced amount of damage with a slight fibrotic septum. Insignificant penetration of lymphocytes was observed in these liver sections groups. Moreover, the histopathological sections demonstrated remarkable regenerative parenchymal nodules, which are boarded with fibrous tissue as well as noteworthy growth in the cells-fat storing, bile ducts, and Kupffer cells (Fig. 2, H&E (c-e)). Hepatic tissues stain Masson trichrome to measure levels of tissue fibrosis. There was no collagen deposition observed in the normal control liver section (Fig 3, MT (a)). TAA group has presented a regeneration of bile duct with notable septa of dense fibers and increased the accumulation of collagen fibers surrounding the congested central vein, which are referred to severe fibrosis in the hepatic tissue (Fig. 3, MT (b)). The silymarin and *T. flagelliforme* clusters illustrated a reduction in the number of fibrous septa and regeneration nodules. In addition, the collagen fibers in all these three groups were observed to be homologous, which indicated the hepatoprotection activity of *T. flagelliforme* extract (Fig. 3, MT (c-e)).

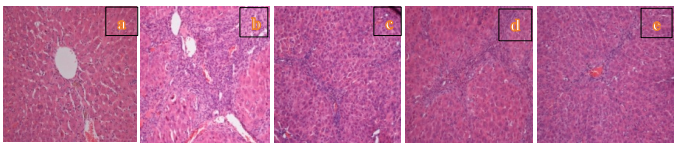

Fig. 2: Histopathology slices of the livers stained with H & E stain. (a) Normal histology construction was understood as a hepatic ordinary collection. (b) Extensive organizational injury development pseudo lobules abundant fibrous septum and propagation bile duct central lobular damage hepatic TAA assembly. (c) The minor inflammatory fibrous septum was shown hepatic parenchyma hepatoprotection rats inoculated TAA + silymarin. (d) Partial conserved hepatic cells construction minor portion of injuries and thin fibrotic septum occurred in the liver of the rat injected TAA + 250 mg/kg of the T. flagelliforme. (e) Partial conserved hepatocytes construction slight parts minor damage experiential hepatic rats inoculated TAA + 500 mg/kg T. flagelliforme (H&E stains 10x).

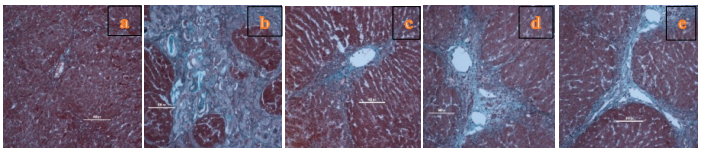

Fig. 3: Histology slices of liver stained with Masson Trichrome. (a) Normal assemblage illustrations usual hepatic construction. (b) TAA cluster demonstrations propagation bile duct, compact fibrosis septum (c) Rodents injected TAA + silymarin expressions negligible fibrous septum. (d) Rat treated with TAA + 250 mg/kg T. flagelliforme displays slight fibrous septum and uneven renewing nodes. (e) Rats inoculated TAA + 500 mg/kg T. flagelliforme confirmations slight fibrous septum. Masson Trichrome stains (amplification 10x).

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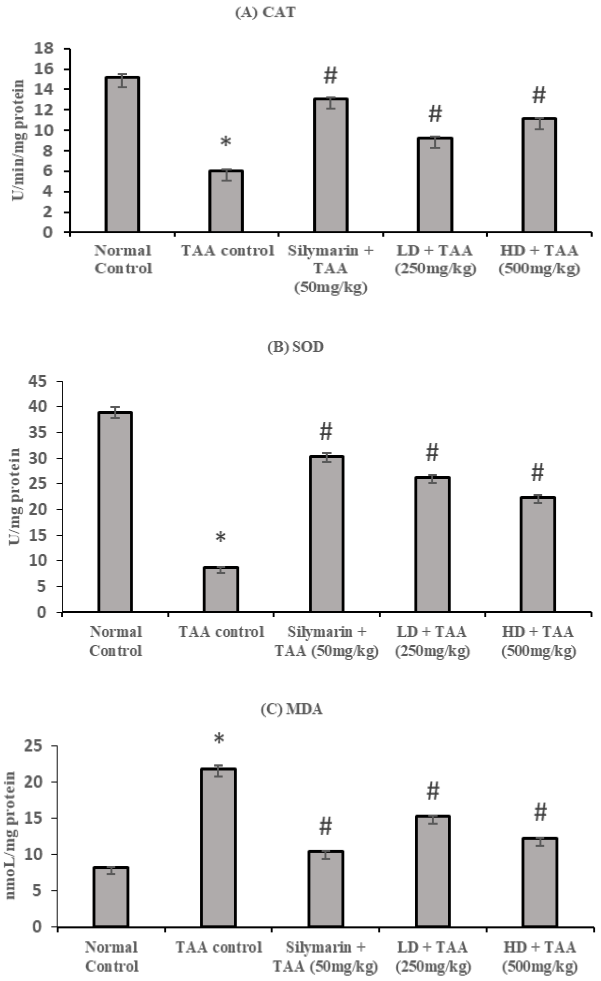

*Fig. 4: Effects of T. flagelliforme on antioxidant enzyme actions MDA amount liver. Actions of SOD, CAT, contented MDA, amount hepatic liver cells. Information stated mean ± SEM. (A) CAT (B) SOD (C). MDA. Substantial alteration normal collection at *p < 0.001, Important change TAA assemblage at #p < 0.001.*

DISCUSSION

In the present study, the hepatotoxic group was related to a visible increase in activities of liver markers in blood circulation such as ALP, ALT, AST bilirubin levels. Raise hepatic function markers imitates hepatic impairment. Similarly, increases in liver markers activities and bilirubin levels in hepatotoxic group were previously reported by several researchers [3, 17, 29]. Morals meaningfully condensed nearly usual standards after nourishing with *T. flagelliforme* extract. With the consistency of the results of our study several co-workers who used various plant extracts showed decreased in liver function enzymes activities and bilirubin level has been previously reported elsewhere [13, 30]. The hepatoprotective achievement may be due to its effect against cells leakage and injury of hepatocytes covering. TAA stated burden RNA initiative nucleus to the cytoplasm, initial exterior damage results upsurge serum hepatic pointers [4]. Current training, total protein and albumin quantities serum condensed TAA control cluster. However, silymarin or *T. flagelliforme* nourishing collections evoke these values in closely ordinary amount. Similarly, huge numbers of scientists displayed that rats' gavage silymarin or various plant extracts brought the albumin and protein to almost normal levels [11]. In the present study, Endogenous enzymes, SOD and CAT, in liver tissues homogenate suggestively condensed hepatotoxicity assemblage comparison ordinary cluster. Both enzymes become flagged by free radicals's resulting in liver weakening [30]. Meanwhile, *T. flagelliforme* expressively raised attentiveness serum CAT, SOD, via self-protective hepatic injurious influence free radicals likened TAA control collection. Analogous outcomes described formerly uncountable investigators [8, 16, 31].

Malondialdehyde (MDA) as a lipid peroxidation marker is a usual damaging procedure [17]. MDA level raised improved lipid peroxidation. Upsurge MDA initiating damages and tragedy of anti-oxidant protection to prevent the expansion of additional free radicals [3, 18]. The existing search exhibited TAA yield increase in MDA amount has been promisingly condensed by *T. flagelliforme* feeding. Parallel results have been previously reported by various academics elsewhere [11, 32]. Reduction of hepatic SOD and CAT activities in the hepatotoxic group might possibly explain elevated MDA.TAA produced liver fibrosis in rodents [33, 34]. Nonetheless, rat's gavage with *T. flagelliforme* could dramatically hasten retrieval the hepatic damages suggestively prevent effect TAA intoxication. These results consistence former trainings stated abundant inventers utilizing diverse medicinal herbs [35]. Results of the existing study presented decrease collagen deposition in *T. flagelliforme* fed groups in tissue section-stained Masson trichrome staining. Similar to consequences of present study numerous investigators used many plant extracts confirmed reduction of collagen fibers compared to TAA control group [18, 36].

CONCLUSION

According to the results the current study *T. flagelliforme* exposed significant hepatoprotective effect in reduction of TAA toxicity in rats as acknowledged by biochemical liver parameters, endogenous enzymes and histology. *T. flagelliforme* intensely raises the CAT & SOD activities, whereas significant reduction of hepatic MDA. Hepatoprotective effect of *T. flagelliforme* attributed ability avoid hepatic cells propagation, lessening oxidative stress lipid peroxidation, antioxidant free radical forager properties.

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STATEMENT OF OPPOSING ATTENTION

Writers announce that they have no recognized rival monetary benefits or individual relations could have seemed to effect effort stated in this manuscript.

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