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Research Article

# Protective Effects of Tribulus Terrestris L Extract Against Kidney Injury Induced By Sorafinib in Rats

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**Abstract:** Medicinal plants or their secondary metabolites have shown different biological effects with a wide range of pharmacological properties, one of these medicinal plants is *Tribulus terrestris* (Tt). The purpose of this research was to evaluate the possible protective effects of Tribulus terrestris fruit aqueous extract against nephrotoxic effect of Sorafinib (Sor), Sorafinib an oral anti-cancer drug approved for the treatment of advanced renal cell carcinoma (RCC). Albino Wistar rats were divided into normal control, Sorafinib alone treated group, Interaction groups and *Tribulus terrestris* alone treated group. The extract was administered at a dose of 300 mg/kg body weight, 600 mg/kg body weight for 4 weeks orally by gavage and Sorafinib was administered at a dose of 60 mg/kg body weight for three weeks orally by gavage. The findings showed that administration of Sorafinib caused a significant increase in Urea, Uric acid and Creatinin levels in comparison to negative control, Additionally significant decreases in this levels in Interaction groups compared in comparison with the positive group. The present study demonstrated the therapeutic effect of aqueous extract of *Tribulus terrestris* fruit on oxidative stress-induced nephrotoxicity of sorafenib in experimental rats.

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## INTRODUCTION

The use of herbal medicines is extensively increasing in the world due to their natural property and minimum or no side effects. Plants and their derivatives play a key role in the world health and have long been known to possess biological activity (Kumari & Singh., 2015). Tribulus terrestris is a plant that is indigenous to many parts of the world, including Europe, Asia, and Africa (Rahman and Husen., 2021). It's been used for a very long time in traditional Chinese medicine, Ayurvedic medicine, and sports nutrition to improve health and performance (Lazaro et al., 2022). Due to its medicinal qualities and possible health advantages, the fruit of T. terrestris is very significant in medicine (Khalid et al., 2022).

Many compounds with a variety of biological properties and chemical structures have been identified in Tt extract, especially steroidal saponins, flavonoids, tannins, terpenoids, polyphenol carboxylic acids, and alkaloids (polysaccharides, amino acids, and vitamins) (Semerdjieva and Zheljazkov., 2019).

Terrestris contains phytochemicals, mainly flavonoids, which have been proven to have antioxidant and anti-inflammatory effects (Stefanescu et al., 2020). These could prevent the start and spread of cancer by reducing inflammation, fighting oxidative stress, and protecting cells from harm (Kilany *et al.*, 2020).

Sorafenib tosylate is an anti-cancer agent which belongs to a family of drugs known as kinase inhibitors ,Sorafenib tosylate has been authorized by the USA Food and Drug Administration for three types of cancer advanced hepatocellular carcinoma and renal cell carcinoma and differentiated thyroid cancer (Pethe & Yadav.,2019). The efficacy of sorafenib is quite high even in patients who failed other treatments o or had only minimal response to chemotherapy (Raoul et al., 2019). It is a multi targeted molecule demonstrating its action thanks to the inhibition of proliferation and angiogenesis of tumor cells by its multi-kinase inhibitory property (Hajighasemlou et al., 2020). Sorafenib and other tyrosine kinase inhibitors cause a variety of side effects in nearly all treated patients, among them: hypertension, gastrointestinal disturbances ,diarrhea, abdominal pain, nausea, vomiting, skin reactions rashes, acne, hand-foot syndrome, fatigue and weight loss (Park et al., 2020). Among the adverse effects of Sorafenib, hepato-renal toxicity is also a common event leading to the discontinuation of the treatment (Williet et al., 2017). Several researchers attempted to minimize the dose of Sorafenib by combining it with other agents such as Chinese herbal medicines, thereby ameliorating the toxic side effects (Ting et al., 2017).

## MATERIAL AND METHOD

### The Plant Tribulus terrestris L

The fruit of Tribulus terrestris L was purchased from the local market of Hilla city and described and authenticated kindly identified as Tribulus terrestris L. by Ministry of Agriculture\ Directorate of seed Testing. the fruits were cleaned and rinsed well with water to remove dust and contaminated materials then air dried at room temperature in dark and grinded into fine powder for the experimental study.

### Plant Extraction

The hot boiled aqueous extract was prepared by dissolving 100 g of dry plant powder in an erlenmeyer flask and adding 500 ml of boiling distilled water. Then the mixture was shaken for two hours using an electric shaker before leaving it at room temperature for 24 h. The mixture was filtered with four layers of gauze and placed in a tube, then the solution was placed in a centrifuge for 10 min at 2000 rpm. The supernatant was filtered by millipore filters (0.22 μm). To achieve a dry raw extract, the filtrate mixture was concentrated by the oven for 72 h to obtain crud extract. This extract was kept at 4 °C in a clean, dark container

until used (Zheng Mu *et al.*, 1990). The aqueous crude extract was dissolved in sterile distilled water to prepare two doses (300 and 600 mg/ kg body weight) which were administered orally to laboratory rats through gavage tube (Goel et al., 2023**).**

### Drug: Sorafenib

(Nexavar., 200® mg) obtained from Bayer Healthcare (Leverkusen, Germany) was used. Pills were ground in a tissue mill. The resulting powder was mixed with distilled water and applied via gavage to rats by stomach tube.

**Dose:** A dose of (60 mg/kg body weight) was given orally and daily for 3 weeks (AbdElla & AbdelLatif., 2019).

### Laboratory Anima

Healthy adult male wistar rats *(rattus norvegicus*) were the laboratory animals that were employed in carrying out the experiments of the study. They were supplied by the animal house belongs to the Faculty of Science/Kufa University, and their age at the start of experiments was 2.5-3 months, and their weight was 165-260 grams. They were divided into groups, and each group was kept in a separate plastic cage. They were kept in well-ventilated house conditions temperature 28-31°C , humidity 50-55%, photoperiod: 12h natural light and 12h dark.

### Experimental Design

Thirty-two male albino rats were divided into eight groups :included: group I:4 rats as a normal negative control, group 2:4 rats were administrated Sorafinib orally at dose 60 mg/ kg body weight for 3 weeks (as positive control), group 3:4 rats were administrated Tribulus terrestris 300mg/ kg body weight orally for 4 weeks before reciving Sorafinib orally at dose 60 mg/ kg body weight for 3 weeks, group 4:4 rats were administrated Tribulus terrestris 600mg/ kg body weight orally for 4 weeks before reciving Sorafinib orally at dose 60 mg/ kg body weight for 3 weeks.

Group 5:4 rats were administrated Sorafinib at dose 60 mg/ kg body weight orally for 3 weeks before reciving Tribulus terrestris orally 300mg/ kg body weight for 4 weeks, group 6:4 rats were administrated Sorafinib at dose 60 mg/ kg body weight orally for 3 weeks before reciving Tribulus terrestris orally 600mg/ kg body weight for 4 weeks, group 7:4 rats were administrated Tribulus terrestris 300mg/ kg body weight orally for 4 weeks , group 8:4 rats were administrated Tribulus terrestris 600mg/ kg body weight orally for 4 weeks.

### Biochemicaltests

After the last treatment at least 24 hours from the end of the experimental period, all rats used were weighed and sacrificed under anesthesia by heart puncture. Blood samples were collected in clean and dry centrifuge tubes Sera were separated by centrifugation at 3000 rpm for 10 minutes and then frozen quickly at 20 ° C for biochemical analysis. three biochemical tests were carried out in the sera of investigated animals. They were Urea (Young., 2000), Uric acid (Tietz., 1999) and Creatinin (Young., 1995).

### Statistical analysis

Statistical analyses were performed using SPSS v. 23 and the results are expressed as the mean ± standard error of the mean. Statistical significance of differences between the control and treated groups was determined by one-way analysis of variance. ($P<0.05$) was considered to indicate a statistically significant difference between groups.

## RESULTS & DISCUSSION

In the current study, Sorafinib treatment resulted in nephrotoxicity that was evident with significant increment in serum creatinine, blood urea nitrogen, and uric acid levels in table 1 ,


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this elevation due to oxidative stress due to renal morbidity in addition to the damage caused by free radicals which in turn causes functional disturbance to the glomerular capillary in the kidney and makes it unable to filter and subtract waste, increase urea and creatinine and decrease its subtraction with urine (Yaribeygi *et al.*, 2018; Oliva *et al.*, 2019).

Because of the inability of the naphronate to subtract them with urine, due to the damage done in the twisted tubes, which has disrupted the efficiency of the naphron in clearing the body of cellular metabolite waste. The kidney 's ability to subtract creatinine and urea is an important biomarker in assessing kidney performance ( Srinivasan *et al.*, 2015).

The rise in urea and creatinine levels may also be attributed to the loss of energy source (glucose) as a result of the loss of insulin, forcing the animal to use proteins as an alternative source of energy, which results in an increase in urea and creatinine, and also agreed with (Farhan., 2017) which explained why it was elevated was due to chronic complications in some organs of the body caused by high sugar Diabetic nephropathy which is characterized by negative changes in kidney function and consequently results in its high level.

In addition to the fact that uric acid is a strong non-enzymatic antioxidant that inhibits the lipid peroxide process by binding to iron or copper or by its direct interaction with free radicals, Hyperuric acid is associated with insulin resistance, pancreatic cell dysfunction and therefore with the development of chronic kidney disease and type 2 diabetes as a result of its association with metabolic, renal and cardiovascular disorders through pathogenic mechanisms such as oxidative stress and inflammation (Lytvyn et al., 2015 ; Sayari et al., 2018; Roumeliotis et al., 2019; Shabana et al., 2022; Tatsugami et al., 2018). Who reported that treatment with Sorafinib may induce a decrease in renal function.

The present results are supported by Hussein et al., (2022) showed that treatment with Tribulus decreases significantly the creatinine levels, blood urea nitrogen, and uric acid in treated groups compared with sorafinib group in table 1. The current study agree with (Kaushik et al., 2019), who found that treatment with an aqueous extract of TT can reduce uric acid levels, with an increase in glomerular filtration rate (GFR) and a decrease in the accumulation of nitrogenous wastes in the blood. (Sharma et al., 2019) stated that the administration of a hydroalcoholic extract of TT at a dose of 300 mg/kg significantly decreased serum creatinine levels. It was found that TT alone improves the renal functions in cisplatin-induced nephrotoxic rats.

**Table 1** Changes in the levels of kidney functions parameters in experimental rats.

| Treatments | Urea (mg/dL) | Uric acid(mg/dL) | Creatinin(mg/dL) |
|---|---|---|---|
| Mean±S.D | | | |
| G1 \ Control | 2.66±0.2 | 7.222 | 0.93±0.1 |
| G2\Sorafinib | 4.52±0.5 a | 9.05±2.3 a | 1.14±0.2 a |
| G3\Tt300+S | 3.03±0.5 b | 8.29±0.1 | 0.99±0.04 b |
| G4\Tt600+S | 2.71±0.2 b | 8.73±1.1 | 0.95±0.3 b |
| G5\S+Tt300 | 3.11±0.8 b | 8.35±0.6 | 0.86±0.1 b |
| G6\S+Tt600 | 2.99±0.7 b | 6.26±2.1 b | 0.97±0.1 b |
| G7\Tribulus 300 mg\kg | 3.23±0.3 | 7.44±2.3 | 0.93±0.2 |
| G8\Tribulus 600 mg\kg | 2.73±0.2 | 8.15±1.2 | 0.76±0.1 |
| L.S.D(0.05) | 0.504 | 1.289 | 0.098 |

Letter(a) refers to significant difference comparison with the negative group

Letter(b) refers to significant difference comparison with the positive group

standard.deviation S.D

Also, our results agree with (Kamboj et al., 2020) who showed that Tribulus lowered the levels of free radicals that cause lipid peroxidation, lowering the malondialdehyde. This is because TT can eliminate free radicals.

Another experiment reported that the protective effect of Tribulus terrestris could be contributed to its ability to eliminate free radicals and induce the antioxidant enzymes expression as well as the down-regulation of pro-inflammatory markers in cellular injuries (Ali et al., 2018).

The current results are in agreement with a previous study by (Abdel-Kader *et al* 2016) who confirmed the positive effect of the plant on the kidney tissues and function. These results may be due to presence of abundant bioactive phytochemicals as glycosides, saponins, flavonoids, phytosteroids, alkaloids, glycosides, and numerous constituents in Tribulus. (Shama *et al.*, 2019). Several studies have shown that this plant had direct effects on the urinary tract as a diuretic and a uricosuric (Akram *et al.*, 2011). The herbal extract of Tribulus terrestris improves kidney function and reduces cellular oxidative stress (Najafi *et al.*, 2014). Another study found the capability of this plant to protect kidneys against heavy metals that cause kidney damages (Manikandaselvi et al., 2012).

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