Artículo original

# The protective effect of *Descurainia sophia* seed extract on oxidative stress and nephrotoxicity induced by acetaminophen in mice

El efecto protector del extracto de semilla de *Descurainia sophia* sobre el estrés oxidativo y la nefrotoxicidad inducida por paracetamol en ratones

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## ABSTRACT

**Introduction:** Acetaminophen is the most common known agent which leads to hepatic and renal toxicity at an over dose in human and experimental animals.

**Objective:** The purpose of the current study was to investigate the protective effect of *Descurainia Sophia* seed extract on oxidative stress and nephrotoxicity induced by acetaminophen in mice.

**Methods:** In this study, 60 male albino mice were randomly assigned into six groups of ten mice, and DS seed extract was administered to mice for seven days in doses of (50,100,200 and 400 mg/kg) respectively. Toxicity was induced by acetaminophen (i.p. 500 mg/kg) for 7 days. 24 hours after the acetaminophen administration the mice were sacrificed under mild anesthesia and their blood was collected to estimate blood urea nitrogen (BUN), Creatinine, Uric acid and malondialdehyde (MDA) levels also, kidneys were removed for histopathological examination.

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**Results:** Administration of acetaminophen significantly increased the BUN, creatinine, uric acid and MDA levels as compared to control group($p<0.05$). DS seed extract pre-treatment significantly decreased serum BUN, Creatinine, Uric acid and MDA levels as compared to acetaminophen group ($p<0.05$). In histopathological examination DS extract restored the damage that cause by acetaminophen especially in dose of 400 mg/kg.

**Conclusions:** Our result demonstrate that the oral administration of DS seed extract has protective effect against acetaminophen nephropathy.

**Keywords:** acetaminophen; mice; *Descurainia sophia* seed, protective effect.

## RESUMEN

**Introducción:** El acetaminofeno, también conocido como paracetamol, es un medicamento que produce toxicidad hepática y renal en dosis excesivas en humanos y animales de experimentación.

**Objetivo:** Definir el efecto protector del extracto de semilla de *Descurainia sophia* sobre el estrés oxidativo y la nefrotoxicidad inducida por paracetamol en ratones.

**Métodos:** En este estudio, 60 ratones machos albinos fueron asignados al azar en seis grupos por igual y se les administró extracto de semilla de *Descurainia sophia* durante siete días en dosis de 50, 100, 200 y 400 mg/kg. La toxicidad se indujo con paracetamol (i.p. 500 mg/kg) durante 7 días. 24 h después de la administración de paracetamol, los ratones se sacrificaron bajo anestesia suave y se recolectó su sangre para estimar los niveles de nitrógeno ureico en sangre, creatinina, ácido úrico y malondialdehído, y se extrajeron los riñones para un examen histopatológico.

**Resultados:** La administración de paracetamol aumentó significativamente los niveles de niveles de nitrógeno ureico en sangre, creatinina, ácido úrico y malondialdehído en comparación con el grupo control ($p<0,05$). El pretratamiento con extracto de semilla de *Descurainia sophia* redujo significativamente los niveles séricos de nitrógeno ureico en sangre, creatinina, ácido úrico y malondialdehído en comparación con el grupo de paracetamol ($p<0,05$). En el examen histopatológico, el extracto de *Descurainia sophia* restauró el daño causado por el paracetamol, especialmente en dosis de 400 mg/kg.

**Conclusiones:** La administración oral de extracto de semilla de *Descurainia sophia* tiene un efecto protector contra la nefropatía por paracetamol.

**Palabras clave:** acetaminofeno; ratones; semilla de *Descurainia sophia*; efecto protector.

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# Introduction

Acetaminophen (N-acetyl-p-aminophenol, APAP), is a widely used analgesic and antipyretic drug with only weak antiinflammatory properties.[1] APAP is safe and effective when administered at therapeutic doses although, previous studies have shown that overdose of this drug in humans and experimentally in animals can also lead to hepatotoxic and nephrotoxic effects.[1] It is mainly metabolized by conjugation with chloroconic acid (60%) and sulfate (35%). A small fraction of the drug is converted to hepatotoxic metabolites under the C-chromium 450 P reactions. This intermediate metabolite is detoxified by conjugation with glutathione and is excreted by cysteine and mercapturic acid conjugates.

Taking toxic doses of acetaminophen or its therapeutic doses for a long time saturates the sulfate and glucuronide pathways of conjugation, resulting in the production of more toxic metabolites and lead to GSH depletion.[2] Exhausted GSH levels allow NAPQI free to bind with other targeted cellular proteins which aggravate cellular oxidative stress and indulge in the cellular necrosis process.[2] APAP induced hepatotoxicity has been studied wildly however, APAP induced nephrotoxicity has not been clearly understood. N acetyle Cyctein-NAC is used for the treatment of liver toxicity and leads to increased liver glutathione levels but it is not able to protect the kidneys against APAP.[3]

Since kidney damage caused by APAP can induced liver and renal damage, it is necessary to find a combination that can neutralize its effect.[4] *Descurainia Sophia* (DS) seed, also known as flixweed, is a member of family Brassicaceae. DS can grow in most parts of the world especially in, Asia, Europe, northern Africa, and North America. (DS) is a popular herbal medicine which is use in China (TCM),[5,6] India and Iran for treatment of many diseases. Some medical benefits, and properties of DS extract include: asthma and cough, promote urination, analgesic, alleviate edema, and strengthen cardiac function, purgative, febrifuge, antipruritic, anthelmintic,[7] expectorant, astringent, litholytic agent[8] and internal hemorrhages.[9]

According to previous reports, *Descurainia* seeds have laxative and antiinflammations effect. it can excrete of ascarid and renal calculus,[10,11] flowers and leaves are source of

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vitamin C.[6] Although, few studies have shown the medical efficacies, mechanism and material of this plant. The effect of DS on cough, asthma, chest tightness, and palpitation was reported.[5,12] The aim of this study is evaluating of administration of high dose of acetaminophen on kidney of mice, and the protective effect of *Descurainia sophia* seed on kidney tissue against nephrotoxicity as preliminary study in human.

# Methods

## Animal

Animals male swiss albino mice (6-8 weeks old) weighing 20-25g were purchased from Pasteur Institute. Mice were kept under standard condition (temperature 23±2°C) (55±10% humidity) with 12 h light/dark cycle and provided standard pellet diet and free access to water for the experiments. The animals get addicted to the environment for 1 week before the start of experiment.

## Plant extract preparation

*Descurainia sophia* seed extract was prepared from herbarium of Medicinal Plant Research Center of Islamic Azad University, Shahrekord Branch (Sh.67D-149). In order to prepare the required extract, the dried seeds were pulverized into fine powder using a homemade grinder, the powdered grain was poured into an Arlene and then ethyl alcohol 96% was added (22 g per 21 ml of ethyl alcohol) and placed on a shaker for 24 hours. The extract was condensed using a rotary device to remove alcohol, and then was placed in an oven for 22 hours at 61°C to dry.[13]

## Study design

Experimental protocol mice were divided randomly into six groups and each group contained ten mice (A to F). Group A: as the control group received NACL 9% (i.p. 200 mg/kg) for 7 days. Group B: mice were received acetaminophen (i.p 500 mg/kg) for 7 days; Group C: mice were received acetaminophen (i.p 500 mg/kg) for 7 days, following administration of DS extract (50 mg/kg, orally) for 7 days. Group D: mice were received acetaminophen (i.p 500 mg/kg) for 7 days, following administration of DS extract (100 mg/kg, orally) for 7 days. Group E: mice were received acetaminophen (i.p 500 mg/kg) for 7 days, following administration of DS extract (200 mg/kg, orally) for 7 days and

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Group E: mice were received acetaminophen (i.p 500 mg/kg) for 7 days, following administration of DS extract (400 mg/kg, orally) for 7 days.

The treated mice received DS seed extract twice a day every 12 hours in doses of (50,100,200 and 400 mg/kg). The doses and duration of treatment were selected based on previous reports.[5,14,15] On the 9th day, animals were sacrificed 24 hours after the acetaminophen administration and their blood was collected to estimate blood urea nitrogen (BUN), creatinine, uric acid and MDA levels. Kidneys were removed and stored in 10% formalin for histopathological examination.

## Biochemical analysis

### Urea, creatinine and uric acid measurement

Their blood was taken from their heart after 24hr of acetaminophen injection. The serum was separated by centrifugation using centrifugation at 3500 rpm at 30°C for 10 minutes. urea, creatinine and uric acid concentration were measured spectrophotometrically with commercial reagent kits according to procedure provided by manufacturer (pars azmon kits) by auto analyzer machine (alfa classic).

### Malondialdehyde measurement

To measure MDA as a lipid peroxidation index, Buege and Aust (1978) method was used. In this method, the serum is mixed with an identifier (0.375% solution of thiobarbituric acid, 15% chlorostatic solution and 0.25% normal hydrochloric acid solution) and after storage in hot water bath and centrifuge, The OD was measured on 532 nm in spectrophotometer.

### Histopathological assessment

The kidney tissues were fixed in phosphate buffered formalin 10% and the pathological sections prepared by H&E staining, according to conventional methods. Sections observed under light microscope and the histological feature alteration were graded.[16]

## Statistical analysis

Statistical analyses were done using the statistical SPSS V22. The results were expressed as mean ± SE and one-way analyses of variance (ANOVAs), followed by Duncan's-test. The statistical significance of difference was taken as $p \leq 0.05$.

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# Results

## BUN, creatinine and uric acid measurement

The level of acetaminophen group significantly increased in BUN, creatinine and uric acid as compared to control group ($p<0.05$). In the levels of BUN and uric acid, we found significant decrement in E, F and D group after administration of DS seed extract compare to acetaminophen group also, there was not any significant difference between C as compared to the control group ($p>0.05$). In the creatinine level there was not any significant difference in treatment groups however administration of DS seed extract caused significant decreased in the E and F groups as compared to acetaminophen group. The best treatment was observed in the F group, (400mg/kg) as compared to the control group in BUN, creatinine and uric acid levels ($p>0.05$) (Table1).

## Lipid peroxidation (MDA) activity

Chronic administration of acetaminophen caused a significant increase in the level of MDA levels. In mice pre-treated with DS seed extract significant reduction was showed in groups of E, and F compared to acetaminophen group. ($P<0.05$), however, there was a significant difference between E and F groups as compared to the control group ($p<0.05$) (Table 1).

**Table 1 -** Treatment with different doses of *Descurainia sophia* seed extract (50, 100, 200 and 400 mg/kg) on serum levels of blood urea nitrogen, uric acid, malondialdehyde and creatinine.

| Groups | BUN (mg/dl) | Uric acid (mg/dl) | Creatinine (mg/dl) | MDA |
|---|---|---|---|---|
| Control (A) | $20.40\pm1.98^{a}$ | $7.40\pm0.392^{a}$ | $0.60\pm0.57^{a}$ | $1.00\pm0.24^{a}$ |
| B | $50.40\pm3.64^{e}$ | $12.82\pm0.703^{d}$ | $1.61\pm0.111^{d}$ | $2.61\pm0.71^{d}$ |
| C (50mg/kg) | $46.30\pm3.314^{ce}$ | $11.97\pm0.883^{cd}$ | $1.54\pm0.0093^{d}$ | $1.54\pm0.53^{d}$ |
| D (100mg/kg) | $40.50\pm3.152^{cd}$ | $10.43\pm0.553^{bd}$ | $1.41\pm0.110^{cd}$ | $1.36\pm0.10^{cd}$ |
| E (200mg/kg) | $32.10\pm1.728^{bc}$ | $9.01\pm0.495^{ab}$ | $1.10\pm0.148^{bc}$ | $1.20\pm0.48^{bc}$ |
| F (400mg/kg) | $26.90\pm3.816^{ab}$ | $8.68\pm0.504^{ab}$ | $0.98\pm0.125^{b}$ | $0.90\pm0.15^{b}$ |

Nephrotoxicity was determined 24 h later by quantifying the BUN, uric acid and creatinine. Each value represents the mean ± SD. abcd significant difference between the groups was shown after the Duncan post-test. Each letter representing a group. The confidence level is 95%.

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## Histologic examination

In the histopathological studies, the control group exhibited the normal architecture of kidneys. In the B groups, inflammatory cell infiltration, congestion, vacuolar degeneration, and necrosis were observed, which demonstrate significant renal damage. D group, was similar to C with less damage severity. In the E and E group mild vacuolar degeneration and necrosis was seen. In the group of F (400 mg/kg), Mild necrosis with minimal tissue damage were observed. Histopathologic parameters for kidneys tissues were graded in Table 2.

**Table 2 -** Histopathologic changes induced by Acetaminophen and different doses of treatment groups of DS seed extract in kidney tissue.

| Group | Inflammatory cell infiltration | Congestion | Degeneration | Necrosis |
|---|---|---|---|---|
| Control (A) | - | - | - | - |
| B | + | + | ++ | ++ |
| C (50mg/kg) | + | + | ++ | ++ |
| D (100mg/kg) | + | + | + | + |
| E (200mg/kg) | - | - | + | + |
| F (400mg/kg) | - | - | - | + |

Histopathologic assessments of the experimental parameters were graded as follows: (-) showing no changes and (+), (++) and (+++) indicating: mild, moderate and severe changes respectively.

# Discussion

The result of present study showed that acetaminophen administration resulted in a significant increase in the BUN, creatinine, and uric acid levels, indicating a significant damage to the kidneys accompanied by degeneration of tubular epithelium and inflammatory cell infiltration in the kidneys. The results of histological studies are also agreeing with biochemical findings. Histopathology of kidneys confirms the protective activity of DS extract against the acetaminophen-induced renal toxicity as it is shown by the reduction of kidney lesions such as inflammatory cell infiltration, congestion, edema, degeneration and necrosis especially at the dose of 400 mg/kg of DS extract.

Other studies have also evaluated protective effects of various herbal medicine against acetaminophen-induced toxicity and reported similar findings as increased serum BUN

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and creatinine levels in animal models.[17,18] The histopathological lesions in kidney following acetaminophen administration may be related to reduction of creatinine clearance and renal blood flow that mentioned in previous reports.[19]

MDA is one of the most well-known secondary products of lipid peroxidation, and it can be used as a marker of cell membrane injury.[20] Further, MDA is associated with the increased production of free radicals or decreased antioxidant defense system activities.[21]

The mice treated with acetaminophen have shown higher levels of MDA. this finding is agree with other reports.[22,23] Many antioxidants have showed their effects in renal toxicity by reducing oxidative markers via promoting anti-oxidative system.[24] In this regard, the antioxidative effects of DS have been established in multiple reports.[25,26]

Propagation of oxidants within renal tissue leads to structural changes in proteins, lipids, DNA, as well as functional exhaustion of critical organelles such as mitochondria.[27] According to studies, acetaminophen damages tubular tissue in kidneys resulting in functional disturbances of tubular cells in regulating the balance of electrolytes and other molecules.[28] Subsequently, these molecular events can induce adverse pathological lesions and tubular necrosis as one of the main causes of acetaminophen-induced nephrotoxicity.[29]

Therefore, using antioxidants such as bioactives in DS can be helpful to prevent negative effects of acetaminophen on kidneys. Acetaminophen also recruits inflammatory mediators to promote its nephrotoxic effects. This is supported by studies that showed beneficial effects of anti-inflammatory agents in preventing acetaminophen-induced renal toxicity.[30] Elevated levels of inflammatory cytokines such as interleukins have been described in renal tissue of models of acetaminophen -induced renal toxicity.[31]

On the other hand, DS seeds extract decreased the expression of IL-4, as a major marker of type 2 helper T response and inflammation, in mouse model of asthma.[32] In mouse model of asthma, DS seeds extract also downregulated VEGFa expression.[33] Other protective mechanisms by DS may be related to the processes initiated by acetaminophen. For example, the plant extract through its active ingredients can modulate signaling pathways such as endoplasmic reticulum stress (i.e. unfolded protein response), and PI3k/Akt/mTOR pathways.[34] Helveticoside; an active ingredient of DS was shown to role as a potent regulator of intracellular signaling pathways and gene expression.[35]

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Finally, ethanolic extract of DS seeds suppressed the activity of cytochrome P450 isoforms which are essential enzymes participating in metabolization of drugs.[36,37,38] Furthermore, the exact mechanism of DS extract and its ingredient in preventing of biological destruction of renal tissue are not identified. In the histopathological and biochemical results, our study demonstrate that *Descurainia sophia* seed extract has a protective effect on acetaminophen-induced nephrotoxicity and oxidative stress in mice's kidneys. The extract had potential protective effect in all doses but the most significant protection was seen in 400 mg/kg. Further studies are required to confirm the mechanisms responsible for nephroprotective activity of *Descurainia sophia.*

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## Conflicts of interest

There is no conflict of interest regarding this paper.

## Authors' contribution

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