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Original Research Article

THE EFFECT OF CRUDE *Nigella sativa* OIL AGAINST THE ACUTE TOXICITY OF DICLOFENAC SODIUM AND IBUPROFEN ON THE LIVER OF ALBINO MICE

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Abstract: The present research work is an investigation of the effect of *Nigella sativa* oil against the acute toxicity induced by the drugs diclofenac and ibuprofen on the liver enzymes, body weight and Hepatosomatic index of Swiss albino mice. Thirty-six healthy, adult Swiss albino mice were used to assess diclofenac- and ibuprofen-induced hepatotoxicity and the hepatoprotective effect of *N. sativa* oil. The animals were divided into the control group and five experimental groups. The animals in the control group were given saline (0.9 percent of NaCl) only, whereas the animals in experimental groups were given single sub-lethal doses of diclofenac, ibuprofen and *N. sativa* oil alone and together. A significant ($p<0.05$) reduction in the body weight of the diclofenac- and ibuprofen-treated groups was recorded. The hepatosomatic index showed significant ($p<0.05$) changes in the combined treated groups. Hepatotoxicity can be confirmed by comparing the significant ($p<0.05$) and highly significant ($p<0.01$) increase in liver enzymes in all the treated animals. The hepatoprotective effect of *N. sativa* oil was confirmed.

Key words: diclofenac; ibuprofen; hepatotoxicity; hepatoprotective; *N. sativa oil*

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are responsible for roughly 10 percent of the total of cases of drug-induced hepatotoxicity (1). NSAIDs induce anti-inflammatory activity. The mechanism of action of NSAIDs occurs via the inhibition of the cyclooxygenase enzyme (COX), thus inhibiting prostaglandins synthesis and inducing its anti-inflammatory action (2). NSAIDs induce liver damage due to the formation of reactive oxygen species (ROS), such as HO, H_2O_2, NO, and O_2. Recent studies have revealed that the administration of NSAIDs significantly increases the lipid peroxidation (LPO) by decreasing the glutathione level, which induces hepatotoxicity due to the generation of free radicals (3). A group of enzymes found in cytosol is released into the blood due to the disturbance of hepatocytes transport functions, and it results in increased enzyme levels in the blood serum, which indicates hepatocellular damage (4).

Nigella sativa (*N. sativa*), popularly known as 'black seed', is used as a spice and food preservative, and its oil extract has been reported

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to possess a plethora of activities that include anti-inflammatory, anti-cancer, anti-diabetic, anti-hyperlipidemic, anti-oxidant, nephroprotective and hepatoprotective actions (5). Thymoquinone, an active constituent of *N. sativa*, acting as an antioxidant, provides significant protection against free radical-induced lipid per oxidation (LPO) and DNA damage (6). A broad range of studies proving the hepatoprotective effects of *N. sativa* exist. Recently, Ait Mbarek *et al.* (2007) demonstrated *N. sativa* decreases hepatic metastasis from tumours, such as mastocytomas (7). Thymoquinone exhibits a hepatoprotective effect against liver damage induced by carbon tetrachloride (8) and prohibits tertbutyl hydroperoxide (TBHP)-induced depletion of glutathione (GSH). GSH is an antioxidant that depletes free radicals; however, thymoquinone increases the activities of antioxidant enzymes and protects against various forms of cancer (9).

N. sativa, through thymoquinone, increases the ratio of helper to suppressor T cells, has a stimulatory effect on macrophages, and enhances the natural killer cell activity and production of interleukin 3 (IL-3) (10). Mohamed and co-workers reported the harmful effect of dimethylaminoazobenzene (DAB) on the livers of Swiss albino mice and the protective effect of *N. sativa* oil treatment on these animals (11). *N. sativa* oil administration showed improvement in the elevation of liver enzymes induced by malathion in albino rats (12). The current study was designed to investigate the hepatoprotective effects of *N. sativa* oil against the hepatotoxicity induced by the oral administration of diclofenac and ibuprofen.

Material and methods

Housing and feeding conditions

Thirty-six healthy, adult, (12 weeks old) female Swiss albino mice, weighing 23-41 grams (g), were purchased from a local market in Lahore, Pakistan. They were kept in clean iron cages in the animal house of the Department of Zoology, Lahore College for Women University, Lahore. The study duration was 24 hours. All mice were maintained on a 12-h light/dark cycle with the temperature maintained at 22 °C (±3 °C). Mice were fed with commercial rodent chow in pellet form; drinking water was provided *ad libitum* throughout the experiment. The experiments were approved by the Research Ethical Review Committee of Lahore College for Woman University, Lahore on 4th of June, 2015 (Memo number RERC - ZOO - 099).

Chemical used

- Diclofenac: Dicloran (Diclofenac Sodium) (50 mg) SAMI Pharmaceuticals Pakistan Ltd.
- Ibuprofen 200 mg was purchased from a pharmacy. (Abbott Laboratories Pakistan Ltd).
- Crude *N. sativa* oil (TOP TREATMENTS, Pakistan Ltd).

Experiment protocol/ Dosage

The LD_{50} of diclofenac sodium in albino mice is 95mg/kg B.W, as reported by Basavraj *et al.* (2012) (13). In the current study, 20 mg/kg B.W (~1/5th of LD_{50}) of diclofenac sodium was administered to the animals. According to Zayed and Hassan (2014), the LD_{50} of ibuprofen is 740 mg/kg B.W (14). In the current study, 74 mg/kg B.W (~1/10th of LD_{50}) of ibuprofen was used. *N. sativa* oil was administered as 2.5 mL/kg B.W (15). Both drugs were first converted to powdered form, dissolved in distilled water for the preparation of the stock solution, and were finally diluted in distilled water in order to make the final volume 0.3 ml for each animal. The dose was administered using gavage after two hours of feeding.

Experiment Design

After the five days of acclimatization, the thirty-six mice were randomly divided into six groups; each group consisted of six mice.

Group 1 (Control): All the animals received 0.3 ml (0.9 percent w/v) normal saline.

Group 2 (Diclofenac treated): Mice were orally administered with sub-lethal dose i.e. 20 mg/kg B.W.

Group 3 (Ibuprofen treated): Mice received a single dose of 74 mg/kg B.W of ibuprofen orally.

Group 4 (*N. sativa* oil treated): Mice received 2.5 ml/ kg B.W of crude oil of *N. sativa.*

Group 5 (Diclofenac and *N. sativa* oil): Single oral dose of 20 mg /kg body weight of diclofenac along with 2.5 ml/kg B.W of crude oil of *N. sativa* oil was administered.

Group 6 (Ibuprofen and *N. sativa* oil): Single oral dose of 74 mg /kg B.W of ibuprofen along with 2.5 ml/kg of crude oil of *N. sativa* oil was administered.

Blood Sampling

Twenty-four hours after treatment, the mice were anesthetized, and their blood samples were collected through cardiac puncture; finally, the mice were dissected. Blood samples were centrifuged at 3000 rpm for 10 min to separate the serum, which was stored at -40 °C. The liver was removed and weighed using an electronic balance; this weight was then used to calculate the hepatosomatic index (HSI) using the formula given below.

$$\text{HSI: } \frac{\text{liver weight}}{\text{Mice weight}} \text{ x } 100$$

Biochemical parameters (ALT, AST, and ALP)

Serum alanine aminotransferases (ALT), serum aspartate aminotransferases (AST) and serum alkaline phosphatases (ALP) were analysed using standard protocols. Analysis was carried out using a semi-automated chemistry analyser (URIT 800 chemistry analyser URIT Medical Co., Ltd Guangxi, China). AST and ALT estimation was carried out using the IFCC (International Federation of Clinical Chemistry) method using AST kit by Crescent Diagnostics, Jeddah Industrial City, Phase III, Jeddah Kingdom of Saudi Arabia. According to DGKC, optimized standard method ALP was measured using Fluitest ALP DGKC ALP diagnostic kits, Analytical Biotechnologies AG 35104 Lichtenfels, Germany. Then, assay values were compared with biochemical control (ELI Tech Clinical Systems). After every ten samples, quality control was run for the calibration of equipment.

Statistical Analysis

Data were analysed using (SPSS version 19) one-way ANOVA of variance followed by the Tukey *post hoc* test for establishing a significant difference between treated groups. $p<0.05$ was considered significant, and $p<0.01$ was considered highly significant. Data were presented as mean $\pm$ S.E.M.

Results

The current study was undertaken to evaluate the hepatoprotective effects of *N. sativa* by observing changes in body weight, the hepatosomatic index, and biochemical parameters. The data in Table 1 demonstrate a significant decrease in the mean body weight of animals treated with diclofenac, ibuprofen, and diclofenac plus *N. sativa*, while the effect of *N. sativa* alone or in combination with ibuprofen was not significant (Table 1). The percentage changes in the mean body weight of respective groups are shown in Table 1.

The changes in the hepatosomatic index showed a non-significant ($p>0.05$) reduction in the groups treated with the diclofenac (D), ibuprofen (B), *N. sativa* oil (N) as compared to the control group. In contrast, the combined treatment of both diclofenac and ibuprofen with *N. sativa* (DN, BN) showed a significant change ($p < 0.05$) (Table 1).

Serum biochemical analysis

The effects of *N. sativa* on diclofenac- and ibuprofen-induced hepatotoxicity were evaluated by recording changes in serum AST, ALT, and ALP levels. There was an increase in the serum AST levels in diclofenac- and ibuprofen-treated animals in comparison to the control group. This effect was reversed in one group that received *N. sativa* along with diclofenac (Table 2).

The data in Table 2 demonstrate a trend of increased levels of serum ALT in the diclofenac- and ibuprofen-treated animals in comparison to the control. This effect was reversed in the group that received *N. sativa* along with ibuprofen (Table 2).

There is an increase in serum ALP levels in diclofenac- and ibuprofen-treated animals in comparison to their control group. This effect was reversed in both groups of *concomitant treatment of N. sativa* with diclofenac and *N. sativa* with ibuprofen. In contrast, mice treated with *N. sativa* alone remained within normal levels in comparison to the control group (Table 2).

Table 1: Comparison of the percentage increase or decrease in mean Body Weight (B.W) before and after the treatment (Mean ± SEM) and Hepatosomatic Index in the control and experimental group (D, B, N, DN and BN) after 24 hours of treatment (n=6 each group)

Treatment	Mean Body Weight			
	Before treatment(g)	After Treatment(g)	Percentage Increase or Decrease	Hepatosomatic Index (HSI)
Control (C)	23.67 ± 0.67	24.33 ± 0.67	2.78	10.06± 0.952
Diclofenac (D)	29.83 ± 0.87	27.17 ± 0.95*	8.91	9.11 ± 0.57
Ibuprofen (B)	26.50 ± 0.81	24.33 ± 0.715*	8.19	9.35 ± 0.337
N. sativa oil (N)	36.17 ± 0.703	35.33 ± 0.558	2.32	7.98 ± 0.378
Diclofenac + *N. sativa* oil (DN)	34.17 ± 0.70	32.33 ± 0.67*	5.38	7.22 ± 0.19*
Ibuprofen + *N. sativa* oil (BN)	35.83 ± 0.946	34.83 ± 1.014	2.79	7.07 ± 0.213*

*$P<0.05$

Table 2: Serum level of AST, ALT, and ALP (IU/L) enzymes following 24 h after' different treatments (n=6 each group)

Treatment	AST(IU/L)	ALT (IU/L)	ALP (IU/L)
Control (C)	91.8 ± 3.20	50.13 ± 1.67	47.64 ± 1.40
Diclofenac (D)	163.4 ± 4.22**@@	90.37±4.25**	143.20 ± 2.86**@@
Ibuprofen (B)	109.68± 3.93*##	78.24± 3.61**	106.08 ± 3.79**##
N. sativa oil (N)	96.7 ± 2.67##	61.88 ± 3.05##@	56.62 ± 2.43##@@
Diclofenac +*N. sativa* oil (DN)	143.4 ± 4.50**#@@	82.60 ± 3.70**	121.38 ± 3.80**##@
Ibuprofen +*N. sativa* oil (BN)	102.19 ± 4.32##	69.27± 3.92##@	81.74 ± 3.72**##@@

*= in comparison to C, # in comparison to D, @ in comparison to B, *, #, @ p< 0.05, **, ##, @@ p<0.01

Discussion

The current study has shown a decrease in mean body weight, which might be due to tissue damage, because it was previously reported that significant decreases in the body weights of the broiler chicks and pigeons were observed in all diclofenac-treated animals, indicating its dose-dependent toxicity (16). Recently, Mohamed et al., 2010 observed the significant decrease in body weight in DAB and DAB plus *N. sativa* treated groups compared to the untreated control group (11). Al-Khafaji (2013) also reported significant decreases in the body weight of mice that received paracetamol and crude oil of *N. sativa* together (17). In our study, the decrease in body weight might be due to the acute dose of *N. sativa oil*, as the metabolism of fats commences with the administration of this oil, and the digestion of fats (oil) requires more energy. In this case, it first reduced the body weight and then its protective effect began. *N. sativa* also produced a significant reduction in the blood level of cholesterol, triglycerides, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) in albino rats after 4 days of treatment (18). The rats treated with *N. sativa* oil showed decreased body weight which might be due to reduced food intake, thus diminishing serum lipids and glucose levels (19, 20). In another study, *N. sativa* oil treatment

showed a slight decrease in the mean body weight of Sprague-Dawley rats (21). According to Al-Khafaji (2013), liver weight is not affected by non-steroidal anti-inflammatory drugs (NSAIDs) and *N. sativa* oil in all treatments (17). In the current study, a comparison of hepatosomatic indexes among all groups has shown a non-significant decrease in liver weight, except the treated group of concurrent administration. The liver was already undergoing oxidative stress, so it could not metabolize oil as it should have if it were functioning normally. Liver weight in the combined treatment group significantly decreased, which may be due to the plethora of activities associated with *N. sativa*. Thymoquinone (an active ingredient of *N. sativa*) can increase the expression of antioxidant enzymes (e.g. GSH peroxidase and superoxide dismutase), thus reducing the NADH/NAD+ ratio leading to an inhibition in lipogenesis in the hepatocytes (22). Guiloski and co-workers (2015) reported that the diclofenac caused a non-significant reduction in the liver size (HSI) of fish (23).The current study has shown an increase in serum enzyme levels in the treated groups (i.e., diclofenac and ibuprofen), which might be due to hepatotoxicity caused by diclofenac and ibuprofen (24, 25). These enzyme levels are generally used in toxicological studies to assess hepatic function (26). It has been suggested that the raised AST levels occur due to extensive tissue necrosis, in the case of liver disease (27). Increased levels of these enzymes might be due to cellular leakage or the loss of functional integrity of cell membrane in liver (28). It was previously reported that diclofenac sodium-treated animals showed increased LPO (29, 30). Previous studies showed that the elevation of serum enzymes after ibuprofen is indicative of cellular injury to the liver (31). The current study has shown that the *N. sativa* treatment alone showed normal liver enzyme levels as that of the control group. Moreover, the biochemical results of the current study demonstrate that the combination of diclofenac and *N. sativa* attenuates the toxic effect of diclofenac as indicated by their serum AST and ALP levels. It also prevented hepatotoxicity induced by ibuprofen, as shown by their serum ALT and ALP levels. Previously, it was reported by Al-Khafaji (2013) that combined treatment of *N. sativa* with paracetamol prevents a rise in serum AST, ALT, and ALP levels because of its antioxidant properties (17). In another study, *N. sativa* oil maintained the serum levels of AST and ALT close to normal, and it showed a hepatoprotective effect against D-Galactosamine (D-GalN)/Lipopolysaccharide-induced hepatotoxicity and oxidative stress in rats (32). The severity of diclofenac is greater than that of ibuprofen because of its high dose in comparison to ibuprofen. *N. sativa* oil offers greater protection against diclofenac in comparison to ibuprofen. Previous studies showed that higher doses and longer durations of ibuprofen exposure increased hepatic toxicity (31). It was found that *N. sativa* treatment prevented CCL4-induced hepatotoxicity in rats by decreasing the lipid peroxidation and increasing the antioxidant defence system activity (8). In a study carried out for 24 hours on mice, similar findings were reported as that of the current study, which showed that the concurrent administration of *N. sativa* oil along with diclofenac and ibuprofen moderately affects serum enzyme levels (17).

Conclusion

From the results of the current study, it is concluded that when treated groups were compared with the control group, all enzymes (AST, ALT, and ALP) increased in both drug-treated groups. This elevation showed moderate decrement toward control values when herbs were combined with drugs (diclofenac and ibuprofen).

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VPLIV OLJA ČRNE KUMINE (*Nigella sativa*) NA AKUTNO ZASTRUPITEV JETER, POVZROČENO Z NATRIJEVIM DIKLOFENAKOM IN IBUPROFENOM, PRI ALBINO MIŠIH

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Povzetek: Predstavljena raziskava opisuje učinke olja črne kumine (*Nigella sativa*) na aktivnost jetrnih encimov, telesno težo in hepatosomatski indeks pri švicarskih albino miših pri akutni zastrupitvi, povzročeni z natrijevim diklofenakom in ibuprofenom. Za oceno škodljivega učinka diklofenaka in ibuprofena na jetra ter zaščitnega učinka olja *N. sativa* na jetra je bilo testiranih šestintrideset zdravih odraslih miši. Živali so bile razdeljene v kontrolno skupino in v pet poskusnih skupin. Živali v kontrolni skupini so prejele fiziološko raztopino (0,9 % NaCl), medtem ko so dobile živali v poskusnih skupinah različne subletalne odmerke diklofenaka in ibuprofena samostojno ali pa v kombinaciji z oljem črne kumine. Rezultati so pokazali statistično značilno ($p < 0,05$) znižanje telesne mase pri skupinah mišk, ki so dobivale diklofenak in ibuprofen. Pri vseh skupinah, tretiranih z diklofenakom in iboprufenom, so se pokazale statistično značilne razlike med kontrolno in tretiranimi skupinami, kar potrjuje hepatotoksični vpliv tretiranja. Hepatosomatski indeks je pokazal statistično značilne ($p < 0,05$) razlike med skupinami, ki so bile tretirane s kombinacijo učinkovin, in skupinami, ki so prejemale tudi olje črne kumine, kar kaže na hepatoprotektivni učinek olja črne kumine.

Ključne besede: diklofenak; ibuprofen; hepatotoksičnost; hepatoprotektivnost; olje *N. sativa*