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**Original article:**

# ACUTE AND SUB-CHRONIC TOXICOLOGICAL EVALUATION OF HYDRO-METHANOLIC EXTRACT OF *CORIANDRUM SATIVUM* L. SEEDS

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## ABSTRACT

*Coriandrum sativum L.* (CS) seeds are known to possess therapeutic potentials against a variety of physiological disorders. This study assesses acute and sub-chronic toxicity profile of hydro-methanolic extract of CS seeds using OECD guidelines. In acute toxicity study, mice were once orally administered 1000, 3000 and 5000 mg/kg body weight of CS extract. There were no any behavioral alterations or mortality recorded in CS treated groups. The $LD_{50}$ value was more than 5000 mg/kg body weight. In the sub-chronic oral toxicity study, the animals were orally administered with CS extract (1000, 2000 and 3000 mg/kg body weight) daily for 28 days whereas; vehicle control group received 0.5 % carboxy methyl cellulose. There was significant reduction in food intake, body weight gain and plasma lipid profiles of $CS_2$ and $CS_3$ (2000 and 3000 mg/kg body weight respectively) groups as compared to the control group. However, there were no alterations in haematological profile, relative organ weights, histology and plasma markers of damage of vital organs (heart, liver and kidney). The overall finding of this study indicates that CS extract is non-toxic up to 3000 mg/kg body weight and can be considered as safe for consumption.

**Keywords:** *Coriandrum sativum* L., hydro-methanolic seed extract, acute toxicity, sub-chronic toxicity

## INTRODUCTION

The traditional systems of medicine such as the Ayurveda, Unani and Sidda have been a treasure trove for development of majority of modern medicines. Also the medicinal research relies on ethnobotany and ethnopharmacognocy for discovery of new molecules for that conventionally result in drugs developments (Gurib-Fakim, 2006). World Health Organization (WHO) estimates that approximately 80 % of the developing world's population is using traditional medicine for primary healthcare (Bannerman, 1982). However, there is a prevalent misunderstanding that herbal medicines are devoid of toxic effects (WHO, 2004). Adverse effects of herbs have been reported including allergic reactions, hepatotoxicity (Saad et al., 2006), nephrotoxicity (Colson and De Broe, 2005; Kwan et al., 2006; Zhu, 2002; Vanherweghem, 1998), cardiac toxicity (Horowitz et al., 1996; Moritz et al., 2005; Gaibazzi et al., 2002), neurotoxicity (Ernst, 2003; Benjamin et al., 2001) and even death (Jensen and Allen, 1981) have been reported. Therefore, a pre-clinical toxicity study is

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indispensible to validate their safe medicinal use.

*Coriandrum sativum* L. (Apiaceae) (CS) is an annual herb, that is widely distributed. Its fresh leaves and dried seeds are extensively used in Middle Eastern, Mediterranean, Indian, Latin American, African and Southeast Asian cuisines. Decoction and tincture of powdered seeds of CS alone or in combination with other herbal agents are recommended for dyspeptic complaints, loss of appetite, convulsion, insomnia and anxiety (Grieve, 1971). It is also used as medication against diabetes, indigestion, flatulence, renal disorders and a diuretic agent (Grieve, 1971; Emamghoreishi et al., 2005). Its therapeutic potential in the treatment of urethritis, cystitis, urinary tract infection, urticaria, rashes, burns, sore throat, vomiting, indigestion, nosebleed, cough, allergies, hay fever, dizziness and amoebic dysentery has also been reported (Grieve, 1971; PDR for Herbal Medicines, 1998).

Phytochemical constituents of CS seeds have been studied extensively and their analysis had revealed presence of polyphenols (rutin, caffeic acid derivatives, ferulic acid, galic acid, and chlorogenic acid), flavonoids (quercetin and isoquercetin) and β-carotenoids (Melo et al., 2003). The essential oil obtained from CS seeds contains α and β-pinene, camphor, citronellol, coriandrol, *p*-cymene, geraniol, geranyl acetate, limonene, linalool, myrcene, α and β phellandrene and α and β-terpinene along with many fatty acids. Presence of water soluble compounds such as monoterpenoid glycosides, monoterpenoid glucose sulfate and other glycosides have been reported (Sergeeva, 1975; Ishikawa et al., 2003). The pharmacological activities of various extracts and essential oils of CS seeds have been studied wherein; the essential oils have been found to possess antimicrobial (Baratta et al., 1998) and antifungal properties (Garg and Siddiqui, 1992). Its efficacy as a hypoglycemic (Gray and Flatt, 1999), hypolipidemic (Chithra and Leelamma, 1997, 1999; Lal et al., 2004), hypocholesterolemic (Dhanapakiam et al., 2008), antihypertensive (Medhin et al., 1986), antioxidant (Melo et al., 2003; Ramadan et al., 2003; Bajpai et al., 2005), antimutagenic (Cortes-Eslava et al., 2004), anxiolytic (Emamghoreishi et al., 2005), antimicrobial (Kubo et al., 2004; Cantore et al., 2004), larvicidal (Consoli et al., 1988) and post-coital antifertility agent (Al-Said et al., 1987) have also been reported.

We had recently reported anti-insulin resistance (Patel et al., 2011) and cardioprotective (Patel et al., 2012) potentials of CS seed extract. Since toxicological evaluation of CS seed extract is not studied, the present study evaluates possible toxicity of CS seed extract using Economic Co-operation and Development (OECD) guidelines.

## MATERIAL AND METHODS

### *Plant material and preparation of extract*

Seeds of CS were collected (in the month of February and March) and identified by Dr. P.S. Nagar, Department of Botany, The M.S. University of Baroda. A herbarium of plant was deposited in the Department of Botany. One hundred grams of powdered dry seeds were soaked in methanol:water (80:20 v/v) at room temperature and allowed to stand for seven days. The resultant extract was filtered through a muslin cloth and then concentrated in a rotary evaporator under reduced pressure to obtain a thick semisolid brown paste (Hashim et al., 2005). The final yield was 8.3 g (w/w).

### *Experimental animals*

Adult female Swiss albino mice (20-25 g) were obtained from Zydus Cadila Research Centre, Ahmedabad, Gujarat, India. They were housed under standard animal house conditions (temperature: 23 ± 2 °C; photoperiod: 12 h light and 12 h dark; humidity: 45-50 %). They were fed with standard laboratory pellets (M/S Pranav agro, Ltd., Baroda, India) and water *ad libitum*. The animals were maintained as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) India and the experimental protocol approved by the

animal ethical committee of the Department of Zoology, The M. S. University of Baroda, Vadodara (Approval No.827/ac/04/ CPCSEA).

### *Acute oral toxicity*

Acute oral toxicity study was conducted according to the guidelines of Organization for Economic Co-operation and Development (OECD, 401). Twenty four animals were randomly allocated into four groups of six animals each. Group I (Control): animals were administered orally with vehicle (0.05 % Carboxy methyl cellulose; CMC). Remaining groups (II, III and IV) were administered with 1000, 3000 and 5000 mg/ kg body weight of CS extract respectively via gastric intubation. Doses were prepared using 0.05 % CMC and dose volume was not more than 1 ml/kg body weight. Cage side observations (tremors, convulsions, salivation, diarrhea, lethargy, sleep and coma) were recorded during first four hours and mortality was recorded after 24 h.

### *Sub-chronic oral toxicity*

The sub-chronic oral toxicity study was conducted according to the guidelines of the Organization for Economic Co-operation and Development (OECD, 407). Twenty four animals were randomly divided into four groups of six animals each. Group I ($CS_0$) served as a control and received 0.5 % CMC (vehicle) for 28 days whereas the remaining groups (Group II- $CS_1$, Group III- $CS_2$ and Group IV- $CS_3$) were orally administered 1000, 2000 and 3000 mg/kg body weight respectively of CS extract daily for 28 consecutive days. Food and water intake were recorded daily, whereas, body weight was recorded once in a week throughout study period.

### *Plasma isolation and haematology*

At the end of 28 days, blood samples were collected from overnight fasted animals through retro-orbital sinus puncture in ethylene diamine tetra acetic acid (EDTA) coated vials and plasma was separated by cold centrifugation (Plasto Crafts Superspin-R centrifuge) at 3000 rpm for 10 min. Blood was also collected for the analysis of haematological parameters such as white blood cell (WBC) count, red blood cell (RBC) count, haemoglobin (Hb) levels, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and red cell distribution width (RCDW) using BC 2300 Haematology Analyzer (Shezhen Mindray Biomedical Electronics Co., Ltd., China).

### *Plasma biochemical parameters*

Creatinine kinase-MB (cardiac damage), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, total protein (liver damage) and urea and creatinine (kidney damage) were analyzed using commercially available kits (Recon diagnostic Ltd., Vadodara, India). Also, plasma glucose and lipid profile [total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL-C)] were assessed and low density lipoprotein (LDL-C) and very low density lipoprotein (VLDL-C) were calculated by Friedewald's formula (Friedewald et al., 1972).

### *Relative organ weights and histopathology*

Animals were later sacrificed by cervical dislocation under mild ether anesthesia for autopsy and liver, kidney, heart, lung and spleen were excised, rinsed in 0.9 % saline and weighed. After sacrifice, organ weights (lungs, heart, liver, kidney and spleen) were recorded and relative organ weights (ROW) were calculated as follows.

$$\text{ROW} = \frac{\text{Absolute organ weight (g)} \times 100}{\text{Body weight on the day of sacrifice (g)}}$$

Tissue pieces of vital organs (heart, liver and kidneys) were fixed in 10 % paraformaldehyde for paraffin histology and processed in paraffin embedding as per the standard protocol. 7 µm thick sections of each tissue were stained with hematoxylin and eosin, and observed for possible histopathological damages.

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## RESULTS

### *Acute oral toxicity*

Cage side observations did not record any behavioral changes such as tremor, convulsion, salivation, diarrhea, lethargy or sleep during the first four hours of CS extract (1000, 2000 or 3000 mg/kg body weight) administration. After 24 h there was no mortality recorded in plant extract administered groups. However, urine output was found to be increased in CS treated animals (1000, 2000 or 3000 mg/kg body weight) as compared to the control (data not shown).

### *Sub-chronic oral toxicity*

### *Body weight gain, food and water intake*

$CS_1$ and $CS_2$ groups did not record any significant alterations in body weight gain. However, $CS_3$ group (3000 mg/kg body weight) recorded significant ($p<0.001$) decrement in body weight gain. Further, there was significant ($p<0.05$ and $p<0.001$ respectively) reduction in food intake of $CS_2$ and $CS_3$ groups as compared to $CS_0$. Water intake was significantly ($p<0.05$, $p<0.01$ and $p<0.001$ respectively) increased in all the CS extract administered groups as compared to $CS_0$ group (Table 1).

### *Haematology*

The haematological parameters (RBC, WBC, Hb, MCV, MCH, MCHC, RCDW, monocytes, lymphocytes, eosinophil) did not record any significant alterations in any of CS administered groups (Table 2).

### *Biochemical parameters*

Plasma glucose recorded moderate non-significant decrement in $CS_2$ and $CS_3$ groups. Also, plasma TC, TG, LDL and VLDL levels recorded moderate to significant reductions in all the CS treated groups but, plasma HDL levels were unaltered (Table 4). Plasma marker of creatinine kinase-MB, AST, ALT, bilirubin, total protein, urea and creatinine did not record significant alterations in any of the CS treated groups as compared to the $CS_0$ group (Table 3).

### *Relative organ weights and histopathology*

There were no significant changes in ROW of CS treated groups as compared to $CS_0$ group (Table 5). A detailed scrutiny of histoarchitecture of the heart, liver and kidney did not reveal any observable cellular damage. The cellular morphology, nuclear characteristics and tissue integrity of organs of CS treated groups were comparable to the $CS_0$ group (Figure 1).

**Table 1:** Effect of *Coriandrum sativum* L. seed extract sub-chronic oral administration on food intake, water intake and body weight

| Groups | Body weight (gm) | | Weight gain gm | Food intake gm/day | Water intake ml/day |
|---|---|---|---|---|---|
| | Initial | Final | | | |
| $CS_0$ | 21.78±0.76 | 25.10±0.70 | 3.32±0.25 | 5.22±0.21 | 7.47±0.83 |
| $CS_1$ | 23.87±0.65 | 26.12±0.38 | $2.82±0.22^{ns}$ | $4.43±0.33^{ns}$ | $10.80±0.63^{*}$ |
| $CS_2$ | 23.32±0.41 | 25.64±0.40 | $2.30±0.35^{*}$ | $3.78±0.39^{*}$ | $11.27±0.39^{**}$ |
| $CS_3$ | $24.48±0.39^{*}$ | 26.24±0.34 | $1.68±0.23^{***}$ | $3.24±0.24^{***}$ | $11.46±0.56^{**}$ |

where n=6. Data were expressed as mean ± S.E.M. * ($p<0.05$), ** ($p<0.01$), *** ($p<0.001$) and ns (not significant) when $CS_0$ v/s $CS_1$, $CS_2$ and $CS_3$

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**Table 2:** Effect of *Coriandrum sativum* L. seed extract sub-chronic oral administration on haematological parameters

| Parameter | Groups | | | |
|---|---|---|---|---|
| | $CS_0$ | $CS_1$ | $CS_2$ | $CS_3$ |
| RBC (x $10^{12}$/l) | 8.70±0.20 | 8.52±0.07$^{ns}$ | 8.72±0.29$^{ns}$ | 8.93±0.10$^{ns}$ |
| Hb (g/dl) | 16.14±0.29 | 16.22±0.17$^{ns}$ | 16.42±0.53$^{ns}$ | 16.62±0.13$^{ns}$ |
| MCV (fl) | 44.73±0.92 | 44.23±0.93$^{ns}$ | 44.17±0.73$^{ns}$ | 42.80±0.15$^{ns}$ |
| MCH (pg) | 18.72±0.19 | 18.94±0.18$^{ns}$ | 19.02±0.34$^{ns}$ | 18.64±0.26$^{ns}$ |
| MCHC (g/dL) | 44.56±0.55 | 44.62±0.59$^{ns}$ | 43.78±0.98$^{ns}$ | 43.00±0.57$^{ns}$ |
| RCDW ( %) | 18.00±0.19 | 17.60±0.30$^{ns}$ | 17.67±0.26$^{ns}$ | 17.45±0.25$^{ns}$ |
| WBC (x $10^3$/µl) | 16.33±0.48 | 16.27±0.23$^{ns}$ | 16.43±0.83$^{ns}$ | 16.53±0.21$^{ns}$ |
| Monocytes ( %) | 2.02±0.15 | 2.16±0.20$^{ns}$ | 2.12±0.15$^{ns}$ | 2.05±0.16$^{ns}$ |
| Lymphocytes ( %) | 7.34±0.15 | 7.30±0.25$^{ns}$ | 7.18±0.24$^{ns}$ | 7.06±0.18$^{ns}$ |
| Eosinophils ( %) | 2.34±0.23 | 2.10±0.43$^{ns}$ | 1.79±0.21$^{ns}$ | 1.88±0.27$^{ns}$ |
| Platelet (x $10^3$/µl) | 678.60±29.43 | 669.40±24.14$^{ns}$ | 667.40±20.00$^{ns}$ | 661.20±15.83$^{ns}$ |
| MPV (fl) | 10.06±0.09 | 9.98±0.06$^{ns}$ | 10.02±0.14$^{ns}$ | 10.00±0.09$^{ns}$ |

RBC: Red blood corpuscle, Hb: Haemoglobin; MCV: Mean corpuscular volume, MCH: Mean corpuscular haemoglobin, MCHC: Mean corpuscular haemoglobin concentration, RCDW: Red cell distribution width, WBC: white blood corpuscle, MPV: Mean platelet volume, where n=6. Data were expressed as mean ± S.E.M. ns (not significant) when $CS_0$ v/s $CS_1$, $CS_2$ and $CS_3$

**Table 3:** Effect of *Coriandrum sativum* L. seed extract sub-chronic oral administration on plasma markers of heart, liver and kidney damage

| | | Groups | | | |
|---|---|---|---|---|---|
| | | $CS_0$ | $CS_1$ | $CS_2$ | $CS_3$ |
| Cardiac damage markers | Creatinine kinase-MB (U/L) | 40.60±5.42 | 43.72±7.40$^{ns}$ | 45.27±4.88$^{ns}$ | 40.79±4.06$^{ns}$ |
| Hepatic damage markers | Aspartate transaminase (U/L) | 29.50±2.06 | 26.50±2.07$^{ns}$ | 27.17±2.94$^{ns}$ | 30.83±3.34$^{ns}$ |
| | Alanine transaminase (U/L) | 22.60±2.20 | 19.40±2.40$^{ns}$ | 21.20±1.49$^{ns}$ | 21.60±3.23$^{ns}$ |
| | Bilirubin (mg/dl) | 1.86±0.22 | 1.79±0.14$^{ns}$ | 1.83±0.15$^{ns}$ | 1.97±0.10$^{ns}$ |
| | Total protein (g/dl) | 4.66±0.12 | 4.59±0.03$^{ns}$ | 4.85±0.25$^{ns}$ | 4.86±0.19$^{ns}$ |
| Kidney damage markers | Urea (mg/dl) | 58.69±6.39 | 58.92±4.44$^{ns}$ | 65.45±6.92$^{ns}$ | 62.30±6.96$^{ns}$ |
| | Creatinine (mg/dl) | 0.32±0.03 | 0.32±0.05$^{ns}$ | 0.36±0.04$^{ns}$ | 0.38±0.05$^{ns}$ |

where n=6. Data were expressed as mean ± S.E.M. ns (not significant) when $CS_0$ v/s $CS_1$, $CS_2$ and $CS_3$

**Table 4:** Effect of *Coriandrum sativum* L. seed extract sub-chronic oral administration on plasma glucose, lipid profile and lipoprotein profile

| | Groups | | | |
|---|---|---|---|---|
| | $CS_0$ | $CS_1$ | $CS_2$ | $CS_3$ |
| Blood glucose (mg/dl) | 146.20±4.97 | 155.7±7.06$^{ns}$ | 139.2±5.52$^{ns}$ | 134.2±4.71$^{ns}$ |
| TC (mg/dl) | 60.33±3.99 | 51.50±5.11$^{ns}$ | 44.17±5.40$^{ns}$ | 45.83±3.09* |
| TG (mg/dl) | 16.50±1.26 | 11.83±1.38* | 11.17±1.32* | 10.33±2.15* |
| VLDL-C (mg/dl) | 3.30±0.25 | 2.36±0.31* | 2.23±0.23* | 2.06±0.30* |
| LDL-C (mg/dl) | 33.21±4.57$^{ns}$ | 25.61±5.62$^{ns}$ | 20.52±4.24$^{ns}$ | 20.74±3.34$^{ns}$ |
| HDL-C (mg/dl) | 23.55±1.14$^{ns}$ | 24.03±1.03$^{ns}$ | 23.30±0.66$^{ns}$ | 23.03±0.78$^{ns}$ |

where n=6. Data were expressed as mean ± S.E.M. ns (not significant) when $CS_0$ v/s $CS_1$, $CS_2$ and $CS_3$

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**Table 5:** Effect of *Coriandrum sativum* L. seed extract sub-chronic oral administration on relative organ weight

| Organs (gm) | Groups | | | |
|---|---|---|---|---|
| | $CS_0$ | $CS_1$ | $CS_2$ | $CS_3$ |
| **Lungs** | 0.51±0.01 | 0.54±0.01$^{ns}$ | 0.54±0.03$^{ns}$ | 0.54±0.02$^{ns}$ |
| **Heart** | 0.42±0.01 | 0.43±0.01$^{ns}$ | 0.42±0.01$^{ns}$ | 0.40±0.01* |
| **Liver** | 3.58±0.13 | 3.72±0.08$^{ns}$ | 3.61±0.11$^{ns}$ | 3.50±0.10$^{ns}$ |
| **Kidney** | 1.10±0.05 | 1.16±0.05$^{ns}$ | 1.12±0.02$^{ns}$ | 1.00±0.03$^{ns}$ |
| **Spleen** | 0.30±0.01 | 0.27±0.01$^{ns}$ | 0.29±0.02$^{ns}$ | 0.30±0.17$^{ns}$ |

where, n=6. Data were expressed as mean ± S.E.M. ns (not significant) when $CS_0$ v/s $CS_1$, $CS_2$ and $CS_3$

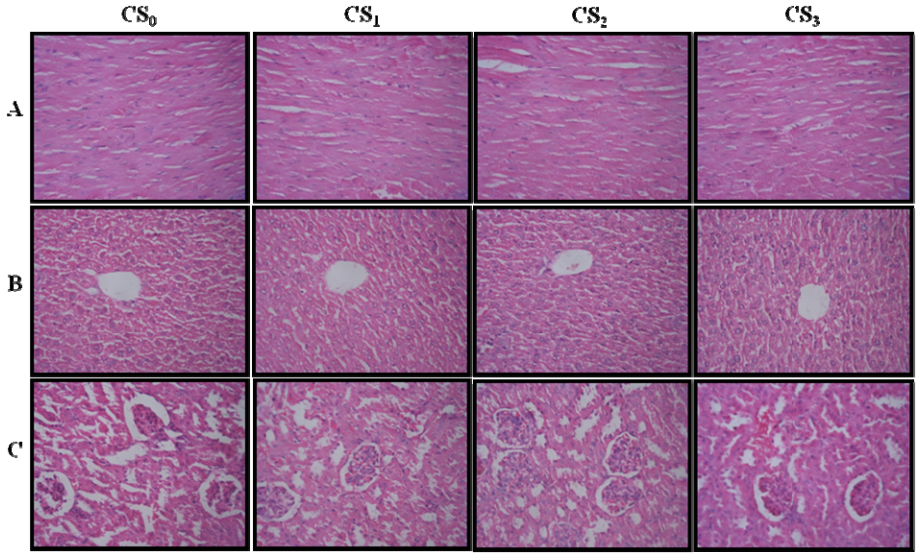


**Figure 1:** Photomicrographs of the sections of the heart (A), liver (B) and kidney (C) of control ($CS_0$) and CS administered ($CS_1$, $CS_2$ and $CS_3$) mice for 28 days showing no histoarchitecture change in CS treated groups as compared to control

## DISCUSSION

Acute toxicity study recorded zero mortality at the end of 24 h period, following CS extracts administration. No behavioral alterations were recorded during the first four hours after administration of CS extract. Hence, the $LD_{50}$ of CS extract is thought to be greater than 5000 mg and therefore CS extract can be considered as non-toxic up to the said dose (OECD 401).

Sub-chronic oral toxicity studies have provided information on drugs that can possibly pose health risks (Ministério de Saúde/Brasil, 2004). Twenty eight days of oral administration of CS ($CS_2$ and $CS_3$) extract showed significant decrement in food intake and body weight gain as compared to $CS_0$ mice. Significant reduction in food intake is suggested as responsible for the observed decrement in body weight gain. Loss of appetite is often synonymous with weight loss due to disturbances in carbohydrate, protein or fat metabolisms (Klaassen, 2001) and the same might be a possible reason for the weight loss in our study. CS ($CS_2$ and $CS_3$) treated mice also showed significant decrement in plasma TC, TG, LDL and VLDL whereas glucose and HDL levels were unchanged. These results indicate that higher doses of CS ($CS_2$ and $CS_3$) results in a reduction of food

intake and subsequent decrement in lipid profile whereas a lower dose ($CS_1$) does not lead to any such negative impact on metabolism.

CK-MB is an enzyme present in the myocardium that leaks out only under conditions of massive myocardial damage resulting from disintegration of contractile apparatus and increased sarcoplasmic permeability (Mair et al., 1994). Observed normal levels of CK-MB under all doses CS administration is reflective of its normal functional status and negligible damage. The same is further validated through the histology of heart of CS treated groups that reveals presence of intact myocardium. However, marginal increment in ROW of heart in $CS_3$ group is inexplicable and warrants further scrutiny.

High levels of AST and ALT are reported in liver diseases or hepatotoxicity (Brautbar and Williams, 2002). Plasma AST, ALT and bilirubin of $CS_0$ and CS treated groups were comparable thus indicative of normal functional status of liver. The ROW and histopathological observations of liver showed no significant changes following CS treatment.

Renal dysfunction can be assessed by concurrent measurements of urea and creatinine and their normal levels reflect at reduced likelihood of renal problems (Davis and Bredt, 1994). In the present study, changes in plasma urea and createnine levels in CS treated groups showed non-significant differences on a dose dependent manner indicating a normal renal function. Healthy status of the kidneys of CS treated groups was further confirmed by their histoarchitecture and ROW. However, higher urine output observed in $CS_2$ and $CS_3$ treated groups can be attributed to its diuretic property as reported earlier by other research groups (Aissaoui et al., 2008; Jabeen et al., 2009).

The haematopoietic system is one of the most sensitive targets for toxic compounds and hence it is mandatory to record any possible alterations resulting from a test substance (Olson et al., 2000). Change in haematological parameters has a higher predictive value, when the data of drug toxicity on animal studies are translated for clinical usage (Adeneye and Adokiye, 2008). A normal haematological profile of CS treated groups also further justified the non-toxic nature of CS extract.

## CONCLUSION

In light of these findings, we may conclude that CS extract is not toxic in all the doses studied herein. This study is the first report that evaluates toxicity of CS extract and defines it as non-toxic up to a dose of 3000 mg/kg body weight.

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