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EVALUATION OF HEPATOPROTECTIVE ACTIVITY OF NANOSUSPENSION CONTAINING *CORIANDER SATIVUM* EXTRACTS

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ABSTRACT

Liver is a highly susceptible organ to damage because of its vital role in the bio transformation and clearance of drugs/chemicals. Hepatotoxicity is the major factor responsible for drug withdrawal from the market. There is no doubt that hepatotoxicity requires considerable attention and that every viable measure to be taken towards an efficient mechanism for hepatoprotection. Among that the Nanosuspension containing *Coriander sativum* extracts will enhance the Hepatoprotective activity of male swiss albino mice with hepatotoxic liver, which was induced by Carbon tetra chloride (CCl_4).

Key words: *Coriander sativum*, Hepatoprotective activity, Carbon tetra chloride etc.

INTRODUCTION

Medicinal plants have been acknowledged and are extremely valued all over the world as a prosperous source of bioactive for the prevention and treatment of ailments. Herbal medicines arebeing used by about 80% of the world population primarily in the developing countries for primary health care. They have stood the test of time for their safety, efficacy, cultural acceptability and minimal side effects.

Nanosuspensions differ from Nanoparticles, which are polymeric colloidal carriers of drugs (Nanospheres and nanocapsules), and from solid-lipid nanoparticles (SLN), which are lipid carriers of drug. The key difference from conventional formulations of suspensions is that the particle size distribution of the solid particles in nanosuspensions is usually less than 1µm (i.e. 0.1nm-1000nm), with an average particle size range between 200–600 nm. On the other hand, the particle diameter required in most good pharmaceutical suspensions, is 1 to 50 µm. In nanosuspensions, the overall bioavailability is improved by an increase in surface area and saturation solubility via particle size reduction. This system cannot be achieved by the conventional milling techniques (Elaine M *et al*., 2008).

The oral route is the preferred route for drug delivery because of its numerous well-known advantages. The efficacy or performance of the orally administered drug generally depends on its solubility and absorption through the GIT. Hence, a drug candidate that exhibits poor aqueous solubility and/or dissolution-rate limited absorption is believed to possess low and/or highly variable oral bioavailability. Owing to low oral bioavailability, such a drug candidate would have to be administered in a larger excess than actually required if it were completely bioavailable in order to achieve a therapeutically active concentration, thus making the therapy costly (Date AA *et al*., 2004).

Nano-sizing of such drugs can lead to a dramatic increase in their oral absorption and subsequently bioavailability. The amelioration in oral bioavailability can be attributed to the adhesiveness of the drug nanosuspension, increased surface area (due to reduction in particle size by 10–50 fold), and increased saturation

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solubility, leading to an increased concentration gradient between the gastrointestinal tract lumen and blood, and increased dissolution velocity. This enhancement in bioavailability will lead to a subsequent reduction in drug dose, rendering the therapy cost-effective and obliterating any undue drug dumping in the body (Kumar MS *et al*., 2011).

MATERIALS AND METHODS

Extraction process by using soxhlet apparatus

The coarse powder of whole plant of *Coriander sativum* was extracted with Dichloromethane in herb: menstrum ratio of 1:6 by hot solvent extraction by heating with it for 12 hr. The methanolic extract was concentrated under reduced pressure to obtain a dark green coloured sticky mass.

Screening of phytochemical constituents of crude extract

The phytochemical constituents are screened by Phyto Chemical Test, Thin Layer Chromatography (TLC).

Formulation of Nanosuspension containing *Coriander sativum* crude extract

The crude extract was dissolved in an organic solvent and this solution was mixed with a miscible anti-solvent for precipitation. In the water-solvent mixture, the solubility is low and the drug precipitates. Precipitation has also been coupled with high shear processing. This is accomplished by a combination of rapid precipitation and high-pressure homogenization.

In order to produce the nanosuspension, the drug *Coriander sativum* extract (40 mg) was dissolved in glacial acetic acid (5 ml). Surfactant like sodium lauryl suphate and span 60 was dissolved in water (10ml). This solution was homogenized at various RPM, meanwhile the solution containing drug was incorporated drop wise and the homogenizing process was continued until the particle size is reduced. The size reduction process resulted in a suspension in the nanometer range, i.e. a nano suspension. High shear and/or thermal energy is required for this process. Rapid addition of a drug solution to an anti-solvent leads to sudden super saturation of the mixed solution, and generation of fine crystalline or amorphous solids. Precipitation of an amorphous material may be favoured at high super saturation when the solubility of the amorphous state is exceeded. The basic principles are precipitation and homogenization. A combination of these techniques results in smaller particle size and better stability in a shorter time. The major drawback of the precipitation technique, such as crystal growth and long-term stability, can be resolved in this process (Date AA *et al*., 2004).

Acute toxicity studies

According to the guideline 423 acute toxicity studies were performed for the crude extract of *Coriander sativum.* Two groups of albinomice such that A and B were selected in each containing 6 mice. 1g/kg body drug were given to each mice and observed for 24 hrs[9].

Experimental Design

Animals were divided into five groups (n = 6). Considering human dose (HD) of Livogen (HD-15 ml daily) and, the mice dose was calculated on the basis of weight of the mice.

Group I: Normal control vehicle i.e. distilled water, Group II: Negative control CCl4 (0.5 ml/kg, i.p.), Group III: Livogen (0.216 ml/kg, p.o.), Group IV: Extract treated (20 mg / kg)

Group V: Nanosuspension treated (0.216 ml/kg), treatment duration was 13 days, and the dose of CCl_4 (30% v/v in olive oil) is administered after every 24 hrs. CCl_4 is given orally for 5 days to induce hepatotoxicity. On 6^{th} day the dose is given to Group III, IV, and V according to the weight of the mice. This dose is given orally for 7 days. Animals were sacrificed on 13^{th} day. Blood was collected, allowed to clot and the serum is separated. The liver was dissected out and used for biochemical studies (Kaplowitz N, 2001; BegumTN, 2011; Wagner H *et al*., 1986).

Biochemical Estimation

The blood was obtained from all the animals by puncturing the retro-orbital plexus. The blood samples were allowed to clot for 45 min at room temperature. Serum was separated by centrifugation at 2500 rpm for 15 min at 30°C and utilized for the estimation of various biochemical parameters, namely, SGOT, SGPT, Total Protein (Beacon diagnostic kit, Navsari) and Billirubin (Bio lab diagnostic kit, Maharashatra) (Roberts L *et al*., 1998; Bhawna S and Kumar SU, 2009; Mannering GJ, 1968).

RESULTS AND DISCUSSION

In this study, mice treated with a single dose of CCl_4 developed significant hepatic damage and oxidative stress, which was observed from a substantial increase in the activities of Serum, SGOT, SGPT, Total protein and Bilirubin. This is indicative of cellular leakage and loss of the functional integrity of the cell membrane in liver. CCl_4 is one of the most commonly used heaptotoxin for experimental study of liver disease. The lipid peroxidative degradation of biomembrane is one of the principle cause of hepatotoxicity of CCl_4. This is evident from an elevation in the serum marker analysis, namely AST, ALT, total proteins and bilirubin. The formulations significantly reduced this serum enzyme in groups. The simultaneous administration of formulations and CCl_4 produced significant recovery of the liver damage induced by CCl_4.

Table 1. *In-vivo* studies showing the difference in biochemical parameters in infected and drug treated liver

Group	SGOT (IU/L)	SGPT (IU/L)	Total Protein (g/dl)	Total Bilirubin (mg/dl)	Liver Weight (g/100 b.w)
I – Control Group	21.54 ± 0.15^{a}	41.53 ± 0.16^{a}	6.34 ± 0.02^{a}	0.80 ± 0.000^{a}	5.01
II – Negative control	$26.09 \pm 0.80^{***}$	$46.47 \pm 1.07^{***}$	$9.10 \pm 0.47^{***}$	$1.98 \pm 0.002^{***}$	6.03
III – Livogen groups	$22.98 \pm 0.54^{***b}$	$43.94 \pm 0.54^{***b}$	$7.77 \pm 0.12^{*** a}$	$1.44 \pm 0.002^{***b}$	5.48
IV – Extract treated group	$24.52 \pm 0.39^{**b}$	$45.58 \pm 0.96^{*b}$	$7.46 \pm 0.02^{*** a}$	$1.24 \pm 0.002^{***b}$	5.51
V – Nanosuspension treated group	$22.92 \pm 0.83^{***b}$	$42.55 \pm 0.12^{***b}$	$6.85 \pm 0.05^{*** a}$	$0.94 \pm 0.002^{***b}$	5.16

a = Group I Vs Group II; b = Group II Vs Group III – V; $p< 0.001$ (***); $p < 0.01$ (**); $p < 0.05$ (*).
All the values are shown are mean ± SEM, n=6.

The hepatotoxic effect of CCl_4 is largely due to its active metabolite trichloromethyl radical that binds to the macromolecule and induces peroxidative degradation of the membrane lipids of endoplasmic reticulum that is rich in polyunsaturated fatty acids. This leads to the formation of lipid peroxide, which in turn produces a toxic aldehyde that causes damage to liver. This was evident by an increase in the level of lipid peroxidation in the CCl_4 group and there was a significant decrease in lipid peroxidation in the groups treated with CCl_4 and formulations.

The comparative histopathological study of the liver from different groups of mice corroborated the hepatoprotective efficacy of formulations. Various pathological changes such as steatosis, centrilobular necrosis and vacuolization observed in group II mice were prevented to a moderate extent in groups III, IV and V. All the effects of formulations were comparable with Livogen as a positive control.

The biochemical studies in albino mice revealed that CCl_4-induced hepatic injury was inhibited significantly by extract and nanosuspension containing *Coriander sativum*. All the results can be compared with the standard drug Livogen. The above results also state that nanosuspensions containing *Coriander sativum* has shown significant hepatoprotective activity in comparison to Livogen. In support, the histopathological reports also revealed that there is a regenerative activity in the liver cells.

The present study is to investigate the nanosuspension containing *Coriander sativum* extracts against the hepatotoxic activity. And results shown that the nanosuspension shows very significant effect on hepatotoxic liver of male Wistar albino mice induced by CCl_4. When compared to Negative control group, Extract group and nanosuspension group shown Hepatoprotective effect based on SGOT, SGPT, Bilirubin and Total protein datas. When compared to extract group Nanosuspension group shows very significant Hepatoprotective activity.

CONCLUSION

Results conclude that nano suspensions containing *Coriander sativum crude* extract was a better and efficient dosage form than marketed available Livogen syrup.

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