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Pharmacological Evaluation of Coriander Seeds against High Fat Diet-Induced Cholelithiasis

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Abstract

Coriander (*Coriandrum sativum L.*) seeds have been documented for their traditional use in lowering cholesterol. The seeds were evaluated for their anticholelithic effects as no satisfactory pharmacological treatment is yet available for cholelithiasis, except cholelithotomy. Cholelithiasis was induced in albino mice by feeding them with high fat diet (HFD) for eight weeks. Treatment group was given 10 % coriander seeds powder (CsS) added in HFD. Experimental animals were analyzed for percent weight gain, total cholesterol levels and cholesterol gallstone grade. Histopathological analysis of gallbladder was also performed. CsS was found to be effective in reducing cholesterol gallstone incidence, preventing hypercholesterolemia and excessive weight gain in experimental animals. The data obtained from the current study justified the therapeutic importance of *Coriandrum sativum* against cholelithiasis. However, further studies are required to explore the underlying mechanism and to separate active compound(s) responsible for the antilithic potential of *C. sativum*.

Keywords: Cholelithiasis; *Coriandrum sativum*; High fat diet; Gallstone grade

Introduction

Cholelithiasis or gall stone formation is a highly prevalent gastrointestinal disorder that occurs due to altered homeostasis of biliary and hepatic cholesterol [1]. It is a major health problem in developing countries like Pakistan with a prevalence rate of approximately 4% in males and 14% in females [2]. Gallstones are formed when cholesterol concentration in gallbladder reaches super-saturation point or abnormal synthesis of conjugated bilirub in that may be due to discharge of calcium ions from necrotic bile duct, bacterial β-glucuronidase or a result of erythrocytes lysis. Gall bladder stasis, enhanced cholesterol nucleation and reduction in biliary lipids are important factors in predisposing a person to gallstones. Choleliths or gallstones are aggregates of biliary components and are of two main types; 80% are composed of cholesterol called cholesterol gallstones, while 20% are made up of calcium and bilirubin known as pigment stones. Cholelithiasis remains asymptomatic until stones reach detectable size with any of the symptoms such as prolonged deep ache in right upper abdomen accompanied with fever, emesis and jaundice. Clay colored stools along with intolerance to high calorie food is also an indication of gallstones. It can be diagnosed by complete blood test, determining cholesterol and bilirubin levels in serum. To confirm the presence of stones and inflammation or blockade due to stones, various imaging techniques are employed. Cholecystectomy and lithotripsy are the only medical interventions to treat this disease; but, associated with lifelong complications and recurrence.

The use of plant-derivedmedicineshas gained popularity worldwide as these arenon-toxic, cost effective and readily accessible [3]. *Coriandrum sativum L.* (Family: Apiaceae/ Umbelleferae) is edible herb, found all over Asia, especially in Pakistan.Its seeds are excellent source of minerals.The seed oil consists of a number of compounds; the major components are anethol, borneol, bornyl acetate,camphor, camphene, carvone, cineole, cymene, coriandrin, dihydrocoriandrin [4], coriandrones A, B, C&E, p-hydroxybenzoic acid, limonene, linoleic acid, myrcene, myristic acid, myristicin, oleic acid, palmitic acid, phellandrene, terpinene, terpineol, umbelliferone,pinene, quercetin, rutin, sitosterol and stigmasterol [5], linalool (37.7%), γ-terpinene(14.4%) and geranyl acetate (17.6%) [6].

The reported activities of *Coriandrum sativum* includeanti-inflammatory [7], antioxidant [8], hepatoprotective [9],

hypolipidemic [10], anthelmintic, anti-bacterial [11], anti-fungal [12], anti-anxiety [13], anticonvulsant [14], sedative and hypnotic [15], mutagenic [10], anti-cancer [16], anti-diabetic [17], antihypertensive and diuretic [18], gastric mucosal protective [19], antifertility [20] and metal detoxification [21]. Although *Coriandrum sativum* has been evaluated for a number of diseases yet no experimental data is available related to its evaluation againstcholelithiasis.

Materials and Methods

Plant material

Coriandrum sativum L. commonly called as 'Cilantro', 'Chinese parsley' or 'Dhaniya' belongs to the family 'Apiaceae' or 'Umbelliferae'. The seeds of *Coriandrum sativum* were purchased from the local market of Bahawalpur, Pakistan, by the authentic herb supplier. Dried seeds sample was submitted to the herbarium of Pharmacology research laboratory, department of Pharmacy, the Islamia University of Bahawalpur, Pakistan, and voucher number was issued; i.e. CS-SD-04-15-89, and kept for future reference.

Experimental animals

Experiments were performed in compliance with Institutional Animal Ethics Committee; i.e. Pharmacy Research Ethics Committee (PREC) with the reference number 33-2015/PREC. Swiss albino mice (20-25 g) were housed at the animal house of the department of Pharmacy, the Islamia University of Bahawalpur, Pakistan, kept in polycarbonate cages with saw dust (renewed after every 48 h), under controlled temperature of 23–25^{0}C and 12 h light/dark cycle.

Chemicals and kits

Different chemicals utilized during research work were purchased from different sources; i.e. cholesterol, and cholic acid from Sigma Aldrich (USA), formalin from Riedel-de Haen(Germany), ketamine from chemical works of Gedeon Richter Ltd, Budapest(Hungary) and xylazine from Prix Pharmaceutica, Lahore(Pakistan). The cholesterol kit was purchased from Human Diagnostics(Germany).

Model of cholelithiasis

The antilithogenic potential of *Coriandrum sativum* seeds (CsS) was evaluated against high fat diet (HFD)-induced cholelithiasis in mice. The animals (weighing 15-20g) were divided into different groups (each comprising often animals). Cholesterol gallstones were induced by feeding lithogenic diet (HFD); i.e. diet containing1% cholesterol and 0.5% cholic acid, to the intoxicated group. The treatment group was fed with the diet containing 10% *C. sativum* seeds, CsS, (coarsely powdered) mixed in HFD and the normal control group was on normal diet; free access to drinking water was provided to all the groups throughout the experimental period of eightweeks [22]. At the end of study, animals were sacrificed to collect blood through cardiac puncture and cholecystectomy was performed.

Analysis of serum

Serum was prepared by centrifugation of blood at 4000rpm for 10min. Total cholesterol levels were analyzed by using commercially available kit.

Grades of gallstones

Each gallbladder was trimmed of extraneous tissue, washed with normal saline and placed under illuminator to examine gallstones, visually, by the help of magnifying glass. The size of gall bladder from each animal was measured and the grading of stones was done on five point scale; i.e. from Grade 0 (no gallstone), Grade I (a few fine crystals), Grade II (≃10 fine crystals), Grade III (fine crystals occupying half of the gall bladder), Grade IV (Leaflet or stratified crystals occupying over a half of the gall bladder) to Grade V (Round gallstones) [23].

Histopathological Examination

The gallbladder of each animal was preserved in 10% formalin and analyzed histopathologically. Fixed tissues of gallbladder were embedded in paraffin, sectioned, and then stained using Haematoxylin and Eosin. Histopathological changes of untreated (intoxicated) group were compared with treated and normal control groups by viewing the prepared slides under the resolution of 100X using microscope.

Statistical Analysis

The results obtained were represented as mean±SEM of 10 observations in each group. One way ANOVA was employed to assess statistical significance; i.e. P value<0.05 was considered significant. The data was compiled and statistically analyzed by using Graph pad prism.

Results

Percent change in weight

Change in weight of lithogenic mice fed on cholesterol-supplemented diet for eight weeks was compared with normal control group and found to be significantly (P<0.001) increased. Treatment group fed on 10% CsS mixed in lithogenic diet showed statistically significant decrease in body weight as compared to the intoxicated group.

Total cholesterol levels

There was significant difference in the levels of serum cholesterol between the normal and intoxicated groups. Coriander seeds decreased the serum cholesterol levels in highly significant manner as compared to the lithogenic group.

Size of gall bladder

The mean size of gall bladder in normal control group was 1×3mm but the gall bladder of intoxicated group was found to be 5.5×3mm. The gall bladders of treatment group were smaller in size than that of the intoxicated group (3.3×3mm), measured using calibrated scale.

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Gallstone grade

Approximate degree of visualized cholelithiasis (gallstone grade) was calculated by observing the gall bladder for the presence of rhomboid monohydrate cholesterol stones. At the end of eight weeks, the grade in intoxicated group was found to be increased; i.e. between grade IV and V showing that gallstones were clustered in more than half of the gall bladder.

Histopathology

The gallbladder of lithogenic animal showed irregular cellular arrangement, tissue inflammation, edema, and cellular necrosis; whereas, the treatment group (10% CsS) prevented dystrophy and the cellular integrity remained intact.

Discussion

Gall stone formation is a complicated and multi factorial process. It is associated with various metabolic and genetic factors such as aging, gall bladder hypomotility, and imbalance in nucleating and antinucleating factors, cholecystokinin (CCK) deficiency and mutation in Lith gene [24]. Studies have shown that cholesterol and cholic acid produce cholesterol gallstone disease [25]. In present research, high fat diet model of cholelithiasis was used to induce cholelithiasis in mice with slight modifications [24]. The comparison of the groups; i.e. control, intoxicated/ lithogenic and treated (10% coriander seeds mixed with HFD), showed highly significant difference in percent change in body weight, serum total cholesterol levels and cholesterol gallstones grades. The study was designed to evaluate the anticholelithic potential of *C. sativum* and it was found to be highly effective in normalizing the serum cholesterol levels, preventing gall stone formation and decreasing percent change in body weight.

HFD has been reported to increase the hepatic cholesterol levels, the major portion of which is secreted into bile. The super-saturation of cholesterol in bile results in cholesterol precipitation. Hypercholesterolemia and obesity are the major causes of cholesterol gall stone formation. The addition of coriander seeds powder (10%) in HFD significantly prevented hypercholestrolemia and excessive weight gain, as coriander has already been reported for its hypocholesterolaemic and hypolipidaemic effects [26]. Hypocholesterolemic activity of coriander is considered to be due to the degradation of cholesterol to fecal bile and neutral sterols by increasing the activity of lecithin cholesterol acyltransferase.

The gallstone grade of treatment group at the end of the study showed that coriander decreased significantly the grade but not completely prevented the gallstone formation. It can be assumed that there might be several other factors involved in cholesterol super-saturation and stone formation that are unaffected by coriander constituents. Coriander seeds have been reported to contain triglyceride oil; i.e. petroselinic acid, a rich source of lipids, which could be the reason behind [27].

Lithogenic diet-treated mice showed tissue inflammation, edema and cellular necrosis, showing that HFD can cause biliary change and as a result, epithelial cell injury with stone formation. Human gallbladder with stones show mucosal hyperplasia, which suggests that this is a reactive process to mucosal irritation, which occurs due to tension produced by stones on gallbladder wall. Coriander seeds at 10% concentration in diet showed protection from hyperplasia (Figure 1) which could be because of lowering mucosal proliferation [24].

The cholesterol crystallization and gallstone formation has been reported to be due to increased cholesterol levels and decreased biliary phospholipids and bile acid levels. Coriander seeds contain antioxidants which have been studied to dissolve and prevent gallstones but it is recommended to confirm this theory by biochemical analysis of hepatic bile [27,28]. Coriander seeds have been used as a spice and similar spices have been evaluated and reported to lower biliary cholesterol and simultaneously raise the bile acid levels, resulting in diluted bile which delays the cholesterol crystal aggregation time [29,30]. Anticholelithic activity of coriander may also be due to the presence of alkaloids as according to previous studies, piperine (an alkaloid) can lower cholesterol levels. Coriander is rich in magnesium that has also been reported to prevent the stone formation [24].

The current findings suggest that dietary strategy to prevent gall stones incidence was quite effective as the coriander seeds were found to significantly normalize the serum cholesterol levels. It is thus concluded that coriander has anticholelithic potential for prevention of gallbladder stones. However, further studies are highly encouraged to explore the exact mechanism(s) of *Coriandrum sativum* (Coriander) against lithi as is and to isolate the active compounds accountable for its anticholelithic effects (Figure 1 & Table 1).

Table 1: The comparison of percent changes in body weight, serum cholesterol levels and grade of cholelithiasis in animals treated with the crude powder of *Coriandrum sativum* seeds (CsS, 10%) with those on normal diet and HFD-induced cholelithiatic mice.

Groups	Percent Change in Body weight of Mice	Serum total Cholesterol Levels (mg/dl)	Grade of Cholelithiasis
Control group (Normal diet)	43.7±6.4	69.63±3.4	0.2±0.1
Intoxicated group (HFD)	92.9 ± 10.6###	127.5###±4.3	4.6±0.2###
Treatment group (HFD + CsS (10%)	57.8±7.9**	100.3***±4.1	2.3±0.1***

(**) p<0.01 more significant, (***) p<0.001 highly significant; when compared with intoxicated group, and,

(###) p<0.001 highly significant; when compared with normal group.

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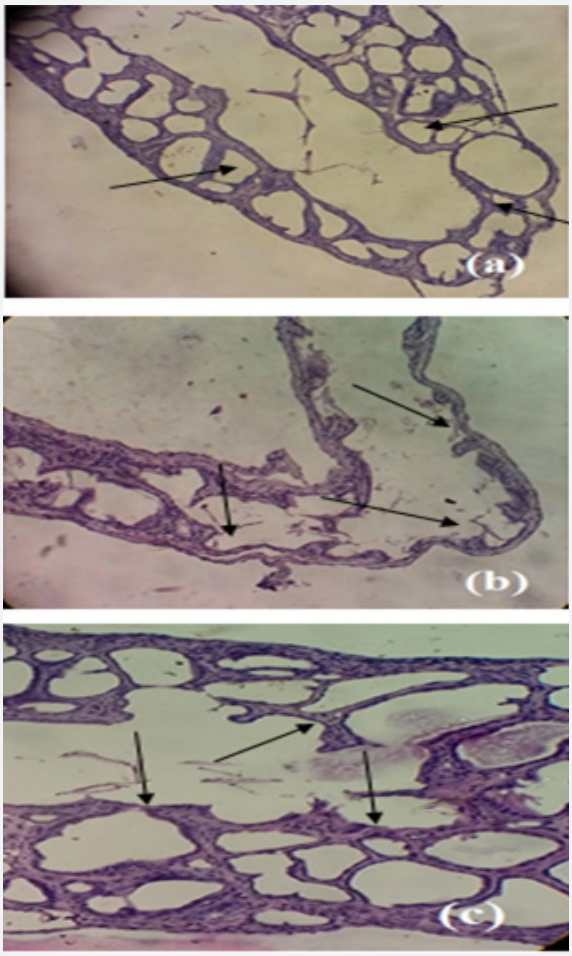

Figure 1: The comparison of histological features of gall bladders of animals treated with the crude powder of *Coriandrum sativum* seeds (CsS, 10%) with those on normal diet and HFD-induced cholelithiatic mice;(a) For control animal, showing intact epithelial architecture and cellular morphology, (b)for intoxicated animal(HFD) depicting irregular cellular architecture and inflammation of epithelial lining, and (c) treatment group (HFD+10% CsS) showing the restoration of normal architecture of epithelial layer and morphology of cells.

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