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Research Article

Protective and Therapeutic Effect of *Ocimum basilicum* (Basil) Ethanolic Extract on Chlorpromazine - Induced Hepatic Cholestasis in Wistar Albino Rats

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Abstract

Aim: This study aimed to investigate the protective and therapeutic effects of *Ocimum basilicum* (Basil) ethanol extract on chlorpromazine - induced hepatic cholestasis-in Wister albino rats.

Methodology: Forty Wister albino rats were divided randomly into four - groups (A, B, C, D) with 10 rats each. Group A (negative control) was given tap water and basal rats diet throughout the experiment. Group B (positive control) was given chlorpromazine at dose (40 mg/kg) orally for 21 days. Group C (protective group) was treated with both the ethanolic extract of *Ocimum basilicum* at dose (400 mg/kg) and Chlorpromazine at dose (40 mg/kg) simultaneously for 21 days, then chlorpromazine was stopped and rats were treated with ethanolic extract of *Ocimum basilicum* for the next 14 days. Group D (treatment group) was given chlorpromazine at dose (40 mg/kg) orally for 21 days and then rats were treated with an oral dose of ethanolic extract of *Ocimum basilicum* at dose (400 mg/kg) for the next 14 days. Blood samples were collected from the Retro-orbital plexus of rats` eyes using heparinized capillary tubes at days (0, 21 and 35). Serum levels of Total Bilirubin, Alkaline phosphatase (ALP), Gamma-Glutamyl Transpeptidase (GGT) and Total Cholesterol, were measured at days (0, 21 and 35).

Results: The findings revealed a significant decrease ($P \leq 0.05$) (at day 35) in serum total bilirubin, GGT and ALP of groups (C and D) treated with *Ocimum basilicum* as compared to the positive control which was not treated by *Ocimum basilicum*, while the level of serum cholesterol revealed a non-significant change in all groups except group (C) which revealed a significant decrease ($P \leq 0.05$) (at day 35) as compared to day 0 of the same group.

Conclusion: Based on the findings of this study, it can be concluded that *Ocimum basilicum* can provide protection and treatment of liver disorders such as hepatic cholestasis.

Keywords: *Ocimum basilicum (Basil); Chlorpromazine; Hepatic Cholestasis; Wister Albino Rats*

Introduction

Liver disorder (LD) is a term used in any condition, disease and infection that affects the structure, or function of the liver. Liver diseases are major global concern and this type of disease/disorder still has extremely poor prognosis and high mortality because of the lack of effective preventive and treatment options [1]. Liver disorder or Liver disease causes serious public health problems because of its high prevalence worldwide and poor long-term clinical outcome [2]. Cholestasis constitutes one of the most common and severe manifestations of acquired or inherited liver diseases [3]. Cholestasis can be defined as a clinical and biochemical syndrome caused by an impaired bile flow often associated with clinical manifestations such as jaundice, itching and biochemical disturbances such as elevated alkaline phosphatase levels [4]. It can be caused by sepsis, lymphomas, tuberculosis, sarcoidosis, amyloidosis and drugs.

Chlorpromazine (CPH) drug is used for patients with psychiatric disorders and this agent has been recognized as a cause of cholestatic hepatitis in humans. CPH is extensively metabolized by the liver and undergoes enterohepatic recirculation. CPH and its metabolites produce multiple effects on hepatic ultrastructure and function. Its hydroxylated metabolites, mainly 7, 8-dihydroxychlorpromazine, can cause inhibition of bile flow [5]. In recent years, researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support liver function and treat diseases of the liver [6]. One of these plants is *Ocimum basilicum* (Basil) which is named commonly as sweet basil. It is a popular herb belonging to the Lamiaceae family. *Ocimum basilicum* is being known by different names in different languages around the world. In Hindi and Bengali, it is known as Babui Tulsi. In English, it is known as Basil, Common Basil or Sweet Basil. In Arabic the plant is known as Badrooj, Hebak or Rihan [7]. It is originally native to India and other Asian regions. Today, it is cultivated all over the world. Traditionally, the basil leaves are used in folk medicine as remedy for a large number of diseases [8]. *Ocimum basilicum* has a huge spectrum of pharmacological activities. Crude extracts and essential oil of various parts of plant have been used for their antibacterial, anticancer, anticonvulsant, antidiabetic, anti-hyperlipidemic, anti-inflammatory, antioxidant, anti-stress, hepatoprotective and immune modulatory properties [7].

Materials and Methods

Study plant: *Ocimum basilicum* (*O. basilicum*).

Experimental animals: Adult male Wistar albino rats.

Methods

Ethanolic extraction of *Ocimum basilicum* (Basil)

The extract was obtained by maceration of the plant in ethanol 80% and water 20% for three days then the extract was evaporated to dryness at (65°C) by a rotary vacuum evaporator. The residue obtained was kept in dry clean bottles till used for pharmacological study [9]. The extract was suspended in convenient volume of distilled water and administered orally to rats using Oro-Gastric feeding tube.

Induction of hepatic cholestasis in rats

Chlorpromazine 40 mg/kg body weight was administered orally for rats for 21 days to induce hepatic cholestasis.

Doses of *Ocimum basilicum* and chlorpromazine:

Based on the study of [10] 400 mg/kg of *Ocimum basilicum* ethanolic extract and 40 mg/kg chlorpromazine were calculated for each rat individually, according to its body. Doses were administered to the rats orally using Oro-Gastric feeding tubes.

Study groups

- Group A: negative control
- Group B: positive control
- Group C: protective group
- Group D: treatment group

Experimental design

In this study four groups of albino rats were subjected to different treatments. The study was conducted through two stages. Stage one (21days) handled the toxic effect of oral chlorpromazine on the liver. Stage two (14days) dealt with treatment using oral dose of *Ocimum basilicum*. In all groups, selected biochemical parameters related to cholestasis, were measured and compared to their related controls. Results obtained were presented in tables.

Experimental procedures

All rats were kept under the same environmental conditions. Rats were divided randomly into four - groups (A, B, C and D) of 10 rats each: Group A: (negative control) was given tap water and basal rats- diet. Group B: (positive control) was given chlorpromazine daily at

dose 40 mg/kg orally for 21 days. Group C:(protective group) was treated daily with both the ethanolic extract of *Ocimum basilicum* at dose (400 mg/kg) and Chlorpromazine at dose (40 mg/kg) orally for 21 days and then chlorpromazine was stopped and rats were treated with ethanolic extract of *Ocimum basilicum* for the next 14 days. Group D: (treatment group) was given chlorpromazine daily at dose (40 mg/kg) orally for 21 days and then rats were treated with an oral dose of ethanolic extract of *Ocimum basilicum* at dose (400 mg/kg) for the next 14 days. Blood samples were collected from all rats at days (0, 21and 35) for determination of total bilirubin, alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT) and total cholesterol.

Collection of Blood samples and preparation of serum

Blood samples were collected from the Retro-orbital plexus of rats eyes using heparinized capillary tubes. Then serum was separated from whole blood by centrifugation at 300rpm for 15 minutes. Then it was collected in Eppendorff tubes and kept in refrigerator at 4°C till analysis.

Serum biochemical analysis

Serum total bilirubin was analyzed according to the method demonstrated by Biosystem kits [11]. The absorbances (A) of samples were read at 555 nm against the blank. Bilirubin concentration was calculated using the following general formula:

(A) sample x10 =mg/dl bilirubin in the sample

Serum gamma-glutamyltransferase (GGT)

Serum GGT concentration was determined using (Biosystem kits) [12]. The difference between consecutive absorbances was recorded and the average absorbance difference per minute (ΔA/min) was calculated using the following general formula:

$$\frac{(R1\text{-}R2) + (R2\text{-}R3) + (R3\text{-}R4)}{3} \text{ X } 1111 \text{ U/L}$$

Serum alkaline phosphatase ALP

Serum ALP concentration was determined using (Biosystem kits). The concentration was measured using spectrophotometer at 405 nm [13]. The initial absorbance was recorded at 1 minute intervals for 3 minutes. The difference between consecutive absorbances was recorded and the average absorbance difference per minute (ΔA/min) was calculated using the following general formula:

$$\frac{(R1\text{-}R2) + (R2\text{-}R3) + (R3\text{-}R4)}{3} \text{ X } 2764 \text{ U/L}$$

Serum total cholesterol

Serum cholesterol concentration was determined using Biosystem kits [14]. The following general absorbances (A) of standard and samples were read at 500 nm against the blank. The colour is stable for at least 2 hours. Cholesterol concentration in samples was calculated using the formula:

$$\frac{\text{A sample}}{\text{A standard}} \text{ X Standard concentration}$$

Data availability statement

Data used to support the findings of this study are included within the article and are expressed as Means ± SE.

Ethical consideration

An ethical clearance certificate was obtained from the veterinary council.

Statistical analysis

Data obtained were analyzed using the Statistical Analysis System (SAS) version (SAS-9). Data were expressed as mean ± standard error (SE). Analysis of variance (ANOVA) test was applied for testing the significant of difference among different means. P-value equal or less than 0.05 ($P \leq 0.05$) was considered being statistically significant.

Results

Effect of *Ocimum basilicum* on the level of serum total bilirubin

After induction of hepatic cholestasis results of this study revealed a significant increase ($p \leq 0.05$) in the levels of serum bilirubin of groups B and D (which were treated with chlorpromazine only) and group C (which was treated with chlorpromazine and *Ocimum basilicum* together) at day 21 compared to negative control. At day 35 the levels of serum bilirubin of the groups treated with *Ocimum basilicum* (C and D) revealed a significant decrease ($P \leq 0.05$) in the levels of the serum bilirubin compared to positive control group B (which was not treated by *Ocimum basilicum*). The results are presented in table 1.

Test groups	Day zero	Day 21	Day 35
A (Negative control)	0.15 ± 0.01 a	0.15 ± 0.06 aA	0.16 ± 0.003 aA
B (Positive control)	0.21 ± 0.02 a	0.34 ± 0.04 bB	0.35 ± 0.07 bB
C (Protective Group)	0.21 ± 0.04 a	0.41 ± 0.05 bB	0.22 ± 0.07 aC
D (Treatment Group)	0.27 ± 0.01 a	0.46 ± 0.02 bB	0.20 ± 0.06 aC

Table 1: *Effect of Ocimum basilicum on the level of serum total bilirubin.*

Data is expressed in terms of Means ± SE.

The mean values with different (small letters within a row and capital letter within column) indicate significant differences ($P < 0.05$).

Small letters compared between days.

Capital letters compared between groups.

Effect of *Ocimum basilicum* on the level of serum gamma-glutamyltransferase (GGT)

After induction of hepatic cholestasis results of this study revealed a significant increase ($P \leq 0.05$) in the levels of serum GGT of groups B and D (which were treated with chlorpromazine only) and a none significant decrease in group C which was treated with chlorpromazine and *Ocimum basilicum* together) at day 21compared to negative control. At day 35 the levels of serum GGT of the groups treated with *Ocimum basilicum* (C and D) revealed a significant decrease ($P \leq 0.05$) in the levels of the serum GGT compared to positive control group B (which was not treated by *Ocimum basilicum*). The Results are shown in table 2.

Test groups	Day zero	Day 21	Day 35
A (Negative control)	3.40 ± 0.42 a	1.63 ± 0.71 aA	1.85 ± 0.00 aA
B (Positive control)	2.73 ± 0.54 a	3.49 ± 0.51 aB	2.72 ± 0.51 aB
C (Protective Group)	2.96 ± 0.23 a	2.55 ± 0.51 aA	1.11 ± 0.34 bA
D (Treatment Group)	3.70 ± 0.45a	5.07 ± 0.90bC	1.30 ± 0.40 cA

Table 2: *Effect of Ocimum basilicum on the level of serum gamma-glutamyltransferase (GGT).*

Effect of *Ocimum basilicum* on the level of serum alkaline phosphatase (ALP)

After induction of hepatic cholestasis results of this study revealed a significant increase ($P \leq 0.05$) in the levels of serum ALP in groups Band D (which were treated with chlorpromazine only) and a none significant decrease in group C (which was treated with chlorpromazine and *Ocimum basilicum* together) at day 21 compared to negative control. At day 35 the levels of serum ALP of the groups treated with *Ocimum basilicum* (C and D) revealed a significant decrease ($P \leq 0.05$) in the levels of the serum ALP compared to positive control group B (which was not treated by *Ocimum basilicum*). Results are shown in table 3.

Test groups	Day zero	Day 21	Day 35
A (Negative control)	104.80 ± 8.76a	67.07 ± 30.85aA	113.32 ± 25.53aA
B (Positive control)	84.30 ± 8.68a	131.35 ± 14.96bB	151.56 ± 14.01bB
C (Protective Group)	116.61 ± 12.47a	114.31 ± 20.34aA	64.36 ± 23.82bA
D (Treatment Group)	98.58 ± 11.79a	123.06 ± 21.41aB	88.68 ± 26.10aA

Table 3: *Effect of Ocimum basilicum on the level of serum alkaline phosphatase (ALP).*

Effect of Ocimum basilicum on the level of serum total cholesterol

After induction of hepatic cholestasis results of This study revealed anon significant change in the levels of serum cholesterol in groups B and D (which were treated with chlorpromazine only) and group C (which was treated with chlorpromazine and *Ocimum basilicum* together) at day 21 compared to negative control. At day 35 the levels of serum cholesterol in the groups treated with *Ocimum basilicum* C and D revealed anon significant change in the levels of serum cholesterol compared to positive control group B (which was not treated by *Ocimum basilicum*). Results are shown in table 4.

Test groups	Day zero	Day 21	Day 35
A (Negative control)	44.50 ± 3.24 a	36.97 ± 3.30 aA	34.98 ± 3.03 aA
B (Positive control)	35.01 ± 2.34 a	31.43 ± 1.61 aA	38.99 ± 4.28 aA
C (Protective Group)	43.78 ± 4.49 a	32.63 ± 2.39 bA	34.76 ± 2.77 bA
D (Treatment Group)	46.55 ± 1.89 a	38.69 ± 1.80 Aa	42.28 ± 1.77 aA

Table 4: *Effect of Ocimum basilicum on the level of serum total cholesterol.*

Discussion

This study was carried out to evaluate the protective and therapeutic effect of *Ocimum basilicum* (Basil) ethanol extract on chlorpromazine - induced hepatic cholestasis in Wistar albino rats. The parameters under investigation, were: total bilirubin, Gamma-glutamyltransferase (GGT), Alkaline phosphatase (ALP) and total Cholesterol. Hepatic cholestasis was induced in rats by administration of chlorpromazine.

Effect of chlorpromazine on the level of serum total bilirubin, GGT, ALP and total cholesterol of study rats

In this study chlorpromazine was used to induce hepatic cholestasis in wistar albino rats. Cholestasis was indicated by a significant increase ($P \leq 0.05$) in the levels of serum total bilirubin, GGT and ALP of groups B, C and D as compared to the negative control at day 21. The level of serum Cholesterol revealed a non-significant change between the different groups but revealed a significant decrease ($P \leq 0.05$) in group C at day 21 as compared to day zero of the same group. A similar finding was reported by [10] who suggested that chlorpromazine at dose 40 mg/kg showed a significant increase in the level of serum Total Bilirubin, Alanine Transaminase (ALT) and Aspartate Transaminase (AST). Movitt E., *et al*. [15] reported that chlorpromazine - induced liver injury elevated serum ALP. Shehta A and Dina S [5] suggested that chlorpromazine at dose 30 mg/kg and Ethinylestradiol (EE) revealed a significant increase in the level of serum total bilirubin, gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and a significant decrease in the level of total cholesterol, while Yang Q., *et al*. [16] reported that chlorpromazine at dose 3.6 ml/kg revealed a significant increase in the level of serum total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), total albumin and total cholesterol.

The mechanism by which chlorpromazine - induced hepatic cholestasis can be attributed to the fact that it causes alteration of cell membrane permeability leading to accumulated bile salt in hepatocytes which can result in oxidative stress and cell death.

Effect of Ocimum basilicum extract on the level of serum total bilirubin, GGT, ALP and total cholesterol of study rats

All the determined parameters (total bilirubin, GGT, ALP and total Cholesterol) were adjusted after treatment with *Ocimum basilicum* extract. This current study revealed a significant decrease ($P \leq 0.05$) in serum total bilirubin, GGT and ALP of groups (C and D) treated with *Ocimum basilicum* as compared to the positive control (group B) which was not treated with *Ocimum basilicum.* This findings indicate the efficacy of *Ocimum basilicum* extract in decreasing the level of elevated serum total bilirubin, GGT and ALP. This result agrees with [17] who reported that *Ocimum basilicum* aqueous and ethanol extract at dose 400 mg/kg reduced the level of serum ALT, AST, ALP and GGT significantly. Their study suggested that the hepato protective effects of *Ocimum basilicum* extracts may be linked to their antioxidant activities. Belgeis A., *et al.* [9] reported that *Ocimum basilicum* ethanol extract at dose 200 mg/kg showed a significant decrease in the levels of serum enzyme ALT, AST, ALP and also total bilirubin. They attributed the hepato protective effect of the extract of *Ocimum basilicum* its antioxidant property due to its high content of flavonoids, tannins, sterols and triterpenes and due to its superoxide radical and nitric oxide radical scavenging activities. Galila A., *et al.* [18] suggested that *Ocimum basilicum* aqueous and ethanol extracts at dose 200 mg/kg lowered the levels of serum enzyme ALT, AST, ALP significantly. The hepato protective and treatment effect on the fibrotic liver rats is possibly due to its antioxidant effect and free radical scavenging properties. Sakr S., *et al.* [19] proved that *Ocimum basilicum* extract at dose 20 ml/kg had an ameliorative effect against liver injury produced by CCl_4 due to its antioxidant activity. Dasgupta T., *et al.* [20] reported that *Ocimum basilicum* aqueous ethanol extract at doses 200 mg/kg and 400 mg/kg increased the activity of xenobiotic metabolizing phase I and phase I1 enzymes and was very effective in elevating antioxidant-enzyme response by increasing significantly the hepatic glutathione reductase, superoxide dismutase and catalase activities, reduced glutathione (GSH). The major intracellular antioxidant showed a significant elevation in the liver and also in all extra hepatic organs. They also reported a significant decrease in lipid peroxidation and lactate dehydrogenase activity in the liver of mice. The protective effect of the extract is probably related to these mentioned evidences. Chinnasamy S., *et al.* [21] reported that the protection of *Ocimum basilicum is* due to its anti-inflammatory property which reduced formation, release and activity of inflammatory mediators such as cytokines, histamine, prostaglandins, and interleukins and also attributed to its antioxidant activities.

Regarding the effect of *Ocimum basilicum* on the level of total cholesterol, the level of serum cholesterol of protective group (C) which was given *Ocimum basilicum* extract since day zero till day 35, revealed a significant decrease in the level of serum cholesterol between day zero and day 35. This result is agrees with [22] who reported that *Ocimum basilicum* extract at dose 100 mg/kg reduced serum total cholesterol. Zeggwagh N., *et al.* [23] reported that the extract of *Ocimum basilicum* whole plant has a hypolipidemic effect.

These findings can be attributed to the antioxidant activities of *Ocimum basilicum* which is attributed mainly to its high content of flavonoids which is known for its hypolipidemic effect as it lowers absorption of dietary cholesterol.

Conclusion

Based on the findings of this study, it can be concluded that the ethanol extract of *Ocimum basilicum* whole plant at dose 400 mg/kg on daily basis, can be a potent was hepatoprotective and therapeutic ligand.

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