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A randomized controlled trial on albino rats treated with chicory plant to improve liver efficiency

Adeela Hameed[1], Rabia Shabir Ahmad[1]*, Ali Imran[1], Adeela Yasmin[1] and Syed Ali Raza Naqvi[2]

[1]Department of Food Science, Government College University, Faisalabad, Pakistan
[2]Department of Chemistry, Government College University, Faisalabad, Pakistan

Abstract: Chicory can be used as herbal medicine against different ailments and also added to daily diet as vegetable or animal feed. An efficacy trial was conducted to assess the potential of this plant against liver disorders using rodent modeling. The trials comprised two modules *i.e.,* normal diet and chicory-based supplemented diet. Moreover, experimental animals (rats) were divided into six groups with both modules including C_0 (control diet), C_1 (Chicory root containing diet), C_2 (chicory seed containing diet), C_3 (chicory stem containing diet) and C_4 (chicory leaf containing diet). During 56 days of the trial period, serum lipid profile, liver and renal functioning tests were performed. The highest feed and water intake, as well as weight gain, was noted in control (C_0) trailed by C_1, C_2, C_3, C_4 and C_5group in an experimental trial, respectively. The resultant diet C_2 lowered the liver alkaline phosphatase level (ALP) from C_0 (240.72±3.35) to 203.52±2.08 (C_2), respectively. Similarly, C_2 significantly lowered the ALT from 60.28±2.23 (C_0) &57.58±0.91 (C_2) in rats. Moreover, C_2 treatment showed a maximum reduction of AST from 145.13±2.10 (C_0) to 134.52±1.24 (C_2), respectively. Convincingly, chicory-based diet may be employed as an alternative to medication in the prevention and treatment of hypercholesterolemia and hepatic malfunctioning.

Keywords: Chicory, efficacy trial, hypercholesterolemia, hepatic malfunctioning, nephroprotective.

INTRODUCTION

The importance of natural compounds extracted from medicinal plants are known to us and have been used since human civilization (Naqvi *et al.,* 2020; Farah *et al.,* 2018; Asif *et al.,* 2017). Variety of diseases were treated with the help of phytochemicals (Anwar *et al.,* 2021; Naqvi *et al.,* 2020; Shahzad *et al.*, 2021; Bukhari *et al.,* 2015). Hepatotoxicity is currently the most prevalent disease globally, reporting approximately 83% of overall ailments and is the gravest health issue. Preventive approaches employing nutritional strategies have been considered effective in curbing metabolic syndromes (Golmohammadi *et al.,* 2020). In developed countries, the incidence of non-alcoholic fatty liver disease (NAFLD) is nearly 20% to 30% in the overall population, while up to 75% in obese people. In history, herbs have earned much attention as they are considered a valuable source of phytochemicals. These phytochemicals may include polyphenols, alkaloids, terpenoids, tannins, essential oils, and vitamins. These functional ingredients are extracted from the raw plants using organic solvents or water. Mixtures and pure compounds from plants applied in different researches have exhibited therapeutic biological properties *i.e.,* antioxidant, anticancer, antifungal and antimicrobial, etc. (Abbas *et al.,* 2021*;* Khoobchandani *et al*., 2010; Sahar *et al.,* 2013; Tahir *et al.*, 2019).

Cichorium intybus L., generally termed as Chicory, is one of the therapeutic plants from the family Asteraceae. The plant consists of six species cultivated throughout Asian and European countries. Out of these six, widely used species is the *Cichorium intybus,* utilized for its medicinal properties against many diseases since ancient times (Singh and Chahal, 2018).This non-woody herbal plant is grown throughout the globe. Specifically in Pakistan, it is locally termed as Kasani, of the phytochemicals found in the Chicory plant, the major ones are flavonoids, sesquiterpene, lactones, coumarins, tannins and inulin (Nwafor *et al*., 2017). Naturally, a fresh root of Chicory fruit consists of 68% of inulin, 5% of cellulose, 14% of root contains the highest percentage of inulin followed by sucrose, cellulose, protein, ashand some other compounds as 68, 14, 5, 6, 4, and 3%, respectively (Perović *et al*., 2021).

Earlier investigations on the extract of chicory and its formulations consisting of the roots and leaves established the hepatoprotective (Krylova *et al*., 2006), antioxidant (Rossetto *et al*., 2005), antihyperglycemic (Petlevski *et al*., 2003) and anti-diabetic effects (Pushparaj *et al*., 2007). In this regard, a study was carried out to investigate the effect of celery leaves along with barley grains and chicory leaves on hepatoprotective parameters using hypercholesterolemic rats. It was observed that dietary supplementation of celery, barley and chicory @ 5% concentration may be valuable to patients suffering from liver diseases and high cholesterol levels (Abd El-Mageed, 2011).

**Corresponding author:* e-mail: rabiaahamd@gcuf.edu.pk

A stable diet and sufficient level of physical activity are suggested as the best ways to improve NAFLD. Drugs used for the treatment of liver ailments can have side effects on the liver when used for a long time (Kalantari and Rastmanesh, 2009). Therefore, its need of the era to develop medicines using natural therapeutic properties plants which will cause minimum or no harmful effect on liver functioning. In this connection, the current investigation was designed to probe the therapeutic effect of chicory against hypercholesterolemia and resultant liver dysfunction. The exploration is unique in the sense that it will highlight the synergistic role of different parts of the chicory plant.

MATERIALS AND METHODS

Procurement of raw material

Chicory seed, root, stem and leaves were procured from fields near Faisalabad. Plant identification was done by the expert botanist, from the Department of Botany, Government College University, Faisalabad. The kits for *in vitro* trials were procured from Sigma Aldrich, Bioassay (Bioassays Chemicals Co. Germany).

Efficacy study plan

The raw materials obtained were cleaned thoroughly to remove any dust, dirt or foreign matter. In the current investigation, the therapeutic effect of the chicory plant against the fatty liver disease was observed using rat modeling. For induction of fatty liver disorder, rats were given a high fat diet (40% fat) in place of normal diet that otherwise provide 10% fat. For the control group, other ingredients of experimental diet contained cellulose and protein and all components constituted 20% while other ingredients used were corn starch (66%), mineral (3%) and vitamin mixture (1%). For experimental diets, different parts of the chicory plant were used in powder form such as chicory seed (CSD), chicory leaf (CLF), chicory stem (CST) and chicory root (CRT), which were scrutinized as therapeutic agents on experimental albino rats. In the present investigation trial, a hepatoprotective diet was administered to rats. Moreover, rats were distributed into six groups for each module based on the type of diet including C_0 (control), CSD (Chicory Seed Diet), CLD (chicory leaf containing diet), CST (Chicory stem containing diet), CRT (chicory root containing diet) and CI (Diet containing all parts of chicory seed, chicory leaf, chicory stem and chicory root). At the commencement of the experimental trial, some rats were dissected to get the reference values whilst the remaining rats were sacrificed at the end of the trial (56^{th} day). Water and feed intakes were examined on a daily basis where as, body weight gain was evaluated every week. The Whole efficacy study was repeated and results are mentioned as Trial 1 and Trial 2.

Biochemical profile

Physical parameters

The feed intake of rats was measured on daily basis by subtracting the spilled from the total diet trial period (Wolf and Weidbrode, 2003). The water consumption of each group of rats was also observed daily, by calculating the differences from the graduated bottles.

Serum lipid profile

CHOD–PAP method (Stockbridge *et al.*, 1989) was used for the measurement of serum cholesterol level while triglycerides and low-density lipoproteins (LDL) were measured following the method elaborated by Kim *et al.* (2011), while high-density lipoprotein (HDL) was assessed by adopting the method of Alshatwi *et al.* (2010).

Liver functioning tests

Liver functioning tests including alanine transferase (ALT), aspartate transferase (AST) and alkaline phosphatase (ALP) were also done by following the procedure of Basuny, 2009.

Ethical approval

For animal study the ethical approval for this research was obtained from the Ethical Review Committee of the Government College University, Faisalabad.

STATISTICAL ANALYSIS

The data of analyzed physical parameters, serum lipid profile and liver functioning tests were subjected to statistical analysis and a software package (Statistic 8.1) was used (Steel *et al.,* 1997). The mean of the three runs was recorded as the experimental value along with standard deviation. Moreover, Duncan's multiple range (DMR) test was used to calculate the level of significance at an approximation level of 5% that existed between the experimental means.

RESULTS

Serum lipid profile

The results affecting total cholesterol (table 1) in different groups of rats, explicated that the obvious elevated level of cholesterol level was 165.49±0.35 mg/dL in C_0group that decreased to 151.36±1.19 (C_3\), 149.54±2.56 m/dL (C_1), 146.39±2.22 mg/dL (C_5), 144.16±1.58 mg/dL (C_4) and 143.20±0.98 mg/dL (C_2) groups, accordingly. Mean values pertaining to serum LDL levels of different groups of rats were presented. Indicated maximum LDL (low density lipoprotein) level in C_0 group as 63.47±1.51 mg/dL noticeably lowered in C_2 (55.62±1.55mg/dL). Along the study duration, serum LDL level elevated as a function of time but this elevation was evident in control groups as compared to the groups fed with chicory-based interventional diet. Mean values in table 1 depict that

HDL (high-density lipoprotein) was considerably affected by treatments and study intervals in all the groups of rats. It can be observed that the mean HDL values at the end of trial 1 were 60.12±3.17, 63.32±1.65, 63.67±2.76, 63.47±2.90, 63.26±1.55 and 63.45±1.57mg/dL for C_0, C_1, C_2, C_3, C_4 and C_5 groups of rats, respectively. A similar trend was noticed in trial 2. The highest incline was noted in C_2 (control diet) whereas, the lowest was observed for C_5 (Diet containing all parts of chicory seed) group of rats. Likewise, mean values for triglycerides showed changes in serum triglycerides values as 100.73±3.26, 102.75±1.37, 94.40±1.59, 95.90±1.71, 94.62±2.64 and 94.87±2.84 mg/dLfor C_0, C_1, C_2, C_3, C_4 and C_5, respectively. The quantities of triglycerides progressively increased from the start to the end of the study period. This rise in TG was clearer in control and supplementation of chicory plant interventional diet showed considerable reduction in TG (triglycerides).

Liver functioning profile

Mean values regarding ALP level of various groups of rats (table 2) portrayed values of ALP level as 240.72±3.35, 211.21±4.43, 203.52±2.08, 241.00±3.09, 204.22±2.31 and 208.23±4.44 IU/L for groups feeding on C_0, C_1, C_2, C_3, C_4 and C_5diets, respectively in trial 1, whilst nearly similar tendency of decline in serum ALP of rats was noticed in trial 2 and the maximum ALP level 222.82±2.56IU/L was found for groups relying on a normal diet and the minimum was recorded 192.92±2.56IU/L for the group relying on C_5 diet.

Mean values pertaining to serum ALT levels of rats (table 2) represent devalues as 60.28±2.23 for C_o, and the least 57.58±0.91IU/L for C_2. Likewise, a trend was noticed in trial 2.In this hepatoprotective study level, AST of different groups of rats was decreased from 145.13±2.10 IU/L (C_0) to 136.42±1.35, 134.52±1.24, 136.73±1.54, 135.26±1.42 and 135.46±1.41 IU/L with ingesting diets C_1, C_2, C_3, C_4 and C_5, respectively (table 2). Similarly, AST levels of rats in trial 2 followed declining trend from C_0 to C_5, accordingly.

Serum kidney functioning profile

Mean values regarding serum creatinine level at the end of the study are shown in the control (C_0) group as 0.97±0.03 mg/dL whereas rats fed on chicory supplemented diet indicated slight reduction for C_1, C_2, C_3, C_4 and C_5 as 0.96±0.01, 0.93±0.01, 0.97±0.02, 0.94±0.03 and 0.95±0.01 mg/dL, respectively (table 3).

During the trial period, a mildrise was noted in creatinine level, however, this elevation was much more obvious in control groups than that of groups fed chicory-based interventional diet. Mean values related to serum urea at the end of trial 1exhibited the highest value for C_0 as 32.47±1.12, while the lowest was recorded for C_2 (29.89±1.45). Mean values regarding serum glutathione (table 3) at the end of trial 1 showed values for C_0, C_1, C_2, C_3, C_4 and C_5 as 39.89±1.12, 45.39±1.45, 46.79±0.82, 44.54±0.78, 46.24±0.70 and 45.84±0.41 mg/dL, correspondingly.

DISCUSSION

The liver is one of the vital organs that contribute greatly to transformation and eliminating chemicals hence is more susceptible to toxicity from these compounds. Recently, there has been growing interest in the use of herbal therapies/ medicine for hepatic disorders and toxicity (Chan *et al*., 2020). *Cichoriuminty bus* was earlier used for its medicinal properties and is specifically significant for its tonic effects upon the digestive tract and liver (Perović *et al*., 2021). Nonalcoholic fatty liver disease (NAFLD) is considered a metabolic syndrome as most of the physiological disorders contribute to the development of this disease like hypercholesterolemia, type-II obesity, diabetes both insulin resistance and type II (Jennison *et al*., 2019). In the present investigations, we observed that in response to different parts of chicory, the bodyweight increased significantly. This could be linked with the fact that chicory extract-based compounds provide protection from hepatoxicity and thus contribute to the overall health of rats, which ultimately results in weight gain.

The response of chicory on the blood cholesterol is mainly due to inulin, an active compound present in chicory. Inulin is a polymer of fructose (monosaccharide) that possesses glycosidic linkage of beta (1-2) (Kocsis *et al*., 2019). Inulin is derived from the root of chicory that has anti-hepatotoxic and anti-inflammatory properties and is used as a liver-protecting medicine (Kalantari *et al*., 2019). An earlier study on dietary supplementation with chicory inulin (2%) or dehydrated chicory root (4%)showed moderated expression of hepatic proteins involved in the cholesterol synthesis pathway, triglyceride metabolism and oxidative stress prevention in young animals (Lepczyński *et al*., 2021). It has been observed that plant-based compounds including flavonoids can inhibit the activity of HMG CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), an enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, a critical step in the biosynthesis of cholesterol. Thus, the cholesterol-reducing effects of chicory in the present study could be attributed to flavonoids and polyphenolic compounds like chicoric acid, which is the main phenolic compound of chicory plants.

The anti-inflammatory, antioxidant and free radical scavenging potential of the chicory plant attenuated the effect of oxytetracycline on serum LDH activity through scavenging the free radicals, minimizing the lipid peroxidation, hence preventing the membrane damage (Ziamajidi *et al*., 2013). Moreover, chicory roots have

Table 1: Effect of chicory-based functional diet on serum lipid profile of rats

Parameters (mg/dL)	Groups of rats on experimental diet					
	C_0	C_1	C_2	C_3	C_4	C_5
Cholesterol						
(Trial 1)	165.49±0.35a	149.54±2.56bc	143.20±0.98d	151.36±1.19b	144.16±1.58d	146.39±2.22cd
(Trial 2)	154.29±0.35a	144.06±2.56bc	137.86±0.35bc	145.72±2.56b	138.34±1.24bc	136.09±2.56c
LDL						
(Trial 1)	63.47±1.51a	58.23±2.0c	55.62±1.55d	60.43±1.81b	56.34±1.72d	57.91±3.07d
(Trial 2)	61.261±5.9a	56.26±2.5bc	53.70±3.21c	58.35±4.2ab	54.21±4.5c	53.46±2.7c
HDL						
(Trial 1)	60.12±3.17b	63.32±1.65a	63.67±2.76a	63.47±2.90a	63.26±1.55a	63.45±1.57a
(Trial 2)	58.40± 1.48b	61.90± 2.01a	62.15± 2.23a	62.06±2.19a	42.611±1.34c	61.468±2.11ab
Triglycerides						
(Trial 1)	100.73±3.2a	102.75±1.3a	94.40±1.59b	95.90±1.71b	94.62±2.64b	94.87±2.84b
(Trial 2)	99.01±8.91a	93.95±8.71b	92.82±7.65b	94.30±8.67b	92.74±8.25b	90.58±8.64b

Table 2: Effect of chicory-based functional diet on liver functioning tests (LFTs) of rats

Parameters (IU/L)	Groups of rats on experimental diet					
	C_0	C_1	C_2	C_3	C_4	C_5
ALP						
(Trial 1)	240.72±3.35a	211.21±4.43bc	203.52±2.08d	241.00±3.09b	204.22±2.31d	208.23±4.44cd
(Trial 2)	222.82±2.56a	195.60±2.56bc	188.47±2.56d	198.18±2.56b	188.42±2.56d	192.92±2.56cd
ALT						
(Trial 1)	60.28±2.23a	58.14±0.99b	57.58±0.91b	58.54±1.06b	57.74±0.38b	57.87±2.16b
(Trial 2)	57.46±0.98a	55.44± 0.99b	54.91±1.52b	55.83±1.87b	54.89± 1.45b	55.32±1.32b
AST						
(Trial 1)	145.13±2.10a	136.42±1.35b	134.52±1.24b	136.73±1.54b	135.26±1.42b	135.46±1.41 b
(Trial 2)	137.43±1.35a	129.23±2.10 b	127.44±1.35b	127.47±2.10b	127.72±1.35b	128.65±2.10 b

Table 3: Effect of chicory-based functional diet on kidney functioning tests of rats

Parameters (mg/dL)	Groups of rats on experimental diet					
	C_0	C_1	C_2	C_3	C_4	C_5
Creatinine						
(Trial 1)	0.97±0.03ab	0.96±0.01ab	0.93±0.01c	0.97±0.02a	0.94±0.03bc	0.95±0.01abc
(Trial 2)	0.91±0.03a	0.90±0.06ab	0.87±0.09c	0.91±0.05a	0.88±0.04bc	0.87±0.06c
Urea						
(Trial 1)	32.47±1.12a	29.89±1.45b	28.80±0.82c	30.20±0.78b	29.00±0.70c	29.51±0.41bc
(Trial 2)	29.89±1.45a	27.53±1.42b	25.31±1.25d	27.89±1.65b	26.63±1.63c	27.21±1.45bc
Glutathione						
(Trial 1)	39.89±1.12d	45.39±1.45bc	46.79±0.82a	44.54±0.78c	46.24 ±0.7ab	45.84±0.41ab
(Trial 2)	39.03±1.16d	44.38±1.45bc	45.76±3.36a	43.56±3.25c	45.09±1.12ab	45.0±1.12ab

Values are given as means ± SD (n =5); means sharing same letters in a row do not differ significantly at $P < 0.05$.

been documented to have antimicrobial, anti-hyperglycemic, immune stimulant, antitoxic, anti-inflammatory, and tumor-inhibitory activities. That is why it helps in hepatoprotection (El-Sayed *et al*., 2015). In a similar investigation by El-Sayed *et al*. (2017), chicory root extract was used to study its ability to ameliorate CCl4 (carbon tetrachloride) induced oxidative stress in rats. For this purpose, they divided rats into four groups and provided them saline as control and for the treatment group, 100 mg/kg body weight daily chicory extract was given orally for 15 days. They demonstrated that as chicory extract is a rich source of antioxidants, therefore it was able to diminish CCl4-induced hepatic injury. They narrated that it may be due to free radicals scavenging, over expression of encoding genes for antioxidant enzymes and enhanced endogenous antioxidant defense system. In an earlier research trial, ethanolic extract of chicory parts given orally @ 6, 18, and 54 mg/kg body weight per day displayed a substantial hepato-protective impact by lowering the hepatic enzymes *i.e.,* AST and ALT. The results were highly profound at the dose of 54 mg/kg body weight per day (Li *et al*., 2014).

Results regarding kidney functioning tests in current research are also in line with the recent findings of Epure *et al*. (2021). They studied cardio-protective effects of

Romanian chicory extract ongentamicin-induced renal failure and myocardial ischemia induced by isoprenaline involving rats. They evaluated oxidative stress, inflammation and renal functions in serum and in the urine of rats. It was summarized that gentamicin-induced acute kidney injury, creatinine and urea were attenuated by treatment with chicory.

The decline in serum urea and creatinine levels with chicory consumption may be attributed to the higher antioxidant activity of chicory. The obtained results in our study are also in line with Fortin (2004), who noticed that Chicory revealed antioxidant activity and comprised significantly higher levels of phenolics.

CONCLUSION

In the present investigation, efficacy trial was conducted to assess the potential of different parts of the chicory plant (leaves, roots and seeds) against hepatic disorders using rodent modeling. The hypercholesterolemic, hepatic and nephroprotective properties were investigated through lipid profile, liver and kidney functioning indicators. The results obtained for chicory seed are more promising in attenuating these parameters in rats, as compared to other parts. Our findings may stretch new directions for further research to establish a scientific basis for the medicinal uses of indigenous plants.

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