Ameliorative effects of *Trigonella foenum-graecum* seed powder on atherosclerosis ratios, anti-inflammatory enzymes and intestinal histological changes in rats

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ABSTRACT

Fenugreek (*Trigonella foenum-graecum*) has been used as a spice worldwide to enhance the organoleptic quality of foods. Several health- beneficial physiological properties of fenugreek seeds have been seen in animal studies as well as human experiments. This study aimed to investigate anti-inflammatory activities and lower the cholesterol, low density lipoprotein, and triglyceride of Trigonella foenum graecum seed powder in four groups of rats. Rats were divided into four groups (each group with six rats). Group A (negative control) was administrated with a normal diet and water, Group B (positive control) was administrated with water containing ethanol 10% and a normal diet, Group C& D administrated with water containing ethanol 10% and basal diet 10% &15% fenugreek seed powder, respectively. Physiological studies were conducted using haematological parameters, lipid profile, liver function, anti-inflammatory enzymes and histopathological examination of the small intestine. The results demonstrated that the animals treated with ethanol for 4 weeks showed a significant increase in RBC count, hemoglobin concentration, hematocrit value and platelets count, while insignificant differences between MCV, MCH, and MCHC as compared to the control group. The results also showed that the treatment of male rats with ethanol resulted in significant increases in the serum concentrations of cholesterol, triglycerides, LDL-c, and VLDL-c, and a significant decrease was observed in serum HDL-c compared with the control group. In rats that received fenugreek seeds powder, the serum ratios of proatherogenic levels of rats significantly decreased and the serum HDL-c significantly increased compared with the control group. Administration of fenugreek with

ethanol caused improvement in serum liver function and histological structure of the small intestine when compared with the positive group. Anti-inflammatory enzymes; COX-1, and COX-2 increased by exposure to ethanol in rats. This study highlighted the biotoxicity of ethanol through biochemical, and histological parameters on one hand and the protective role of fenugreek seeds on the other hand. Thus, this work could be a pilot study that will encourage using fenugreek seeds as a detoxifying diet supplement for domestic animals.

Keywords: *Trigonella foenum-graecum* seeds, rats, Ethanol toxicity, histology, Anti-inflammatory enzymes, COX-1, COX-2, lipid profile, cyclooxygenases, proatherogenic ratios.

1. INTRODUCTION

Fenugreek, a member of the Fabaceae family, is widely used in the Mediterranean basin, and on the southern coasts of the Black Sea **(Ghedira et al., 2010)**. It is an annual legume that has been used as a spice worldwide to enhance the sensory quality of foods **(Su 2020)**. The fenugreek herb, seeds, powder, and extracts have many nutritional and medicinal properties **(Singh et al., 2020)**. Several bioactive compounds beneficial to health have been identified in fenugreek seeds. These compounds have multiple health beneficial effects, including anti-hyperlipidemic, and anti-cancer **(Sharma & Choudhary 2017)**, as well as anti-obesity, and anti-type 2 diabetes **(Su 2020)**.

Comparing the physical-chemical properties of different fenugreek origins herbs, **Dilshad (2017)** found that Yemen seeds showed higher values of moisture, oil, and total phenolic content, while Egyptian seeds recorded higher ash content along with sodium, iron, and copper. Among the minerals, calcium and magnesium were the most abundant minerals, followed by potassium and sodium in both studied herbs.

Fenugreek seeds contain protein with a desirable amino acid profile, lipids, and biogenic elements, and are also a rich source of saponins, flavonoids, choline, carotene, essential oils containing trigonelline, and other functional components **(Murlidhar & Goswami 2012).**

Increased levels of low-density lipoprotein cholesterol (LDL-c) have also been linked to the onset and development of atherosclerosis, according to experimental research **(Amarenco et al., 2007).** Consequently, it is important to observe not only HDL-c or LDL-c alone but also their ratio for predicting the progression of atherosclerosis as a high LDL-c/HDL-c ratio is a strong predictor of cardiovascular events **(Nicholls et al., 2007).**

The beneficial physiological effects including the antidiabetic and hypocholesterolemia effects of fenugreek are mainly attributable to the presence of dietary fiber, which has promising nutraceutical value **(Khorshidian et al., 2016).** Hypertriglyceridemia, usually associated with increased levels of plasma VLDL-triglyceride (TG) and fatty acids, is another major contributing factor to atherosclerosis **(Scordo & Pickett, 2017).**

In addition to a large amount of fiber, phospholipids, glycolipids, oleic, linolenic, and linoleic acids, choline, vitamins A, B1, B2, and C, nicotinic acid, and niacin are among the many beneficial substances found in fenugreek seeds. Its use is safe and various health benefits can be obtained from this natural herb **(Singh et al., 2020).**

Ethanol consumption is a major cause of gastric ulcers. Oxidative stress and depletion of antioxidants have been considered crucial steps in alcohol-induced mucosal damage. Thus, considering that ethanol is involved in the formation of extracellular and intracellular oxidative stress **(Mary & Merina, 2015). Coker et al., (2020)** confirmed that ethanol caused liver inflammation in animal models.

Administration of polyphenol extract from fenugreek seeds has shown a positive influence on both lipid profile, and the quantitative and qualitative properties of collagen in alcoholic liver disease, and the protective effect is presumably attributable to the bioactive phytochemicals in fenugreek seeds **(Kaviarasan et al., 2007).** Polyphenols present in the seeds have been also demonstrated to prevent oxidative haemolysis, and lipid peroxidation induced by hydrogen peroxide in vitro, in human erythrocytes **(Pandey & Awasthi 2015).**

The polyphenolic compounds of fenugreek seeds can be considered cytoprotective during ethanol-induced liver damage

(Kaviarasan et al., 2006). A wide variety of antioxidants and diverse diets have been tested to mitigate the oxidative stress induced by ethanol abuse **(Ramírez-Farías et al., 2008).** The hepatoprotective effect of fenugreek seeds, mainly restricted to studies on ethanol toxicity and diabetes, has also been elucidated through the literature **(Sushma & Devasena 2010).**

Regardless of fenugreek being a familiar spice that has been added to human foods, literature has also proven that the use of this natural tonic to cure several types of lifestyle-related disorders such as cardiovascular diseases, hypercholesterolemia, hyperglycemia, cancer, liver ailments, and sexual disorders such as testosterone deficiency syndrome **(Thorat & Gaikwad 2019).**

In addition, fenugreek can stimulate humoral and cellular immune mechanisms **(Guardiola et al., 2018),** and regulate body immunity **(Wani & Kumar 2016).** Recently, **Syed et al., (2020)** concluded that fenugreek mucilage supplementation resulted in oedema inhibition by decreasing the activities of inflammatory enzymes due to its anti-arthritic potential, and improving the conditions of hyperlipidemia, liver malfunction, and insulin resistance **(Khound et al., 2018).**

The present investigation was designed to study the potential of using Trigonella foenum - graecum seeds powder and its protective effects against ethanol toxicity and inflammation in rats.

2. MATERIALS AND METHODS

2.1. Materials

2.1.1. Fenugreek powder

Seeds of *Trigonella foenum graecum* (fenugreek) were purchased from the local market in Giza, Egypt. Seeds were carefully cleaned, finely powdered, and kept in jars until use.

2.1.2. Chemicals

Kits for biochemical analysis of serum AST, ALT, ALP, total cholesterol, high density lipoprotein-cholesterol (HDL-c), and triglyceride were purchased from the Gamma Trade Company for Pharmaceutical and Chemicals, Dokki, Egypt.

2.1.3. Diets

The basal diet was prepared according to **Reeves et al., (1993),** the compositions of vitamin and mineral mixture were according to **(AOAC, 2016).**

2.1.4. Animals

The animal experiment was conducted in an animal house at the Faculty of Veterinary Medicine, Cairo University. The study included 24 male Wistar rats weighing 160±5 g, provided from the animal house. Animals were housed in polypropylene rat cages in an animal room, with a controlled temperature (24±2°C). The rats had unlimited access to food and water, and a 12-hour cycle of light and dark was maintained.

2.2. Methods

2.2.1. Experimental Design

Rats were divided into the following four groups (each group consist six rats):

Group A: negative control group administrated with a normal diet and water.

Group B: positive control group administrated with water containing ethanol 10% and normal diet.

Group C: administrated with water containing ethanol 10% and basal diet containing 10% fenugreek seed powder.

Group D: administrated with water containing ethanol 10% and basal diet containing 15% fenugreek seed powder.

The experimental animals were fed different diets for one month. At the end of the experiment, all rats were euthanized. The blood samples were taken from each animal by cardiac puncture. The samples were transferred into two tubes containing ethylenediaminetetraacetic acid (EDTA) as the hematology anticoagulant and clot tube for biochemical analyses. The clot tube was centrifuged at 5000 rpm for 10 min to extract serum. The blood serum samples were separated and stored in a freezer at -٢0 °C until use for biochemical analysis, the small intestine was kept in formalin solution (10%) for the histopathological examination.

2.2.2. Biochemical analysis

Hematocrit value, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count, differential leucocyte count, and blood platelet count are among the blood parameters that are measured were determined using Neubarer Hemocytomter.

The serum was separated and kept in a deep freezer at -20◦C for biochemical analysis. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities, total cholesterol (TC), triglycerides (TG) and high-density lipoprotein HDL-cholesterol concentration were determined using colorimetric methods as described in the kit's instruction (Diamond Co, Hannover, Germany). The concentrations of very low-density lipoprotein (VLDL-cholesterol) and low-density lipoprotein (LDL-cholesterol) were estimated using the Friedewald equation **(Friedewald et al.,1972).**

HDL-C was subtracted from total cholesterol to determine non-HDL. Ratios of proatherogenic lipoprotein measurements, including total cholesterol to HDL-C (TC/HDL), LDL to HDL (LDL/HDL), LDL+VLDL/HDL and TG to HDL (TG/HDL) were calculated.
Cyclooxygenase-1 COX-1 and cyclooxygenase-2 COX-2 assays were performed according to the procedure previously described by **Gautam et al., (2010).**

2.2.3. Histopathological analysis

Fresh pieces of the small intestine from each rat were kept in 10% formalin and then cut to obtain paraffin blocks. Sections of 4-micron thickness were stained with haematoxylin and eosin stain (H+F) according to the methods described by **Drury & Wallington (1980)** and examined by light microscopy. The histopathological results of the different groups were recorded and photographed.

2.2.4. Statistical analysis

Values were illustrated as mean ± SD. analysis of variance (ANOVA) was used for data comparison among the studied groups. The findings were considered statistically significant at the level of $p<0.05$. This was done using the software SPSS 21.0.

3. RESULTS

The effects of fenugreek administration on the hematological parameters of the different groups in male rats are presented in **table (1&2).**

Table 1: Effect of fenugreek on Hb, RBC count, Haematocrit, MCV, MCHC % and Platelets count in normal and alcoholic induced rats

Groups	Hemoglobin g/dl	RBC count 10^6/mL	Haematocrit %	MCV	MCH	MCHC %	Platelets Thousand/µm
Group A	13.15±0.05^{c}	7.63±0.05^{b}	38.40±0.10^{b}	50.50±0.50^{a}	17.00±0.00^{a}	34.00±0.00^{a}	432.50±208.50^{b}
Group B	14.65±0.45^{a}	8.39±0.64^{a}	43.50±2.77^{a}	51.00±1.00^{a}	17.50±0.50^{a}	34.00±1.00^{a}	623.0±21.00^{ab}
Group C	14.00±0.40^{b}	8.01±0.15^{ab}	40.50±2.00^{ab}	50.50±1.50^{a}	17.50±0.50^{a}	34.50±0.50^{a}	677.00±119.00^{a}
Group D	14.50±0.10^{ab}	8.58±0.23^{a}	42.25±0.25^{a}	49.00±1.00^{a}	17.00±0.00^{a}	34.00±0.00^{a}	691.00±51.00^{a}

The mean ± SD of each value.
Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).
Mean values in each column with same letters are not significantly different
Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

Table 2: WBC count, Lymphocytes, Monocytes, Eosinophils, Basophils and Neutrophils in normal and alcoholic-induced rats

Groups	WBC count thousand/µm	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %	Neutrophils %
Group A	13.30±1.07^{a}	62.00±6.00^{b}	8.00±0.00^{a}	1.00±0.00^{a}	0.00±0.00^{a}	17.50±4.50^{b}
Group B	10.12±0.44^{b}	72.50±4.50^{a}	6.00±1.00^{b}	1.00±0.00^{a}	0.00±0.00^{a}	30.00±5.00^{a}
Group C	8.32±0.86^{c}	62.00±2.00^{b}	6.00±0.00^{b}	1.00±0.00^{a}	0.00±0.00^{a}	30.00±2.00^{a}
Group D	6.25±0.75^{d}	67.00±3.00^{ab}	7.50±0.50^{a}	1.00±0.00^{a}	0.00±0.00^{a}	23.50±2.50^{ab}

The mean ± SD of each value.
Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).
Mean values in each column with same letters are not significantly different
Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

As shown in **Table 1&2**, adding two levels of fenugreek did not significantly affect the serum MCV, MCH, MCHC, Eosinophils, and Basophils contents ($P > 0.05$), compared to group A.

Male rats that received fenugreek with ethanol for 30 consecutive days had a higher number of RBCs in the blood,

hemoglobin concentration, hematocrit value, platelets, and monocytes, and neutrophils compared to the negative control group.

The results of the study showed that the administration of ethanol to male rats concurrently with fenugreek seeds, daily for 30 consecutive days, led to a significant increase in the number of white blood cells as compared to the positive control group **(Table 2).**

Table 3 showed the effect of fenugreek on lipid profile in normal and alcoholic- induced rats.

Table (3) illustrates that rats that received 10% ethanol-water (positive control) for 30 days had a significant increase ($P<0.05$) in serum concentrations of total cholesterol, triglycerides, LDL, and VLDL, as compared to the control group. In rats receiving fenugreek seeds powder, the serum total cholesterol and LDL were significantly decreased, while the serum HDL was significantly increased compared with the positive control group. On the other hand, serum HDL concentration was significantly lower than those of the negative control group.

Table 3: Lipid profile in normal and alcoholic-induced rats

Groups	T. C.	T. G.	HDL	LDL	VLDL
	mg/dl				
Group A	35.00 ± 0.40^{c}	47.50 ± 5.50^{b}	8.00 ± 1.00^{b}	17.50 ± 2.50^{c}	9.50 ± 1.10^{b}
Group B	57.40 ± 0.80^{a}	54.50 ± 1.50^{a}	6.00 ± 2.00^{c}	40.50 ± 1.50^{a}	10.90 ± 0.30^{a}
Group C	41.30 ± 3.90^{c}	49.00 ± 3.00^{b}	12.50 ± 2.50^{a}	19.00 ± 2.00^{c}	9.80 ± 0.60^{b}
Group D	51.00 ± 8.20^{b}	47.50 ± 3.50^{b}	8.50 ± 1.50^{b}	33.00 ± 6.00^{b}	9.50 ± 0.70^{b}

The mean $\pm$ SD of each value.

Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).

Mean values in each column with same letters are not significantly different

Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

The effect of fenugreek on Ratios of proatherogenic lipoprotein measurements of rats compared with control groups is illustrated in **table 4.**

Table 4: Ratios of proatherogenic lipoprotein measurements in normal and alcoholic- induced rats

Groups	TC/HDL	LDL/HDL	TG/HDL	LDL+VLDL/HDL	Non-HDL
Group A	4.45 ± 0.61^{b}	2.26 ± 0.59^{b}	5.94 ± 0.05^{b}	3.45 ± 0.61^{b}	27.00 ± 1.40^{c}
Group B	10.71 ± 3.43^{a}	7.68 ± 2.8^{a}	10.12 ± 3.12^{a}	9.71 ± 3.43^{a}	51.40 ± 1.20^{a}
Group C	3.37 ± 0.36^{b}	1.55 ± 0.15^{b}	4.13 ± 1.06^{b}	2.37 ± 0.36^{b}	28.80 ± 1.40^{c}
Group D	6.01 ± 0.09^{b}	3.87 ± 0.02^{b}	5.69 ± 0.59^{b}	5.01 ± 0.09^{b}	42.50 ± 6.70^{b}

The mean ± SD of each value.
Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).
Mean values in each column with same letters are not significantly different
Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

From **table 4**, it could be noticed that the mean values of proatherogenic lipoprotein measurements in the positive control group were significantly higher than those of the negative control group. All ratios of proatherogenic treatments indicated statistically significant differences when compared with the control (+) group. Groups C&D (10% and 15% fenugreek seeds powder) were found to be the best groups for decreasing ratios of proatherogenic levels of rats so close to the control (-) group when compared.

Serum ALT, AST, and ALP activities of the different groups are shown in **table 5.**

Data in **Table 5** showed the effect of different treatments on serum ALT, AST, and ALP activity. Mean serum AST, ALT, and ALP activities were significantly changed in the control group compared with all groups with each other and in between.

Table 5: Liver functions (ALT, AST, and ALP) in normal and alcoholic- induced rats (U/L)

Groups	ALT	AST	ALP
	U/L		
Group A	24.00 ± 5.00^{c}	57.00 ± 13.00^{b}	30.00 ± 1.00^{c}
Group B	51.50 ± 1.50^{a}	78.50 ± 1.50^{a}	64.50 ± 6.50^{a}
Group C	33.50 ± 2.50^{b}	60.50 ± 1.50^{ab}	56.50 ± 13.50^{b}
Group D	36.50 ± 1.50^{b}	67.00 ± 1.00^{ab}	53.00 ± 2.00^{b}

The mean ± SD of each value.
Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).
Mean values in each column with same letters are not significantly different
Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

COX1 and COX2 of the different groups are shown in **table 6.**

Table 6: Inhibition of COX-1 and COX-2 enzymatic activity by fenugreek

Groups	COX1	COX2
	NG/ML	
Group A	1.61±0.27^{c}	1.18±0.07^{d}
Group B	10.50±2.10^{a}	7.65±0.75^{a}
Group C	4.50±0.60^{b}	3.70±0.30^{b}
Group D	3.95±0.25^{b}	2.85±0.25^{c}

The mean ± SD of each value.
Significant differences exist between the values in each column with a different superscript at ($p < 0.05$).
Mean values in each column with same letters are not significantly different
Group A (Negative Control), Group B (Positive Control), Group C (Group 10% fenugreek), and Group D (15% fenugreek)

Data presented in **Table 6** indicated the inhibition of COX-1 and COX-2 by fenugreek. Fenugreek at a high concentration (15%) showed great potential to efficiently inhibit COX-1 as well as COX-2.

Results of Histopathological Examination:

Histopathological examination of the small intestine is shown in **Photos (1-4).**

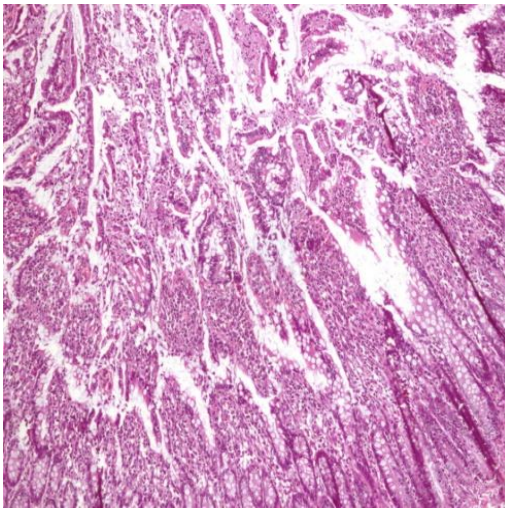

Photo. 1: Photomicrograph of rat small intestine from negative control group showing healthy villi and crypts, (H&E X 100).

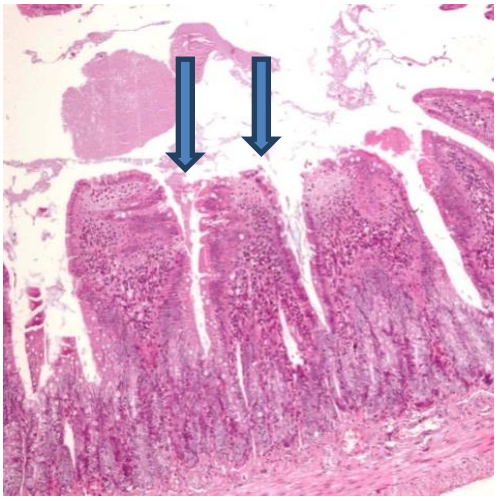

Photo. 2: Photomicrograph of rat small intestine from positive control group showing necrosed Villar epithelium (arrows), (H&E X 200).

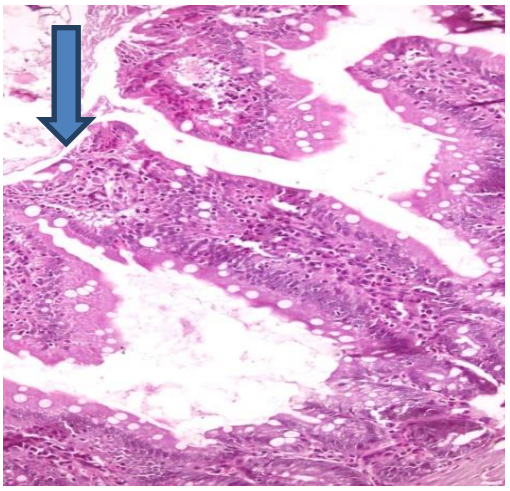

Photo 3: Photomicrograph of rat small intestine from low dose diet group showing improved Villar epithelium than the control positive group (arrow), (H&E X 200).

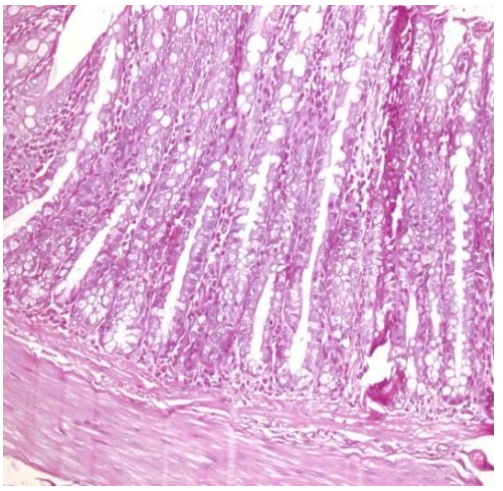

Photo 4: Photomicrograph of rat small intestine from high dose diet group showing apparently normal Villar epithelium and improved than low dose diet group, (H&E X 200).

The negative control group showed that the small intestine showed no histological changes with normal villi and crypts **(Photo. 1).** The second Group (the positive control group) declared that the small intestine showed necrotic villar epithelium and crypts **(Photo. 2).**

Concerning fenugreek groups, the third group (10% FSP diet) showed that the small intestine showed improvement in the epithelium of the villus and crypts **(Photo. 3).** However, the fourth group (15% of the FSP-treated group) proved that the small intestine showed normal villous epithelium and crypts **(Photo. 4).**

4. DISCUSSION:

In hematological parameters of the different groups respect, the study of **Rosioru et al., (2010)** illustrated that treatment of rats with 10% ethanol in drinking water for 30 days caused a significant increase in RBCs count, Haematocrit value, and Hb concentration, and WBC count as compared to the control animals. The addition of 10% fenugreek flour to the diet of ethanol-intoxicated rats for 30 days showed a tendency to restore the control values.

The obtained findings confirmed those reported by **Kandhare et al., (2015)** that fenugreek seeds affected the hemoglobin, which

improved hematopoietic function. Similarly, **Al-Amri & Alrasheedi (2016)** demonstrated that feeding rats on a diet supplemented with fenugreek seeds at a concentration of 5% for 14 days of radiation exposure significantly resulted in a significant increase in hemoglobin percentage compared to the control group.

In this regard, **Abdel-Rahman et al., (2016)** suggested that the administration of fenugreek powdered seeds was responsible for the improvement of the immunological profile through the increased phagocytic index, the phagocytic capacity of macrophages, and humoral immunity.

Fenugreek treatment may enhance haematological indicators because the flavonoids in fenugreek seeds have antioxidant properties, which increase the body's ability to fight free radicals in the blood. The high iron content of fenugreek seed flour stimulated hemoglobin synthesis, and thereby fenugreek seeds may improve immunity as they play a role in protecting the spleen, and increasing the lymphocytes **(Elghazaly et al., 2019).**

The obtained data are in the line with those made in a previous study that demonstrated the hypolipidemic effect of fenugreek powder in experimental animals like rabbits, rats, etc. **(Sharma & Choudhary 2014).**

Similarly, the intake of fenugreek seeds and extracts lowered total cholesterol (TC), triglycerides, and low-density lipoprotein cholesterol (LDL). It is possible that these effects were attributed to saponin, which increased bile cholesterol excretion, which in turn reduced cholesterol levels. The lipid-lowering effect of fenugreek may also be attributed to its estrogenic components, which indirectly increase thyroxine (T4) **(Khan et al., 2018).**

The obtained results also confirmed the results of **Hou et al., (2010)** who observed that ethanol intake led to a significant increase in the hepatic index, and elevated serum levels, triglycerides and total cholesterol, noting that ethanol intake caused typical fatty liver.

The first stage in reverse cholesterol transfer, which is proposed to be a key mechanism by which HDL mediates its atheroprotective effects, is the formation and release of HDL in the peripheral vascular **(Ragbir & Farmer 2010).**

However, Increased levels of LDL and VLDL lead to an increased risk of cardiovascular diseases **(Jaiswal et al., 2013).** As

Oxidative stress products could stimulate the production of oxidized low-density lipoprotein. Hypercholesterolemia, especially LDL-C, could cause endothelial dysfunction, and increased permeability of the endothelial layer; inducing oxidative stress injury, and vascular inflammation, which consequently leads to atherosclerosis **(Sun et al., 2014).**

The increase in the concentration of TC and TG in the serum indicates that the body fat metabolism is abnormal, or that the accumulation of fat in the animal body increases, leading to an increase in serum lipid content **(Tan et al., 2020).** LDL-c and HDL-c are lipoproteins associated with cholesterol transport linked to atherosclerosis and cardiovascular disease **(Pizzini et al., 2019).**

Worth mentioning, the use of fenugreek extracts significantly reduced the levels of TC, TG, and LDL in plasma while increasing the plasma levels of HDL-c in plasma **(Belguith-Hadriche et al., 2010). Begum et al. (2016)** added that fenugreek seed extract has a significant increase in serum HDL-c concentration. Recently, fenugreek seed extract can control blood lipids and lower serum total cholesterol **(Huang et al., 2022).** Furthermore, **Algridi & Azab (2021)** assured that the use of fenugreek seed powder by humans may be considered beneficial in alleviating dyslipidemia.

The results obtained regarding the effect of fenugreek on liver function are consistent with those observed in some studies. Fenugreek administration caused a marked decrease in the level of serum lipid hydroperoxides, and lowered activities of AST, ALT, and ALP as compared to rats fed only with ethanol **(Thirunavukkarasu et al., 2003),** AST and ALT activities **(Al-Wabel et al., 2008),** and restored the levels of serum ALP, AST and ALT activities **(EI-Tawil 2009).**

The aqueous extract of fenugreek seeds significantly reduced the elevated ALT and AST levels, which were increased in rats treated with monosodium glutamate as it was attributed to its protective effect on hepatic tissues **(Kumar & Bhandari 2013).** Similarly, **Belaïd-Nouira et al., (2013)** upheld that fenugreek seeds powder can ameliorate hepatic function through the significant amelioration of ALT and AST activities in the liver and plasma as well as the prevention of cholestasis. The administration of fenugreek seed

extract in CCl4-treated rats caused a reduction in Serum ALT, AST, and ALP levels **(Das 2014).**

Serum ALT and AST activities are considered toxicity markers in hepatotoxicity investigations, and an increase in these enzymes' activities is referred to as the early detection of toxic hepatitis **(Abushofa et al., 2019).**

The two isoforms of the COX enzyme; cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) catalyze the conversion of arachidonic acid to eicosanoids, (like prostaglandins and thromboxanes) via the formation of endoperoxides. The COX1 isoform synthesizes prostaglandins that are required for normal physiologic functions like gastrointestinal cytoprotection, and platelet activity. COX2 is not detectable in most normal tissues; however, it is induced at sites of inflammation by cytokines, growth factors, tumor promoters and other agents. Both isoforms are also responsible for the synthesis of prostaglandin E2 (PGE2), and there is evidence for the correlation between increased levels of PGE2, and tumorigenesis **(Janakiram & Rao 2008).**

The anti-inflammatory properties of fenugreek may be due to the existence of flavonoids and saponins as antioxidants and inhibitors of cyclooxygenase (COX), and lipoxygenase **(Sharififar et al. 2009).**

The expressions of the genes hitch play role in prostaglandin biosynthesis (COX1, COX2) were downregulated as a result of fenugreek containing nutriment. These biologically active compounds of fenugreek may be tools of chemopreventive strategies as well, such as the possible inhibition of prostaglandin of the metabolic pathway with cyclooxygenase (COX) enzymes **(Varjas et al., 2011).**

The inhibitory activity may be due to the natural phenolic and flavonoid compounds, which play antioxidant activities by different mechanisms. The high contents of these phytochemicals in fenugreek seed extracts can exhibit anti-inflammatory activity **(Bairagi et al., 2012).** The anti-inflammatory and antinociceptive activity of alkaloid and flavonoid fractions of fenugreek seeds was probably due to their ability to inhibit pro-inflammatory enzymes, namely cyclooxygenases (COXs) and lipooxygenases **(Mandegary, et al., 2012).**

Nagulapalli et al., (2017) reported that Trigonella foenum-graecum (fenugreek) seed extracts had potential anticancer properties. **El-Taib et al., (2020)** indicated that the fenugreek seed extracts can be used as an anti-inflammatory agent to reduce inflammation, and alleviate pain. This plant may play an important role in discovering new anti-inflammatory natural drugs. Also, these medicinal plants can be subjected to further investigations as anticancer natural products.

Similarly, **Bakheet et al., (2020)** found that dietary supplementation with fiber that is a source of butyric acid production, such as fenugreek seed, represents a new, effective, non-invasive way to avoid and reduce the severity of gastrointestinal problems. The mechanisms that contribute to the improvement of intestinal resistance to inflammation by anti-inflammatory action may be enhanced by the improvement of intestinal lymphoid tissues and the increase in the production of immunoglobulin A, revealing that fenugreek seeds are a good candidate for the formulation of synbiotic. **Kheirandish et al., (2011)** demonstrated that the integrity of the intestinal mucosa with fenugreek remained almost in the normal group, which conforms to **Abdeen et al., (2011)** who used different antioxidant agents in the same animal model.

5. CONCLUSION

This study clearly showed that the fenugreek seeds in a dose-dependent manner could protect cell structure and function from the toxic effects of ethanol. Fenugreek seeds powder administration resulted in an overall improvement in the intestine histology of rats, and showed a protective effect on the liver enzymes, the hematological parameters and hypocholesterolemia and anti-atherogenic. Humans can benefit from the usage of fenugreek seed powder in the treatment of dyslipidemia. Fenugreek seeds were potent inhibitors of the tested enzymes with efficacy decreasing COX-1 and COX-2. The evidence that fenugreek seeds were a better inhibitor of COX-1 and COX-2 could contribute to its cardioprotective effect. It may be due to the presence of various phytoconstituents present in *Trigonella foenum-graecum* like phenolics, flavonoids, tannins, and alkaloids, which are already reported to possess immunomodulatory activity. The above-

mentioned studies on fenugreeks' functional, nutritional and therapeutic characteristics of fenugreek can be exploited further in the development of healthy products. Further studies are needed to better evaluate these activities and the potential of *Trigonella foenum-graecum.*

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التأثيرات التحسينية لمسحوق بذور الحلبة على نسب تصلب الشرايين والإنزيمات المضادة للالتهابات والتغيرات الهستولوجية للامعاء الدقيقة في الفئران

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الملخص العربي

يتم استخدام الحلبة (*Trigonella foenum-graecum*) كتوابل في جميع أنحاء العالم لتعزيز الجودة الحسية للأطعمة. وجدت العديد من الخصائص الفسيولوجية المفيدة للصحة لبذور الحلبة في الدراسات التي أجريت على الحيوانات وكذلك الانسان. استهدفت هذه الدراسة التحقق من الأنشطة المضادة للالتهابات وخفض الكوليسترول والبروتين الدهني منخفض الكثافة والدهون الثلاثية لمسحوق بذور الحلبة فى أربع مجموعات من الفئران. تم تقسيم الفئران إلى أربع مجموعات (كل مجموعة بها ستة فئران). المجموعة أ (الضابطة السالبة) تم تغذيتها على الوجبة الاساسية والماء، المجموعة ب (الضابطة الموجبة) أعطيت الماء المحتوي على الإيثانول ١٠٪ ونظام غذائى عادى (الوجبة الاساسية)، بينما أعطيت المجموعتين ج ود الماء المحتوى على الإيثانول ١٠٪ والنظام الغذائي الأساسي المضاف له ١٠٪ و ١٥٪ مسحوق بذور الحلبة على التوالي. وقد أجريت الدراسات الفسيولوجية باستخدام قياسات الدم، ونسبة الدهون، ووظائف الكبد، والإنزيمات المضادة للالتهابات والفحص الهستولوجي للأمعاء الدقيقة. بينت النتائج أن الفئران التي تناولت الإيثانول لمدة ٤ أسابيع أظهرت زيادة معنوية في عدد كرات الدم الحمراء وتركيز الهيموجلوبين وقيمة الهيماتوكريت وعدد الصفائح الدموية بينما كانت الفروق غير معنوية بين MCV و MCH و MCHC مقارنة بالمجموعة الضابطة. كما أدت إلى زيادة معنوية في تركيزات الكوليسترول والدهون الثلاثية و LDL-c و VLDL-c في الدم، ولوحظ انخفاض معنوي في HDL-c في الدم مقارنة مع المجموعة الضابطة. وقد وجد أن عند أضافة مسحوق بذور الحلبة، انخفضت نسب معدل تصلب الشرايين في الفئران بشكل ملحوظ بينما زاد HDL-c في الدم بشكل ملحوظ مقارنة بمجموعة الضابطة الموجبة. أدى تناول الحلبة مع الإيثانول إلى تحسن في وظائف الكبد في الدم والبنية النسيجية للأمعاء الدقيقة عند مقارنتها بالمجموعة الإيجابية. زادت الإنزيمات المضادة للالتهابات COX-1 و COX-2 نتيجة تناول الإيثانول في الفئران. سلطت هذه الدراسة الضوء على السمية الحيوية للإيثانول من خلال المقاييس البيوكيميائية والهستولوجية من جهة والدور الوقائي لبذور الحلبة من جهة أخرى. وبالتالي، يمكن أن يكون هذه الدراسة تجريبية من شأنها أن تشجع استخدام بذور الحلبة كمكمل غذائي لإزالة السموم من الحيوانات.

الكلمات الدالة: بذور الحلبة، الفئران، سمية الإيثانول، الهستولوجي، الإنزيمات المضادة للالتهاب، COX-1، COX-2، الدهون، انزيمات الأكسدة الحلقية، معدل تصلب الشرايين.