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Antidyslipidemic Effect of Fenugreek Seeds Powder against Sodium Fluoride-Induced Dyslipidemia in Male Rabbits

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Abstract

Background: Although fluoride is everywhere in the environment, the major environmental sources of population exposure to elevated levels of fluoride are water, food, beverages, air, food supplements, and dental products. Fluoride is a well determined non-biodegradable and moderate pollutant, which at high levels causes serious health problems.

Objectives: The present study aimed to evaluate the anti-dyslipidemia effect of fenugreek seeds powder against dyslipidemia induced by sodium fluoride in male rabbits.

Materials and Methods: This study included twenty-four adult male rabbits, which were divided into 4 groups, 6 rabbits for each. Group I (control group): Animals were provided with tape water and fed with normal diet for 30 days. Group II (Fenugreek seeds powder group): Fenugreek seeds powder was given to rabbits in food at a dose of 10 g per kilogram of diet weight/kg of body weight/day for 30 Days. Group III (sodium fluoride group): Rabbits were injected intraperitoneally with sodium fluoride at a dose of 15mg/kg of body weight/day for 30 consecutive days. Group IV (Sodium fluoride/fenugreek co-administered group): Fenugreek seed flour was added at a rate of 10 g per kilogram of diet weight, and rabbits were injected with intraperitoneally with sodium fluoride at a dose of 15mg/kg of body weight/day for 30 consecutive days. After thirty days, blood samples were taken for biochemical analysis. Biochemical analyzes were performed to measure of the serum concentrations of cholesterol, triglycerides, HDL-C, LDL-C, and VLDL-C in all groups.

Results: The results of the study showed that the treatment of male rabbits with sodium fluoride resulted in a significant increase (P<0.01) in the serum concentrations of cholesterol, triglycerides, LDL-C, and VLDL-C, and a significant decrease was observed (P<0.01) in serum HDL-C compared with the control group. In rabbits received fenugreek seeds powder only, the serum triglycerides and VLDL-C were significantly (P<0.01) decrease and the serum HDL-C was significantly (P<0.05) increase compared with the control group. A significant decrease (P<0.01) was observed in serum cholesterol, triglycerides, LDL-C, and a significant increase was observed vertice. A significant increase was observed (P<0.01) in serum HDL-C was significant increase was observed (P<0.01) in serum HDL-C was significant increase was observed vertice.

Conclusion: The results showed that injection of rabbits with sodium fluoride led to serum dyslipidemia, and the injection with sodium fluoride and treatment of fenugreek seeds powder alleviate dyslipidemia induced by sodium fluoride. The use of fenugreek seeds powder by humans can be considered beneficial in the alleviation of dyslipidemia. It is recommended that humans exposed to sodium fluoride should be advised to take Fenugreek seeds powder as a rich source of antioxidant to prevent serum dyslipidemia induced by sodium fluoride. Further studies are necessary to elucidate exact mechanism of the antidyslipidemic effect of Fenugreek seeds powder as a protective agent against sodium fluoride induced dyslipidemia in clinical trials.

Keywords: sodium fluoride, dyslipidemia, lipid profile, fenugreek seeds powder, antidyslipidemic effect, male rabbits

1. Introduction

Fluoride is a well determined non-biodegradable and moderate pollutant, which at high levels causes serious health problems [1]. Fluorides are released into the environment due to human activities and naturally from natural sources. The manufacturing of steel, brick, ceramic, glass, aluminum, copper, nickel, glues, adhesives, and the production of hydrogen fluoride, chlorofluorocarbon and phosphate fertilizer and use of

fertilizer released fluoride into the environment (air, water, plants, animals, rocks and soil) [2, 3]. Combustion of fluoride impurities containing coals as well as the use of fluoride containing pesticides and controlled fluoridation of drinking water supplies also release fluoride into the environment [3]. Mining activities and deep wells of springs may release a large amount of fluoride into the atmosphere. Fluorides also released into the environment naturally through weathering and

dissolution of fluoride-bearing minerals like fluorite, rock phosphate, fluorapatites, and topaz [3, 4]. Fluorides are released into the environment through atmospheric emissions from volcanoes and sea water [3]. Traces of fluorides are present in many waters; higher concentrations are often associated with underground sources. In seawater, a total fluoride concentration of 1.3 mg/litre has been reported. In areas rich in fluoride containing minerals, well water may contain up to about 10 mg of fluoride per litre. Fluorides may also enter a river as a result of industrial discharges [5]. In ground water, fluoride concentrations vary with the type of rock the water flows through but do not usually exceed 10 mg/litre [6].

Sodium fluoride is the most commonly used compound in oral caries prevention in the form of fluorinated drinking water, salts or milk, tooth pastes, mouth washes and fluoride tablets that adversely affects liver functions parameters [7]. Although fluoride is everywhere in the environment, the major environmental sources of population exposure to elevated levels of fluoride are water, food, beverages, air, food supplements, and dental products [3, 8, 9]. Fluoride salts generate free oxygen radicals which cause lipid peroxidation resulting in cell membrane damage and toxicity [10].

Heart disease or cardiovascular disease is a global of chronic human disease and over the past centuries, cardiovascular disease has been remained as common public health problems throughout the world [11]. To date, cardiovascular disease is still remaining a leading cause of death in both developed and developing countries [12] and by 2020, it is predicted to be main causes of morbidity and mortality in most developing countries [13]. Lipids play an important role in virtually all aspects of biological processes in the body. Disturbances of their level in tissues and serum are usually associated with many abnormalities, including atherosclerosis, and coronary artery disease [14]. As people grow older, fat, cholesterol, and calcium build up in the walls of arteries and form hard structures called plaques. The process of calcium accumulation in blood vessels resembles bone formation and involves maintaining a balance between bone-forming cells called osteoblasts and bone-destroying cells called osteoclasts. The resulting plaques cause arteries to become narrow and stiff and can obstruct blood flow. As a consequence, oxygen-starved tissue can become damaged or die, leading to heart attack and stroke [15]. Afolabi et al., [16] suggested that the association between fluoride exposures with cardiovascular diseases may be related to its ability to disturb lipid homeostasis and oxidative stress.

Modern lipid lowering agents i.e. statins (atorvastatin, cimvastatin, rosuvastatin etc.) are expensive. The most important adverse effects of statins are liver and muscle toxicity. Other risk factors are hepatic dysfunction, renal insufficiency, hypothyroidism, advanced age and serious infections [17, 18]. Liver and kidney functions may be modified [18].

In the present century modern medicine draws its nourishment from the rich legacy of traditional medicine [19]. Herbal agents like fenugreek, is economical and easily available in many countries like Bangladesh, India, Nepal, Pakistan and Mediterranean region and South African countries [18, 20]. Fenugreek (Trigonella foenumgraecum) is one of the oldest medicinal plants, dating back to Hippocrates and ancient Egyptian times [20, 21]. Fenugreek seed is one of the well-known spices in human food which is cultivated worldwide as a semiarid crop. It belongs to the family of Fabaceae. Fenugreek provides natural food fiber and other nutrients required in human body. Aromatic and flavourful fenugreek seed is a popular spice and is widely used for well recognized culinary and medicinal purposes [3]. The chemical composition of fenugreek (such as seeds, husk and cotyledons) showed that endosperm had the highest (4.63g/100g) saponin and (43.8g/100g) protein content [22, 23]. Fenugreek can be recommended for the diet and must use in daily habit for its medicinal health benefits and its safe use. The functional, nutritional and therapeutic characteristics of fenugreek can be use further

in the development of healthy life and nutritional value of medicinal plants [23]. Fenugreek seed is used in physiological utilization for the treatment of antibacterial, anticancer, hypocholesterolemic, hypoglycemic antioxidant, and antidiabetic agent [3]. The antihyperlipidemic properties of oral fenugreek seed powder has been suggested [19, 24].

2. Objectives

The evidences reporting the antidyslipidemic effects of fenugreek seeds powder against sodium fluoride induced dyslipidemia in male rabbits are hardly found. So, the present study aimed to evaluate the antidyslipidemia effect of fenugreek seeds powder against dyslipidemia induced by sodium fluoride in male rabbits.

3. Materials and Methods

3.1. Animals

24 adult male rabbits, aged between 35-37 weeks and weighing 1.5-1.8 kg, were used in the current study. The rabbits were housed in a room under standard conditions of ventilation, temperature (25 ° C \pm 2), and humidity (60 - 70) %, rabbits were separated in a plastic cage, the animals were provided with free drinking water and standard commercial food.

3.2. Chemicals

Sodium fluoride was purchased from Sigma Chemicals Company, and rabbits were injected intraperitoneally with sodium fluoride at a dose of 15mg/kg of body weight/day for 30 consecutive days [25].

3.3. Fenugreek seeds

Fenugreek seeds was purchased from the Zawia market, and the fenugreek seeds were ground and added at a rate of 10 gm of fenugreek seeds powder per kilogram of diet weight that was provided to rabbits for 30 days.

3.4. Experimental Design

After one week of acclimation, the animals were randomized and divided into four groups (6 rabbits for each) as follows: Group I (control group): Animals were provided with tape water and fed with normal diet for 30 days. Group II (Fenugreek seeds powder group): Fenugreek seeds powder was given to rabbits in food at a dose of 10 g per kilogram of diet weight/kg of body weight/day for 30 Days. Group III (sodium fluoride group): Rabbits were injected intraperitoneally with sodium fluoride at a dose of 15mg/kg of body weight/day for 30 consecutive days. Group IV (Sodium fluoride/fenugreek co-administered group): Fenugreek seed flour was added at a rate of 10 g per kilogram of diet weight, and rabbits were injected with intraperitoneally with sodium fluoride at a dose of 15mg/kg of body weight/day for 30 consecutive days. At the end of the experiment and 24 hours after the last dose, all animals were anesthetized with ether and blood samples were collected by heart puncture.

3.5. Biochemical Analysis

The blood sample was collected in clean dry tube and centrifuged at 3000 rpm for 15 minutes then, serum was separated and kept in a deep freezer at -20°C until biochemical measurements were carried out. Total cholesterol concentration was estimated according to Allain *et al.* [26], triglycerides concentration also by the method of Fossati and Prencipe [27] and HDL-cholesterol by Burstein *et al.* [28]. VLDL-cholesterol and LDL-cholesterol concentrations were estimated by using the Friedewald equation [29].

3.6. Statistical Analysis

The values were presented as means \pm SD of different groups. One-way analysis of variance (ANOVA) was carried out. For the comparison of significance between groups, Duncan's test was used as a post hoc test

according to the statistical package program (SPSS version 25.0). The results were considered statistically significant when P < 0.05.

4. Results

Rabbits that received intraperitoneal injection of sodium fluoride only (15mg/kg of body weight/day) for 30 days had significantly (P < 0.01), increased the serum concentrations of triglycerides, cholesterol, LDLc, and VLDLc (Table. 1 & Fig.1, 2, 4, 5), as compared with the control group. On the other hand, serum HDLc concentration was significantly (P < 0.01) decreased as compared with the control group (Table. 1 &

Fig.3). In rabbits received fenugreek seeds powder only, the serum triglycerides and VLDL-C were significantly (P < 0.01) decrease and the serum HDL-C was significantly (P < 0.05) increase compared with the control group (Table.1 &Fig.1, 3, 5).

A significant decrease (P < 0.01) was observed in the serum cholesterol, triglycerides, LDL-C, and VLDL-C, and a significant increase was observed (P < 0.01) in the serum HDL-C in rabbits treated with sodium fluoride and received fenugreek seeds powder compared with the sodium fluoride group, but these measurements did not reach normal levels in the control group (Table.1 & Fig.1-5).

Groups	Control	Fenugreek Seeds	Sodium Fluoride	Sodium Fluoride + Fenugreek Seeds
Parameters	Mean + SD	Mean + SD	Mean + SD	Mean + SD
Triglycerides concentration (mg/dl)	66.2 ± 2.6	$62.5 \pm 1.9^{**}$	$91.3 \pm 2.0^{**}$	$71.3 \pm 2.0^{**\#}$
Cholesterol concentration (mg/dl)	55.5 ± 2.7	52.8 ± 2.6	$97.8 \pm 4.3^{**}$	$60.5 \pm 2.7^{* \# \#}$
High-density lipids concentration (mg/dl)	27.2 ± 1.7	$29.3 \pm 1.5^{*}$	$18.8 \pm 1.5^{**}$	$24.3 \pm 1.6^{**\#}$
Low-density lipids concentration(mg/dl)	15.1 ± 3.9	11.0 ± 3.8	$60.7 \pm 5.4^{**}$	21.9± 3.4*##
Very low-density lipids concentration (mg/dl)	13.2 ± 0.5	$12.5 \pm 0.4^{**}$	$18.3 \pm 0.4^{**}$	$14.3 \pm 0.4^{**\#}$

*: Significant at (P<0.05) when compared with control group, **: Significant at (P<0.01) when compared with control group, ##: Significant at (P<0.01) when compared with Sodium Fluoride group.

Table 1. Effect of administration of sodium fluoride and/or fenugreek seeds powder on serum lipid profile parameters concentrations in male rabbits.



Figure 1. Effect of administration of sodium fluoride and/or fenugreek seeds powder on serum Triglycerides concentration in male rabbits.



Figure 2. Effect of administration of sodium fluoride and/or fenugreek seeds powder on serum cholesterol concentration in male rabbits.





Figure 3. Effect of administration of sodium fluoride and/or fenugreek seeds powder on serum HDL-cholesterol concentration in male rabbits.

Figure 4. Effect of administration of sodium fluoride and/or fenugreek seeds powder on serum LDL-cholesterol concentration in male rabbits.





5. Discussion

High fluoride could cause metabolic disorders of rabbits, thus lead to hypercholesterolemia. Hypercholesterolemia, especially LDL-C, could cause endothelial dysfunction, increase the permeability of the endothelial layer; induce oxidative stress injury and vascular inflammation, consequently resulting in atherosclerosis [30, 31]. It has been reported that lipid, lipoprotein and apolipoprotein levels in both fluorosis patients and experimental rats showed abnormal changes [31, 32]. Also, previous studies recorded that fluoride exposure disturbs lipid metabolism [16, 33-35]. Additionally, chemical liver injury caused by chronic fluorosis can lead to damage, steatosis, eosinophilic and inflammatory responses of hepatocytes, resulting in abnormal catabolism of blood lipids and lipoproteins and elevating blood lipids [31, 36].

The results of the current study showed that the treatment of male rabbits with sodium fluoride resulted in a significant increase (P < 0.01) in the serum concentrations of cholesterol, triglycerides, LDL-C, and VLDL-C,

and a significant decrease was observed (P < 0.01) in serum HDL-C compared with the control group. These results run parallel to those reported by many of previous studies in rabbits [31], rats [37, 38], mice [39], and Guinea pigs [40, 41]. Afolabi *et al.*, [16] reported that exposure of rats to 50 mg/L and 100 mg/L of fluoride through drinking water for seven weeks led to hypercholesterolemia while the 100 mg/L concentration induced hypertriglyceridaemia. High density lipoprotein (HDL) cholesterol levels dropped in the exposed rats. Also, Rupal and Narasimhacharya [42] reported significant high level of total cholesterol, LDL-C, and VLDL-C after exposure of rats to 100ppm of sodium fluoride for four weeks. Fluoride was found to have an inhibitory effect on hepatic cholesterol and free fatty acid synthesis in fluoride treated rabbits [43, 44].

Cholesterol is an essential part of every cell in the body. It is necessary for formation of new cells and for older cells to repair themselves after injury. It is also used by the adrenal glands in the synthesis of some hormone, such as cortisol, by the testicles to form testosterone, and by the

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ovaries to form estrogen and progesterone [45]. The high cholesterol level in plasma may be due to increased uptake of exogenous cholesterol and subsequent deposition and decreased cholesterol catabolism as evidenced by a reduction in bile acid production and turnover of bile acids. The metabolism of free and ester cholesterol are impaired in liver, spleen and thymus tissue and the rate of turnover was specifically decreased in all tissues of hyperlipidemic rats [46]. Increase in LDL, VLDL levels are increase the risk of cardiovascular diseases [47].

The hypertriglyceridemic effect of fluoride may be related to lower hydrolysis of triglyceride, attributable to fluoride-induced reduction in the activity of lipoprotein lipase [16, 48]. Hypetriglyceridemia may be due to stimulation of hepatic synthesis of very low density lipoprotein, which is a consequence of increased hepatic fatty acid synthesis, activation of adipose tissue lipolysis, and/or suppression of fatty acid oxidation and ketogenesis [16, 49].

Excess intake of fluoride was found to increase LPO and MDA levels significantly and accumulate the products of oxidative stress [31, 50, and 51]. So, oxidative stress caused by excess intake of fluoride might play an important role in the development of hypercholesterolemia in experimental animals [31]. The products of oxidative stress could induce the production of oxidized low density lipoprotein, and the atherogenic effect of oxidized low density lipoprotein is stronger than that of LDL [31, 52]. Firstly, oxidized low density lipoprotein can injure endothelial cells, causing degeneration, necrosis and shedding. Secondly, oxidized low density lipoprotein can induce hyperplasia of endothelial cells and smooth muscle cells [31, 53].

The observed abnormalities in lipoprotein profile after exposure to NaF might be due to over-production of VLDL by the liver or to the decrease in removal of VLDL and LDL from the circulation [44, 54]. It could be suggested that the abnormal activities of lipases enzymes seemed to be one of the chief and responsible factors for the rise in serum triglycerides and cholesterol. It appeared that enzymes inhibited by fluoride, such as triglyceride lipase, unspecific esterase and pyrophosphates [33, 44] lead to weaken lipid metabolism and a case of dyslipidemia. Moreover oxidative stress induced by NaF [44, 55] could be claimed. NaF intoxication registed an increased in lipid peroxidation and loss of membrane integrity which might be important in altered lipid metabolism and closely associated with observed hyperlipidemia [44, 56]. Besides, fluoride was found to cause hypercholesterolemia due to lower insulin level [44, 57].

The synthesis and release of HDL into the peripheral vasculature is the first step in reverse cholesterol transport that is proposed to be a major mechanism by which HDL mediates its atheroprotective effects [58]. HDL has also been demonstrated to improve endothelial function, maintain the integrity of vascular endothelium and may induce the production of vasodilators, such as prostacyclin, by the endothelium. HDL has also been demonstrated to exhibit anti-thrombotic and anti-inflammatory activities [59]. HDL acts as a transporter of a variety of fat-soluble vitamins, including vitamin E, and also as a natural anti-oxidant protecting for LDL in a multifactorial manner. Moreover, HDL are associated with enzymes with anti-oxidant capacity like paraoxonase that is a major contributor to the anti-oxidant activity of HDL [58].

HDL-C inversely correlates with the risk of coronary heart disease and its reduction by fluoride reflects changes in HDL metabolism that could lead to defective reverse cholesterol transport, eventually promoting atherogenesis. The dyslipidemic effect of fluoride reflected in hypercholesterolemia, hypertriglyceridemia, increased levels of triglyceride-rich lipoproteins, and HDL depletion may well contribute to

its atherogenic tendencies, as dyslipidemia has been well implicated in cardiovascular disease [16, 60].

In recent years, there has raised public concern about damage to the cardiovascular system, especially atherosclerosis and hypertension, which caused by excessive exposure to fluoride [31]. Excessive exposure to fluoride can cause a metabolic, structural and functional damage to the cardiovascular system [31, 32, 61-62]. Atherosclerosis is an inflammatory process of the vascular wall, characterized by the accumulation of lipids and fibrous elements in the large and medium-sized elastic and muscular arteries [31, 63]. Previous studies have shown that chronic exposure to high levels of fluoride can not only influence lipid metabolism, but also affect oxidative stress [31, 64, and 65].

Fenugreek seeds may be useful in hyperlipidemic states of patients with hypertension, atherosclerosis, ischemic heart diseases etc [19].

Results of the present study which have shown that co-administration of fenugreek seeds powder with sodium fluoride induced a significant reduction in the serum triglycerides, cholesterol, LDL-cholesterol, and VLDL- cholesterol concentrations and elevation in the serum HDLcholesterol concentration. Similar observations were also made in a study that demonstrated hypolipidemic effect of fenugreek powder in experimental animals like rabbits, rats, etc [18, 19, and 66]. These results are in concordant with those of Moosa et al., [19] who reported that administration of fenugreek seed powder of 25 gm orally twice daily for 3 and 6 weeks produces significant (p<0.001) reduction of serum triglycerides, total cholesterol, and LDL-cholesterol in hypercholesteremic group but the change of serum HDL-cholesterol was not significant. Researchers suggest that fenugreek seed powder would be considered as effective agent for lipid lowering purposes. Also, there was a reduction in total blood cholesterol, LDL, VLDL level, and triglycerides and there was an increase in HDL cholesterol level after the consumption of sprouted fenugreek seeds in Albino rabbits [23]. Fenugreek seed administration and its extracts significantly decreased plasma cholesterol, triglyceride, and LDL cholesterol [23, 67]. The inclusion of fenugreek seeds as a diet component for the mice aided in reducing cholesterol level up to 42% and 58% both in control group and in hypocholesterolemic group, respectively [23, 68]. Also, Umarani et al., [69] recorded that supplementation of dietary rutin has been shown to reduce the bioavailability of fluoride in rats, reduced clinical signs of fluoride poisoning and reduced fluoride accumulation and prevented the damage through its free radical scavenging activity. Similarly, Emejulu et al., [70] reported that aqueous fruit juice extract of Irvingia gabonensis has hypolipidemic effect on NaF induced dyslipidemia. The extract was able to normalize lipoprotein phenotype altered by NaF-induced toxicity in albino rats by enhancing HDL-C concentration and lowering serum LDL-C concentration. Which may be due to its reportedly rich vitamin C content and plant polyphenolics [70-72]. Also, this could be related to presence in the plant of alkaloids, saponins, flavonoids and polyphenols commonly known to reduce serum lipids in animals [70, 73].

Fenugreek seeds lower serum triglycerides, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C). These effects may be due to sapogenins, which increase biliary cholesterol excretion, in turn leading to lowered serum cholesterol levels. The lipid-lowering effect of fenugreek might also be attributed to its estrogenic constituent, indirectly increasing thyroid hormone (T4) [23, 74]. Sharma [75] demonstrated that fenugreek administration increased excretion of bile acids and neutral sterols in feces, thus depleting the cholesterol stores in the body in experimental rats.

This lipid lowering effect of the fenugreek powder may be due to the sapogenins which it contains, which increase the biliary cholesterol excretion [18, 76]. Its triglyceride lowering effect may be due to the pectin component of the fenugreek extract that absorbs the bile acids [18, 77].

The fenugreek seeds contain the phenolic compounds, mainly flavonoids. An amino acid compound, 4-hydroxyisoleucine, was identified in the fenugreek extract by using an LC-MS apparatus in the positive ionization mode [18, 78]. The hypolipidaemic effect of the fenugreek seeds could be attributed to the presence of 4-hydroxy isoleucine, an atypical, branched chain amino acid [18, 79]. The lipid lowering effect of fenugreek is due to its action on the adipocytes and the liver cells, which leads to decreased triglycerides and cholesterol synthesis in addition to an enhanced low density lipoprotein (LDL) receptor mediated LDL uptake [18, 80].

Fenugreek seeds able to prevent from lipid peroxidation and restoration of GSH and SOD in various causes of oxidative stress [81-84]. It is likely that lipid peroxidation in the liver is owing to antiradical and antioxidant potential of fenugreek seeds emphasized through *in vitro* and *in vivo* experiments [84-86]. Shang *et al.* [87] identified five different flavonoids namely vitexin, tricin, naringenin, quercetin and tricin-7-O- β -d-glucopyranoside to be present in fenugreek seeds. The scavenging activities of the phenolic substances are attributed to the active hydrogen-donating ability of the hydroxyl substitutions [84, 88]. Quercetin, one of the identified flavonoids in fenugreek seeds, was found able to protect rat hepatocytes against oxidative damage induced by ethanol [84, 89].

6. Conclusion

The results showed that injection of rabbits with sodium fluoride led to serum dyslipidemia, and the injection with sodium fluoride and treatment of fenugreek seeds powder alleviate dyslipidemia induced by sodium fluoride. The use of fenugreek seeds powder by humans can be considered beneficial in the alleviation of dyslipidemia. It is recommended that humans exposed to sodium fluoride should be advised to take Fenugreek seeds powder as a rich source of antioxidant to prevent serum dyslipidemia induced by sodium fluoride. Further studies are necessary to elucidate exact mechanism of the antidyslipidemic effect of Fenugreek seeds powder and potential usefulness of fenugreek seeds powder as a protective agent against sodium fluoride induced dyslipidemia in clinical trials.

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