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Fenugreek [Trigonella foenum-graecum] linn- a reducer of glucose and lipid profile in diabetic subjects

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ABSTRACT

Back ground: Recently use of herbal medicines, have been considered as an alternative for therapeutic usage. *Fenugreek (Trigonella foenum graecum Linn),* used as traditional medicine and natural additive food, has been shown to exert significant antiatherogenic, antidiabetic, antianorexic, antioxidant, anticarcinogenic, antihyperlipidemic, galactogogue and anti-inflammatory effects in several human and animal models. ***Objective:*** Taking this lead, an evaluation was done for the effect of fenugreek on blood glucose and lipid profile in Type 2 diabetic subjects. ***Methodology***: Forty diabetics, both sex (14 male and 26 female), of 1-5 years duration, on treatment with oral anti-diabetic drugs, without any complications were included in this open trial, conducted for a period of eight weeks. They were divided into two (20 in each) groups. First group were treated with 15 grams of *Fenugreek seeds (5 grams in each pocket)* in 3 divided doses per day after meals, along with their oral anti-diabetic drugs, while the second group were allowed to continue with regular oral anti-diabetic medications only, without fenugreek. Pre and post-test, fasting blood sugar, total cholesterol, triglycerides, low density, high density and very low-density cholesterol were taken. ***Results:*** Statistical analysis showed significant reduction in blood sugar and lipid profile. ***Conclusion***: Fenugreek supplementation with oral anti- diabetic drugs has produced significant fall in fasting blood sugar and modulations in lipid levels.

Key words: Fenugreek, Oral Anti-diabetic Drugs, Blood glucose, Lipid profile.

INTRODUCTION

Diabetes mellitus or simply diabetes is a metabolic disorder wherein the body does not produce/adequately use the hormone insulin leading to impaired regulation of glucose. The disease is growing at epidemic rate, affecting over 220 million people worldwide, and is expected to double by 2030. In 2010, 10.9million people over 65 years of age had diabetes and 215000 people under the age of 20 years had either type 1 or type 2 diabetes. About 366 million people around the World suffer from diabetes. The more alarming news is that about 7 million of those 25.8 million diabetics remain undiagnosed until they develop a major complication such as stroke, peripheral circulatory disorders, atherosclerosis, neuropathy, nephropathy, retinopathy, amputation or blindness, which further adds to the economic burden of diabetes on society. In addition, diabetes is a polygenic disorder, and the pathogenesis of diabetes involves magnitudes of both genetic and environmental factors that adversely affect insulin secretion and tissue response to insulin. Genomic explorations have attempted to identify genetic variants that may contribute to the development of diabetes. A thorough understanding of the intricate mechanistic aspects of diabetes and its complications will help the clinicians/ scientists to design effective therapeutic strategies to curb the epidemic. Diabetes is characterized primarily by metabolic dysfunction mediated through carbohydrate metabolism, manifested by hyperglycemia resulting from compromised insulin secretion or impaired insulin action. If untreated, diabetes may lead to a series of complications affecting the vascular system, eyes, nerves and kidneys leading to cardiomyopathy, neuropathy, nephropathy, retinopathy, limb amputation or even mortality. Type 1 diabetes is a condition wherein the pancreas produces little or no insulin, whereas type 2 diabetes (T2D), the more prevalent form results from, either body becomes resistant/ does not produce sufficient insulin. Management of

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diabetes with various pharmacological agents that targets the underlying pathogenesis of diabetes have serious adverse effects. To counteract that, scientists have suggested alternative therapies including balanced diets enriched in fresh fruits, vegetables, dietary fiber, anti-oxidants and structurally diverse phytopharmaceuticals in conjunction with regular physical exercise) [1]. ***Fenugreek (Trigonella foenum-graecumLinn) seeds*** are one such, that have demonstrated novel anti-diabetic efficacy in various human and animal experimental models and has strong anti-diabetic potential. Furthermore human studies also confirmed blood glucose and cholesterol lowering property of *fenugreek seeds* and *leaves* [2,3]. *Fenugreek seeds* are high in soluble fiber which helps to lower blood sugar by slowing digestion and absorption of carbohydrate and reduce gastrointestinal absorption of glucose, which suggests that it might be effective in the treatment of diabetes. Fenugreek seeds are also rich sources of vitamins, minerals and anti-oxidants, which help to protect the cells from free- radical induced oxidative injury [4].

Fenugreek is one of the oldest medicinal plants, originating in India and Northern Africa. The health benefits and medicinal properties of herbal food products are known since antiquity. *Fenugreek*, a seed spice used to enhance flavor, color and texture of food, is employed for medicinal purposes in many traditional systems. A number of epidemiological experimental studies and laboratory research have unraveled the biological actions of fenugreek. It is estimated that about two-third of world population depend on traditional medicine for primary medical needs. *Fenugreek* is a short-living annual medicinal plant belonging to *Fabaceae* family, is used extensively in various parts of the world as herb, food, spice and traditional medicine [5,6]. *Fenugreek* is considered as one of the oldest, small medicinal plant with big benefits and its health-promoting effects have been cited in Ayurveda and traditional Chinese medicine [7,8,9]. Plant-derived natural products have long-standing utility towards treating degenerative diseases. The investigations into the chemical composition and pharmacological actions have seen a renaissance in recent years. Extensive preclinical and clinical research have outlined the ***pharmaceutical uses of fenugreek*** as ***antidiabetic, antihyperlipidemic***, antiobesity, anticancer, anti-inflammatory, antioxidant, antifungal, antibacterial, galactogogue and for miscellaneous pharmacological effects, including improving women's health [10]. The pharmacological actions of fenugreek are attributed to diverse array of phytoconstituents. The phytochemical analysis reveals the presence of steroids, alkaloids, saponins, polyphenols, flavonoids, lipids, carbohydrates, amino acids and hydrocarbons which offers the potential of fenugreek, for disease prevention and health improvement with special emphasis on cellular and molecular mechanisms. Challenges and new directions of research on fenugreek are very much essential in the medical field [11,12].

Newer research has identified hypocholesterolemic, antilipidemia, antioxidant, hepatoprotective, anti-inflammatory, antibacterial, antifungal, antiulcer, antilithigenic, antiasthmatic, anticarcinogenic, antioxidant properties and other miscellaneous medicinal effects of *fenugreek*. Although most of these studies have used whole seed powder or different forms of extracts, some have identified active constituents from seeds and attributed the medicinal values for different indications [13,14,15]. ***Metabolic syndrome***, pre-diabetes and T2DM are increasing dramatically, not only in the U.S. but around the world. These metabolic states lead to significant increased risk of cardiovascular disease and mortality. Diet, exercise and weight management are at the core of a management strategy, but a simple dietary supplement such as *fenugreek seeds* that can modulate glucose, cholesterol, LDL cholesterol and triglycerides is extremely appealing. *Fenugreek* is native to the Mediterranean, India, China, Northern Africa and Ukraine, and is widely cultivated in those regions. Cultivated commercial products in the United States come mainly from Morocco, Turkey, India and China and it is one of the oldest medicinal plants because there are recorded information, that dates back to ancient Egypt, when it was mentioned as a plant to ***induce childbirth, abortifacient*** as well as an ***embalming agent*** [16,17]. ***Other uses includes***: as an, appetite stimulant, baldness, boils, breast enhancement, bronchitis, cellulites, constipation, cough, diarrhea, eczema, flatulence, galactagogue, hepatitis, hernia, indigestion, leg ulcers, menopausal symptoms, myalgia, postmenopausal vaginal dryness, hyperglycemia, tuberculosis and wound healing and more modern uses including its hypoglycemic, hypocholesterolemic and galactagogue properties. The leaves and seeds are used as powders and extracts for medicine use [18,19,20].

Fenugreek seeds contain 45-60% carbohydrates, most of which is a mucilaginous fiber which is 30% soluble and 20% insoluble fiber. It also contains about 20-30% proteins that are high in lysine and tryptophan, a small amount of oils (5-10%), a small amount of pyridine alkaloids (mostly trigonelline), and a few flavanoids, free amino acids, sapogenins, vitamins and volatile oils. Constituents in *fenugreek* that are thought to be

responsible for its hypoglycemic effects include the ***testa*** and ***endosperm*** of the ***defatted seeds*** called the ***A subfraction*** **the** ***4-hydroxyisoleucine*** may promote glucose metabolism and inhibit absorption of cholesterol and the fiber. ***The probable mechanism*** of action might be, it decreases the total body and adipose tissue, and flushes out the carbohydrates from the body before they enter the blood stream resulting in weight loss. The high proportion of soluble fiber forms a gelatinous structure (similar to gaur gum) which may have effects on slowing the digestion and absorption of food from the intestine and creates a sense of fullness in the abdomen, thus suppresses appetite and promotes weight loss. The 4-hydroxyisoleucine component of fenugreek extract may also decrease plasma triglyceride consequently leading to prevention of obesity induced by a high-fat diet [21,22]. Furthermore some chemical constituents of fenugreek may directly stimulate insulin secretion from ß-cells resulting in reduction of blood sugar. It is also thought that the saponins in the seeds are transformed in the gastrointestinal tract into sapogenins which is responsible for the lipid lowering effects [23]. Research on fenugreek in recent years has identified a number of health benefits and physiological attributes in both experimental animals as well as clinical trials in humans. Hence this current human trial was undertaken, for the scientific proof regarding the hypoglycemic and hypolipidaemic properties of fenugreek seeds in Type 2 diabetic subjects.

MATERIALS AND METHODS

This open, prospective, experimental design trial has recruited forty subjects, both male (14) and female (26) diagnosed with Diabetic Mellitus, with a duration of 1-5 years, without any complications, attending the outpatient department, which was conducted for a period of eight weeks. Study was conducted after getting necessary approval from Institutional Ethics Committee. Informed consent obtained from all the study subjects. They were divided into two groups, 20 subjects in each group. There was no wash out period. The first trial group, were treated with fenugreek seeds 5 grams, 3 times daily after each meals, along with their regular oral hypoglycemic agents (OHAs) and the second control group, were put on routine oral anti-diabetic medications only, without any fenugreek supplementation for eight weeks. Base line fasting blood sugar (BGLU), total cholesterol, triglycerides (TGL), low density (LDL), high density (HDL) and very low density cholesterol (VLDL) was taken and the same was repeated at the end of the study period. There was no change in their diet and oral anti-diabetic medications in both groups. All the study subjects were advised to come for review on every 15^{th} day, and the test group were advised to handover the empty sachets for medication adherence and compliance, and in-turn they were provided with refill packets during each visits.

Statistical analysis and interpretations: The study subjects namely study and control groups were compared in their pre-test glucose level and lipid profiles between them in respect of their homogeneity. The reduction of glucose and lipid profile of both groups were studied by student paired‘t’test. The significant reductions of within the groups were further compared between the groups to find out the significant reduction by student independent‘t’test. The above statistical analysis and interpretations have been performed by the statistical package namely IBM-SPSS statistics-20. The P-values less than or equal to 0.05 ($P \leq 0.05$) have been fixed as level of significance.

RESULTS

The study and control groups were compared in respect of their age and lipid profile before undergoing fenugreek administration to study group to interpret the homogeneity of two groups as shown in Table-1 and comparison of Blood Glucose and lipid profile reduction within the groups is shown in Table-2. The Improvements of blood glucose, TGL and HDL between the two groups are shown in Table-3.

DISCUSSION

Among the two groups, who were included in this trial the means differences in variable’s, were not statistically significant ($P>0.05$) and the two groups were homogeneous and comparable as shown in table-1. Findings of this trial showed that, the mean reductions of fasting blood glucose, total cholesterol, triglyceride and VLDL in pre and post tests were statistically significant ($P<0.001$).Similarly there was an increases in HDL in pre test 39.9±3.3 and post 44.7±2.4 and the increase was statistically very highly significant ($P<0.001$). The pre- test and post-test LDL reductions were not statistically significant ($P>0.05$). Regarding the control group the pre and post tests level of Blood Glucose, Triglyceride and LDL reductions were statistically significant ($P<0.001$), while the pre and post test HDL was 41.5±2.8 and 42.2±2.7 just statistically significant ($P<0.05$). Similarly the Cholesterol and VLDL differences within the pre to post tests were not statistically significant ($P>0.05$) as shown in table-2. Likewise table-3 indicates, a significant reduction of BGLU ($P<0.001$), and very high

statistically significant increase in HDL ($P<0.05$) when improvements were compared between groups. Our study does not correlate with one previous study wherein they demonstrated no significant differences between groups in mean glucose tolerance test values with hydro-alcoholic extract of fenugreek seeds, and our findings have proved, that there was statistically very highly significant reduction of fasting blood glucose and increase of HDL between groups [24].

In another study the safety/adverse effects of *fenugreek* reveals no reports of clinically significant harmful adverse effects. Although fenugreek has traditionally been considered safe and well tolerated, some side effects have been associated with its use. Apart from hypoglycemia which is an expected effect, fenugreek contained in curry powder was found to be an allergen in a patient who reported severe bronchospasm, wheezing, and diarrhea, flatulence and decreased body weight in some, has also been reported and also there was a decrease in triidothyronine (T_3) levels which is in contrast with the present study [25]. Our study is on par with another study which showed significant reductions of fasting blood glucose levels in more than 80% of the study subjects and 62% in control group, and also they had demonstrated 49% reduction of dosage of anti-diabetic drugs in the study subjects than the control group showing that fenugreek is efficacious in ameliorating the symptoms of T2D in humans [26]. Study done by Muralidara et al in their acute and subacute toxicity studies on *Trigonella* in mice has illusterated, no significant alterations either in relative organ weights/their histology and *fenugreek* had failed to induce any signs of toxicity or mortality up to a maximum practical dosage of 2 and 5 g/kg body weight. No variations in haematological/histoarchitecture constants, food intake/growth and no alterations in biochemical parameters, and had concluded that fenugreek does not produce any significant acute and cumulative toxicity at the doses administered which is well in accordance with this current research as there was no dropout suggesting the better compliance among our study subjects. The only side effect reported among few study subjects was flatulence which was very much tolerable and there was no discontinuation from the study [27].

Chronic studies with *Trigonella* on long-term use has evidenced, that consumption of fenugreek induced some serious toxicological side effects such as teratogenic effects like congenital malformations to death, were reported in human, rodent, rabbit, and chick [28]. Moreover, results obtained in rats, mice and rabbits showed a testicular toxicity and anti-fertility effects in male associated with oxidative stress and DNA damage, as well as anti-fertility, anti-implantation and abortifacient activity in females related to saponin compound of fenugreek, which suggest that fenugreek is not recommended for use during pregnancy[28,29,30,31]. Indeed, the consumption of fenugreek should be avoided for persons having peanut and chickpeas allergy because of possible cross-reactivity as well as chronic asthma. Accumulating evidence has also suggested that fenugreek may produce neurodevelopmental, neurobehavioral and neuropathological side effects on prolonged use. It is suggested that future long-term human clinical trials are needed in this regard, to identify the molecular and cellular mechanisms underlying the toxicological properties of *fenugreek* [32]

CONCLUSIONS

This clinical trial has confirmed the hypoglycaemic and hypolipidaemic potential of fenugreek seeds as it has produced significant reductions in fasting blood glucose with modulations in the lipid profiles, leading to a conclusion, in support of fenugreek seeds as an adjuvant with oral hypogycaemic agents in reducing the hyperglycaemia in diabetic subjects. So further large scale, long-term, detailed clinical trials are needed to strengthen these findings and further clarifications are required to evaluate the potential pharmacological properties, using sufficient doses of well characterized fenugreek preparations for drawing more conclusive evidence on the safety, efficacy, toxicity and possible drug inter-action profiles of *Trigonella foenum- graecum (Fenugreek seeds)*, because many of its effects are subjected to lack of clinical trials confirmation. This in-turn will help to reduce the pharmaco-economic constraints of health care functionaries in the management of diabetes, and adverse effects profile of anti-diabetic drugs, thereby we can avoid complications of diabetic mellitus to a great extent to our suffering community. So *Fenugreek*, as an ***adjuvant herbal medicine*** may hold promise in the future therapy of the silent killer disease, the Diabetes Mellitus.

TABLE-1: COMPARISON OF HOMOGENEITY BETWEEN THE STUDY AND CONTROL GROUPS IN PRE-TEST'S AGE, GLUCOSE LEVEL AND LIPID PROFILE:

VARIABLES	Study group n=20		Control group n=20		Difference b/w means	't'	Df	Sig
	Mean	SD	Mean	SD				
AGE	48.4	4.0	49.8	4.8	1.4	1.038	38	P>0.05
BLOOD GLUCOSE	129.0	5.2	127.8	2.6	1.2	0.969	38	P>0.05
CHOLESTEROL	241.9	27.8	245.3	20.4	3.4	0.441	38	P>0.05
TRIGLYCERIDE	169.7	18.4	169.6	11.9	0.1	0.031	38	P>0.05
HDL	39.9	3.3	41.5	2.8	1.6	1.642	38	P>0.05
LDL	129.4	7.6	131.4	6.4	2.0	0.889	38	P>0.05
VLDL	37.2	3.2	38.4	4.0	1.2	0.996	38	P>0.05

The table-1: states the homogeneity of the study and control groups in respect of their pre test. The mean ages of the study and control groups were 48.4±4.0 and 49.8±4.8 years respectively. The difference was not statistically significant (P>0.05). The mean BGL of both groups were 129.0±5.2 and 127.8± 2.6 mg/dl. The mean Cholesterol of the two groups were 241.9± 27.8 and 127.8±20.4 and that of Triglyceride of the study and control groups were 169.7±18.4 and 169.6±11.9 respectively. The means of HDL of both groups were 39.9±3.3 and 41.5±2.8 and that of the LDL were 129.4±7.6 and 131.4±6.4 respectively. Finally, the mean VLDL of the two groups were 37.2±3.2 and 38.4±4.0. The mean differences of all the above variables were not statistically significant (P>0.05). Hence the two groups were homogeneous and comparable groups.

TABLE-2: COMPARISON OF BLOOD GLUCOSE AND LIPID PROFILE REDUCTION WITHIN THE GROUPS:

GROUPS	VARIABLES	Pre test		Post test		Reductions		"t"	df	Sig.
		Mean	SD	Mean	SD	Mean	SD			
STUDY	**BLOOD GLUCOSE**	129.0	5.2	114.7	6.6	14.3	5.4	11.928	19	P<0.001
	CHOLESTEROL	241.9	27.8	234.2	26.8	7.7	3.6	6.522	19	P<0.001
	TRIGLYCERIDE	169.7	18.4	162.5	19.5	7.2	3.3	9.658	19	P<0.001
	HDL	39.9	3.3	44.7	2.4	4.8	2.8	8.712	19	P<0.001
	LDL	129.4	7.6	127.4	6.0	2.0	4.8	1.859	19	P>0.05
	VLDL	37.2	3.2	36.3	2.8	0.9	2.0	2.139	19	P<0.05
CONTROL	**BGLU**	127.8	2.6	124.5	3.7	3.3	3.2	4.505	19	P<0.001
	CHOLESTEROL	245.3	20.4	241.2	17.0	4.1	10.6	1.742	19	P>0.05
	TRIGLYCERIDE	169.6	11.9	161.1	15.9	8.5	9.0	4.153	19	P<0.01
	HDL	41.5	2.8	42.2	2.7	0.7	1.2	2.371	19	P<0.05
	LDL	131.4	6.4	128.6	5.3	2.8	3.0	4.172	19	P<0.01
	VLDL	38.4	4.0	37.7	3.3	0.7	2.1	1.505	19	P>0.05

The study and control groups were interpreted within groups in ***table-2.*** In respect of study group the mean BGLU of pre and post tests were 129.0±5.2 and 114.7±6.6 mg/dl respectively. The reduction from pre to post was statistically significant (P<0.001). Similarly, the Cholesterol, Triglyceride and VLDL were 241.9±27.8 and 234.2±26.8, 169.7±18.4 and 162.5±19.5 and 37.2±3.2and 36.3±2.8 respectively. The reductions were statistically significant (P<0.001). The HDL at pre test was 39.9±3.3 and post was 44.7±2.4. The increase was statistically very highly significant (P<0.001). The pre- test LDL was 129.4± 7.6 and post was 127.4±6.0. The reduction was not statistically significant (P>0.05). Regarding the control group the pre and post tests level of BGLU, Triglyceride and LDL were 127.8±2.6 and 124.5±3.7, 169.6±11.9 and 161.1±15.9 respectively. The reductions were statistically significant (P<0.001). The pre and post test HDL was 41.5±2.8 and 42.2±2.7. The improvement was statistically significant (P<0.05). The pre and post tests Cholesterol and VLDL were 245.3±20.4 and 241.2±17.0 and 38.4±4.0 and 37.7±3.3 respectively. The differences within the pre to post tests were not statistically significant (P>0.05).

TABLE-3: COMPARISON OF THE IMPROVEMENTS OF BGLU, TGL AND HDL BETWEEN THE TWO GROUPS:

VARIABLES	Study group n=20		Control group n=20		Difference b/w means	"t"	Df	Sig
	Mean	SD	Mean	SD				
BGLU	14.3	5.3	3.3	3.2	11.0	7.897	38	P<0.001
TRIGLYCERIDE	7.2	3.3	8.4	9.1	1.2	0.577	38	P>0.05
HDL	4.8	2.8	0.6	1.2	4.2	6.102	38	P<0.001

The above table-3: compares the variables which showed statistically significant improvements between both groups. The mean BGLU reduction in study group was 14.3±5.3 and control group was 3.3±3.2. The difference between the groups was statistically very highly significant (P<0.001). The reductions of Triglyceride between the two groups was not statistically significant (P>0.05). The mean increase of HDL in study group was 4.8±2.8 and control group was 0.6±1.2. The difference was statistically very highly significant (P<0.05).

REFERENCES

1. Narsingh Verma et al. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (*Trigonella foenum-graecum*) extract (Fenfuro™) in patients with type 2 diabetes Food Nutr Res. 2016; 60: 10.3402/fnr.v60.32382.
2. Kassaian N et al. Effect of *fenugreek seeds* on blood glucose and lipid profiles in type 2 diabetic patients. Int J Vitam Nutr Res. 2009;79(1):34-9.
3. Anand Swaroop et al. Safety, Efficacy and Toxicological Evaluation of a Novel, Patented Anti-Diabetic Extract of *Trigonella Foenum-Graecum Seed Extract (Fenfuro(TM)).* Toxicology mechanisms and methods 2014; 24(7):495-503
4. Hannana JMA et al. Effect of soluble dietary fibre fraction of *Trigonella foenum-graecum* on glycemic, Insulinemic, lipidemic and platelet aggregation status of Type2 diabetic model mice. J Ethnopharmacol 2003; 88: 73-77.
5. Zargari.A. Medicinal plants. Tehran university press 2007; (2): Pp 608. 637-642.
6. Samsamshariat, H. Moattar, F. Medicinal plants and natural plants (medical materia). Mashaal press 2008; Pp: 79,333,336-337.
7. Wan- Li xue et al. Effect of *Trigonella foenum- graecum (Fenugreek*) extract on blood glucose blood lipid and hemorheological properties in streptozotocin induced diabetic mice. Asia PC J clin Nutr 2007; 16 (suppi): 422-426.
8. Venkata KC et al. A small plant with big benefits: Fenugreek (*Trigonella foenum-graecum Linn.*) for disease prevention and health promotion. Mol Nutr Food Res. 2017; Mar 7. doi: 10.1002/mnfr.201600950. [Epub ahead of print]
9. P.Udayasekhara Rao et al. Short term nutritional and safety evaluation of *Fenugreek* ,Nutrition Research -1996; 16(9):1495-1505 ·Biochem Biophys Res Commun. 2017; 22;482(4):1284-1288.
10. Abdo M, Al-Kafawi A. Experimental studies on the effect of *Trigonella foenum graecum*. Planta Med1969;17:14-18.
11. Ashish Toppo F et al. Pharmacological actions and potential uses of *Trigonella foenum-graecum*: A review, Asian Journal of pharmaceutical and clinical Research 2009; 2(4):29-38
12. Yadav UC, Baquer NZ. Pharmacological effects of *Trigonella foenum-graecum L.* in health and disease.Food Chem Toxicol. 2016 ;96:145-54.
13. Piao CH et al. *Trigonella foenum-graecum* alleviates airway inflammation of allergic asthma in ovalbumin-induced mouse model.Pharm Biol. 2014;52(2):243-54.
14. Latha S et al. Acute and Repeated Oral Toxicity of Antidiabetic Polyherbal Formulation Flax Seed, *Fenugreek* and Jamun Seeds in Wistar Albino Rat. J Diabetes Metab 2016; 7:656.
15. Bhatia K et al. Aqueous extract of *T. fenum-graecum l.* Ameliorates additives urotoxicity of buthionine sulfoximine and cyclophosphamide in mice. Food and Chemical Toxicology2005; 44:1477-1750
16. Tori Hudson. *Fenugreek* – An Overview of the Research and Clinical Indications 2009 pp1-6
17. Bordia A et al. Effect of ginger and *fenugreek* on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids1997;56:379-384.
18. Turkyilmaz C et al. The effect of galactagogue herbal tea on breast milkproduction and short-term catch-up of birth weight in the first week of life. J Alternative and Comp Med 2011;17(2):139-142.
19. Ethan Basch et al. Therapeutic Applications of Fenugreek, Altern Med Rev 2003;8(1):20-27

20. Jasim Neem Al-Asadi. Therapeutic Uses of Fenugreek *(Trigonella Foenum-Graecum L*.), Review,American Journal of Social issues and Humanities, American Journal of Social issues and Humanities 2014;21-36.
21. Yang WX et al. Study on chemical constituents in total saponin from *Trigonella foenum-graecum*, Zhongguo ZhongYao Za Zhi 2005; 30: 1428-1430.
22. Yoshikawa M et al. Medicinal foodstuffs. IV, *Fenugreek seed*. (1): structures of trigoneosides Ia, Ib, IIb, IIIa, and IIIb, new furosranol saponins from the seeds of Indian Trigonella foenum-graecum (Fenugreek) seed extract as antineoplastic Agent, phytother. Res 2001; 15: 257-9.
23. Sauvaire Y et al. Implication of steroid saponins and sapogenins in the hypocholesterolemic effect of *fenugreek.* Lipids 1991;26:191-197.
24. Gupta R, Lal B. Effect of *Trigonella foenum-graecum (fenugreek)* seeds on glycemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. J Assoc Physicians India 2001; 49:1057-1061
25. Panda S et al. Inhibition of triiodothyronine production by *fenugreek seed extract* in mice and rats. Pharmacol Res 1999;40(5):405-409.
26. Nithya Neelakantan et al. Effect of fenugreek (*Trigonella foenum-graecum* L.) intake on glycemia: a meta-analysis of clinical trialsNutr J. 2014; 13: 7.
27. Murali Muralidhara Et Al. Acute And Subchronic Toxicity Assessment Of Debitterized *Fenugreek Powder* In The Mouse And Rat food, Chemical Toxicology 1996; 37(8):831-8.
28. R.D.Sharma et al. Toxicological Evaluation of *Fenugreek Seeds*: a Long Term Feeding experiment in Diabetic Patients, Phytotherapy Research 1996 10(6):519 – 520.
29. Zamiri, M. Reproduction physiology. Haghshenas press 2006; Pp112-114,127.
30. Mokhtari M et al. The effect of fenugreek *(Trigonella foenumgreeum L* .) on hormone variation of testosterone and spermatogenesis of rat.Medicinal plants magazine 2007;(25): 12-20.
31. Mehred moderesi et al. The effect of hydro-alcoholic extract of *fenugreek seeds* on female reproductive hormones in mice,International Conference on Applied Life Science,Turkey, 2012; 437-443
32. Ouzir M et al. Toxicity studies on *Trigonella foenum-graecum L*.seeds used in spices and as a traditional remedy for diabetes, Oriental Pharmacy and Experimental Medicine 2010;10(2):66- 78.