Antihyperglycaemic Effect of *Azadirachta indica* Juss. and *Trigonella foenum-graecum* Linn. on Type 2 Diabetes Mellitus

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Abstract

In the present study the combined effect of two well documented and well known herbal drugs *Azadirachta indica* Juss. & *Trigonella foenum-graecum* Linn. have been studied in Type 2 Diabetes mellitus patients. Medicinal plants have been mentioned by various authors for their hypoglycaemic activity. Therefore, we choose two medicinal plants to check the efficacy of these drugs in diabetes mellitus. The drug was given in powder form in the dose of 6gm twice a day for 3months. The results were analysed statistically. There was statistically significant reduction in the fasting and post prandial blood glucose ($t=8.3$, $p < 0.001$) ($t=8.6$, $p<0.001$) respectively. The significance on glycated haemoglobin was ($t=4.4$, $P<0.001$). The significance on total cholesterol was ($t= 5.1$, $p< 0.001$). The significance on effect of drug on glycosuria was ($t=6.1$, $p<0.001$).

Keywords: Unani Medicine, Diabetes, Antihyperglycaemic effect.

Introduction

The word diabetes is derived from "*Ziabitus"* which is a Unani term meaning to run through, while Mellitus is a latin word which means sweet like honey (Ahuja, 1983). Galen believed that diabetes is a disease of kidney; he stated that the sole cause of diabetes is altered hot temperament (*Sue-Mizaj har)* of Kidney. He stated that kidney shows a weakness similar to that of intestine as in case of "lecientria", and also stated that along with altered hot temperament, its power of absorption (*Quwwat-e-jaziba)* is increased (Kirmani, 1935) due to which fluid is diffused more towards kidneys. In addition to this the power of retention (*Quwwat-e-Masika*) of kidneys are weakened and is unable to hold the urine which is excreted out in large quantity and a cycle of thirst and micturition is established (Jafri and Siddiqui, 1995). Review of literature reveals that diabetes was described on the basis of clinical triad of polyuria, polydipsia, and polyphagia, but Avicenna alone has been credited with two additional discoveries, firstly: physical, mental and sexual weakness and secondly: occurrence of carbuncles and gangrene as a complication of the disease (Schadewaldt, 1989). In the 19th century with the advancement of techniques and study of microbiology and advancements in the field of Genetics, type 2 diabetes mellitus has been defined as a "heterogeneous group of disorders characterized by variable degree of insulin resistance, impaired insulin secretion, and increased glucose production". Diabetes

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mellitus usually remains asymptomatic for a considerable period of time. Despite insulin resistance glucose level remains normal because beta cells compensate by increasing insulin output. As the disease progresses, insulin resistance worsens and post prandial hyperglycaemia sets in. Further, there is decline in insulin secretion with persistent insulin resistance resulting in fasting hyperglycaemia. Ultimately beta cells failure may ensue due to glucotoxicity (Braunwald, 2001) and the disease is well established. According to data released by International Diabetes Federation (IDF), the number of people around the world suffering from diabetes has gone up in the last two decades, from 30 million to 230 million and the greatest increase is in the developing countries of Africa, Asia and South America (Santora, 2006). As predicted by the WHO, the prevalence of diabetes in adults worldwide has risen from 135 million in 1995 to 300 million by the year 2025. Epidemiological data in India shows the same upward trend. Presently there are 32 million diabetics. It may increase to 80 million in 2030 (Rao *et al*., 2005). India has thus become the "Diabetic Capital" of the world. Data presented by the endocrinology unit of JNMC, AMU, Aligarh at the Continuing Medical Education in 2006 showed that in Aligarh 15-20% people are affected by diabetes mellitus (Alam, 2006). Some 90% of diabetic individuals have type 2 diabetes mellitus. For the Indian population factors which act as pre-disposing factors for this steep rise include genetic predisposition, urbanization, ethnicity, insulin resistance and central obesity and over and above physical inactivity.

Aims and objectives of the study

1. Although immense advancements in oral as well as in the brand of Insulin in Allopathic medicine has taken place in the recent past which revolutionized the treatment of diabetes mellitus and near normal glycaemic control can be achieved, but we the unani physician cannot use these drugs to the law of land . This prompted us to search an alternative drug in unani medicine.

2. Allopathic drugs have serious side effects if not given b a well versed allopathic physician which may either cause hyper or hypoglycaemia

3. *Trigonella foenum-graecum* Linn. has antilipaemic effect so, it is beneficial in controlling the blood sugar in mild type2 diabetes mellitus and also has advantage of antilipaemia because diabetes mellitus and hyperlipaemia usually go hand in hand.

Methodology

This study was carried out on 30 patients of Type2 Diabetes mellitus who attended the Ajmal Khan Tibbiya College, Hospital. Diagnosis was confirmed by WHO criteria. Patients with known Type1 diabetes mellitus, thyrotoxicosis, chronic renal failure, peptic ulcer, and pregnant ladies were excluded from the study. During the study the following approach was carried out in all the cases, that is detailed clinical history, physical examination, and bio-chemical investigations.

After the informed written consent, the patients were advised to take 6 g. drug in powder form twice a day in the morning and in the evening before meals for 3 months. The drugs were obtained from Dawakhana Tibbiya College, Aligarh MuslimUniversity, Aligarh. The drugs used are *Azadirachta indica* Juss. & *Trigonella foenum-graecum* Linn. in equal amounts.

	Common name	Scientific name	Amount
1.	Neem	*Azadirachta indica Juss. ,* Juss.	1 Part
2.	Methi	*Trigonella foenum-graecum*, Linn	1 Part

Azadirachta indica Juss. (Barg-e-Neem); Family: Meliaceae; Vernacular Names:__Lila, Neem Tree, Nimb, Mahanim, Lilas (Chopra, 1996: Kirtikar,1987; Nadkarni, 1986), Part Used: Leaves; Temprament (Mizaj): Hot, Dry(Husain,1975). Medicinal Properties: Muhalil-e-Warm (anti-inflammatory), Musaffi-e-dum (blood purifier), Dafe Taffun (antiseptic), Qata-e-deedan (antihelminthic), Naf-e-ziabitus (hypoglycaemic), (Anonymous, 1987; Nadkarni, 1986). Chemical constituents: Nimocinol, Nimocinolide, Isonimocinolide, Limonoid, Meliacin, Quercitin, Dehydrosalannol, Glutamic acid, Tyrosine, Glutamin (Anonymous, 1982; Khosla, 1995; Rastogi, 1999).

Trigonella foenum-graecum Linn. (Tukhm-e-Hulba). Family: Papilionaceae; Vernacular Names: Fenugreek, Methi, Mothi, Chandrika (Anonymous, 1982; Anonymous, 1987), Part used: Seeds. Temprament (Mizaj): Hot, Dry (Kabiruddin, YNM; Nadkarni, 1976); Medicinal Properties: Muhalil-e-Warm (antiinflammatory), Mudir-e-Baul wa Haiz (diuretic and emmenagogue), Mulayyin (laxative), Mulattif (demulcent), Naf-e-ziabitus (hypoglycaemic), Naf-e-Fart-e-Tadassum-fi-dum (hypolipidimic) (Kabiruddin, YNM; Nadkarni, 1976; anonymous, 1987; Trivedi, 2004). Chemical constituents: Trigonelline, Choline, Diosgenin, Gitogenin, Togogenin, Yamogenin, Quercitin, Luteolin, Vitexin, Isovitexin, Saponaretin, Homoriein and Vicennin1 &2 (Anonymous, 1982; Khosla, 1995; Rastogi, 1999)

The follow up of patients was performed every fortnightly. Blood sugar (fasting, post prandial) and urine (routine, microscopic) examinations were performed monthly while lipid profile, HbA_1C, blood urea, serum creatinine and liver function test were performed on 0 and 90^{th} day. All the observations and results obtained were statistically evaluated, applying paired t-test, and Z-test.

Observations and Results

In the present study 30 patients of Type 2 Diabetes mellitus were taken. As shown in table 1 that maximum no. of patients belonged to 30-50 yrs of age (66.67%), and most of patients belonged to phlegmatic temperament (66.7%). Thirteen (43.3%) of patients had BMI≥23, and (93.3%) of patients lived sedentary life style.

Effect of drug on symptom and signs

Out of thirty patients five had genital candidiasis which after ninety days of treatment showed an improvement in four patients, that is an improvement of 80% was observed. Another salient presentation was polyphagia which was present in fourteen patients before starting treatment and at the termination of therapy was present only in three patients, that is, there was an overall improvement of 78.5%. Another important symptom was generalised weakness which was seen in twenty seven patients. During the course of the treatment there was gradual improvement and at the end only in nine patients this symptom persist reflecting 66.65% improvement. Although, polydipsia is usually the most common feature of diabetes mellitus but in our study it was present only in seventeen patients which with the treatment over ninety days remain present in six patients, showing an overall improvement by 64.7%. Polyuria and nocturia was the next most common presenting feature which reduces from twenty four patients to nine patients showing an overall improvement of 62.5%. Loss in weight was found in eleven patients before the commencement of therapy. However, at the end of the study it was present only in six patients, that is, an overall improvement of 54.4% was observed. The least common symptom was paresthesia which was present only in six patients and it was only symptom which shows no improvement at all at the termination of trial (Table2).

Table 3 shows effect of drug on glycosuria: As it is evident from table all the patients had glycosuria which persisted only in twelve patients, that is to say in eighteen patients it was absent at the termination of therapy ($t=6.1$, $p<0.001$). The most objective parameter to assess the glycaemic control was estimation of Fasting and Post Prandial blood sugar. At the start of the therapy mean

fasting blood sugar was 195.6mg% which was reduced to 138.37mg% showing a mean differential fall by 57.23mg%. As regard post prandial blood sugar is concerned it was 282.27mg% at the beginning of the therapy which showed a steady fall and became 188.6mg%, showing a difference of 93.67mg% (Table 4) on applying t test it was (t=8.3, p<0.001, t=8.6, p<0.001) for fasting and post prandial blood sugar respectively. Table 5 shows effect of drugs on glycated haemoglobin, the mean glycated haemoglobin before starting the treatment was 8.35mg% which was reduced to 7.31mg% at the end of trial, on applying t test for significance it was (t=4.4, P<0.001). Table 6 shows effect on total cholesterol, before starting the treatment the mean total cholesterol was 195.9mg%, which showed a marginal fall and on the 90th day its level was 183.4mg% on applying 't' test it was (t=5.1, p<0.001). We also tried to observe the effect of the our drug formulation on the normal euglycaemic persons to see whether it causes hypoglycaemia or not during the study it was observed that there was no such effect on the fasting blood sugar (Table 7).

Table 1: Base line demographics

	(n = 30)	
	No. of Patients	Percentage%
a. Male: Female	9:21	30:70
b. Age in yrs: 30-40	8	26.6
40-50	11	36.6
50-60	11	36.6
c. Occupation: Service	6	20
Business	5	16.6
House Wife	13	43.4
Others	6	20
d. Food Habits: Vegetarian	10	33.3
Non Veg.	20	66.7
e. Temperament: Sanguine	0	0
Phlegmatic	20	66.7
Bilious	10	33.3
Melancholic	0	0
f. Risk Factors: +ve Family History	11	36.6
Stress +ve	19	63.3
No exercise	28	93.3
BMI ≥ 23Kg/m2	13	43.3

Table 2: Showing effect on classical symptoms

(n = 30)

Symptoms	0 Day	15 Days	30 Days	45 Days	60 Days	75 Days	90 Days
a. Polydipsia	17	12	4	4	4	6	6
No. of patients improved	-	5	13	13	13	11	11
Improvement %	-	29.4	76.4	76.4	76.4	64.7	64.7
b. Polyphagia	14	13	9	4	2	3	3
No. of patients improved	-	1	5	10	12	11	11
Improvement %	-	7.1	35.77	71.4	85.7	78.5	78.5
c. Polyuria with or without Nocturia	24	21	13	15	11	9	9
No. of patients improved	-	3	11	9	13	15	15
Improvement %	-	12.5	45.6	37.5	54.1	62.5	62.5
d. Weight Loss	11	11	10	10	8	6	6
No. of patients improved	-	0	1	1	3	5	5
Improvement %	-	0	9.09	9.09	27.2	45.45	54.54
e. Weakness	27	27	26	20	11	9	9
No. of patients improved	-	0	1	7	16	18	18
Improvement %	-	0	3.7	25.9	59.2	66.6	66.6
f. Genital candidiasis	5	5	3	2	2	1	1
No. of patients improved	-	0	2	3	3	4	4
Improvement %	-	0	40	60	60	80	80
g.Erectile dysfunction	4	4	4	3	3	2	2
No. of patients improved	-	0	0	1	1	2	2
Improvement %	-	0	0	25	25	50	50
h. Paraesthesia	6	6	6	6	6	6	6
No. of patients improved	-	0	0	0	0	0	0
Improvement %	-	0	0	0	0	0	0

Table 3: Showing effect on glycosuria

(n = 30)

0 Days		30 Days	60 Days	90 Days
Glycosuria	No. of affected	No. of affected	No. of affected	No. of affected
	35	27	18	12
Improvement %		29	48	66

Table 4: Showing effect of formulation on blood sugar.

(n = 30)

	0 days	30 days	60 days	90 days
Mean Blood Sugar Fasting	195.6±40.18	176.23±42.64	149.96±27.34	138.37±28.40
Mean Blood Sugar Post Prandial	282.27±57.18	245.0±57.84	204.1±43.94	188.6±53.71
Mean difference Fasting	-	19.37±26.99	45.63±31.44	57.23±37.83
Mean difference Post Prandial	-	37.27±44.54	78.17±43.97	93.67±59.56

Table 5: Showing effect on glycated haemoglobin

(n = 30)

	0 Days	90 Days
HbA1C	Average 8.35±0.82	Average 7.31±1.36

Table 6: Showing effect on total cholesterol.

(n = 30)

T. Cholesterol	0 Days	90 Days
Average	195.9±32.61	183.4±34.40

Table 7: Showing effect on normal individual

(n = 10)

Mean Blood Sugar Fasting before giving drugs	81.2 mg/dl
Mean Blood Sugar Fasting after giving drug	81.6 mg/dl

Discussion

In the present study thirty patients suffering from type2 diabetes mellitus were selected randomly from the moalejat and ilaj-bit-tadbeer department of Ajmal Khan Tibbiya College, Aligarh Muslim University, Aligarh. After the informed written consent the drugs *Azadirachta indica Juss. & Trigonella foenum-graecum Linn.*was administered in the dosage of 6 g. per orally in the powder form, details of which have been given earlier.

As depicted in table1, maximum no. of patients i.e. (22) were found between 40-60 yrs of age. As it is a well known fact that practically type2 diabetes mellitus which was previously known as maturity onset diabetes is found mainly in the middle and old age. Therefore, our findings are consistent with the classical text. Regarding the occupation housewives numbering (13) were the maximum sufferers the possible reason may firstly be lack of physical exercise and mental stress born by them in the present day of nuclear family. On Temperamental analysis maximum no. of patients i.e. (20) belonged to the phelegmatic temperament, this may be because they are usually obese and relatively physically inactive. When the main risk factors were considered here was a positive family history of diabetes mellitus in eleven (11) patients followed by stress in nineteen (19), and no physical exercise in twenty eight (28) patients. As it is a well known fact that these factors pay a pivotal role in precipitating the pre diabetics into a full blown diabetes mellitus syndrome of type2. Basal metabolic index (BMI) was 23 or more than 23 in thirteen (13) patients. However, according to Indian standards more than (23) is taken as abnormal. So, it also might be a causative factor in precipitating diabetes mellitus.

Decrease in polydipsia, polyphagia was found in 64.7% and 78.5% cases respectively which may be due to the hypoglycaemic effect of the alkaloids present in the *Azadirachta indica Juss.* possessing the insulin like activity (Anonymous, 1978). Obviously, the polyuria also decreased due to the decreased osmotic pressure of filtrate in renal tubule absorbing water from interstitial spaces of the kidneys. This seems to be the most convincing reason for decrase in polyuria (Table2 a,b,c and, d).

With the importance in the glycaemic control decrease rate of weight of loss was found in eleven (11) patients where as decrease in weakness was present in one third of the patients. These effects may again be due to the fall in the blood sugar as per the passage of time i.e. 90 days (Table2 d and e).

There were four (4) patients in whom there were an improvement in genital candidiasis as there was a decrease in blood sugar level as mentioned under (Table 2 a,b and c) here it is worth mentioning that no local or systemic drug administration was given for fungal infection. So, it is concluded that it was hyperglycaemia which predispose the fungal infection (Table 2 f). There was no improvement in paresthesia which may be due to the fact that either our drug combination or a relatively short duration of therapy could not affect the microangiopathy causing the paresthesia (Table2 h). There was an improvement in the erectile dysfunction in two (2) out of four (4) patients which remains to be explained. Probably our drugs either had vasodilator effect or anti-atherosclerotic effect. However, it requires other thorough investigations like Pudendal artery angiography and anti-atherosclerotic activity.

So far the effect of drugs on Fasting, Post prandial and Glycated haemoglobin is concerned there was a steady decline in the blood sugar level there values are depicted in the table 4 and 5, as the glycated haemoglobin reflects the glycaemic control of preceding three months, hence, it is regarded as the most sensitive parameter in diagnosing and degree of control in the blood sugar. As depicted in table 5 average glycated haemoglobin before starting the treatment was 8.35mg% which decreased to 7.31mg%. Many writers describe the hypoglycaemic effect of *Azadirachta indica* Juss. & *Trigonella foenum-graecum* Linn. (Jarald *et al.,* 2008; Rao *et al.,* 2010). The possible mechanism involved in the decline of fasting, post prandial and glycated haemoglobin may be due to the insulin activity present in the Neem and 4-hydroxyisoleucine amino acid present in Methi (Basch *et al.,* 2003) which increase the secretion of insulin from beta cells due to hyperglycocaemia. Although, glycated haemoglobin did not reach within its normal limit and was found to be slightly higher i.e. 7.31. The desired effect may probably be achieved either by readjusting the dose of the given drugs or prolongation in the duration of therapy.

The drug was also screen for its anti lipimic effect and for this purpose total serum cholesterol was estimated before and at the termination of the trial, the mean cholesterol was 195.9mg% which was reduced to 183.4mg%. This marginal fall in cholesterol level was may be due to the fecal excretion of bile acids due to presence of *Trigonella foenum-graecum* Linn.

Conclusion

From the above study it is concluded that our drug combination is by and large effective in decreasing the blood sugar level in type2 diabetes mellitus patients without improving the microvascular complications. Hence, it is suggested

that the quantity of the drug should be reviewed and if needed dose may be readjusted. Long term and collaborative study with interdisciplinary approach is needed, and if after that the drugs are found safe and effective then it must be incorporated in main stream antidiabetic drugs, because these drugs are safe, cost effective, and natural.

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