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Research article

EFFICACY OF AYURVEDIC / HERBAL PATENT MEDICINES IN TYPE 2 DIABETES MELLITUS AS PER THE CLAIM

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ABSTRACT

The study was designed to evaluate the comparative efficacy of a commercially available poly-herbal drug in Indian market to that of a modern sulfonylurea - Gliclazide. Currently, there are many herbal drugs available in market claiming promising results in managing type-2 diabetes mellitus. The aim of this study was to evaluate the efficacy of one among them in type-2 diabetes mellitus along with Gliclazide as control. The present drug being called as Diazen comprising *Gymnema sylvestre (Retz.) Schult*, *Momordia charantia* L, *Eugenia jambolana* Lam., *Tinospora cordifolia* (Willd.), *Trigonella foenogricum* L, *Withania somnifera* (L.) Dunal, *Cassia auriculata* L., *Aegle marmelos* (L.) Correa, *Azadirachta indica* A. Juss, *Curcuma longa* L. For the clinical study, type -2 diabetic patients were selected voluntarily and divided in to 3 groups, each comprising 10 patients. One group supplied only with the sulfonylurea drug Gliclazide, another group supplied only with the herbal drug Diazen whereas the last group supplemented with both the herbal drug Diazen and Gliclazide .The patients were observed for a period of one month. The herbal drug was found to be effective in bringing normoglycemia as per the claim. A review of possible mechanism of anti diabetic activity of the ingredients of Diazen was done.

KEY WORDS: Sulfonylurea, Gliclazide, *Diazen*, Hypoglycaemia,

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INTRODUCTION

About Diabetes mellitus

Diabetes mellitus: often referred to simply as diabetes is a condition in which the body either does not produce enough, or does not properly respond to, insulin, a hormone produced in the pancreas. Insulin enables cells to absorb glucose in order to turn it into energy. In diabetes, the body either fails to properly respond to its own insulin, does not make enough insulin, or both. This causes glucose to accumulate in the blood, often leading to various complications[1].

Treatment and drugs: Several groups of medicines are available in allopathic system of medicine e.g. Sulfonylureas, Biguanides, Thiazolidinediones, Alpha-glucosidase inhibitors, Peptide analogues etc. but herbal extracts are also occupied a category among these groups. Different patent medicines of different manufacturers composed of various combinations of multiple herbs have widely occupied recent pharmaceutical market.

This paper discusses about a trial conducted regarding the efficacy of such herbal formulated drug available in current market.

Status of diabetes in India - India has become the diabetic capital of the world with 50.8 million (7.1%) of its people suffering from diabetes [2, 3].

From the available region wise population based studies it is clear that in the last two decades, there has been a marked increase in the prevalence of diabetes among both urban as well as the rural Indians[4]. Out of the total diabetics the total figure of Type-1/insulin dependent diabetes mellitus is 1–5% and the rest 95–99% are of type -2 insulin independent Diabetic mellitus patients [3, 4].

In a study over one year, it was observed that mortality amongst hospitalised patients with non insulin dependent diabetes mellitus (NIDDM) was nearly 20% and the mean age of death in these patients is 61 year. Ischemic heart disease and cerebro-vascular accident accounted for 80% of deaths in this group[5].

Age group/ Male and Female

Out of total the maximum number of diabetic population comes under the age of 40–50years of both male and female. Maximum diabetic patients are of age ≥ 50years [6].

Table no-1 Statistical data of diabetic peoples suffering type-2 in rural India [6]

SEX	DIABETICS	PRE DIABETICS
MALE	6.20%	13.50%
FEMALE	4.40%	9.60%

Table-2 Age groups (from total diabetic population) suffering with Type 2 diabetes in rural India[6]

40–50 years	43.30%
≥50 years	50%
≤40years	0.70%

The crude prevalence rate of diabetes in urban areas is about 9% and that the prevalence in rural areas has also increased to around 3% of the total population[7].

Use of Allopathic and Ayurvedic drugs in Diabetes mellitus type-2

According to World Health Organization in India 80% of population directly or indirectly use herbal drugs[8]. Although people use

allopathic drugs as principal and emergency medicine they also take some form of herbal/Ayurvedic drugs as an adjuvant therapy[8]. In traditional system of medicine and the tribal populations in India so many different herbs are used in practice for the treatment of diabetes [9]. Most of them are not tested yet for their significant hypoglycaemic properties. In current pharmaceutical market there are a number of herbal drugs available for the treatment of *Diabetes mellitus*. So it is necessary to take the independent clinical trials out of these available drugs to get confirm and to make the people aware about the true efficacy of these drugs[10].

MATERIALS AND METHODS

A herbal drug with the following composition (DIAZEN from the manufacturer Green milk health products, Apex herbal division), which is already available in market was selected and it's efficacy was compared with the standard allopathic drug Gliclazide (Sulfonylurea group) to prove the efficacy.

The safety of this product and the adverse reactions were also studied in this trial. The herbal drug composed of the multiple herbal extracts composing of following herbs. Each soft gelatine capsule of 200 mg (total weight with all the ingredients mentioned in Table-3), Diazen (the trade name) was selected because it's composition is only of herbs and no metallic drugs.

Table-3 List of Ingredients in the Herbal formulation 'Diazen'

Herbs	Common name	Part Used	Mg/200 mg cap.
Gymnema sylvestre (Retz.) Schult.	*Gudmari*	Leaf	15
***Momordia charantia* L.**	*Kalera*	Whole fruit pulp	30
***Eugenia jambolana* Lam.**	*Jamu*	Seed	18.75
***Tinospora cordifolia* (Willd.) Miers**	*Guduchi*	Stem	15
***Trigonella foenogricum* L.**	*Methi*	Seed	10
***Withania somnifera* (L.) Dunal**	*Aswagandha*	Root	20
***Cassia auriculata* L.**	*Avartaki*	Flowers & Roots	25
***Aegle marmelos* (L.) Correa**	*Bael*	Dried fruit pulp	18.75
***Azadirachta indica* A. Juss**	*Neem*	Leaf	7.5
***Curcuma longa* L.**	*Haldi*	Rhizome	3.5

The study duration was one month in which the hypoglycaemic activity was studied. The included subjects were divided into 3 groups each consisting of 10 individuals. The control group was supplied with Gliclazide 80 mg/24hr. The doses /24 hr were given as per the Hyperglycemic condition of the patients. The trial group was administered with soft gelatine Capsules of *Diazen.* Third group patients were administered with the combination of medication composed of the herbal drug with the Sulfonyleurea drug Gliclazide.

In every 15 days interval the blood sugar test for both fasting and postprandial of each patient were repeated. Dietary restrictions were also applied to all these patients.

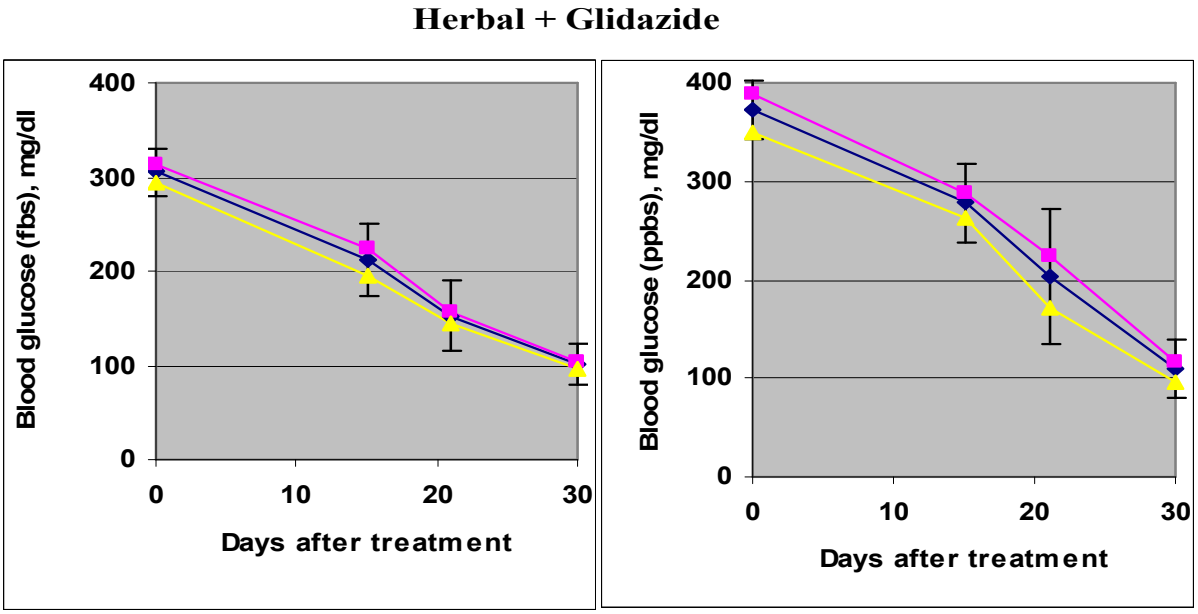
Observation: All the symptoms were noted prior to the trial. Very common among those were constipation, fatigueness, polyurea, polydipsia. The plasma glucose level (both fasting and post prandial) were also recorded. Out of 10 patients 9 patients feeling normal and the complications like constipation, fatigueness, muscle weakness, palpitation, polyurea, polydipsia were also absent. Other symptoms like recurrent urine infection, blurring vision, dyspepsia, were also found in the diabetic patients

Table-4 Results for patients using both herbal drug and Allopathy drug gliclazide-80Mg. (For a duration of one month)

Sl No	Age	Blood glucose		After 15days		22 days		30days		Doses of medicines	
		F.B.S.	P.P.B.S	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	DIAZEN	GLICLAZIDE
		(Mg/Dl)	Mg/Dl	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)		
1	40	341	419	260	340	199	301	145	178	2CAPS B.D.	80Mg B.D.
2	44	306	386	208	269	188	208	108	133	2CAPS B.D.	80Mg B.D.
3	41	290	370	190	250	112	140	79	96	2CAPS B.D.	80Mg O.D
4	45	285	355	170	230	108	126	85	99	2CAPS B.D.	80Mg O.D
5	48	310	365	215	290	171	200	110	156	2CAPS B.D.	80Mg B.D.
6	55	320	380	225	285	182	225	109	129	2CAPS B.D.	80Mg B.D.
7	54	286	330	180	240	126	142	103	134	2CAPS B.D.	80Mg O.D
8	48	330	410	265	332	173	290	111	136	2CAPS B.D.	80Mg B.D.
9	52	322	385	256	310	166	275	98	120	2CAPS B.D.	80Mg B.D.
10	42	260	325	156	236	98	123	66	110	2CAPS/B.D.	80Mg O.D.

Abreviation –B.D.- bis die (BD), a latin term meaning twice per day .O.D.-Once Daily , Mg/Dl- Milligrams per Deciliter.

Table -5 Days after treatment with both Herbal & Allopathic drugs



In this group patients were required low dose of gliclazide. For all patients in this group the blood sugar level came down to normal range with an average of 21 days.

Second group of patients who were receiving herbal therapy only, got the normal blood glucose level but it took time longer duration than patients consuming both herbal therapy and Gliclazide .Within first 15 days the blood sugar decreased but not up to the normal range of (Fasting blood sugar) 70–110 mg/Dl and Post Prandial blood sugar 90–140 mg/Dl. Out of 10 patients in 7 patients the response was up to the desired as the drug able to bring normoglycemic stage.

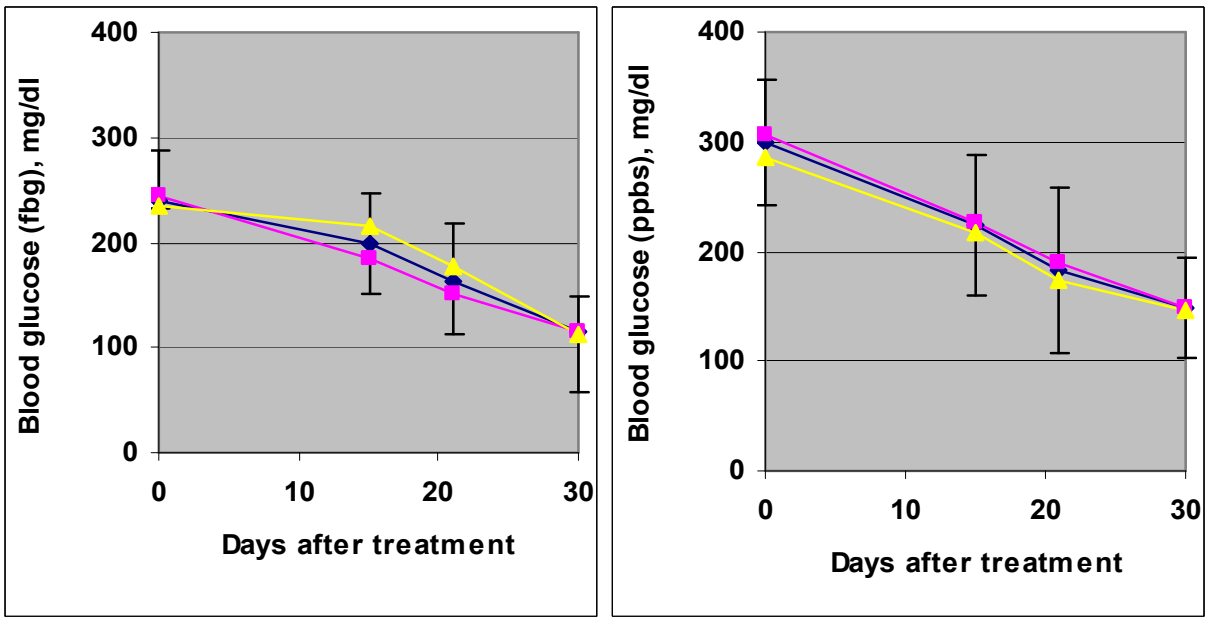
TABLE NO. 6 RESULT WITH IN ONE MONTH OF ONLY HERBAL THERAPY

Sl. no	Age	Blood glucose		After 15days		22 days		30days		Doses of medicines
		F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	DIAZEN
		(Mg/Dl)	Mg/Dl	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	
1	42	268	345	210	250	179	202	126	167	2CAPS B.D.
2	45	305	375	280	330	285	355	200	260	2CAPS B.D.
3	43	190	230	115	136	86	105	79	96	2CAPS B.D.
4	49	220	265	170	230	129	158	103	124	2CAPS B.D.
5	55	258	325	205	230	171	200	115	175	2CAPS B.D.
6	58	210	280	160	204	118	130	96	129	2CAPS B.D.
7	62	176	205	168	198	126	142	105	134	2CAPS B.D.
8	48	196	278	130	167	100	140	99	112	2CAPS B.D.
9	52	290	370	210	270	137	176	98	130	2CAPS B.D.
10	54	285	315	255	290	205	245	125	157	2CAPS/B.D.

Abreviation –B.D.- bis die (BD), a latin term meaning twice per day .O.D.-Once Daily , Mg/Dl- Milligrams per Deciliter.

Table – 7 Days after treatment with Diazen

Herbal



It took more than 1 month to get the glucose level up to the normal range. The Control group or the patients who were supplied with the only sulfonylurea group of medicine Gliclazide got their sugar level normal. Out of 10 patients 8 got their sugar level normal with in the period 30 days from the hyperglycemic condition (Table-No-8 Patient No-3 -10). After the sugar level got to normal range the dose reduced to 80mg per day. The initial doses of medication were Gliclazide 80 mg twice daily.

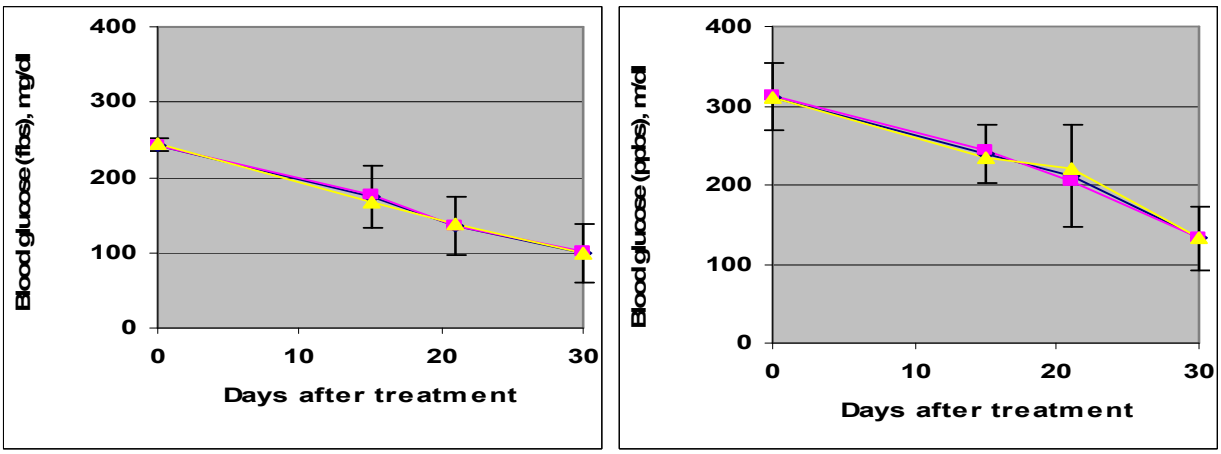
TABLE NO. 8 Patients with the standard drug Gliclazide (BD)

Sl. no	Age	Sex	Blood glucose		After 15days		22 days		30days		Doses of medicines
			F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	F.B.S.	P.P.B.S.	GLICLAZIDE
			(Mg/Dl)	Mg/Dl	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	(Mg/Dl)	
1	44	M	306	376	245	310	200	281	145	210	80Mg B.D.
2	42	F	267	320	196	259	176	255	143	190	80Mg B.D.
3	56	M	256	336	176	250	145	196	109	142	80Mg B.D.
4	67	M	246	316	170	230	108	126	82	99	80Mg B.D.
5	45	F	290	340	210	270	174	200	101	130	80Mg B.D.
6	56	M	210	280	165	245	132	225	106	132	80Mg B.D.
7	49	F	190	269	108	185	86	142	67	90	80Mg O.D.
8	47	F	230	310	155	225	112	290	86	119	80Mg B.D.
9	53	M	259	339	175	235	139	275	93	122	80Mg B.D.
10	59	M	180	225	136	186	88	123	69	89	80Mg O.D.

Abbreviation – B.D.- bis die (BD), a latin term meaning twice per day .O.D.-Once Daily , Mg/Dl- Milligrams per Deciliter.

Table-9

Glidazide



After the glucose level came down to normal state the doses were reduced to 80 mg once/Day from the initial 80mg twice a day dose.

RESULTS AND DISCUSSION

Taking the standard normal blood glucose range (F.B.S.-70 mg/Dl-110 mg/Dl and P.P.B.S.-90 mg/Dl-140 mg/Dl) the comparative study of the herbal drug with the standard drug Gliclazide shows that the herbal drug is effective at least in lowering the blood glucose level up to normal range. No case of severe hypoglycemia has been found in any of the patients. In case where both herbal drug and Gliclazide simultaneously used condition of hypoglycemia may arise (Table-4 patient no-10). In case of high doses of Gliclazide may also cause severe hypoglycemia. The group using both herbal drug and Gliclazide; in case of 1 patient (Table-4 patient no.1) the glucose control was not so effective and took longer time to make the glucose level to normal in spite of in an increased doses .The main possible cause is the Obesity and distorted lipid profiles

Regarding the efficacy of the herbal drug ; there was no contra indicatory undesired effects like nausea, vomiting, body rashes or belching dyspepsia etc. were observed by any of the patients. From this trial it is established that the drug "Diazen" has the desired efficacy to be used in the treatment of diabetes mellitus type-2(NIDDM). The patients who were receiving the only herbal therapy, 6 out of 10 patients got their glucose level normal in one month, 2 out of 10 patients have got moderate result near to normoglycemic state. One out of ten patients was observed not to be up to satisfactory result. There were no such adverse effects noticed in case of patients who used this drug during the trial study

Mechanism of action of Gliclazide

Gliclazide is a sulphonylurea drug with an intermediate half-life of around 11 hours[11]. It is extensively metabolized. The molecule contains an azabicyclo-octyl group which confers special properties on the basic sulphonylurea moiety. Gliclazide stimulates insulin secretion through the beta cell sulphonylurea receptor, and possibly through a direct effect on intracellular calcium transport. It specifically improves the abnormal first phase insulin release in type 2 diabetes, and also has an effect on the second phase. This pattern of insulin release is thought to explain the lower incidence of hypoglycaemic episodes and weight gain compared with some other sulphonylurea. There is also a reduction in hepatic glucose production and improvement in glucose clearance, without changes in insulin receptors. This suggests a possible post-receptor effect on insulin action, perhaps by stimulation of hepatic fructose-2,6-bisphosphatase and muscle glycogen synthesis [12].

Possible mechanism of anti diabetic action of the herbal drug

Gymnema sylvestre (Retz.) Schult. - Sanskrit name: *Meshasringi, Madhunasini;* Familly-Asclepiadacae [13]

Hypoglycemic action mechanisms

Research shows that a water-soluble extract of *Gymnema sylvestre* (Retz.) Schult., causes reversible increases in intracellular calcium and insulin secretion in mouse and human β-cells when used at a concentration (0.125 mg/ml) without compromising cell viability. Hence forth these data suggest that extracts derived from *Gymnema sylvestre* (Retz.) Schult . may be useful as therapeutic agents for the stimulation of insulin secretion in individuals with Type 2 Diabetes. Gymnema leaves raise the production of insulin by regeneration of the cells in the pancreas that produce insulin [14]. Research has shown that Gymnema also improves glucose uptake by cells by increasing the activity of the glucose utilizing enzymes, and stops adrenaline[15] from stimulating the liver to produce extra glucose, thereby controlling blood sugar levels[16].

Momordia charantia L .-Sanskrit name: *Karavellaka*, Family – Cucurbitaceae [17]

Antidiabetic mechanism –

Bitter melon contains a lectin that has insulin-like activity[18]. The insulin-like bioactivity of this lectin is due to its linking together 2 insulin receptors[19]. This lectin lowers blood glucose concentrations by acting on peripheral tissues and, similar to insulin's effects in the brain, suppressing appetite [20, 21].

The proven hypoglycaemic properties through animal trial experiments can be summarized as follows:-

Pancreatic activities-

1. Insulin promoting or mimetic [22].

2. Increased GLUT4 transporter protein of muscles [23-24].

3. Increased glucose utilization in liver and muscle tissues [25].

4. Inhibition of glucose-6-phosphatase and fructose-1, 6-bisphosphatase in the liver [26]

5. Stimulation of red-cell and hepatic glucose-6-phosphate dehydrogenase activities [27]

6. Inhibition of glucose transport at the brush border of the small intestine [28]

Eugenia jambolana Lam. , Sanskrit name: *Jambu*, Family-Myrtaceae [29].

Possible Mechanism of hypoglycaemic action- A study in vitro model systems shows aqueous extracts from *Eugenia jambolana* Lam. (Myrtaceae) seeds have an inhibitory action on carbohydrate hydrolyzing enzymes, namely, porcine pancreatic á-amylase, rat intestinal α-glucosidase, and sucrose. These findings emphasize that inhibition of carbohydrate hydrolyzing enzymes is one of the mechanisms through which *E. jambolana* exerts its hypoglycemic effect in vivo [30]. EJ has been reported to show significant antihyperglycaemic activity in mild diabetes rats which have functioning pancreatic β cells indicating that it may modulate insulin release which have observed with an increase in insulin level with EJ water ext. (*E. jambolana* Lam. water extracts) treatment[31]. Further, the flavonoids also stimulate 16% increase in insulin release in vitro from pancreatic islets[32]. All previous animal model trials are in concordance with earlier reports where EJ was found to increase insulin secretion [33].

Tinospora cordifolia (Willd.) Miers; Sanskrit name-Guduchi, Amrita; Family - Menispermaceae [34]

Anti diabetic mechanism

Aqueous extract causes a reduction in blood sugar in alloxan induced hyperglycaemias in rats and rabbits in the dose of 400 mg/kg. The aqueous extract also exhibits some inhibitory effect on adrenaline-induced hyperglycemias. Ethyl acetate extract of its roots has afforded a pyrrolidine derivative with hypoglycaemic activity in rabbits[35]. The Water extract of *Guduchi* has hypoglycaemic properties and used to treat diabetes mellitus. It has been estimated in animal model that 400 mg/Kg is equivalent to the action of 1unit/kg insulin[36].

Trigonella foenogricum L . , Sanskrit name – *Methika*, Family- Fabaceae [37]

Antidiabetic mechanism

The possible Mechanism behind the hypoglycaemic property is Fenugreek may increase the number of insulin receptors in red blood cells and improve glucose utilization in peripheral tissues, thus demonstrating potential anti-diabetes effects both in the pancreas and other sites[38]. The amino acid 4-hydroxyisoleucine, contained in the seeds, may also directly stimulate insulin secretion. Fenugreek seed has remarkable power to reduce blood sugar level hence used in diabetes[39] .Fenugreek seeds contain alkaloids, including trigonelline, gentianine and carpaine compounds, fibers, 4-hydroxyisoleucine and Fenugreekine, a component that may have hypoglycemic activity[40].

Withania somnifera (L.) Dunnal , Sanskrit name-*Aswagandha/Ajagandha*, Family – Solanaceae[41]

Antidiabetic mechanism

Possible mechanism of Hypoglycaemic action as revealed from different animal model trials are that it has (The root extract and leave extract) got antioxidant properties and free radical scavenging activities[42].

Centuries of Ayurvedic medical experience using *Withania somnifera* (L.) Dunal have revealed it to have pharmacological value as an adaptogenic.

The activities of liver G6P (glucose-6-phosphatase) and serum enzymes like AST (aspartate transaminase), ALT (alanine transaminase), ACP (acid phosphatase) and ALP (alkaline phosphatase) when assayed (method of King) significantly found increase in the diabetic rats when compared to those of normal control rats[43]. But the activities of liver G6P and serum AST , ALT , ACP and ALP significantly decreases in diabetic rats treated with WSREt (*Withania somnifera* (L.) Dunal root extract). WSREt and WSLEt(leaf extract) replenishes liver glycogen stores and suppresses the hepatic gluconeogenesis by decreasing activity of G6P[44] .

Cassia auriculata L., Sanskrit name-*Avartaki*, Family -Fabaceae

The dried flowers and flower buds are used as a substitute for tea in case of diabetes patients. How does it work*? Cassia auriculata* L. might increase the body's production of insulin. This property is confirmed through a laboratory trial upon animal models in the Department of Biochemistry Faculty of Science, Annamalai University.

The possible mechanism by which CFEt (*Cassia auriculata* L. flower extract) brings about its anti-hyperglycemic action may be by potentiating the pancreatic secretion of insulin from β-cell of islets or due to enhanced transport of blood glucose to peripheral tissue. This was clearly evidenced by the increased level of insulin in diabetic rats treated with CFEt.[45-46]

Aegle marmelos (L.) Correa, Sanskrit name-*Bilwa*, Family-Rutacaeae[47]

Possible mechanism of Antidiabetic properties of *Aegle marmelos* (L.) Correa extract.

Aegle marmelos contain the minerals like Cu, Ni, Zn, K, and Na were found to be in trace amounts, whereas Fe, Cr, and V levels were found in marginal levels. These minerals play a role to maintain normoglycemia in blood by stimulating pancreatic beta cells to secret insulin[48].

Azadirachta indica A. Juss , Sanskrit name-*Nimba*, Family –Meliaceae[49]

Possible mechanism of antihyperglycemic effect

Effect of *Azadirachta indica* A.Juss leaf extract on serotonin inhibition in glucose mediated insulin release in rat pancreas was studied in vitro to elucidate the possible mechanism of antihyperglycemic effect of *A. indica* leaf extract. *A. indica* leaf extract blocks significantly the inhibitory effect of serotonin on insulin secretion mediated by glucose[50].

In the animal model experimental trial (tudied in normal and streptozotocin-induced diabetic rabbits) studies it has been proved that, "*A. indica* leaf extract, in itself, was found to have no action on peripheral utilization of glucose or on hepatic glycogen. The reduction in peripheral utilization of glucose and glycogenolytic effect is due to the complete block of epinephrine action by *A. indica* leaf extract. It almost completely block the action of epinephrine (the insulin antagonistic hormone) in diabetic rabbits and to a certain extent in normal ones [50-51]

Aqueous leaf extract also reduces hyperglycaemia in streptozotocin diabetes and the effect is possibly due to presence of a flavonoid, Quercetin [52-53].

Curcuma longa L. , Sanskrit name-*Haridra*, Family: Zingiberaceae[54]

Anti diabetic potentials

The hypoglycaemic property is due to the Curcumin, or diferuloyl methane, is the yellow pigment extracted from turmeric. Curcumin exhibits an even more pronounced anti diabetic action.

The study (in animal models) reveals that curcumin feeding improves the metabolic status in diabetic conditions, despite no effect on hyperglycaemic status or body weight. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence and its antioxidant and free-radical-scavenging properties[55].

CONCLUSION

As the results observed from all the patients based upon the result of fasting blood sugar and postprandial sugar the herbal drug which was chosen out of many herbal Ayurvedic drugs has proved out to have the desired anti-hyperglycemic efficacy. Also it has the composition of standardized herbal extracts to combat day to day diabetic complications like constipation, fatigues, polydipsia, polyurea etc. .Also it has the property to resurrect the lipid profile of blood. So as per the claim the drug has the desired efficacy for use in the treatment of Diabetes mellitus type -2 as per the claim.

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