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Whether the glucose dependent insulin secretion work under the umbrella of *Vata dosha*?

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A B S T R A C T : Impairment in insulin activity and decrease in insulin secretion are mainstay of NIDDM. Apparently, the first is the result of beta cell damage or decrease in beta cell mass. It is well-known fact that in NIDDM, there is less than 30% reduction in beta cell mass. On the other hand, the flaw in insulin secretion is more severe than the defect in beta cell mass. The conclusion is that in NIDDM, the insulin secretory deficiency is due to the loss of insulin secretion. In glucose dependent insulin secretion, the most important role is played by the closure of ATP sensitive potassium channels K (ATP) in the beta cells.In recent times, many *ayurvedic* herbs have been establishedfor their influence on the process of insulin exocytosis byobstructingK (ATP) channel in pancreatic beta cells. We have considered*Kanchanar, Punarnava, Gudmar, Bilva, Latakaranj* and *Lajjalu,* which have analogous*panchabhautic* constitution, for the correlation of the role of *tikta, kashaya rasa,* and*laghu, ruksha* qualities of *Vata*with the glucose dependent insulin secretion, andconcluded that these attributes of *Vata,* have an outright control on the functionality of glucose dependent insulin secretion from the beta cells of pancreas.

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Keywords: insulin-secretion, tikta-Kashay, Vata, laghu-ruksha

1. Introduction

In the World scenario, the population of diabetic patients has raised nearly 4 times, in the last 35 years. In India the proportional mortality from diabetes mellitus is more than 2% of the total deaths [2]. The main cause behind this mortality rate is the increase in blind followers of the modern western society. In last 30 to 40years,young generation of India, have blown off their ancient culture under the influence of westernization, resulting in modernization of life-style. Now the result is that young India is in front of non-insulin dependent diabetes mellitus as a major health problem. One third of the total population in India is still under the poverty line. So it is very difficult to the diabetic general public, who are in low income group, to purchase the immensely high costed modern medicines throughout their life for the treatment of diabetes mellitus. Keeping these realities in mind, it is very necessary to accept alternate strategies for the anticipation and treatment of diabetes mellitus in India. It is assumed that more than 80 percent of Indian population is still dependent on medicinal herbs for their primary health care. In the long run, scientific investigations of many significant medicinal herbs have been carried out productively. Rationally considered interdisciplinary research programs have directed to the development of ethnic medicinal herb resources as practical and cost effective alternatives.
Understanding the Ayurvedic concept of Madhumeha

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In Ayurveda, there are twenty types of Prameha described. The base of these different types of Prameha, is the precise character expressed by the urine, which is develop due to the specific grouping between deranged qualities of the doshas. Madhumeha is one of the four types of the vātaj type of Prameha. In ancient texts, it is explained that in the long run, all types of Prameha are get converted in to Madhumeha. The leading etiological causespronounced in caraka for the disease Prameha, are extremeassimilation of meat from aquatic animals and animals from marshy land, habit to the desire of sedentary life, extra intake of curds, too much intake of freshly harvested grains and freshly prepared alcoholic drinks and preparations of jaggery and all kapha aggravating factors [3]. These etiological factors become responsible for the nourishment and upsurge of the kaphavargiya dhatu in the body, which are Parthiva and Jaliya in their panchabhautika constitution [4]. Vagbhata has cited that intensification in the attributes of one dosha, reasons a decline in the qualities of another dosha [5]. So it is not obligatory every time that, ingesting of madhuradi dravya, will manifest the escalation of the kapha, but it is also possible that symptoms of vatakshaya may be present. In this association, when we say that, the kaphais provoked by the qualities like snigdha, guru, shlakshna, sthula, sthira etc., at the same time the contrasting qualities like ruksha, laghu, khara, sukshma, cala are being weakenedcorrespondingly. In suchbackground, madhukoshakara has clarified that this disproportion is not due to direct imbalance of vata, but due to the augmentedreverse qualities, mainly of derangedkapha, which reduces the normal tasks of vata dosha[6].

So it is very important to understand that, when due to the incorporation of madhura-snigdhadi qualities in the body, percentage of individualities of vata becomes depressed and the normal functioning of vatadoshabecomessusceptible. Though doshavrudhiis more significant for the pathogenesis of any disease, doshakshaya is also having a distinctiveimportance in the pathology of Madhumeha. So due to the lessening of percentage of its qualities as a result of amplified percentage of attributes of its opposite kaphadosha, vatadosha, which was until now in regular physiological condition, is now incapable to work properly or it drops some of its functions in the body. In persistence with the above example of Madhumeha, here we can say that some of the qualities of vata dosha, which are indispensable for facilitating the entry of insulin in the cell through insulin, are vanished due to upsurge of its opposite qualities of kapha dosha and are causing the development of hyperglycemia.

Six Ayurvedic Secretagogues and their qualities

We have deliberated six most extensivelyused medicinal herbs, described in Ayurveda, for this review. The aim of this review is to co-relate the glucose dependent insulin secreting activity of these 6 herbs with the functionality of vata dosha.In the last 30 years, all the medicinal herbs listed in the Table No.1, were confirmed for their secretagouge activity in the diverse in vivo or in vitro model systems.

Table No. 1

No.	Dravya	Rasa	Vipaka	Guna	Action on beta cells
1.	Kanchanar (Bauhinia variegate)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity
2.	Punarnava (Boerhavia diffusa)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity
3.	Gudmar (Gymnema sylvestre)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity
4.	Bilva (Aegle marmelos)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity
5.	Latakaranj (Caesalpinia bonducella)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity
6.	Lajjalu (Biophytum sensitivum)	Tikta, Kashay	Katu	Laghu, Ruksha	Insulin secreting activity

Kanchanar(Bauhinia variegate): -Frankish N and others (2010), studied the insulin-secreting cell line INS-1 for the properties of the crude ethanolic extract of leaves of Bauhinia variegata and its major metabolite (6 S,7 E,9 R)-9-hydroxymegastigma-4,7-dien-3-one-9- beta-glycopyraroside (roseoside) on insulinotropic activity, and found that the crude extracts and the major metabolite increase insulin secretion in a dose-dependent manner [7].

Punarnava(Boerhavia diffusa): - M Amarnath Satheesh and L Pari (2004) found that administration of Boerhavia diffusa leaf extract produced a marked decrease in blood glucose at 200mg/kg body weight in normal as well as in alloxan diabetic rats after 1-month treatment. They concluded the antidiabetic effect of Boerhavia diffusa leaf extract was due to increased `release of insulin from the existing beta cells, similar to that observed after glibenclamide administration [8]. MA Chude and others (2001) found that the aqueous leaf extract of Boerhavia diffusa produced non-dose related decreases in blood glucose level in alloxan-induced diabetic rats. They suggested that the mechanism of action was due to the stimulation of the residual pancreatic beta cell function [9].

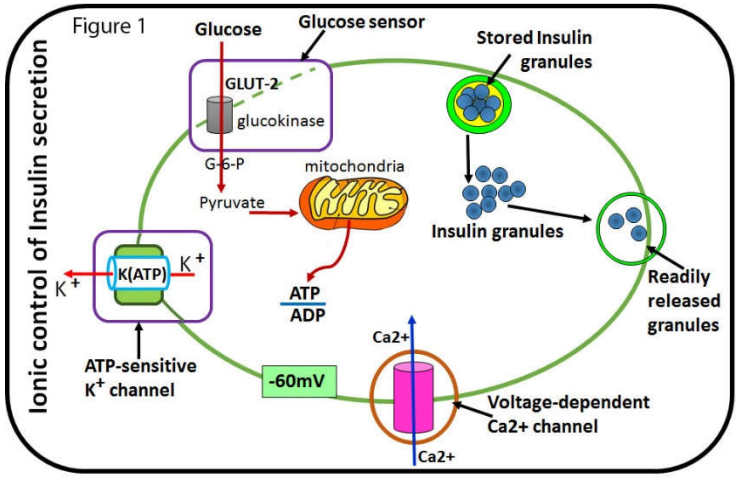
Gudmar (Gymnema sylvestre): - Patel DK and others (2012) found that the alcoholic extract of Gymnema sylvestreencouraged insulin secretion from the rat islets of Langerhans and several pancreatic cell lines [10]. JK Grover and others (2002) established that oral administration of aqueous leaf extract of Gymnema sylvestre to Insulin Dependent Diabetes Mellitus patients on insulin therapy decreased insulin requirements [11]. Mohamed Bnouham and others scrutinized the effects of GS4 (400mg/day) extracted from the leaves of Gymnema sylvestre on the type 2 diabetic patients for 18-20 months as a supplement to the conventional oral drugs. Along with the significant fall in blood glucose and glycosylated haemoglobin, the patientsexhibited a reduction in conventional drug dosage. Nearly 25% of the patients were capable to withdraw their conventional drugs and maintain their blood glucose with GS4 alone. After perceiving the presence of elevated insulin levels in the serum of patients after GS4 supplementation, they resolved the reason behind this activity as the improvement in the functionality and regeneration of the beta cells [12]. Additionally, they utilized GS4 supplementation in type 1 diabetes and proved that GS4 therapy heightened the insulin secretion [13]. M Upendra Rao and others found that extract from the leaves of Gymnema sylvestre encouraged insulin secretion from mouse cells and isolated human islets in vitro [14].

Bilva(Aegle marmelos): - Karunanayake and others (1984) establishedthe hypoglycemic effect of aqueous decoction of the plant root bark in normal fasted rats [15]. Ponnachan and others (1993) proved the antihyperglycemic activity of the aqueous leaf extract of Aegle marmelos in alloxanized rats [16]. Bell RH. and RJ Hye. (1983) established that the upsurge in the plasma insulin, in the Aegle marmelos leaf extract treated Alloxan-diabetic mice, was due to the motivation of the intact functional beta cells of the Langerhans islets to produce insulin or guarding of functional beta cells from further deterioration, so that they persist active and can produce insulin [17]. Afeefa Kiran Ch and others (2016) have established that the aqueous extract of Aegle marmeloscomprises some biomolecules that inspire the beta cells of islets of Langerhans to discharge insulin [18]. Das AV and others (1996) revealed that the treatment of leaf extract on diabetic pancreas presentedenhanced functional state of pancreatic beta-cells, which pointed toward the potential hypoglycemic nature of the leaf extract, serving in regeneration of damaged pancreas [19]. In one another experiment, Upadhya S and others (2004) discovered a significant reduction in blood glucose in diabetic albino rats treated with aqueous extract of Aegle marmelos leaves [20]. Sabu, M.C. and Kuttan, R. (2004) found that 75% methanolic extract of Aegle marmelos significantly minimized serum glucose level in hyperglycemic animals [21]. Kamalakkannan, N and others (2003) evaluated the antidiabetic effect of an aqueous extract of Aegle marmelos fruits in streptozotocin-diabetic Wister rats. They found that the treatment with Aegle marmelos upturned the effects of diabetes by lessening glucose level and glycosylated hemoglobin to normal level. They also found that the plasma insulin level was improved[22]. In another animal experiment, Kamalakkannan, N. and Prince, P.S., (2003) found the hypoglycemic effect of an aqueous extract of Aegle marmelos fruits in streptozotocin-diabetic Wister rats. They confirmed that the effect of the extract at a dose of 250 mg/kg was more concrete than glibenclamide in reduction of blood glucose [23].

Latakaranj(Caesalpinia bonducella): - Sharma and others (1997) studied the properties of the aqueous and 50% ethanolic extracts of *Caesalpinia bonducella* seeds in normal and streptozotocin-diabetic rats. They found that in normal rats, both the extracts exhibited hypoglycemic activity as early as 4 h after administration at a lower dose of 100 mg/kg and in diabetic rats, both the extracts created significant ($P<0.01$) antihyperglycemic effect from day 5 onwards [24]. Chakrabarti, S. and others (2005) assesseddifferent extracts from Caesalpinia bonducella in chronic type 2 diabetic model along with insulin secretagouge activity of five fractions quarantined from the Caesalpinia bonducella seed kernel. They established that both the aqueous and ethanolic extracts have a strong

hypoglycemic activity in chronic type 2 diabetic model. They also revealed that the 2 fractions, namely BM 169 and BM 170 B upsurge secretion of insulin from isolated islets [25].

Lajjalu(Biophytum sensitivum): - Puri D and Baral N (1998) studied the action of the extract prepared from the Biophytum sensitivum leaves by reduction in fasting plasma glucose and enhancement in the oral glucose tolerance test, which displayed significant hypoglycemic effects. They decided that this result is due to pancreatic beta cell stimulating action[26]. Puri D (2001) perceived the effect of the leaf extract of Biophytum sensitivum on glucose homeostasis in rabbits. He established that the serum insulin levels had a significant upsurge in the



treated animals, which proposes a pancreatic mode of action of B. sensitivum. His explanations suggest that the hypoglycemic response of B. sensitivumisfacilitated through stimulating the release of insulin from the beta cells of Langerhans [27]. In 2015, Ananda PK and others studied the effect of aqueous solution of Biophytum sensitivum leaf extract on normal and streptozotocin-nicotinamide-induced diabetic rats, and established that Biophytum sensitivum leaf extract significantly lessened the blood glucose and glycosylated hemoglobin levels in diabetic rats[28].

Considering the insulin secretion

As shown in the figure1, the order of insulin secretion, which is broadly acknowledged can be pronounced as follows: - First glucose is conveyed through assisted diffusion of GLUT2 glucose transporters into beta cells. At mitochondria, this glucose is metabolized to ATP, ensuingtheupsurge in the ratio of ATP/ADP. This elevation in ATP/ADP ratio encourages closure of ATP-sensitive K+ channels. This closure of K (ATP) channels reasonsthe depolarization of cell membrane. Voltage-dependent Ca2+ channels (VDCC) are unlocked due to this depolarization, resulting in extracellular Ca2+ influx into beta cells. Raise in the level of free cytosolic Ca2+, activates the exocytosis of insulin. **********

K (ATP) channel-dependent pathway and GTP-dependent pathway, are the two important pathways,in which glucose stimulation causes the insulin secretion. Fundamentally, potassium channels are inhibited by intracellular ATP, so these channels are called as ATP sensitive potassium channels. These K (ATP) channels accomplishdecisivebiological role in regulating glucose dependent insulin secretion. In the K (ATP) channel-dependent pathway, glucose inspiration increases the entry of extrinsic Ca2+, through voltage-gated channels, by closing down of the K (ATP) channels and depolarization of the beta cell membrane. The consequent upsurge in the intracellular ca2+ boosts insulin exocytosis. The second one is GTP-dependent pathway, in which intracellular Ca2+ is elevated by GTP-dependent proteins, which amplifies the Ca2+ motivated release of insulin.

Secretagogues perform at intermediate steps of these signaling pathways and influence the process of insulin exocytosis. So one can increase insulin release by –

Inhibiting ATP-sensitive K+ channel in pancreatic beta cells,

By release of intracellular calcium

By evoking PKA-mediated Ca2+ influx,

Beta cells are electrically excitable and capable of generating Ca2+ action potentials that are important in synchronizing islet cells activity and insulin release. K (ATP) channels are signal targets for glucose. In addition to this, inducing closure of K (ATP) channels is one of the targets for oral agents in the treatment of type 2 diabetes, for the purpose of stimulating insulin secretion.

Discussion

As shown in table no. 1, insulin secreting activity has been established in all these six ayurvedic herbs, Kanchanar(Bauhinia variegate), Punarnava(Boerhavia diffusa), Gudmar(Gymnema sylvestre), Bilva(Aegle marmelos), Latakaranj(Caesalpinia bonducella), and Lajjalu(Biophytum sensitivum). In the description of these six ayurvedic Secretagogues& their attributes, we have seen that in normal and diabetic animals, all these six medicinal herbs have shown an upsurge in plasma insulin levels, due to the increase in insulin secretion from the pancreatic beta cells.

We know that any type of stimulation comes under the authority of vata dosha activity. Hemadri has also described cala, one of the most important quality of vata dosha, as “prerane calah”.

Approximately 100 Gm serving	Ruksha	Laghu	Shita	Vatakar	Alanine (in mg)	Glycine (in mg)
Peanut [29]	Yes	Yes	Yes	Yes	1.04	0.94
Lentil pink [30]	Yes	Yes	Yes	Yes	1.05	1.01
Flat beans [31]	Yes	No	No	Yes	0.98	1.01
Bengal gram[32]	Yes	Yes	Yes	Yes	0.83	1.55
Red Gram [33]	Yes	Yes	Yes	Yes	1.08	0.82
Red kidney beans[30]	Yes	Yes	Yes	Yes	0.99	0.92
Kidney bean aconite leaved[34]	Yes	Yes	No	Yes	0.98	1.02
Mung beans [35]	Yes	Yes	Yes	Yes	1.04	0.95
French beans [30]	Yes	Yes	Yes	Yes	0.79	0.73

Table No. 2

Anywhere in the body this preranaor stimulation is controlled by cala quality of vata dosha. So when we say that closure of K (ATP) channels, causes depolarization, resulting in opening of VDCC (voltage dependent calcium channels), we have to consider, how the vata doshaacts in this phenomenon. The first thing is that, closing or opening of any channel is an activity of vata dosha. Secondly, when glucose is transported into beta cell and converted into ATP in the mitochondria, the ATP/ADP ratio changes. This change in the ratio is recognized by the vata dosha. Because in the definition of vata[Vaa gati gandhnayo Vayu], it is said that the word vatais originated from Sanskrit word “Vaa”, which is indicative of not only movement, but apart from representing the meaning of movement, this word grammatically also expresses the sense of knowledge & addition. The meaning of this is that vata is also responsible for reasoning, perception, and decision taking. That is the cause, that sushrutahas describe vata as “amohah buddhi karmanah”. So we can say that the changes in ATP/ADP ratio are detected or identified by the attributes of vata dosha, and causes the closure of K (ATP) channels. This is the way by sensing the environs and closing the K (ATP) channels, vata dosha activates the cascade for the secretion of insulin. One more thing to consider is that K (ATP) channels and insulin, both have vayu mahabhuta and akasha mahabhutaas major constituents in their panchabhautic constitution. K (ATP) channels possess an important hydrophobic patch in the inner side of the channel with ruk□a, laghu, khara, sukshma, cala qualities. Shinde S., and Kulkarni D.V. have demonstrated that insulin is in possession of Vayu mahabhutaand Akash mahabhutain its panchabhauticconstitution.

The second important thing which denotes the importance of vata dosha in the secretion of insulin, is the role of alanine & glycine amino acids. These two amino acids work apart from the K (ATP) channels. Simple meaning is that alanine and glycine amino acids trigger the secretion on insulin without any type of involvement of the K (ATP) channel closure. As we are aware of the fact that both these amino acids, alanine and glycine, are hydrophobic in nature and are in possession of ruksha, laghu, khara, sukshma, cala qualities of vata dosha. Secondly it is observed that the food particles which are rich in alanine and/or glycine are responsible for the increase of ruksha, laghu, khara, sukshma, cala qualities in the body. So we can, without any difficulty, say that alanine and glycine amino acids represent the functionality of vata dosha. Now these alanine and glycine amino acids act on the transportation of sodium into the beta cell. They cause influx of sodium into a cell resulting in depolarization of cell membrane. This depolarization activates the opening of Ca2+ channel causing additional influx of calcium into cell. Thus vata dosha is capable of inducing depolarization of cell by opening the Ca2+ channel without involving K (ATP) channel.

Table No. 3	vayu mahabhuta	akasha mahabhuta	pruthvi mahabhuta
Tikta rasa	1 Part	1 Part	------
Kashayarasa	1 Part	------	1 Part
Tikta + kashaya	50%	25%	25%
guna	ruksha, khara, cala	laghu, sukshma	Snigdha, shita

The base of this discussion is described in table no. 3. All the six medicinal herbs are in possession of tikta rasaand kashaya rasa. We know that in pancabhautika constitution of tikta rasa,vayu mahabhutaand akasha mahabhutaare present and in Kashaya rasa,vayu mahabhuta and pruthvi mahabhuta are in existence. Simple meaning is that, in constituents of all these medicinal herbs, 50% manifestation belongs to vayumahabhuta, and 25% appearance goes to each akasha mahabhutaandpruthvi mahabhuta. So it is not a wonder, when we observe all these six medicinal herbs coming under the umbrella of vata dosha. Secondly all these six medicinal plants are also in possession of laghu and ruksha qualities. Similarly,sukshmaand cala attributes present in all these six medicinal plants are due to their Katu Vipaka, which is designed by the combination of agnimahabhutaand vayu mahabhuta.

Conclusion

Considering the above discussion, we have concluded that, the process of ionic control of insulin secretion is the functionality of vata dosha. As in all these 6 medicinal herbs, the combination of 50% manifestation of vayu mahabhuta, and 25% appearance of akasha mahabhuta, acquiring totally 75% portion of the constitution, support to increase the attributes of vata dosha in the body. We have already discussed the fact that, in madhumeha, the etiological factors are responsible for the reduction of the attributes ofvata dosha, resulted in diminished stimulation of insulin secretion. These six medicinal plants, which are established secretagouge of insulin, work due to ruksha, laghu, khara, sukshma, cala qualities attributes of vata dosha.

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