Herbs can Effectively Talk with Diabetogenes

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Summary: Diabetes mellitus type-2 is a sweet killer disease, yet to be conquered. The frequency of this disease is constantly growing, emphasizing the need of new insights into the disorder's ground realities and novel strategies for the treatment of this disease. Many herbs are used to treat diabetes mellitus type-2 in all the areas of world predominantly in Asia and Africa. The main reason which promote investigators to hunt for new anti-diabetic herbs is the side effects coupled with the conventional and non-conventional drugs. Diabetes mellitus type-2 is a complicated and heterogeneous disease due to the mutations in many genes, called diabetogenes. This article is meant to describe the mechanism of action of anti-diabetic herbs in association with diabetogenes. There is a scant amount of scientific data revealing the molecular mechanisms of herbal drugs but lot of efforts are under the way to find out the molecular mechanism of these herbal drugs which will be helpful in discovering the reliable treatment for diabetes mellitus type-2.

Introduction

Most conventional drugs, that are used in the treatment of type-2 diabetes, alleviate a major problem that is manifested by a term "Diabesity" showing a relationship between type-2 diabetes leading to the obesity. These conventional drugs promote the nonselective uptake of glucose by many cells as adipocytes leading to the excess weight gain. So it can be said that on one hand they manage one problem but on the other hand they generate another one. That's why; it is needed to discover those drugs which are anti-diabetic but not the promoter of weight gain [1, 2]

Moreover, conventional drugs are also associated with a number of side effects, therefore, there is a need for emphasizing on the need of searching for safe and alternative drugs. It has been observed that some patients experienced insulin resistance and they do not respond well to conventional drugs but show positive response to natural products which are used as therapeutic measures. [3].

Nutrigenomics is related with the effects of nutritional components on the expression and regulation of several genes and proteins. Nutritional genomics can address with the investigation to identify the molecular targets which are acted upon by specific nutrients. It has been suggested that some nutrients have capability to change the level of gene expression [4]. Four mechanisms are claimed associated with these nutrients (Figs. 1 and 2). Through these mechanisms, nutrients influence the expression pattern of certain genes. First associated with the changes in the chemistry of the cell membrane such as the metabolism of eicosanoids and play a central role in monitoring the function of different receptors present on the cell membrane. Several products of eicosanoids are responsible for controlling the expression level of various genes and responses of cellular environment. Second mechanism is linked with the direct association of nutrients with transcriptional factors which when get entrance inside the nucleus, may couple with the regulatory spots, reside on DNA and ultimately regulate expression of certain genes for example polyunsaturated fatty acids follow this type of mechanism. Third mechanism is coupled with the change in the redox conditions of the cell and affects the function of transcription factors. Fourth possible mechanism is associated with epigenetic alterations for instant methylation of those proteins which are present and glue around the DNA, governing the gene functions [4].

According to WHO, 80% or 4 billion of the population of the world use herbal drugs [7] and recommends the scientific investigation of plant originated drugs for the treatment of diabetes [8]. Plants are used both as food as well as drugs to treat

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various diseases. They contain many substances which are actually not considered as nutrients but they help to maintain the health of individuals, thereby, named "Nutraceuticals". The compounds which act as nutraceuticals are alkaloids, flavonoids, glycosides, steroids, terpenoids, polysaccharides, proteins, saponins, polyphenols, phytoestrogens, polysterols, phytates and polyunsaturated fatty acids. Many of them showed anti-diabetic activity [9-11].

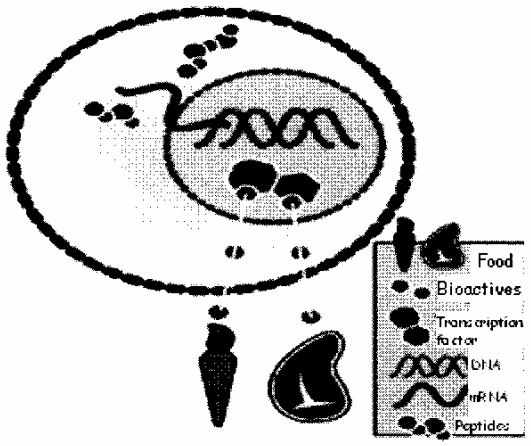

Fig. 1: A hypothetical diagram showing the bioactive ingredients of food after passing through the cellular and nuclear membranes, interact with the DNA either directly or through transcription factors thereby effecting the functions of genes [5].

Anti-diabetic herbs can illustrate their effects by a variety of mechanisms; they

a) restore β-cell function,
b) stimulate the insulin releasing activity,
c) provokes glucose uptake,
d) mediate carbohydrate metabolism [12].

Effect of Anti-diabetic herbs on Diabetogenes

From the stimulation of beta cells to the release of insulin and from the action of insulin on the body cells to the utilization of glucose, a large number of intermediary signaling events are happened. A protein gets the signals from its preceding protein and transferred to the next one thereby a cascade of events occur after a single stimulus. If one of protein's functionality becomes abnormal, whole the process can be effected. Still a number of intermediary proteins are yet to be known but a quite a good number and their corresponding functions are known. Some of them which are known to be associated with diabetes, are described in this review.

1. *Protein Tyrosine Phosphatase -1B (PTP-1B)*

Its protein product catalyzes the de-phosphorylation of insulin receptor and insulin receptor substrate, followed by the modification of insulin action [13]. PTP-1B accounts significantly for insulin sensitivity and fuel metabolism [14]. There are a number of Protein tyrosine phosphatases which can cause dephosphorylation of insulin receptor, followed by reduction in its kinase activity. Two dominant PTPases are PTP-1B and LAR (leukocyte antigen-related phosphatase) [15]. In NIDDM (Non insulin dependent diabetes mellitus) or insulin resistant states, the decreased function of PTPase is observed [16]. In diabetic patients, the PTPase-1B concentration is 38% lower as compared to non-diabetic subjects. The exact mechanism of the scarcity of PTPase 1B is not well-understood but it is supposed that either it increases degradation of PTP-1B or decrease PTPase 1B synthesis [17]. PTP-1B is one of the negative regulators of insulin signaling phenomenon. PTP-1B is a strong candidate to target for the therapy of insulin resistance [18, 19].

Astragalus polysaccharide (APS), a component found in the aqueous extract of *Astragalus membranaceus* roots. It belongs to the family, Fabaceae / Papilionaceae , Scientific name, Astragalus membranaceus and the common name is Huang. APS is a *hazel*-colored and water-soluble powder. A study showed that in type-2 diabetic rats, the level of PTP1B after treatment with APS was reduced by 30% [20, 21]. *Astragalus polysaccharide* (APS) has hypoglycemic and insulin sensitizing activity. They do their action by increasing the expression of *'protein-tyrosine phosphatase 1B'* (PTP-1B) in the skeletal muscles experiencing type-2-diabetes. In a study, type-2 diabetic rat model showed decrease response to insulin and IRS-1 phosphorylation decreased by 37% in skeletal muscles and 35% in the liver. After the administration of APS, the rate of insulin induced IRS-1 tyrosine phosphorylation didn't increase in type-2diabetic rats, on contrary in skeletal muscles, phosphorylation is improved [12].

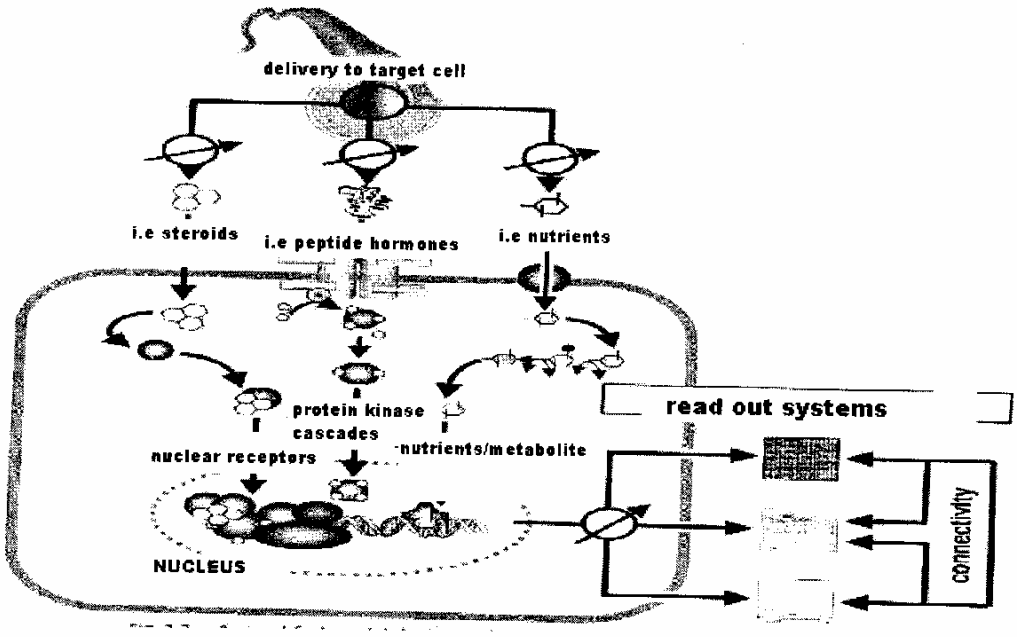

Fig. 2: A simplified model showing the integrative nature of signal processing for transmitting changes in the nutritional environment into the adaptation of the transcriptome, proteome and metabolome of a cell system [6].

A compound urosolic acid (a pentacyclic triterpenoid substance), isolated from the fruit pulp of *Cornus Officinalis*, was found to inhibit the function of PTP1B. Later on, a derivative (UA0713) of Urosolic acid was produced which boosted up IR phosphorylation by 2.6 fold; and raised the insulin-induced phosphorylation of IR-β [22].

2. *Glycogen Synthase Kinase- 3β (GSK-3β)*

Its product is a serine/ threonine kinase protein [23]. GSK-3β is one of the negative regulators of insulin signal transduction in the liver. Inhibition of GSK-3 in the animal model results in improved hepatic peripheral insulin resistance [24]. When insulin is absent, GSK-3 is active and it phosphorylates an enzyme, glycogen synthase. As insulin docks on its receptor, it evokes Akt to perform inhibitory phosphorylation of GSK-3. In this fashion, insulin indirectly activates GS (glycogen synthase) [13]. Glycogen synthase is a master enzyme in the process of glycogen synthesis and its regulation occurs as a result of phosphorylation of sites between Ser641 and Ser653 targeted by GSK3β. GSK-3 also phosphorylates IRS-1 at serine site; as a result it becomes an unfavourable substrate for tyrosine phosphorylation by the insulin receptor so affecting insulin signaling [25]. GSK-3 contributes in the onset of insulin resistance based on its participation in the regulation of glycogen synthesis. Type-2 diabetes is associated with reduction in insulin stimulated GS function and glycogen synthesis [26].

Astragalus polysaccharide (APS), get involved in hepatic transduction by affecting the expression of hepatic '*GSK3β protein*'. It actually causes the under expression of *GSK3β protein*. A study was done with KKAy mice model in which after the treatment with APS, GSK3β phosphorylation at ser9, which is the activated form of this kinase, is stimulated. APS administration leads to the decrease GS phosphorylation at Ser 641 site. On the basis of these results, it can be concluded that APS has positive influence on insulin resistance found in liver [12].

3. *Peroxisome Proliferators Activated Receptor (PPAR)*

It comprises of a family of related receptors. PPARs are divided into 3 isotypes α, β and γ [27]. PPARγ regulates the expression of lipoprotein, fatty acid translocase and fatty acid transport protein [28]. PPARγ can be correlated with insulin signaling on the basis of finding of c-Cbl (Casitas B-lineage lymphoma)-associated protein which is a signaling protein linking with the insulin receptor which could be encoded by a PPAR γ target gene [29]. PPARγ$_2$ is the isoform of PPAR γ which is expressed abundantly in adipose tissues, there this gene monitors the expression of target genes involved in adipocyte differentiation and glucose homeostasis, that is why PPAR γ is a valuable candidate gene for type-2 diabetes and obesity [30]. *'PPAR α'* is widely expressed in muscles, kidneys, intestine and liver, monitoring the expression of genes involved in lipid metabolism [31].

Isohumulones are the bitter compounds extracted from Hop plant *(Humulus lupulush)*. They activate both *PPAR α* and *γ* and improve the insulin sensitivity and lipid metabolism [31]. Farnesol is a usual component of plants and it is normally taken by body *via* diet. It drastically causes the high expression of peroxisome proliferators-activated receptor-α (PPAR- α) and of those genes which are specifically regulated by PPAR-α such as Carnitine palmitoyltransferase 1A, demonstrating that elevated hepatic fatty acid oxidation might decrease triglycerides in serum of rats [32]. *Salacia oblonga* is an Ayurvedic medicine which showed activities against diabetes and obesity. The extracts from its roots correct hyperlipidemia in obese rats which was a genetic model of type-2 diabetes and obesity used in a study. It showed potential of activating PPAR [33]. A study demonstrated that *Pueraria thomsonii* considerably activated PPARα and PPARγ genes. Certain functional compounds from *P. Thomsonii* such as daidzein was extracted by using bioassay-guided fractionation. They all bear PPAR-activating properties [34]. *Lagerstroemia speciosa* is a Southeast Asian tree, also known as Banaba. In a study, water and methanol extracts were used and the functional compounds of Banaba extract are found to be *Ellagitannin lagerstroemin* and penta-*O*-galloyl-glucopyranose (PGG). PGG was determined as a persuasive gallotannin. It provoked drastically the glucose transport in adipocytes. Along with this, PGG also showed anti- adipogenic activity [35]. It induced significant decrease in PPARγ2 mRNA and GLUT-4 protein [36]. There is a large number of herbal compounds which have proved their effect on nuclear receptor signaling for instance, the PPARs. A study used to do work with Labiates herbs, *Sage* and *Rosemary*. From these herbs, two diterpenes were isolated *i.e.* Carnosic acid and Carnosol. Both of these showed their effect by activating PPAR γ gene. Some other herbs also provide as most effective including, *Alisma Plantago, Catharan thus roseus, Acorus calamus, Euphorbia balsamifera, Jatropha curcas, Origanum majorana, Zea mays, Capsicum frutescens* and *Urtica dioica*. So on the basis of this study, it can be concluded that traditional herbs accounts considerably for treating diabetes [37]. *Euonymus alatus* is also known as Gui Jeon Wu, capable of lowering blood glucose level. It increases the sensitivity of tissues to insulin, followed by glucose uptake and normal glucose homeostasis. It augments the amount of PPAR-γ in the fat cells. The genes which are involved in lipolysis and lipogenesis are also acted upon by the ethanol extract of this herb. It causes the downregulation of genes which carried out lipogenesis in the liver *i.e.* SREBP-1a, which permits the normalization of insulin resistance [38].

Different parts of *Pomegranate plant* are used for the treatment of several diseases. But in the Unani and Ayurvedic medication only the flowers of Pomegranate have been assigned as anti-diabetic. The flowers have potential to activate both PPAR-α as well as PPAR-γ. Some of the positive effects are also linked with diabetes associated complications [39, 40].

An analysis used combination diet, containing *Mulberry leaves*, *Korean Red Ginseng* and *Banaba leaf* extracts. This combination diet showed observable improvement in insulin sensitivity. The mechanism behind their effect is to normalize PPAR-mediated lipid metabolism *i.e.* they increase the production of PPAR-α mRNA in liver and PPAR- γ mRNA level in adipose tissues [41].

4. *Phosphoenolpyruvate Carboxykinase* (PEPCK)

Human chromosome number 20 is of great significance with reference to non-insulin dependent diabetes mellitus (NIDDM). Several candidate genes for NIDDM are located on this chromosome. One of

these genes is '*phosphoenolpyruvate carboxykinase gene'*, which is associated with the maturity onset diabetes of the young (MODY) [42]. It is produced abundantly in liver, cortex region of kidney and adipose tissues [43]. It converts oxaloacetate into phosphoenolpyruvate. The production of PEPCK reaches to its peak in all types of diabetes [44].

Researchers used extract of Russian tarragon, *Artemisia dracunculus* in STZ-induced diabetic-rats. They pinpointed that anti-hyperglycemic activity is associated with this extract. This extract causes the under expression of mRNA of *phosphoenolpyruvate carboxykinase* (PEPCK). This therapeutic activity of the herb depends on 2 compounds which are isolated from it that are 6-demethoxycapillarisin and 2', 4'-dihydroxy4-methoxydihydrochalcone [45]. The ethanolic extract of Artemisia dracunculus is known as Tarralin. STZ-diabetic rat models were used in a study in which tarralin was used and it was observed that it lowered the blood glucose. It enhances the insulin effect in peripheral tissues *i.e.* liver, muscle, skeletal muscle or adipose tissues, independently of insulin. Tarralin mimics insulin in the sense that it effects the expression of PEPCK gene [46]. *Trigonella foenum graecum* seed powder was given to diabetic animal models; they showed a significant reduction of glucose concentration in serum. Its administration moderately restored the tainted expression of PEPCK gene. Along with the effect on PEPCK gene, it also improved the changes in the allocation of GLUT4 in the skeletal muscles [47]. *Satureja Khuzestarica Jamzad* is a plant found in Iran, related to the family Lamiacea. A study was conducted to observe the effect of Satureja Khuzestarica essential oil (SKEU). This herb bearing two components, Flavonoids and Carvacrol, showed the effect on PEPCK expression *i.e.* causes the decrease in the PEPCK function [48]. Stevioside is a glycoside present in *Stevia rebaudiana.* In a study, fructose was administered to animal models to see the anti-hyperglycemic effect of Stevioside. It was observed that it decreased the level of glucose. It also down regulates the expression of phosphoenolpyruvate kinase (PEPCK) gene. It showed dual effects *i.e.* stimulation of insulin secretion and improvement in insulin utilization and insulin resistance [49].

5. *Insulin Receptor (INSR)*

One of the major breakthroughs in the genetic study of type-2 diabetes mellitus is the identification of mutation, results in severe insulin resistance. *INSR* is responsible for the availability of specific receptor for insulin binding [50] and subsequent signaling. Insulin receptor has tyrosine kinase activity. When insulin binds to its receptor, it causes conformational changes which provoke the receptor kinase activity through self-phosphorylation of certain tyrosine residues. It phosphorylates other proteins like insulin receptor substrate proteins (IRS). As a result, the pathway of kinase signaling stimulates, *i.e.* PI3K (phosphoinositide 3-kinase and the mitogen- activated protein tyrosine kinase) pathway. Stimulation of PI3K pathway holds an important point in insulin signaling [51].

In a study, dried leaves of *Campsis grandiflora* were used, from them five pentacyclic triterpenoids were extracted *i.e.* CG6 (oleanolic acid), CG7, CG9 (hederagenin acid), CG10 (tormentic acid) and CC11 (myrianthic acid). These pentacyclic triterpenoids has an insulin-sensitizing effect as an IR (insulin receptor), CG7 stimulates the tyrosine phosphorylation of IR. Infact, it provokes and stabilizes the auto phosphorylation of IR, activator [52]. Tannins are the compounds present in Banaba herb extract, polyphenolic in nature. The major ingredients of Tannins are gallotannins also known as Tannic acid (TA). It causes IR (insulin receptor) and Akt phosphorylation, also induces the translocation of GLUT4 which is a glucose transporter molecule [53].

6. *Insulin Receptor Substrate-1and 2 (IRS 1&2)*

IRS-1 is a first intermediate element of the signal transfer pathway initiated by the binding of insulin to its receptor. Whereas IRS-2 is considerably expressed in mouse hematopoietic cells; there it plays an important role in cytokine signaling and mitogenesis. On contrary, IRS-1 is significantly expressed in adipocytes and plays a dominant role in response to insulin signaling [54]. IRS proteins act as immediate substrate for insulin receptor and IGF-1 receptor [14]. IRS-1 and IRS-2 play a critical role in the process of insulin signaling as well as metabolism, growth and survival. The tyrosine phosphorylated IRS-2 behaves as docking protein and allows the complex intracellular signaling molecules to keep in touch with insulin receptor [55]. Various population based studies revealed the fact that Leu 647 to Val polymorphism was found dominantly in type-2 diabetic patients [56]. A study showed that heterozygous IRS-1 and IRS-2 knockout

mice develop severe insulin resistance in liver and muscles [57].

In a study, *Gosha-jinki-gan* (GJG) was used and it was observed that it elevates the concentration of IRS-1 and seizes the tyrosine phosphorylation. *Gosha-jinki-gan* (GJG) administration significantly potentiate the impaired insulin action. The *insulin receptor substrate-1(IRS-1) protein* content was significantly improved by the action of GJG. The mode of action of this herb may be linked with the idea that it improves the anomalous initial step of insulin signaling process [58]. Various studies showed that β-cell malfunctioning is followed by type-2 diabetes. It is coupled with the distortion in the insulin/ IGF-1 signaling flow via IRS-2. A study was carried out to examine the effect of *Rehmanniae radix, Ginseng radix* and *Scutellariae radix,* revealed that these herbs have impact on the expression of multi genes, *i.e.* IRS-2 (insulin receptor substrate-2), PDX-1 (pancreas duodenum homeobox-1) and GK (glucokinase) genes [59].

7. *5'AMP-activated Protein Kinase (AMPK)*

AMPK consists of 3 subunits that together make a functional enzyme. It contributes in the stabilization of cellular energy homeostasis. It is found to be present in liver, brain and skeletal muscles. The ultimate consequences of its stimulation and activation include, inhibition of cholesterol synthesis, lipogenesis (conversion of carbohydrates into fat), initiation of fatty acid oxidation and ketogenesis in liver, inhibition of adipocyte lipolysis (the process of degradation of fats which are stored in fat cells, then release into blood stream), initiation of fatty acid oxidation in skeletal muscle and glucose uptake by muscles, lipogenesis and alteration of insulin efflux by pancreatic cells. So it can be concluded that it is the very skilled and efficient enzyme, monitoring several processes which are going on in a cell such as cellular uptake of glucose [60, 61].

Berberine is an isoquinolone alkaloid isolated from *Cortex phellodendri (huang bai)* and *Rhizoma copidis* plants. Berberine has an effect on *an enzyme* which is activated in muscle and liver that is involved in improving the sensitivity of the tissue to insulin. Infact, Berberine causes the increase in AMPK *i.e. Activated protein kinase.* Investigators used rodent model to analyze the effect of Berberine on insulin resistance and it was proved that Berberine caused improvement in the state of insulin resistance [60, 62]. Cryptotanshinone is the compound pooled from the roots of *Salvia militorrhiza.* It is excessively used in Asia as a drug. It provokes AMPK, followed by enhance translocation of GLUT4 to the plasma membrane and glucose uptake. Along with this it also causes the increase expression of GLUT1. AMPK may be a significant target candidate for the treatment of diabetes and obesity [63].

8. *Progastricsin (PGC1-α and PGC1 –β)*

It encodes for proteins of mitochondria and cell structures. They play a role in energy metabolism. In diabetics, their gene expression is low resulting in reduced activity of a number of genes involved in the metabolism of fats and carbohydrates. The reduced activity of *PGC1-α* and *PGC1-β* may govern the insulin resistance [64]. PGC1 is also involved in gluconeogenesis and glucose uptake. [65].

A study used ethanol or water soluble extract of *Syzgium aromaticum* to observe its effect on hepatocytes and showed that it mimics insulin, down regulates the expression of phosphoenol-pyruvate carboxykinase (PEPCK) gene (takes control on hepatic gluconeogenesis). It has also an effect on PCG-1 gene *i.e.* it reduces the expression of PCG-1 gene, suggesting a mechanism for low expression of PEPCK gene [66].

9. *Lipoprotein Lipase (LPL)*

LPL plays a significant role in the metabolism of triglycerides [67]. Panax ginseng roots are used for curing of type-2 diabetes. Ginsenosides, are the functional components of Panax ginseng. It is a collection of steroidal saponins. Various regions of the Ginseng plant such as leaf, root and berry, bears ginsenosides compounds. A study was carried out with obese insulin resistant mouse model; the obesity was due to the presence of mutation in the obese gene, encodes Leptin. Its administration leads to differential expression of genes engaged in muscles and lipid associated metabolic processes. Phospholipase A2 group VII, is one of the lipid catabolic genes, was increased. On contrary, one of the lipid synthesis genes, fatty acid synthase was reduced. Ginseng also significantly triggered the reduction in the expression of Lipoprotein lipase

(LPL) which is highly expressed in patients experiencing diabetes. The mechanism, through which this herb acts, is still to be known [68, 69]. Mulberry leaves, Korean Red Ginseng and Banaba leaf extracts also exert their effect on LPL enzyme. They elevated the LPL mRNA level in adipose tissues and liver. Mulberry and Banaba leaves water extracts caused increase by 5.1 folds and Korean Red Ginseng by 9.3 folds [41].

10. *Adipocyte Complement Related Protein (ACRP)*

Adipocytes produce certain substances such as a protein known *as Acrp30* [70]. Insulin resistance is generally coupled with obesity. In obese people, if the expression of this gene is reduced then it becomes partially responsible for obesity-associated insulin resistance as it is an insulin sensitizer in liver. Investigators have observed a decreased *Acrp30* level in insulin resistance state [71, 72].

Acrp30 is also known as *Adiponectin.* It is a protein found in plasma, as mentioned earlier that it is synthesized and secreted from adipose tissues in high concentration. [73].

The processed leaves of *Hydrangea macrophylla var. thunbergii (Hydrangeae Dulcis Folium)* contain two, 3-phenyldihydroisocomarins (hydrangenol and phyllodulcin), a 3-phenylisocoumarin (thunberginol A) and a stilbene (hydrangeaic acid). Hydragenol is a major component which extensively increase the concentration of PPARγ2, adiponectin and GLUT4 thereby enhance the adipogenesis of 3T3L1 cells [74].

11. *Glucose 6-Phosphatase*

Glucose 6-phosphatase carries out typical role in the utilization of glucose, gluconeogenesis and glycogenolysis [75]. *Zizyphus* is among the dominant herbs used in Egyptian folk medicine. It has been the remedy of many diseases. It has great capability of reducing glucose level of serum of diabetic rats. It also down regulates the activation of glucose 6-phosphatase, thus affecting the homeostasis of glucose [76, 77].

12. *Alpha Glucosidase*

Alpha Glucosidase is an enzyme found on the intestinal brush border. It acts on carbohydrates present in the food; *i.e.* starch and sucrose and break them into glucose and fructose. They are absorbed in the blood and elevate the blood glucose level. The products which lowers the production of this enzyme, may indirectly affect the absorption of carbohydrates [78].

Sangzhi (Ramuslus mori) is one of these products and is the member of the family Moracea. A study used aqueous extract of Sangzhi on α-glucosidase in the small intestine of rats and mice and was noted that this herb has a great potential to destroy the α- glucosidase activity [78].

13. *Glucose Transporter-4 (GLUT-4)*

To reduce the amount of glucose in the blood, its entrance inside the cell is necessary. For this purpose, GLUT transporter assists glucose. Skeletal muscles form various types of GLUT, but the GLUT4 transporter is the dominant one [79]. GLUT4 trapped in vesicles present within the muscle cells and adipocytes. Whenever, there is a rise in the insulin concentration, GLUT4 turn on, shifts to the plasma membrane and carry glucose inside the cell [80].

Carsolic acid is found in the leaves of *Lagerstroemia speciosa.* An experiment suggested its negative effect on blood glucose level. In Carsolic acid- treated mice the translocation of GLUT4 to the plasma membrane was dominantly increased so it is concluded that it affects the GLUT4 translocation, provokes glucose uptake and ultimately reduction in hyperglycemia [81, 82].

14. *Glucose Transporter-2 (GLUT-2)*

This gene is highly expressed in pancreatic β-cells and hepatocytes, regulating the glucose input and output so called Glucose transporter [83]. The expression of GLUT2 gene found to be greatly reduced in the islets from diabetic patients. [84].

To observe the effect of rhizomes of *Polygonatum officinale*, an investigation was carried out with Wistar fatty rats this herb showed its anti-diabetic activity by down regulating GLUT2 expression in the liver. Some studies also suggested that the activity of *Polygonatum officinale* is coupled with the increase in insulin activity [85].

15. *Glucokinase*

It converts glucose to glucose 6-phosphate and found in the liver, pancreas, gut and brain. It governs the regulation of carbohydrate metabolism and act as a glucose sensor, stimulating alterations in metabolism or cellular activity in response to increase or decrease levels of glucose [86]. Glucokinase is an important stimulator of glucose utilization. Its activity decreases in case of diabetes. When liver glucokinase level falls down, it leads to the release of glucose (synthesized through the process of gluconeogenesis) [87].

Ethanol extracts of variants of *Artemisia princes Pampanini, i.e.* Sajabalssuk (SB) and Sajuarissuk (SS) were used in a study. The results showed anti-diabetic activity by normalizing the level of glucokinase in the liver [87].

16. *Glycogen Synthase*

Excessive glucose stores in the form of glycogen inside the body and provides energy on demand. The concentration of glycogen is firmly governed by glycogen synthase and glycogen phosphorylase. Glycogen synthase engages in the synthesis of glycogen [88].

Aqueous extract of Cinnamon has a tremendous ability to be a successful candidate for the treatment of diabetes. It activates the enzyme glycogen synthase followed by the increase in glycogen synthesis. It activates insulin receptor kinase, enhances the phosphorylation and inhibits the dephosphorylation of insulin receptor. This ultimately results in more and more glucose uptake and improved insulin resistance [89].

The main idea behind the progress of unraveling of new drugs is to understand the variations caused by these drugs. The identification of genetic factors behind the disease and alterations in response to drugs could permit the physicians to pinpoint the appropriate way of treatment. It has been proved that genes and nutrition could talk with each other. There are strong evidences revealing that the modifications in the nutritional substances could alter the activities and expression pattern of certain genes [6]. No doubt, many people throughout the world using several herbs as medicines. Infact, there is no specific hypothesis behind the mechanism of action of many herbs which may become helpful to replace the conventional drugs with these herbs. Although there is a lot of research on exploring the potential therapeutic herbs but there is a minuscule number of studies which determine the mechanism of action of new potential herbs [90].

Conclusion

It is necessary to advent the dissection of molecular pathways which are involved in insulin signaling, so that the diabetogenes become identifiable. These culprit genes could be used as therapeutic targets and this would tackle with the discovery of more advanced and efficient new pharmacological agents that could act on genetic level [91]. The current therapeutic approaches for diabetes are insufficient, unsatisfactory to deal with as the prevalence rate is increasing. That's why; there is an urgent need to sort out the new therapeutic options for this scourge disease.

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