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HERBAL INSULIN SENSITIZERS AS AN ALTERNATIVE IN DISEASES CAUSED BY INSULIN RESISTANCE: AN EVIDENCE BASED REVIEW

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ABSTRACT
Insulin resistance recognized recently as a strong predictor of diseases in adults, and has become the leading element of the metabolic syndrome and renewed as a focus of research. It affects about one-fourth of the population. Obesity and diabetes reach epidemic proportions in the developed world; hence the role of insulin resistance and its consequences are gaining prominence. Insulin resistance pathologically grows through many interactions of genotype, lifestyle change mainly sedentary life and over eating. Physiologically, many circulating factors regulate insulin sensitivity in target tissue such as adipokines, plasma lipid, circulating hormones and their signaling pathways. Insulin resistance is a powerful independent analyst of wide range of serious illnesses, including stroke, type II diabetes, cardiovascular diseases, hypertension and even cancer. The complications associated with insulin resistance, includes particularly the development of diabetes, atherosclerosis, polycystic ovarian syndrome (PCOS) etc, which are potentially fatal in patient care; consequently, the detection and treatment of insulin resistance is rising appropriately. In last decade, many trials has been carried out on herbal drugs which act as insulin sensitizers, effective in improving the insulin resistance in PCOS and other metabolic diseases.

KEYWORDS: Insulin Resistance, Metabolic Diseases, Insulin Sensitizer, Herbal drugs, Unani Medicine.

INTRODUCTION
Insulin resistance is a condition in which, higher than normal insulin concentrations are needed to achieve normal metabolic responses or normal insulin concentrations fail to achieve a normal metabolic response. It is recently recognized as a strong predictor of disease in adults, and has become the leading element of metabolic syndrome and renewed as a focus of research.[1] It affects about one-fourth of the population, one in seven adults have impaired glucose tolerance (IGT) and 50% of them develop diabetes mellitus within 10 years. Gerald Reaven, was the first scientist to name the cluster of hypertension, central or android obesity, and dyslipidaemia as syndrome X in 1988 to highlight the co-occurrence of risk factors for coronary heart disease and type II diabetes mellitus.[2] PCOD is also one of the heterogeneous disorder, with multiple reproductive, cosmetic and metabolic complexities[3] and insulin resistance is the main cause of it.[4]

The condition of insulin resistance exists when insulin levels are higher than expected values relative to the level of glucose. It can be defined as a reduced responsiveness of a target cell or a whole organism to the insulin concentration to which it is exposed,[1] and clinically as inability of known quality of exogenous or endogenous insulin to increase glucose uptake and use in an affected individual as much as it does in normal person.[5] Insulin resistance is a powerful independent analyst of a wide range of serious illnesses, including stroke, type II diabetes, cardiovascular disease, hypertension, and even cancer.[1]

Treatment considerations for patients with insulin resistance must begin by differentiating between efforts focused on improving insulin sensitivity itself and those aimed at treatment of any of the specific manifestations of the insulin resistant. For insulin resistance, both adiposity and level of physical activity are powerful modulators of insulin-mediated glucose disposal. More importantly, in contrast to the other factors that affect insulin action, they are modifiable by safe, straight forward lifestyle changes. Thus, weight loss of 5-10% of body weight and low calorie diet in overweight/obese individuals, will significantly enhance insulin sensitivity, lower ambient plasma insulin concentrations, and improve the manifestations of insulin resistance. There is difficulty in changing lifestyle, and the probable limits of

its efficacy in many individuals, it could be argued that treatment of the insulin resistance would be a drug that could significantly enhance insulin sensitivity, as well as the other manifestations of the insulin resistance.[6] Administration of exogenous insulin does not always match with the cell demands and oral anti-diabetic agents have its own limitations; complete glucose homeostasis may not be established with demand, even chances for drug resistance to develop with long term usage. Hence, the ailing patients search for alternate option which is safe, effective, less expensive and free from side effects such as herbal insulin sensitizer.

In Unani system of medicine, many single and compound poly-herbal formulations having synergistic effects are available and widely used in its management. Although, Unani formulations have been used as herbal remedies for centuries, but only limited research was conducted to evaluate the therapeutic benefits of these herbs. These, herbal remedies may have fewer side-effects but act as natural alternative or as an adjunct therapy to other interventions in the management of diseases caused by insulin resistance.

MATERIAL AND METHODS

The data information related to insulin resistance and medicinal plants were collected from the available guidelines, journals on insulin resistance, classical Unani literature, and various pharmacological studies which proved several plants as anti-diabetic and insulin sensitizer. A database search was carried out using the databases PubMed, Medline, Research Gate, and Google Scholar. In some studies, only abstracts were evaluated due to inability to access the full articles.

Insulin resistance: Insulin is a hormone which promotes anabolism that balances individual caloric need and intake with disbursement. Basically it increases breakdown of excess carbohydrate and protein in the forms of lipids and inhibits the opposite.[7] Insulin resistance may be defined as a condition in which, higher than normal insulin concentrations are needed to achieve normal metabolic responses or normal insulin concentrations fail to achieve a normal metabolic response.[8] It is mainly the impairment in the function of insulin targets cells such as hepatocytes, adipocytes and musculoskeletal cells to react to the insulin action.[7] Insulin resistance is not a disease in itself, but rather a physiological abnormality that increases the risk of developing one or more of the abnormalities.[6]

Mechanism of Insulin resistance: Insulin resistance pathologically grows through many interactions of genotype, lifestyle change mainly sedentary life and over eating. Physiologically, many circulating factors regulate insulin sensitivity in target tissue such as adipokines, plasma lipid, circulating hormones and their signaling pathways. There is neuroendocrine axis involving adipose tissue with brain and gut, which regulate insulin metabolism by adjusting insulin sensitivity in target tissues.[7] The biological action of insulin depends on a cascade of events following the interaction of insulin with its specific receptor. Insulin binding with receptor promotes the auto phosphorylation of the receptor and subsequent tyrosine phosphorylation of IRS proteins (IRS-1 and IRS-2), which initiates a cascade of events finally leading to translocation of a specific transporterie; Glucose transporter-4 from its intracellular pool to the cell membrane. Glucose transporter-4 facilitates glucose transport along the concentration gradient from the extracellular space into the cytoplasm. In this sequence of events, the mechanisms responsible for insulin resistance may involve either insulin binding or IRS proteins, or finally Glucose transporter-4. Abnormalities of cellular glucose uptake appear to result from defects in intracellular signaling. Several factors such as hyperinsulinemia, hyperglycemia, tumor necrosis factor, free fatty acids, ceramide, and transcription factors (e.g., nuclear factor-B) have been implicated in altering insulin signaling in patients. The most likely mechanism of insulin resistance within the muscle cell is cytokine-induced serine rather than tyrosine phosphylation of IRS-1.

In most cases, insulin resistance may be regarded as an energy sparing mechanism favoring survival during limited food availability or increased energy requirement. Insulin resistance and subsequent hyperinsulinemia promote energy accumulation as fat, and reduces energy expenditure. Trauma, sepsis, surgical stress, and chronic diseases cause insulin resistance, as do physiological states (e.g., pregnancy, puberty, physical inactivity, and aging). Over eating and obesity, particularly visceral obesity is the most important environmental causes of insulin resistance. The final balance is the result of the relative contribution of all these factors. Whatever the cause, insulin resistance in concert with hyperinsulinemia favors an increase in fat mass, increased lipolysis, and elevated levels of free fatty acids, further reducing insulin signaling in a dose-dependent manner and increasing both hepatic glucose and lipid production (lipotoxicity).[8]

Diseases associated with Insulin Resistance

- **Type II Diabetes:** 92% people with type II diabetes have insulin resistance. It has been suggested that insulin resistance develops 20-30 years before the onset of type II diabetes.[2] A progressive inability of the β-cells to compensate for the prevailing insulin resistance by sufficient hyperinsulinemia, heralds the clinical onset of this disorder.
- **Metabolic Syndrome:** In 1988 it was proposed that individuals with glucose intolerance, elevated triglycerides, low HDL cholesterol and essential hypertension were at increased risk of cardiovascular diseases. It was initially referred to as Syndrome X, but later as the Metabolic Syndrome.
- **Dyslipidaemia:** The lipid abnormalities associated with insulin resistance affect all lipid fractions. They are characterized by elevated fasting triglyceride

levels, elevated postprandial triglyceride rich remnant lipoproteins, low HDL cholesterol, and small dense LDL particles. This pattern correlates strongly with cardiovascular risk.

- **Hypertension:** Essential hypertension has been associated with insulin resistance in up to 50% of cases. There is a strong correlation of blood pressure with body weight. Proposed mechanisms have included increase adrenal sodium retention and increased sympathetic nervous system activity from compensatory hyperinsulinemia. However, endothelial dysfunction from resistance to insulin mediated nitric oxide formation is thought to be of clearer significance.
- **Polycystic ovarian syndrome (PCOS):** Convincing evidence links insulin resistance to the pathogenesis of this syndrome, the most common endocrine disorder of premenopausal women. The ovarian dysfunction relates to the effects of compensatory hyperinsulinemia increasing pituitary luteinizing hormone secretion and androgen production by the theca cells of the ovary. Aromatization of androgens in the setting of obesity increases production of estrogens, further impairing the function of the HPG- axis. Hyperinsulinemia also suppresses sex hormone binding globulin production by the liver, further elevating free androgens, which in turn aggravates insulin resistance.[9,10]
- **Non-alcoholic Fatty Liver Disease (NAFLD):** Its incidence is increasing among different countries with a reported prevalence rates of 10-24% of general population; however amongst obese individuals, 50-75% is affected. NAFLD may progress to non-alcoholic steatohepatosis, fibrosis or cirrhosis, representing increasing liver damage.
- **Cancer:** Insulin resistance with compensatory hyperinsulinemia has been implicated in the etiology of certain cancers, including colon, endometrial, possibly pancreatic and renal-cell cancers and breast cancer.[9]

Pharmacotherapy for Insulin Resistance

The complications associated with insulin resistance, particularly the development of diabetes and atherosclerosis which are potentially deadly, for patient care the detection and treatment of insulin resistance is increasing rapidly.[11] In last decade, many trials have been held showing the efficacy of insulin sensitizers, mainly biguanides and thiazolidinediones in improving the insulin resistance particularly in PCOS, Type II Diabetes and other diseases.[12]

Biguanides (Metformin): Metformin has been available since 1950s. Its historic roots and origin can be traced back to the guanidine-rich *Galega officinalis* (goat's rue or French lilac) which has traditionally been used in Europe to treat diabetes.[13] Metformin has a variety of clinical actions that extend beyond just the glucose lowering effects such as weight reduction, improving lipid profile and vascular effects. The molecular mechanisms of action have not yet been clearly established. However, it is thought that insulin sensitivity is improved and mediated via modification of post-receptor signaling in the insulin pathway. Hepatic sensitivity to insulin is increased, thereby reducing gluconeogenesis as well as glycogenolysis, which contribute to the postprandial plasma glucose lowering effects. Biguanides are generally considered the drugs of choice in obese type II diabetics. Metformin can be used in combination with any other class of oral anti-diabetic drug or with insulin. It is also used in the treatment of PCOS to improve insulin sensitivity and to lower circulating androgen levels. It improves ovulation and menstrual cyclicity as well. The FDA of USA still considers this an unlicensed indication of this drug in the absence of diabetes. The American Association of Clinical Endocrinologists recommends that metformin be considered as the initial intervention in most women with PCOS, particularly those who are obese and overweight.[11-13]

Contra indications: It should be avoided in the presence of underlying impairment of renal function, conditions predisposing to hypoxia or reduced perfusion because of the increased risk of lactic acidosis, liver disease, alcohol abuse and a history of a previous episode of lactic acidosis.

Side effects: The most common adverse effects are diarrhea, nausea, vomiting, abdominal bloating, abdominal cramping or pain, flatulence, and anorexia. Also headache, agitation, dizziness, and tiredness have been observed. The safety of long-term use of metformin in young women is still unknown.[14] However; the incidence of metformin induced lactic acidosis is extremely rare, with only 0.03 cases per 1000 patient per year reported in the literature. Vitamin B-12 deficiencies owing to decreased GIT absorption can occur.

Thiazolidinediones-TZDs (Pioglitazone, Rosiglitazone, Troglitazone)

Thiazolidinediones represents a novel class of drugs that emerged in 1997.[13] It has been identified to act through improvement of insulin sensitivity and decreasing hyperinsulinaemia.[15] The overall effect of these drugs results from stimulation of a nuclear Peroxisome proliferator-activated receptor (PPAR-γ) that regulates the transcription of genes culminating in an increase in insulin sensitivity. This class of drug can be used as monotherapy in obese as well as non-obese patients who have failed other conservative measures. TZDs can be used in combination with metformin and sulphonylureas. The concurrent use of these drugs in combination with insulin is not recommended as weight gain can be aggravated. In some studies, TZDs have demonstrated a beneficial effect on ovulation in patients with PCOS.

Contraindications: The use of TZDs is contraindicated in acute liver disease owing to the increased risk of hepatotoxicity. In patients with New York Heart

Association (NYHA) class III or IV heart failure it is not recommended in view of the side-effects of fluid retention and weight gain.

Side effects: Troglitazone, was withdrawn in 2000 following reports of fatal hepatotoxicity, and the future of rosiglitazone currently hangs in the balance, owing to a possible increased risk of myocardial infarction and cardiovascular related deaths. Clinicaltrial databases in 2007, reported an increaseof fracture risk in females treated with pioglitazone.[13]

Herbal insulin sensitizers

Mechanism of improving insulin sensitivity with herbs

The main phytochemicals groups improving insulin sensitivity are flavonoids, terpenoids, glycosides and oligosaccharides. These medicinal plants with beneficial action on insulin sensitivity act via various cellular and metabolic targets. The principle sites targeted by these medicinal plants are the peripheral tissues (muscles and adipocytes) or the liver.

In these organs, the medicinal plants have been demonstrated to stimulate.

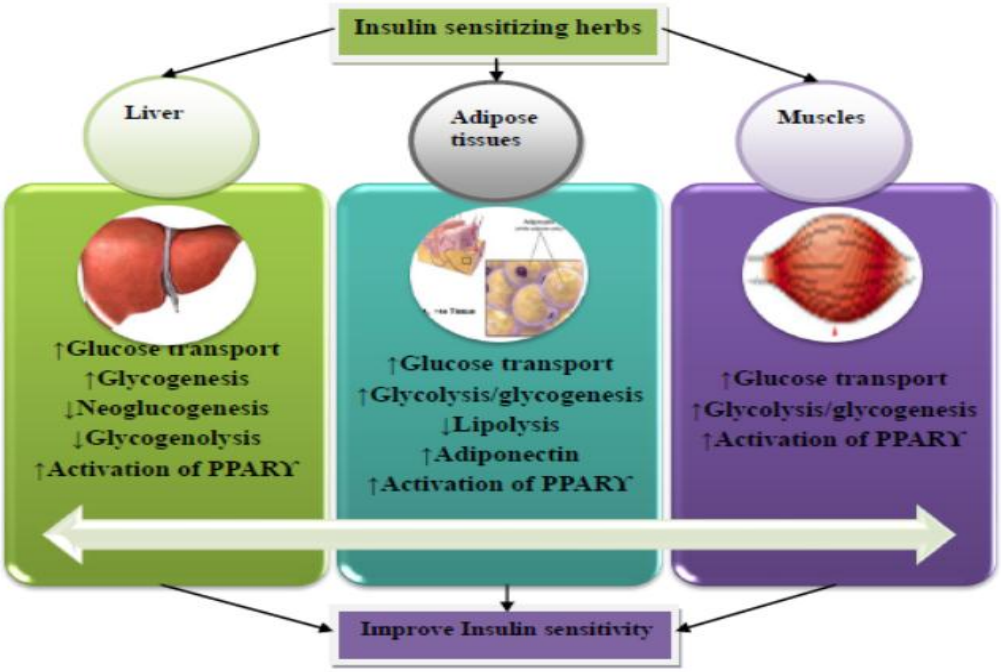

Fig. No-1: Mechanism of Insulin sensitizing Herbs.[15]

Table No-1: Unani drugs proved as insulin sensitizers on experimental studies.

S.No	Unani Drugs	Action & Uses	Active constituents	Effect demonstrated in studies	Authors
1. 1	*Elwa*(*Aloe vera* Linn.)/ *Aloe barbadensis* Miller) 	Hypocholesterolaemic, antidiabetic, antiinflammatory, immune modulator, antioxidant, anticancer [16,17]	Anthraquinones (barbaloin/Aloin), phytosterols[16,17]	-processed Aloe gel prevents the progression of NIDDM related symptoms and significantly decreases plasma insulin level in high-fat diet-fed mice[18]	Kim K et al Kim K et al (2009)[18]
2.	*Asgand*- Indian ginseng (*Withania somnifera* Linn.) 	Hypoglycemic, antiinflammatory, Immuno modulatory, antitumour, antioxidant, hepatoprotective antiageing, anticonvulsant[19]	Alkaloids (withanine, withananine, pseudo-withanine, somnine, somniferine, somniferinine[17,20]	-decreases blood glucose level, prevent hyperinsulinemia & improves glucose tolerance in NIDDM rats by improving insulin sensitivity[21]	Anwer T et al (2007)[21]
3.	Zanjabeel- Ginger (*Zingiber officinale*) 	Antiemetic, antiflatulent, hypocholesterolaemic, antiinflammatory, antispasmodic, expectorant, circulatory stimulant, diaphoretic[20]	Monoterpenes (geranial, neral), Sesquiterpenes (β-sesquiphellandrene, β-bisabolene, ar-curcumene, alphazingiberene)[17] Essential oil, gingerol, shogaol[17,20]	-ginger root supplementation significantly lowers blood glucose and HbA1c levels[22]	Daily JW et al (2015)[22]
4.	Karela *(Momordica charantia)* 	Hypoglycaemic stomachic, emetic, laxative, antibilious, Anthelmintic[17]	Non-bitter & bitter momordicosides, 5-hydroxytryptamine, charantindiosgenin, cholesterol, lanosterol and beta-sitosterol.[17] Glycosides (cucurbitacin)[17,23] Methionine, p-insulin.[23]	-stimulation of peripheral and skeletal muscles glucose utilization, -inhibition of intestinal glucose uptake, -inhibition of adipocyte differentiation, -suppression of key gluconeogenic enzymes, preservation of β-cells,[24] - improve glucose intolerance.[25]	Joseph B et al (2013)[24] Alam MA et al (2015)[25]
5.	Zafran- Saffron *(Crocus sativus* Linn.)	Sedative, antispasmodic expectorant, stomachic,	volatile oil (terpenes, terpene alcohols, esters) crocin,	-act as insulin sensitizer by increasing glucose metabolism	Elgazar AF et al (2015)[26]

		diaphoretic, emmenagogue, nervine tonic, antiatherosclerotic[17]	picrocrocin, crocetin, carotenoids, riboflavin, thiamine[17]	and peripheral glucose uptake[26,27]	Kang C et al (2012) [27]
6.	Kalonji- Black cumin *(Nigella sativa)* 	Stimulant, carminative, diuretic, lactiferous, emmenagogue[17]	Essential oil (nigellone, quinone), fixed oil (carvone), resin, saponin and tannin[17,20] Beta-sitosterol[17]	-amplifies glucose-stimulated insulin secretion, -accelerates β-cell proliferation -increases peripheral glucose uptake by muscle cells[28]	Sultana S et al (2015)[28]
7.	Darchini- Cinnamon *(Cinnamomum zeylanicum* Linn.) 	Antidiabetic, carminative, astringent, antispasmodic, expectorant, haemostatic, antiseptic[17]\	Essential oil,, tannin and mucilage[20]	-improves the disorders caused by PCOS to a significant extent[29,30] including amelioration of hyperinsulinemia, dyslipidemia & hyperandrogenism[29]	Sangal A (2011)[29] Heibashy et al (2013)[30]
8.	Methi- Fenugreek *(Trigonella foenum-graecum)* 	Hypoglycaemic, secretolytic, hyperaemic, antiseptic, demulcent[17]	Alkaloids (trigonelline, gentianine, carpaine), saponins (sapogenins, diosgenin), flavonoids (vitexin), glycosides, esters[17]	-Fenugreek polyphenole extract and quercetin improves the insulin sensitivity and thereby promotes the cellular actions of insulin in rat model[31]	Kannappan S et al (2009)[31]
9.	Neem- Margosa *(Azadirachta indica)* 	Hypoglycemic, antiinflammatory, insecticidal, anthelmintic, antifertility, antimicrobial, antifungal, antiviral, antipyretic, antimalarial, spermicidal[17]	Tetra-nor-triterpenoids[17] β-sitosterol.	-Meliacinolin inhibits α-glucosidase & α-amylase enzymes which lowers the levels of post-prandial hyperglycaemia and prevent the absorption of carbohydrates.[32]	Perez- GRM et al (2012)[32]
10.	Gurmar- Gymnema *(Gymnasyl vestre)*	Antidiabetic, diuretic, antihyperlipidemic, emetic,	Gymnemagenin, Gymnemic acids[17]	-antidiabetic action is due to its combined effect of insulin	Bhansali S et al (2013)[33]

		antibilious, expectorant, astringent, stomachic, Gastroprotective[17]		sensitizing, and peripheral utilization of glucose by increasing cell permeability[33,34]	Persaud SJ et al (1999)[34]
11.	Zaitoon- Olive (*Oleaeuropaea* L.) 	Hypotensive, astringent, diuretic, demulcent[17]	Iridoidmonoterpenes (oleuropein, oleuroside), triterpenes (oleanolic, maslinic acids), flavonoids (luteolin&apigenine derivatives)[17]	-improve insulin sensitivity and pancreatic β-cell secretory activity in overweight middle-aged men[35,36] -ability to restrain the oxidative stress[36]	de Bock M et al (2013)[35] Hashmi MA et al (2015)[36]
12.	Soya bean (*Glycine Max*) 	Hypocholesterolaemic, hypoglycaemic, anticancer[17]	Glycinin, betaconglycinin, saponins, isoflavones[17]	-improvement in glucose metabolism and better glucose tolerance on OGTT and insulin tolerance test (ITT) in streptozotocin-nicotinamide induced type-2 diabetis in rat model.[37] -reduces hyperinsulinemia by stimulating insulin secretion to a lower extent[38]	Bhattamisra SK et al (2013)[37] Tripathi MK et al (2013)[38]
13.	Haldi- Turmeric (*Curcuma longa*) 	Anti-inflammatory, cholagogue, hepatoprotective, antioxidant, stomachic, carminative[17]	Alkaloids (curcumin), volatile oil (turmerones)[17]	-Curcumin increases insulin mediated glucose uptake by 30-50% in patients with type-2 diabetes mellitus[39]	Santosh kumar J et al (2013)[39]
14.	Gilo- Tinospora (*Tinospora cardifolia*) 	Hypoglycaemic, antipyretic, hepatoprotective, spasmolytic, antiinflammatory, antirheumatic[17]	Alkaloidal (berberine), bitter principles (columbin, chasmanthin, palmarin, tinosporon, tinosporic acid, tinosporol)[17,20]	-decreases blood glucose level as well as serum lipids[40]	Sinha K et al (2004)[40]
15.	Tukhme Hayat (*Withania coagulans*)	Sedative, CNS depressant, diuretic, antibilious, emetic,	Withanolides, withacoagin, coagulan, withasomidienone[17]	-Shows modulation of insulin levels and related enzyme	Shukla K et al (2012)[41]

		antiasthmatic, emmenogogue, antiinflammatory, antibacterial[17]		activities.[41] - reduces the levels of blood glucose, HbA1c, and insulin in T2DM rats.[42]	Bharti SK et al (2012)[42]
16.	Khurfa- Purslane (*Portulacaoleracea*) 	Hypogycaemic, refrigerant, mild spasmodic, diuretic, antiscorbutic, antidysenteric[17]	Organic acid, flavonoids, alkaloids, terpeneansteroid, hydroxybenzene, saponin, polysaccharide[43]	-reduction in fasting plasma glucose, serum triglyceride levels - alleviate the blood glucose -improve the abnormal glucose metabolism[44] -increase insulin secretion by restoring the impaired pancreas β-cells in alloxan-induced diabetic rats[43]	Gao D et al (1997)[43] Esmaillzadeh A et al (2015)[48]
17.	Sumaq- Sumac (*Rhuscoriaria*) 	astringent, styptic,[17]	Limonene, nonanal and dec-2 (Z)-enal, betacaryophyllene, patchoulane.[17]	-significant decrease in insulin, HOMA-IR, High sensitive-CRP[45] - decrease in fasting serum insulin levels[46]	Rahideh ST et al (2014)[45] Ardakani MRF et al (2017)[46]
18.	Khulanjan- Galangal (*Alpiniagalanga*) 	Antiinflammatory, antiulcer, antispasmodic[17]	Methyl cinnamate, cineole and *d*-pinene[17]	-controlling blood glucose level and improve lipid profile due to stimulatory effect of methanolic extracts on the regenerating β cells and also on the surviving β-cells.[47]	Verma RK et al (2015)[47]
19.	Kanduri (*Coccinia*  *indica*)	Carminative, antipyretic, Galactagogue[17]	beta-amyrin, lupeol, cucurbitacin-B[17]	-Pre-administration of aqueous extract of *Coccinia indica* leaves significantly prevented the elevation of insulin, glucose and lipid levels in dexamethasone induced insulin resistant rats.[48]	Koyagura N et al (2017)[48]
20.	TukhmeHammaz- Sorrel	Astringent, stomachic,	Anthraquinoneglucosides,	-significantly decreases the	Reddy NS

	(*Rumexvasicarius*) 	antiscorbutic, Diuretic, antidysenteric[17]	emodin, chrysophanol, oxalate, minerals[17]	level of blood glucose in streptozotocin induced rats. -protect pancreatic β-cells from streptozotocin induced damage[49]	et al (2017)[49]
21.	Sandal- Sandal wood (*Santalum album*) 	Diaphoretic, antiseptic diuretic, expectorant, bacteriostatic[17]	Triterpene, α & β-santalol, sesquiterpene, hydrocarbons[17]	*Santalum album* pet ether fraction in streptozotocin-induced diabetic rats reduces blood glucose level[50]	Kulkarni CR et al (2011)[50]
22.	Aqaqia/ Samagh Arabi- Babul (*Acacia arabica*) 	Hypoglycaemic, demulcent, antiinflammatory[17]	Galactose, *l*-arabinose, *l*-rhamnose, aldobiouronic acids, arabinobioses[17]	-significant decrease in levels of serum glucose, insulin resistance in streptozotocin-induced diabetic rats[51]	Hegazy GA et al (2013)[51]
23.	Anar- Pomegranate (*Punica granatum*) 	Hypoglycaemic, astringent, stomachic, digestive[17]	Ellagitannin, punicalagin, punicalin, ellagicacid[17]	-Pomegranate juice and seed had slight reduction in plasma glucose conc. and no impact on plasma insulin -restoration effect on the damaged islets of Langerhans in experimental rats[52]	Rouhi SZT et al (2017)[52]
24.	Muqil- Mukul (*Commiphoramukul*)	Hypocholesteremic, hypoglycemic, antiinflammatory, antithrombotic[17]	Essential oil, Steroids (gugglsterones Z and E, guggulsterols I-V, diterpenoids)[17,20]	-enhancing glucose utilization and decreasing hepatic glucose production[53] -regeneration of β-cells and protect pancreatic islets against the cytotoxic effects of STZ.[54]	Ramesh B et al (2012)[53] Ramesh B et al (2014)[54]

					
25.	Mur- Myrrha (*Commiphora myrrha*) 	Hyporglycemic, hypocholesteremic,[55] antiinflammatory, emmenogogue, expectorant[17,56]	Terpenoids, steroids, flavonoids, lignans, myrrhic acid, gum, volatile oil[17,55]	-significant decrease in blood glucose level in diabetic rats with different histological changes in cells of islets of Langerhans.[57]	Helal EGE et al (2005)[57]

CONCLUSION

Hyperinsulinemia in the basal state of any origin produces widespread insulin resistance. All tissues that have insulin receptor pathways will be affected, including the pancreatic cell, and possibly the brain. Defective insulin signaling at the cell impairs glucose-stimulated insulin release. At steady state, basal hyperinsulinemia generates and sustains insulin resistance, irrespective of where the pathology started. Many chemical agents are available to control and treat hyperinsulinemia, but total recovery has not been reported till date. In addition, most of the oral hypoglycemic drugs are costly and have a lot of side-effects. Alternative to these synthetic agents, plants provide a potential source of hypoglycaemic drugs and are widely used in several traditional systems of medicine to prevent diabetes. During the past few years; many phytoconstituents responsible for antidiabetic effects have been isolated from hypoglycaemic plants. Several medicinal plants had beneficial effects on insulin sensitivity; however, there is still insufficient evidence to draw definitive conclusion about their efficacy in the treatment of diabetic patients through improvement of insulin sensitivity. Hence, advanced studies are needed to identify the relationship between the active principles and bioactivity in other disorders related with insulin sensitivity. Further, well-designed randomized controlled trials with long-term consumption and follow up are recommended to prove scientifically the efficacy and safety of these medicinal plants.

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REFERENCES

1. Shanik MH, Yupingxu, Skrha J, dankner R, zick Y, roth J. Insulin Resistance and Hyperinsulinemia. Is hyperinsulinemia the cart or the horse? Diabetes Care, Feb 2008; 31(2).
2. Agarwal AK, Yadav P. Insulin Sensitizers beyond Glycaemic Control. Medicine Update, 2005; 281-85.
3. Tehrani FR, Gandevani SB. Polycystic ovary syndrome. Contemporary Gynaecology Practice, 2005; 81-102.
4. Farshchi H, Rane, Love, Kennedy RL. Diet and nutrition in polycystic ovary syndrome (PCOS): Pointers for Nutritional Management. Journal of Obstetrics and Gynaecology, Nov 2007; 27(8): 762-73.
5. Agarwal N, Gangopadhyay S, Koch N, Gupta A, Batra A, Kabi BC. Polycystic ovarian syndrome and insulin resistance: a North Indian study. International Journal of Research in Medical Sciences Agarwal N et al. Int J Res Med Sci, June 2015; 3(6): 1321-1324.
6. Chaney TL, Sissy HC. Crabtree, Horn WA, Jones DC. ACE Position Statement on the Insulin Resistance Syndrome, *Endocr Pract*, 2003; 9(3): 240-52.
7. Mohammed IAA. Pathophysiology of insulin resistance. Individual Report for Module 1, The Post Graduate Diploma in Diabetes University of Cardiff, Wales June 2015.
8. Bugianesi E, McCullough A J, Marchesini G. Insulin Resistance: A Metabolic Pathway to Chronic Liver disease. Concise review in mechanisms of disease. Hepatology, Nov 2005; 42: 987-1000.
9. Wilcox G. Insulin and Insulin Resistance. Clin Biochem Rev, May 2005; 26: 19-39.
10. Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningum FG. Williams Gynaecology. 1st ed. China: McGraw Hill companies, 2008.
11. Goodarzi MO, Korenman SG. The importance of insulin resistance in polycystic ovary syndrome. Fertility and sterility, Aug 2003; 80(2): 255-58.
12. Dhindsa G, Bhatia R, Dhindsa M, Bhatia V. Insulin resistance, insulin sensitization and inflammation in polycystic ovarian syndrome. J Postgrad Med, 2004; 50: 140-4.
13. Bösenberg LH, van Zyl DG. The mechanism of action of oral antidiabetic drugs: A review of recent literature. Journal of Endocrinology, Metabolism and Diabetes of South Africa, Dec 2008; 13:3, 80-88.
14. Zonneveld PV. Position of alternatives: insulin sensitizers and others. International Congress Series, 2005; 1279: 31–34.
15. Eddouks M, Bidi A, El Bouhali B, Hajji L, Zeggwagh NA. Antidiabetic plants improving insulin sensitivity. Royal Pharmaceutical Society, Journal of Pharmacy and Pharmacology, Feb 2014; 2-18.
16. Pothuraju R, Sharma RK, Onteru SK, Singh S, Hussain SA. Hypoglycemic and hypolipidemic effects of Aloe vera extract preparations: a review. Phytotherapy research, Nov 2015.
17. Khare C.P. Indian medicinal plants- An illustrated dictionary. New Delhi: Springer, 2007.
18. Kim K, Kim H, Kwon J, Lee S, Kong H, Im S et al. Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine-Elsevier, 2009; 1-8.
19. Qamar Uddin, Samiulla L, Singh VK, Jamil SS. Phytochemical and Pharmacological Profile of Withaniasomnifera Dunal: A Review. Journal of Applied Pharmaceutical Science, Jan 2012; 2(1): 170-175.
20. Central Council for Research in Unani Medicine. The Unani pharmacopeia of India. Rakmo Press New Delhi, Aug 2007.

21. Anwer T, Sharma M, Pillai PP, Iqbal M. Effect of Withaniasomnifera on Insulin Sensitivity in Non-Insulin-Dependent Diabetes Mellitus Rats. Nordic Pharmacological Society. Basic & Clinical Pharmacology & Toxicology, Aug 2007; 102: 498–503.
22. Daily JW, Yang M, Kim DS, Park S. Efficacy of ginger for treating Type 2 diabetes: A systematic review and meta-analysis of randomized clinical trials Journal of Ethnic Foods, Feb 2015; 2: 36-43.
23. Kandunuri KK, White K, Smith E. An overview on the efficacy of herbs used in ayurvedic formulations for the treatment of type 2 diabetes. International Journal of Herbal Medicine Aug 2016; 4(5): 116-121.
24. Joseph B, Jini D. Antidiabetic effects of Momordicacharantia(bitter melon) and its medicinal potency Asian Pac J Trop Dis, Feb 2013; 3(2): 93-102.
25. Alam MA, Riaz Uddin, Subhan N, Rahman MM, Jain P, Reza HM. Beneficial Role of Bitter Melon Supplementation in Obesity and Related Complications in Metabolic Syndrome. Hindawi Publishing Corporation Journal of Lipids, Dec 2014; 1-18.
26. Elgazar AF, Rezq AA, Bukhari HM. Anti-Hyperglycemic Effect of Saffron Extract in Alloxan-Induced Diabetic Rats European Journal of Biological Sciences, May 2013; 5(1): 14-22.
27. Kang C, Lee H, Jung ES , SeyedianR, MiNa Jo , Kim J,Kim JS, Kim E. Saffron (Crocus sativus L.) increases glucose uptake and insulin sensitivity in muscle cells via multipathway mechanisms. Food Chemistry, June 2012; 135: 2350-2358.
28. Sultana S, Asif HM, Akhtar N, Iqbal A, Nazar H, Rehman R. *Nigella sativa:* Monograph Journal of Pharmacognosy and Phytochemistry, October 2015; 4(4): 103-106.
29. Sangal A. Role of cinnamon as beneficial antidiabetic food adjunct: a review. Advances in Applied Science Research, 2011; 2(4): 440-450.
30. Heibashy, Mazen, Shahin. Metabolic Changes and Hormonal Disturbances in Polycystic Ovarian Syndrome Rats and the Amelioration Effects of Metformin and/or Cinnamon Extraction Journal of American Science, 2013; 9(12): 54-62.
31. Kannappan S, Anuradha CV. Insulin sensitizing actions of fenugreek seed polyphenols, quercetin& metformin in a rat model. Indian J Med Res, April 2009; 129: 401-408.
32. Perez GRM, Damian GM. Meliacinolin: a potent α-glucosidase and α-amylase inhibitor isolated from *Azadirachtaindica*leaves and *in vivo* antidiabetic property in streptozotocin- nicotinamide-induced type 2 diabetes in mice. Biol Pharm Bull, June 2012; 35(9): 1516-1524.
33. Bhansali S, Shafiq N, Pandhi P, Singh AP, Singh I, Singh PK et al. Effect of a deacylgymnemic acid on glucose homeostasis & metabolic parameters in a rat model of metabolic syndrome. Indian J Med Res, June 2013; 137: 1174-1179.
34. Persaud SJ, Al-Majed H, Raman A, Jones PM. Gymnemasylvestre stimulates insulin release in vitro by increased membrane permeability. Journal of endocrinology, 1999; 163: 207-212.
35. de Bock M, Derraik JGB, Brennan CM, Biggs JB, Morgan PE et al. Olive (Oleaeuropaea L.) Leaf Polyphenols Improve Insulin Sensitivity in Middle-Aged Overweight Men: A Randomized, Placebo-Controlled, Crossover Trial. PLOS ONE, March 2013; 8(3): 1-8.
36. Hashmi MA, Khan A, Hanif M, Farooq U, Perveen S. Traditional Uses, Phytochemistry, and Pharmacology of *Oleaeuropaea*(Olive) Hindawi Publishing Corporation, Evidence-Based Complementary and Alternative Medicine, Jan 2015; 1-29.
37. Bhattamisra SK, Mohapatra L, Panda BP, Parida S. Effect of isoflavone rich soya seed extract on Glucose utilization and endurance capacity in Diabetic rat. Diabetologiacroatica, 2013; 2: 42-52.
38. Tripathi MK, Kumar V, Yadav MK, Yadav D, Pandey S. Beneficial Role of Soybean Phytoestrogens. Octa Journal of Biosciences- An International peer-reviewed journal, Nov 2013; 1(2): 170-176.
39. Santoshkumar J, Manjunath S, Mariguddi DD, Kalashetty PG, Dass P, Manjunath C. Anti-Diabetic Effects Of Turmeric In Alloxan Induced diabetic rats. Journal of Evolution of Medical and Dental Sciences, March 2013; 2(11): 1669-1679.
40. Sinha K, Mishra NP, Singh J, Khanuja SPS. *Tinosporacordifolia* (Guduchi), a reservoir plant for therapeutic applications: A Review. Indian journal of traditional knowledge, July 2004; 3(3): 257-270.
41. Shukla K, Dikshit P, Shukla R,. Gambhir JK. The Aqueous Extract of Withaniacoagulans Fruit Partially Reverses Nicotinamide/Streptozotocin-Induced Diabetes Mellitus in Rats. Journal Of Medicinal Food, April 2012; 15(8): 718-725.
42. Bharti SK, Kumar A, Sharma NK, Krishnan S, Gupta AK, Padamdeo SR. Antidiabetic effect of aqueous extract of *Withaniacoagulans* flower in Poloxamer-407 induced type 2 diabetic rats Journal of Medicinal Plants Research, Nov 2012; 6(45): 5706-013.
43. Gao D, Li Q, Fan Y. Hypoglycemic effects and mechanisms of *Portulacaoleracea* L. in alloxan-induced diabetic rats Journal of Medicinal Plants Research, Oct 2010; 4(19): 1996-2003.
44. Esmaillzadeh A, Zakizadeh E, Faghihimani E, Gohari M, Jazayeri Sh. The effect of purslane seeds on glycemic status and lipid profiles of persons with type 2 diabetes: A randomized controlled cross-over clinical trial. J Res Med Sci, 2015; 20: 47-53.
45. Rahideh ST, Shidfar F, Khandozi N, Rajab A, Hosseini SP, Mirtaher SM. The effect of sumac (*Rhuscoriaria L.*) powder on insulin resistance, malondialdehyde, high sensitive C-reactive protein

and paraoxonase 1 activity in type 2 diabetic patients. J Res Med Sci, Aug 2014; 19: 933-8.
46. Ardakani MRF, Vahidi AR, Nazari EK, Dehghani A, Nadjarzadeh A. Effect of RhusCoriaria L. on Glycemic Control and Insulin Resistance in Patients with Type 2 Diabetes Mellitus Iranian Journal Of Diabetes And Obesity, Aug 2017; 8(4): 172-78.
47. Verma RK, Mishra G, Singh P, Jha KK, Khosa RL. Anti-diabetic activity of methanolic extract of Alpiniagalanga Linn. aerial parts in streptozotocin induced diabetic rats. AYU, 2015; 36: 91-5.
48. Koyagura N, Nayak N, Jamadar MG, Patil AM. Protective role of *cocciniaindica*herb against dexamethasone induced. Insulin resistance international journal of scientific research, july-2017; 6(7): 186-88.
49. Reddy NS, Ramanjaneyulu K, Sabbani V, Chodey V. In Vitro and in Vivo Antidiabetic Activity of Rumex Vesicarius Leaves Extract in Streptozotocin Induced Diabetic Albino Wister Rats. Journal of Diabetes and Metabolism an open access journal, June 2017; 8(6): 1-4.
50. Kulkarni CR, Joglekar MM, Patil SB, Arvindekar AU. Antihyperglycemic and antihyperlipidemic effect of Santalum album in streptozotocin induced diabetic rats, Pharmaceutical Biology, Dec 2011; 50(3): 360-365.
51. Hegazy GA, Alnoury AM, Gad HG. The role of Acacia Arabica extract as an antidiabetic, antihyperlipidemic, and antioxidant in streptozotocin- induced diabetic rats, Saudi Med J, May 2013; 34(7): 272-33
52. Rouhi SZT, Sarker MMR, Rahmat A, Alkahtani SA, Othman F. The effect of pomegranate fresh juice versus pomegranate seed powder on metabolic indices, lipid profile, inflammatory biomarkers, and the histopathology of pancreatic islets of Langerhans in streptozotocin-nicotinamide induced type 2 diabetic Sprague–Dawley rats BMC Complementary and Alternative Medicine, 2017; 17: 156.
53. Ramesh B, Karuna R, Sreenivasa RS, Sudhakara G, Saralakumari D. Ethanolic extract of Commiphoramukul Gum Resin Attenuates Streptozotocin-Induced Alterations in carbohydrate and lipid metabolism in rats. EXCLI Journal, June 2013; 12: 556-58.
54. Ramesh B, Karuna R, Sreenivasa Reddy S, Haritha K, Sai Mangala D, et al. Effect of Commiphoramukul gum resin on hepatic and renal marker enzymes, lipid peroxidation and antioxidants status in pancreas and heart in fructose fed insulin resistant rats. Beni-Suef University Journal of Basic and Applied Sciences, Nov 2015; 4: 269-278.
55. Nadkarni KM. Indian MateriaMedica. Mumbai: Popular Prakashan Pvt. Ltd, 2009.
56. Bisset NG. Herbal drugs and phytopharmaceuticals-A handbook for practice on a scientific basis. 2nd ed. MedpharmGbbH scientific publishers Stuttgart, Germany, 2001.
57. Helal EGE, Mahmoud A, El-Badawy EE, Kahwash AA. Effect of Commiphoramyrrha extract on some physiological parameters and histological changes in diabetic albino rats. The Egyptian Journal of Hospital Medicine, Sep 2005; 20: 148-162.