UK Journal of Pharmaceutical and Biosciences

Available at www.ukjpb.com

Management of Diabetes and Complication: Herbal Therapies

Triveni Kanwar, Amit Roy, Pushpa Prasad*

Columbia Institute of Pharmacy, Tekari, Raipur, Chhattisgarh – 493111, India

Abstract

Diabetes mellitus is a universal metabolic disease characterized by means of hyperglycemia, hyperlipidemia, hyper aminoacidemia and hypoinsulinaemia. It leads to diminish in insulin, secretion and insulin action. Insulin is natural hormone secreted commencing the β- cells of pancreas which help out the cells to uptake glucose molecules from the blood flow. Diabetes mellitus is a chronic autoimmune disease related by selective damage of insulin-producing pancreatic β-cells. There are lots of multiple agents obtainable to control and to care for diabetic patients, although total recovery from diabetes has not been reported up to this time. Alternative in the direction of these synthetic agents, plants and nutrients supply a potential source of hypoglycemic drugs and are extensively used in some traditional systems of medicine toward prevent diabetes. Conventional systems of medicines with the perspectives of protection, efficiency, and quality will controls.

1 Introduction

Diabetes mellitus is a systemic metabolic disease characterize by hyperglycemia (increase glucose level), hyperlipidemia (increase lipid level), hyper aminoacidemia, and hypoinsulinaemia (decrease insulin level) it leads to reduce in insulin, release and insulin action[1]. human body do not produce or accurately us insulin, a hormone toward is required to exchange sugar, starches, and supplementary food interested in energy. Diabetes mellitus is characterized in continuous high levels of blood glucose (sugar). Human bodies have to maintain the blood glucose levels lying on a extremely narrow range which is done with insulin and glucagon. The purpose of glucagon is causing the liver to discharge glucose seeing as its cells into the blood for the making of energy[2]. Chronic hyperglycemia is associated through long-standing damage, dysfunction, and failure of dissimilar organs, especially eyes, kidneys, nerves, heart, and blood vessels[3]. It is estimated to facilitate in the year 2010 more than 200 million public worldwide will consist of DM and 300 million people will after have the disease in 2025[4,5].

2 Etiology/Contributing factors

Type 1 Diabetes

1. Cause during the immune destruction of the beta cells of the pancreas.

2. Antibodies to islets cells and insulin are present on diagnosis.

3. Insulin secretion infrequently diminishes.

4. May nearby every age, but most common in early days and adolescence.

5. Insulin by injection is compulsory meant for survival

Contributing factors

1. Genetic predisposition

2. Environmental triggers (infection or else additional stress)

Type 2 Diabetes

1. Caused during insulin resistance in the liver and skeletal muscle, greater earlier than glucose production in the liver, over production of free fatty acids by fatty cells and relative insulin paucity.

2. Insulin secretion decrease through gradual beta cell failure.

3. Reductions in blood glucose levels frequently care for achieved through changes in food eating and physical activity patterns. Oral medication and/or insulin injections are ultimately required.

Contributing factors

1. Fatness

2. Age (onset of puberty is allied through increased insulin resistance).

3. Not comprise of physical activity.

4. Genetic predisposition.

5. National/ethnic background (African American, Native American, Hispanic and Asian/Pacific Islander).

6. Conditions associated through insulin resistance, (e.g., polycystic ovary syndrome[6,7].

3 Types of mellitus (DM)

1. TYPES 1 DIABETES: (insulin-dependent diabetes mellitus, IDDM or immune-mediated or juvenile-onset diabetes): It is because by an auto-immune reaction universally the body's defense system destroys the insulin-producing β-cells.Community with type 1 diabetes turn out very little or no insulin. The disease repeatedly occurs in children or young adults. Patients totally depend on the exogenous insulin to control the levels of glucose in their blood. Genetic factors be thought to go on the main reason of it[7].

2. TYPE 2 DIABETES**:** (non-insulin dependent diabetes mellitus, NIDDM or adult-onset diabetes): It accounts designed for at least 90% of all cases of diabetes. It is characterized by insulin resistance and relative insulin deficit. This occurs mainly appropriate to loss of functional β-cells. Type 2 diabetes is associated by means of very serious life cease complications[8].

3. GESTATIONAL DIABETES (GDM): An appearance of diabetes consisting of high blood glucose levels throughout pregnancy. It develops in 2-4% of pregnancies generally in 2nd or 3rd trimester[9].

4. PREDIABETS: This is body's declaration of warning sign to make some health change. Pre-diabetes is diagnosed following the level of glucose in the blood is higher than the normal limits but not quite high enough to diagnose as Type-2 diabetes[10] (Table:1).

4 Insulin

Insulin plays an important role for the storage of excess energy in the body, Insulin is a natural hormone buried as of the β- cells of pancreas which helps the cells to uptake glucose molecules commencing the blood flow. Hence deficiency of insulin results in the breakdown of glucose utilization by the cells and leading to its increased concentration in blood[12].

Table 1: Normal and Diabetes blood glucose level[11]

	Normal	Diabetes
Fasting blood sugar	80-99 mg/dl	126 mg/dl and more than
Random blood sugar	80-139 mg/dl	200 mg/dl and more than
2hour glucose tolerance test	80-139 mg/dl	200 mg/dl and more than

Mechanisms of insulin

Coupled to several additional protein kinase signal

1. Pathways signaling all the draw near during PI 3-kinase and phosphatidylinositol (3,4,5)P3 (PI-3 kinase and protein kinase B/Akt).

2. Mitogen-activated protein kinases (MAPKinases).

NB: Both group 1and 2 signals furthermore activate protein kinase Cγ and Protein kinase Cζ.

3. Possible interaction by kinases not coupled to IRS proteins[13].

It have been suggested that the majority dominant is the first group (PI 3-kinase) which converts phosphatidylinositol 3,4 bisphosphate (PIP2) or [PI(3,4)P2] to phosphatidylinositol 3,4,5 triphosphate PIP3 or (PI 3,4,5)P3. These nucleotides act on the same time as anchors, binding down-line protein kinases to the plasma membrane and activating them. Insulin binds the first alpha subunits and lead to auto phosphorilation of beta subunits which extending cytoplasm by have bonds of two subunits, and induces converting active protein kinase[14, 15].

Symptom of diabetes

1. being especially thirsty

2. urinating often

3. feeling extremely hungry

4. feeling very tired

5. losing weight underprovided trying

6. sores that heal slowly

7. dry, itchy skin

8. Approach of pins and needles in your feet

9. losing feeling in your feet

10. blurry eyesight[16, 17].

Causes

Diabetes as the two major causes of diabetes seem to be diet and exercise.

1. Obesity/overweight (especially overload visceral adiposity)

2. Excess glucorticoids (Cushing's disorder or steroid treatment)

3. Excess augmentation hormone (acromegaly)

4. Lipodystrophy (acquired or genetic, associated with lipid accumulation in liver)

5. Auto antibodies to the insulin receptor

6. Mutations of insulin receptor

7. Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)

8. Hemochromatosis (a hereditary disease that cause tissue iron accumulation)[18, 19].

5 Pathogenesis of type 1 Diabetes

Type 1 diabetes mellitus is a chronic autoimmune disease linked through selective destruction of insulin-producing pancreatic β-cells. The onset of clinical infection represents the end stage of β-cell destruction primary to type 1 diabetes mellitus[20] (Fig 1).

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islet;

2. Association of susceptibility to disease with the class II (immune response) genes of the most important histocompatibility complex (MHC; human leucocyte antigens HLA);

3. Presence of atoll cell specific auto antibodies;

4. Alterations of T cell mediated immune regulation, in exacting in CD4+ T cell compartment;

5. The attachment of monokines and TH1 cells producing interleukins in the illness process;

6. Response to immunotherapy

7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their relatives members[21, 22].

6 Pathogenesis of type 2 diabetes

In type 2 diabetes these mechanisms break down, among the consequence that the two most important pathological defects in type 2 diabetes are impaired insulin secretion throughout a dysfunction of the pancreatic β-cell, and impaired insulin action during insulin resistance[23].

i) Folks through normal glucose tolerance.

ii) Chemical diabetes (called impaired glucose tolerance).

iii) Diabetes through minimal fasting hyperglycemia (fasting plasma glucose a smaller amount than 140 mg/dl).

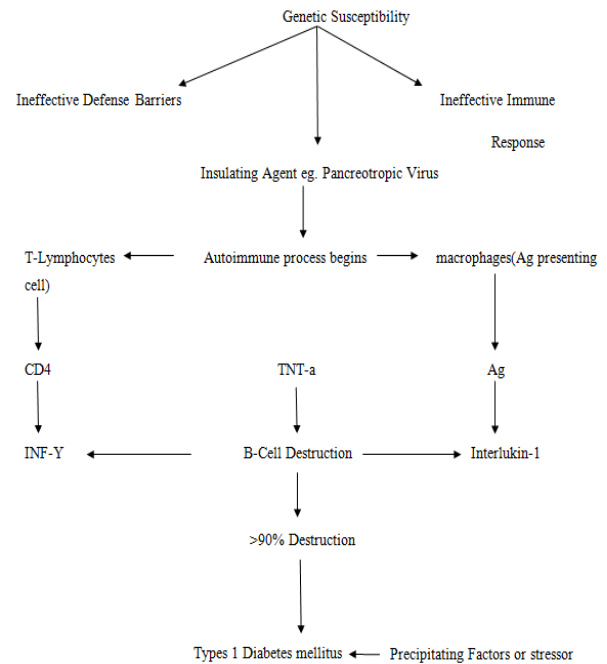iv) Diabetes mellitus in association through overt fasting hyperglycemia (fasting plasma glucose greater than 140 mg/dl)[24].

Fig 1: **Pathogenesis of type 1 Diabetes mellitus**

7 Complications in diabetes

The most important reason for this is because diabetes causes problems with the nerves as well as problems with the flow of blood during the blood vessels that supply energy for each organ. These two problems affect each organ in the human body[25]. So, when the blood glucose levels are not maintain because of unsuccessful or poor self-care, this can trigger the problems with blood vessels and nerves.

Diabetes is related with many complications similar to micro vascular (retinopathy, neuropathy and nephropathy), macro vascular (stokes, peripheral vascular diseases and coronary heart disease) and supplementary large blood vessel diseases similar to atherosclerosis[26].

8 Diagnosis of disease

The blood glucose levels of a strong man are 80mg/dl on fasting and uptown 160mg/dl in the post prandial state. Diabetes mellitus is characterized by recurrent or persistent hyperglycemia and able to be diagnosed by any one of the subsequent tests:

1. A fasting plasma glucose (FPG) test: events blood glucose in a person who has not eat everything for at least 8 hours. (>162 mg/dL).

2. An oral glucose tolerance test (OGTT): measures blood glucose subsequent to a person fasts at smallest amount 8 hours and 2 hours after the person takes 75g oral glucose load(>200mg/dL).

3. A casual plasma glucose test: also called the person individual tested last (200>mg/dL).

4. Impaired Glucose Tolerance (IGT): To replace this grouping of intermediate hyperglycemia by an generally risk assessment for diabetes, cardiovascular disease, or both, which include a measure of glucose as a uninterrupted variable[27-28].

Table 2: Herbal drugs and mechanism of action[34-64]

Botnical name	Common name	Family	Part used	Chemical constitute	Mode of action
Momordica charantia	Karela	Cucurbitaceae	Fruit	Charantin, sterol	Decrease blood glucose level.
Aloe barbadensis	Aloe vera	Aloe barbadensis	Whole plant	Aloe-emodin, aloetic-acid, anthranol, aloin A and B	Stimulation of synthesis and liberate of insulin beginning pancreatic beta cells.
Azadirachta india	Neem	Meliaceae	Whole plants	Azadiracthin, nimbin, nimbinin, nimbolide, nimbilic acid.	decrease blood glucose level by regeneration of β cells.
Allium sativum	Garlic	Alliaceae	Bulbs	S-allyl cystein sulfoxide (SACS), allin.	Increased the insulin approximating activity of plasma.
Aegle marmelos	Bael	Rutaceae	Leaf	aegelin & aegelinin and marmesin	Increases utilization of glucose, direct stimulation of glucose uptake, conciliation of enhanced insulin secretion, Account for the hypoglycemic potential.
Eugenia jambolana	Indian goosebery jamun	Myrtaceae	Seed powder	Tri-terpenoids, tannins, gallic acid, and oxalic acid	It exhibits normoglycemia and better glucose Tolerance.
Zingiber officinale	Ginger	Zingiberaceae	Leaves	6-Gingerol, tannins, polyphenolic, flavonoids.	Decrease blood glucose level.
Allium cepa	Onion	Liliaceae	Bulb	Sulfar containing amino acid s methyl cysteine sulphoxide	Lowers blood glucose level, potent Antioxidant activity, which may account for the hypoglycemic potential.
Mangifera indica	Mango	Anacardiaceae	fruit	Mangiferin, mangifera	Hypoglycemic action.
Ocimum sanctum	Tulsi	Labiatae	whole plant	eugenol and caryophyllene, rosmarinic acid and ursolic acid	created potent hypoglycaemic and hypolipidemic effect.
Tinospora cordifolia	Gaduchi	Menispermaceae	Root	Alkaloids, diterpenoid lactones,	Decreases the blood glucose intensity and increases glucose

				glycosides, steroids, Sesquiterpenoid,	tolerance.
Acacia arabica	Babhul	Mimosaceae	bark	galactopyranose, L-arabofuranose and aldobionic acid 6- -d-glucuronosido-d-galactose	hypoglycemic effect, initiating release insulin from pancreatic beta cells.
Cinnamomum	Indian Cassia	Lauraceae	Bark	Cinnamaldehyde, eugenol	Promoting the insulin release from the undestroyed β-cells.
Swertia punicea	Chirayita	Gentianaceae	Whole plant	Methyl swertianin and Bellidifolin	α-glucosidase inhibitors.

Table 3: Allopathic drug and mechanism of action[65-72]

Drug	Mechanism of Action
Insulin secretagogues Sulfonylureas (glibenclamide, gliclazide, glipizide, glimepiride)	Attach to an ATP-sensitive K^+ (K_{ATP}) channel, slow down a boost, hyperpolarizing efflux of potassium, depolarization open voltage-gated Ca^{2+} channels, better secretion of (pro)insulin.
Insulin sensitisers: Biguanides (metformin)	Glucose-lowering achieve by inhibiting hepatic gluconeogenesis and opposing the act of glucagon. The inhibition of mitochondrial complex I consequences in defective cAMP and protein kinase A signalling in respond to glucagon. Inspiration of 5′-AMP-activated protein kinase.
Thiazolidinediones (pioglitazone, rosiglitazone)	Binding to the PPAR-γ receptor through the purpose of expressed predominantly in adipocytes, TZDs, like metformin, need the presence of insulin to mediate a blood glucose-lowering generate.
New drug modalities: Incretins (exendin-4, liraglutide, vildagliptin, sitagliptin)	The small intestine secrete glucagon-like peptide-1 (GLP-1) as vigorous as glucose-dependent insulin tropic polypeptide (GIP), These hormones excite insulin secretion, insulin gene expression**,** pancreatic beta-cell expansion.

9 Diabetes care and medication

Diabetes is not completely curable it wants a being time commitment to do what is necessary to manage diabetes. Through proper management it can be controlled to a greater amount. This entire factor is organized. And in the casing of Type-2 diabetes[29], It can be totally controlled in various cases with diet and exercise**.** Daily monitoring of blood glucose level through a glucometer.

1. Insulin injections and additional medications to be taken as directed.

2. Organization of diet and weight control.

3. Managing a everyday exercise plan.

4. Daily monitoring and organization of skin and foot think about.

5. Every day oral hygiene.

6. Regular visit to the eye doctor as glowing as the dentist.

7. Regular remedial for blood pressure etc.

10 Diabetes know how to be managed with different types of medications

1. Exogenous insulin.

2. Oral hypoglycaemic mediator.

3. Alternative medicines resembling herbal treatment, Yoga, Unani medicines etc[30, 31].

11 Mechanism of Action of Herbal Antidiabetic

1. The ant-diabetic activity of herbs depends upon diversity of mechanisms. The mechanism of action of herbal anti-diabetic may be.

2. α –amylase inhibition.

3. Inhibition in renal glucose reabsorption.

4. Stimulation of insulin secretion beginning beta cells of islets or/with

5. inhibition of insulin derivative process.

6. Cortisol lowering actions.

7. Insulin resistance reduction. Providing assured necessary fundamentals like calcium, zinc, magnesium, manganese and copper intended for the β -cells.

8. Regenerating and/before repairing pancreatic β cells.

9. Increasing the amount and numeral of cells in the atoll of Langerhans.

10. Stimulation of insulin emission.

11. Stimulation of glycogenesis amid hepatic glycolysis.

12. Inhibition of β -galactocidase among α–glucocidase.

13. Protective consequence on the destruction of the β cells.

14. Improvement in digestion alongside with reduction in blood sugar and urea.

15. Prevention of pathological alteration of starch to glucose[31, 33] (Table 2 and Table 3).

12 Conclusion

Herbal therapies used for diabetes have been followed all-over the World effectively. Herbs are used to manage Type I and Type II diabetes and their complications. The potency of herbal drugs is considerable & they include negligible side effects than the synthetic ant-diabetic drugs. So it was concluded to facilitate these herbal formulation is supportive to lower glucose level during treatment of diabetes patients. Thus lots of different plants contain be used individually or in formulations used for treatment of diabetes.

13 Conflict of interests

The author declared none

14 Author's contributions

TK and PP carried out literature review and draft the manuscript. AR participated in collection of data. All authors read and approved the final manuscript.

15 References

1. Dwivedi C, Daspaul S. Antidiabetic Herbal Drugs and Polyherbal Formulation Used For Diabetes: A Review. Journal of Phytopharmacology. 2013;2(3):1-7.

2. Bolla K, Santhi KV, Afnan KS, Veni PK, Kusuma M. Effect Of Diet Counseling On Type 2 Diabetes Mellitus.

3. Gnanu N, Divagar M, Juliet L. Evaluation of invitro anti diabetic activity of seendhil herbal formulation. Asian Journal of Pharmaceutical and Clinical Research. 2013 Dec 29;1(2):91-3.

4. King H, Aubert R, Herman W. Global burden of diabetes, 1995-2025. Prevalence, numerical estimates and projections. Diabetes Care 1998; 21:1414-1431.

5. Zimmet P. Globalization, coca-colonization and the chronic disease epidemic: can the Doomsday scenario be averted? J Intern Med. 2000; 247: 301- 310.

6. Diabetes mellitis: Type 1 and Type 2 Emily Loghmani chapter 14 page no.164.

7. Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. Diabetes Care 1999;22(2):345-354.

8. Diagnosis of Diabetes. National Diabetes Information Clearinghouse, US department of health and human services, National institute of diabetes and digestive and idney diseases. *www.diabetes.niddk.nih.govpp 1-2.*

9. Bailey CJ, Day C.Traditional plant medicines as treatments for diabetes;Diabetes Care. 1989; 12: 553-564.

10. World Health Organization: Report of a WHO consultation: definition of metabolic syndrome in definition, diagnosis and classification of diabetes and its complications. I.Diagnosis and classification of diabetes mellitus. Geneva, World Health Organization, Department of Non-communicable Disease Surveillance, 1999.

11. Khan A, Ali S, Ahmad J. Antidiabetic activity of traditional herbal formulation. Int J drug form res. 2011; 2(1):96-104.

12. Kumari K, Augusti KT: Antidiabetic and antioxidant effect of S-methyl cysteine sulfoxide isolated from onion *(Allium sepa* Linn) as compared to standard drug in alloxan diabetic rats. Indian Journal of Experimental Biology. 2002; 40(9):1005- 1009.

13. Washington DC. 20016. Pathophysiology of type 2 diabetes mellitus R. Leibel Naomi Berrie Diabetes Center 25 February 2008.

14. Mechanism-Based Modeling of the Glucose-Insulin Regulation during Clinical Provocation Experiments ISSN 1651-6192.

15. Molecular and Cellular Endocrinology. entitled Functional role of Rab11 in GLUT4 trafficking in cardiomyocytes, M. Uhlig, W. Passlack ahd J. Eckel. 2005; 1-9.

16. Zhao M, Wan ZL, Whittaker L. Design of an insulin analog with enhanced receptor-binding selectivity. Rationale, structure, and therapeutic implications. J BiolChem 2010;285:11755-59.

17. Park S, Hong SM, Ahn IS. Exendin-4 and exercise improve hepatic glucose homeostasis by promoting insulin signaling in diabetic rats. Metabolism 2010;59(1):123-33.

18. Gayatri College of Pharmacy, Jamadarpali, Sambalpur, Odisha, India. 2 Roland Institute of Pharmaceutical Sciences, Berhampur, Odisha, India, 3 School of Pharmaceutical Education & Research, Berhampur University, Berhampur 760007, Odisha, India.

19. Jane Kelly. MD – Director. National Diabetes Education Program CDC National Center for Chronic Disease Prevention and Health Promotion Phone: 404-639-3286.

20. The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. 2013; 4(4): 46-57.

21. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, Hu FB. Diabetes in Asia; epidemiology, risk factors, and pathophysiology. JAMA. 2009; 301: 2129-2140.

22. Comi RJ, Grunberger G, Gorden P. Relationship of insulin binding and Insulin-stimulated tyrosine kinase activity is altered in type II diabetes. J. Clin. Invest. 1987; 79:453-62.

23. Campbell IT, Kay TWH, Oxbrow L, Harrison TC. Essential role for Interferon Gama and interleukin 6 in autoimmune, insulin-dependent diabetes in NOD/Wehi mice. J. Clin. Invest. 1991; 87:739-742.

24. Evephart JE, Pettit DJ, Bennett PH, Knowler WC. Duration of obesity increases the incidence of NIDDM. Diabetes. 1992; 41:235-240.

25. Knowler WC, Pettitt DJ, Sadd M, Bennett PH. Diabetes mellitus in the Pina Indians: incidence, risk factors and pathogenesis. Diabetes/Metab. 1990; Rev 6:1-27.

26. Rao CHV, Mishra SB, Ojha SK, Vijayakumar M, Verma A. An analytical review of plants for anti-diabetic activity with their phyto constituent & mechanism of action. International Journal of Pharmaceutical sciences and research. 2010; 1: 29-46.

27. Sachdeva SD. Indians are more susceptible to diabetes. The Sunday Times of India 2002; New Delhi: 11.

28. *suryadas2007@rediffmail.com*

29. Diagnosis of Diabetes, National Diabetes Information Clearinghouse, US department of health and human services, National institute of diabetes and digestive and idney diseases.www.diabetes.niddk.nih.govpp 1.

30. Pulok KM, Kuntal M, Kakali M, Peter JH. Leads from Indian medicinal plants with hypoglycemic potentials. J Ethnopharmacol 2006;106:1–28.

31. Mohamed B, Abderrahim Z, Hassane M, Abdelhafid T, Abdelkhaleq L. Medicinal plants with potential antidiabetic activity-A review of ten years of herbal medicine research (1990-2000). Int J Diabetes Metabol 2006;14:1-25.

32. Manisha Modak, Priyanjali Dixit, Jayant Londhe, Saroj Ghaskadbi, and Thomas Paul A. Indian Herbs and Herbal Drugs Used for the Treatment of Diabetes., J. Clin. Biochem. Nutr. 2007; 40: 163–173.

33. https://en.wikipedia.org/wiki/Drug. MHRA. Retrieved, 2008-11-05.

34. Rao CHV, Mishra SB, Ojha SK, Vijayakumar M, Verma A. An analytical review of plants for anti-diabetic activity with their phyto constituent & mechanism of action. International Journal of Pharmaceutical sciences and research. 2010; 1: 29-46.

35. Chattopadhyay RR. A comparative evaluation of some blood sugar lowering agents of plant origin. J Ethnopharmacol. 1999; 67: 367-372.

36. Chattopadhyay RR, Chattopadhyay RN, Nandy AK, Poddar G, Maitra SK. The effect of fresh leaves of *Azadirachta indica* on glucose uptake and glycogen content in the isolated rat hemi diaphragm. Bulletin of the Calcutta School of Tropical Medicine. 1987; 35:8–12.

37. Chattopadhyay RR. Possible mechanism of antihyperglycemic effect of *Azadirachta indica* leaf extract, part IV. General Pharmacology. 1996; 27:431–434.

38. Chattopadhyay RR. A comparative evaluation of some blood sugar lowering agents of plant origin. Journal of Ethnopharmacology. 1999; 67:367–372.

39. Gholap S, Kar A. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. Pharmazie. 2004; 59:876–878.

40. Chattopadhyay RR, Chattopadhyay RN, Nandy AK, Poddar G, Maitra SK. Preliminary report on antihyperglycemic effect of a fraction of fresh leaves of Azadirachta indica (Beng. Neem). Bulletin of the Calcutta School of Tropical Medicine. 1987a; 35:29–33.

41. Sharma SR, Dwivedi SK, Swarup D. Hypoglycemic, antihyperglycemic and hypolipidemic activities of *Caesalpinia bonducella* seeds in rats. Journal of Ethnopharmacology. 1997; 58:39–44.

42. Singh KN, Chandra V, Barthwal KC. Letter to the editor: hypoglycemic activity of *Acacia arabica, Acacia benthami* and *Acacia modesta* leguminous seed diets in

normal young albino rats. Indian Journal of Physiology and Pharmacology. 1975; 19:167–168.

43. Wadood A, Wadood N, Shah SA. Effects of *Acacia arabica* and *Caralluma edulis* on blood glucose levels of normal and alloxan diabetic rabbits. Journal of Pakistan Medical Association. 1989; 39, 208–212.

44. Augusti KT. Studies on the effects of a hypoglycemic principle from *Allium Cepa* Linn. Indian Journal of Medical Research. 1973; 61:1066–1071.

45. Babu PS, Srinivasan K. Influence of dietary capsaicin and onion on the metabolic abnormalities associated with streptozotocin induced diabetes mellitus. Molecular and Cellular Biochemistry. 1997; 175:49–57.

46. Kinghorn AD, Compadre CM. Less common high-potency sweeteners. In: Nabors L O'Brien, editor. Alernative Sweeteners, 2nd ed. New York: Marcel Dekker; 1991.

47. Asare-Anane H, Huang GC, Amiel SA, Jones PM, Persaud SJ. Poster Presentations - Stimulation of insulin secretion by an aqueous extract of Gymnema sylvestre: role of intracellular calcium. Endocrine Abstracts. 2005; 10:1.

48. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. Journal of Ethnopharmacology. 1990b; 30 (3):265-279.

49. Chattopadhyay RR. A comparative evaluation of some blood sugar lowering agents of plant origin. Journal of Ethnopharmacology. 1999; 67 (3):367-372.

50. Gholap S, Kar A. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. Pharmazie. 2004; 59: 876–878.

51. Rai V, Iyer U, Mani UV. Effect of Tulsi (*Ocimum sanctum*) leaf powder supplementation on blood sugar levels, serum lipids and tissue lipids in diabetic rats. Plant Foods and Human Nutrition .1997; 50:9–16.

52. Wadood N, Wadood A, Shah SA. Effect of Tinospora cordifolia on blood glucose and total lipid levels of normal and alloxan-diabetic rabbits. Planta Medica. 1992; 58:131–166.

53. Prince PS, Menon VP. Antioxidant activity of *Tinospora cordifolia* roots in experimental diabetes. Journal of Ethnopharmacology. 1999; 65:277–281.

54. Stanely P, Menon VP, Gunasekaran G. Hypolipidaemic action of *Tinospora cordifolia* roots in alloxan diabetic rats. Journal of Ethnopharmacology. 1999; 64:53–57.

55. Stanely P, Menon VP. Hypoglycemic and other related actions of *Tinospora cordifolia* roots in alloxan-induced diabetic rats. Journal of Ethnopharmacology. 2000; 70:9–15.

56. Stanely P, Menon VP. Antioxidant action of *Tinospora cordifolia* root extract in alloxan diabetic rats. Phytotherapy Research. 2001; 15:213– 218.

57. Stanely P, Menon VP. Hypoglycaemic and hypolipidaemic action of alcohol extract of *Tinospora cordifolia* roots in chemical induced diabetes in rats. Phytotherapy Research. 2003; 17:410–413.

58. Rao BK, Kesavulu MM, Giri R, Appa Rao C. Hypoglycemic and hypolipidemic effects of *Momordica cymbalaria* Hook. Fruit powder in alloxan-diabetic rats. Journal of Ethnopharmacology. 1999; 67:103–109.

59. Handa SS, Chawla AS, Maninder NA. Hypoglycemic plants—a review. Fitoterapia. 1989; 15(3):195–224.

60. Rao BK, Kesavulu MM, Apparao C. Antihyperglycemic activity of *Momordica cymbalaria* in alloxan diabetic rats. Journal of Ethnopharmacology. 2001; 78:67–71.

61. Rajasekaran S, Sivagnanam K, Ravi K, Subramanian S. Hypoglycemic effect of *Aloe vera* gel on streptozotocin-induced diabetes in experimental rats. Journal of Medicinal Food. 2004; 7:61–66.

62. Ajabnoor MA. Effect of aloes on blood glucose levels in normal and alloxan diabetic mice. Journal of Ethnopharmacology. 1990, 28:215–220.

63. Achrekar S, Kaklij GS, Pote MS, Kelkar SM. Hypoglycemic activity of *Eugenia jambolana* and *Ficus bengalenesis*: mechanism of action. In Vivo. 1991; 5:143–147.

64. Grover JK, Vats V, Rathi SS. Anti-hyperglycemic effect of *Eugenia jambolana* and *Tinospora cordifolia* in experimental diabetes and their effects on key metabolic enzymes involved in carbohydrate metabolism. Journal of Ethnopharmacology. 2000; 73:461–470.

65. Sharma SB, Nasir A, Prabhu KM, Murthy PS, Dev G. Hypoglycaemic and hypolipidemic effect of ethanolic extract of seeds *of Eugenia jambolana* in alloxan-induced diabetic rabbits. Journal of Ethnopharmacology. 2003; 85:201–206.

66. Ravi K, Ramachandran B, Subramanian S. Protective effect of *Eugenia jambolana* seed kernel on tissue antioxidants in streptozotocin induced diabetic rats.

Biological and Pharmaceutical Bulletin. 2004a; 27:1212–1217.

67. Salonen JT, Nyyssonen K, Tuomainen TP, Maenpaa PH, Korpela H, Kaplan GA, Lynch J, Helmrich SP, Salonen R. Increased risk of non-insulin-dependent diabetes mellitus at low plasma vitamin E concentrations: a four year study in men. Br Med J. 1995; 311:1124-1127.

68. Jain K, McVie R. Effect of glycaemic control, race (white versus black) and duration of diabetes on reduced glutathione content in erythrocytes of diabetes patients. Metabolism. 1994; 43:306-309.

69. Department of Internal Medicine, Kalafong Hospital, School of Medicine, Faculty of Health Sciences, University of Pretoria L H Bösenberg, MB ChB, MMed D

G van Zyl, MB ChB, MSc, FCP December 2008, Vol. 13, No. 3.

70. Hawley SA, Gadalla AE, Olsen GS, Hardie DG. The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotideindependent mechanism. Diabetes 2002; 51(8): 2420-2425.

71. Shaw RJ, Lamia KA, Vasquez D, *et al.* The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. *Science* 2005; 310(5754): 1642-1646.

72. Semple RK, Krishna K. PPAR-and human metabolic disease. J Clin Invest. 2006; 116: 581-586.