Today 415 Million people worldwide are living with diabetes. In 2040 more than half of this is important because India is becoming diabetic capital of the world with more than 62 million patients on record.
INTRODUCTION

Diabetes mellitus (DM) is one of the most important public health challenges of the twenty-first century, producing great social and economic burden [1]. According to the World Health Organization, over 10% of the world’s population is estimated to have DM or be at high risk of developing DM [2]. DM is a leading cause of cardiovascular disease (primarily heart disease and stroke), renal failure, and blindness (due to diabetic retinopathy). Due to reduced blood flow in combination with neuropathy in the feet, DM increases the chance of foot ulcers, infection, and even limb amputation, which is associated with an impaired immune response and a high microbial burden. Diabetes is a condition of multifactorial origin, involving several molecular mechanisms related to the intestinal microbiota for its development. In type 2 diabetes, receptor activation and recognition by microorganisms from the intestinal lumen may trigger inflammatory responses, inducing the phosphorylation of serine residues in insulin receptor substrate-1, reducing insulin sensitivity. In type 1 diabetes, the lowered expression of adhesion proteins within the intestinal epithelium favors a greater immune response that may result in destruction of pancreatic β cells by CD8+ T-lymphocytes, and increased expression of interleukin-17, related to autoimmunity.

OBJECTIVE:
To investigate and prepare safe and effective natural source of “Anti Diabetic Drug” and safeguard adverse/toxic effects of conventional drugs. Further objective is to focus on four pillars / major organs/pathogenesis which is postulated (International Reviews) as the causative platform for Diabetes Mellitus:

1. Islet Cells
2. Liver Dysfunction
3. Gut Microbe
4. Enzyme

MATERIALS (Extracts)

1. Withania coagulant
2. Andrographis paniculata
3. Phyllanthus emblica
4. Ashphaltum

Microbial dysbiosis can actually influence the immune response and pathophysiology of DM (Diabetes Mellitus)

ROLE OF GUT MICROBIOME

It can be foreseen that the gut microbiota will be used not only as a biomarker for diabetes, but also as a target for potential therapeutic treatments. Through the intervention of gut microflora, it will eventually be possible to achieve a more precise and personalized diagnosis as well as treatment of diabetes. Various functions of the gut are regulated by sophisticated interactions among its functional elements, including the gut microbiota. These microorganisms play a crucial role in gastrointestinal mucosa permeability. They control the fermentation and absorption of dietary polysaccharides to produce short-chain fatty acids, which may explain their importance in the regulation of fat accumulation and the subsequent development of obesity-related diseases, suggesting that they are a crucial mediator of obesity and its consequences.
Role of Islet cells in diabetes mellitus

The islets of Langerhans are a cluster of cells within the pancreas that are responsible for the production and release of hormones that regulate glucose levels. A Pancreas, Pancreatic islet cells are the main source of insulin and glucagon, which are produced by β cells and α cell, respectively. The secretion of hormones from pancreatic islets is mainly regulated by the glucose concentration. Pancreatic islet cells are the main source of insulin and glucagon, which are produced by β cells and α cell, respectively. The secretion of hormones from pancreatic islets is mainly regulated by the glucose concentration. The growth and differentiation of hormone-producing cells and the secretion of hormones must be rigorously regulated to maintain glucose homeostasis.

The endocrine pancreas is composed of clusters of cells, or islets, which secrete endocrine factors important for systemic metabolism, including insulin and glucagon. A large proportion of the islet cell mass comprises insulin secreting β-cells, which regulate plasma levels of glucose. In addition, islets contain glucagon secreting α-cells, other endocrine cell populations and immune cells. Autoimmune β-cell destruction leads to type 1 diabetes mellitus, where the pancreas is unable to produce enough insulin. In type 2 diabetes mellitus, β-cells are dysfunctional and cannot produce enough insulin to maintain normoglycaemia in the face of insulin resistance. The purpose of this article series is to highlight developments in islet biology and provide a knowledge hub for the diabetes mellitus research community. Ultimately, increasing our understanding of the cellular composition, function and cell–cell crosstalk in pancreatic islets might lead to the development of novel management strategies for diabetes mellitus and the metabolic syndrome.

The primary function of a beta cell is to produce and release insulin and amylin. Both are hormones which reduce blood glucose levels by different mechanisms. Beta cells can respond quickly to spikes in blood glucose concentrations by secreting some of their stored insulin and amylin while simultaneously producing more. Primary cilia on beta cells regulate their function and energy metabolism. Cilia deletion can lead to islet dysfunction and type 2 diabetes. The triggering pathway of glucose-stimulated insulin secretion

Role Of Liver In Diabetes Mallitus

The liver plays a key role in regulating both glucose and lipid metabolism, derangements of which occur in NAFLD and T2D. In T2D, fasting hyperglycemia results from unopposed endogenous glucose production due to IR and postprandial hyperglycemia from the inability to store glucose as glycogen after a meal. In 38% of cases, DM was subclinical[19]. As liver function deteriorates, the incidence of diabetes increases so that clinical diabetes may be seen as a marker of liver failure.
SGPT and SGOT are certain enzymes that are produced by the liver and its cells. Elevated SGPT and SGOT levels are an indication of liver cell injury or damage

MEDICINAL DIALOGUES (Bioactive)
WITHANIA coagulans:
10,11-dihydroxy-1,2,6a,6b,9,9,12α-heptamethyl-1,2,3,4,4a,5,6,6a,7,8,8a,9,10,11,12,12α,12b,13,14b-icosahydropicene-4α-carboxylic acid
Chemical Formula C30 H48 O4

THERAPEUTIC ACTIVITY
*W. coagulans* resulted in significantly decreased FPG, PPG, and HbA1c (P<.01), whereas serum insulin increased significantly compared with that in diabetic-untreated rats (P<.01). MD and SD animals treated with aqueous *W. coagulans* also showed significant increases in liver and muscle glycogen compared with diabetic-untreated animals (P<.01). Moreover, activities of glucokinase and phosphofructokinase were also significantly increased (P<.01), whereas glucose-6-phosphatase activity was significantly decreased (P<.01) in MD and SD groups treated with aqueous *W. coagulans* compared with diabetic-untreated groups. The most effective dose of aqueous *W. coagulans* was 250 mg/kg of body weight. These results show that the aqueous extract of *W. coagulans* fruit has significant antihyperglycemic effects, which may be through the modulation of insulin levels and related enzyme activities. Phytochemical screening of aqueous *W. coagulans* showed the presence of several bioactive components in the extract (*i.e.*, carbohydrates, glycosides, steroidal compounds, saponins, phenols, tannins, alkaloids, terpenoids, and flavonoids).

Daily treatment with aqueous *W. coagulans* at 250 mg/kg of body weight for 30 days restored plasma glucose, HbA1c, tissue glycogen, and glucose metabolic enzymes to near-normal ranges in both MD and SD animals. The results of this study reveal that the regular administration of aqueous *W. coagulans* extract for 30 days significantly improved glycemic status and nearly normalized plasma glucose concentrations. Therefore, it can be concluded that aqueous *W. coagulans* extract contains active components that have antihyperglycemic effects.


**PHYLLANTHUS emblica: C**
CHEMICAL CONSTITUENTS: Phyllaemblic acid
A large number of the phenols which possess distinct biological activities, *e.g.*, simple benzenoids and flavonoids, are biosynthesized via shikimic acid and acylpolimalonate pathway. The classes of chemical constituents in Plant Extract are follows: Alkaloids, Benzenoid–Corilagin, 3-6-di-O-galloyl Beta-D-glucose-ethyl gallate, Betaglucogallin, 1, 6-di-O-galloyl-beta-D-glucose, Galactaric acid, Furanolactones: ascorbic acid. Diterpene, Triterpene, Flavonoid: Leucodelphinidin. Kaempherol-3-gluco side, rutin, quercetin, quercertin-3-O-beta-D-glucoside, Sterol Beta-sitosterol, carbohydrate. Recently reported biological effects of Phyllanthus emblica L. (Euphorbiaceae).

SHILAJIT –BITUMEN: Botanical name: Ashphaltum punjabionum
Shilajit is a natural substance found mainly in the Himalayas, formed for centuries by the gradual decomposition of certain plants by the action of microorganisms. It is a potent and very safe dietary supplement, restoring the energetic balance and potentially able to prevent several disease.

Shilajit is composed mainly of humic substances, including fulvic acid, that account
for around 60% to 80% of the total nutraceutical compound plus some oligoelements including selenium of antiaging properties. Morphometric study of primary cultured rat hippocampus cells exposed to Shilajit and the Brain Up-10 formulae that contain Shilajit plus complex B vitamins (Vit B6, B9, and B12).

**ANDROGRAPHIS paniculata:** N.O. acanthaceae

**CHEMICAL CONSTITUENTS:**
Andrographolide (Bitter)

Three bitter principles, deoxyandrographolide, andrographolide and neoandrographolide have been shown to stimulate powerful immune responses in living creatures. The immune response may be specific directed at a microbial invader already present in the body, or generally, strengthening the immune system in preparation against future infections. Andrographis strongly stimulates phagocytosis and the production of specific antibodies.

**Hypoglycemic** (blood sugar reducer)

**VOULNTARY PILOT CLINICAL INTERVENTION:** 28 Male 36 Female. The voluntary clinical trials are under continues sailing. The present outcome may be considered as more than 85% success ratio but more clinical trials suggested bringing conclusive results.

**Acknowledgement:**
We are thankful to the NIH, CDC, USFDA and the Royal Botanical Garden KEW, UK. for all the time significant guidelines for series of our drug discoveries since 1986. At the same tenure, we are obliged to Dr. Achyut Padmawar for his noteworthy cooperation in selection of plant bioactive. Mr. Ajay Mishra, Laboratory technician deserve the same praise of thanks. I tender gratitude to my wife Harsha H. Shukla and two daughters Sejal and Kunjal for devoting time to prepare the script and medication.

The project has been funded by Mr. Rajesh N. Doshi and we tender our vote of thanks for his noteworthy financial aid in time, we also pay homage to late Mrs. Ritaben R. Doshi, who has fueled encouragement to her profound visionary projet for us.

**CONFLICT OF INTEREST:** None.

**References (A)**


**Reference: ( B )**

doi:10.1016/j.molmet.2017.06.019. PMC 5605733. PMID 28951820.
19) Hoda Q. Ahmad S. Akhtar M. Najmi AK. Pillai KK. Ahmad SJ. Antihyperglycaemic
and antihyperlipidaemic effect of poly-
constituents, in aqueous and chloroform
extracts, of Withania coagulans Dunal in
experimental type 2 diabetes mellitus in
658. [PubMed] [Google Scholar]
Experimental NIDDM: development of a
new model in adult rats administered
streptozotocin and nicotinamide. Diabetes.
Establishment and pathophysiology
characterization of type 2 diabetic mouse
model produced by streptozotocin and
nicotinamide. Biol Pharm Bull. 2006;
29:1167–1174. [PubMed] [Google Scholar]
22) Harborne JB. Phytochemical Methods—A
Guide to Modern Techniques of Plant
Analysis. 2nd. Chapman and Hall;
Scholar]
23) Ayoola GA, Coker HAB, Adesegun SA, et
al. Phytochemical screening and
antioxidant activities of some selected
medicinal plants used for malaria therapy
in southwestern Nigeria. Trop J Pharm
24) Vialettes B, Vovan L, Simon MC, Lassmann
V, Altomare E, Vague P. Kinetics of fast
haemoglobin in diabetic rats. Diabetologia.
PS. Hypoglycaemic effect of the water
extract of Ficus bengalensis in alloxan
recovered, mildly diabetic and severely
diabetic rabbits. Int J Diabetes Dev
Ctries. 1994;14:78–81. [Google Scholar]
26) Goldstein DE, Little RR, Wiedmeyer HM, England JD, McKenzie EM. Glycated
hemoglobin: methodologies and clinical
B70. [PubMed] [Google Scholar]
27) Good CA, Kramer H, Somogyi M. The
determination of glycogen. J Biol
Chem. 1933;100:485–498. [Google
Scholar]
28) Carroll NV, Longley RW, Roe JH. The
determination of glycogen in liver and
muscle by use of anthrone reagent. J Biol
29) Porter EV, Chassey BM. Glucokinase
from Streptococcus mutans. Methods
30) Racker E. Spectrophotometric
measurement of hexokinase and
phosphohexokinase activity. J Biol
31) Harper AE. Measurement of enzyme
activity: glucose-6-phosphatase. In:
Bergmeyer HU, editor. Methods of
Enzymatic Analysis. Academic Press;
Scholar]
Stimulation of insulin release by
repaglinide and glibenclamide involves
both common and distinct
[PubMed] [Google Scholar]
33) Schmid-Antomarchi H, De Weille J.
Fosset M, Lazdunski M. The antidiabetic
sulphonylurea glibenclamide is a potent
blocker of the ATP-modulated K+ channel
in insulin secreting cells. Biochem Biophys
34) Peter AL, Davidson MB, Schriger DL, Hasseblad V. Meta Analysis Research
Group on the Diagnosis of Diabetes using
Glycosylated Hemoglobin Levels: A
clinical approach for the diagnosis of
diabetes mellitus: an analysis using
glycosylated hemoglobin levels. JAMA.
35) Grover JK, Vats V, Rathi SS. Antihyperglycemic effect of Eugenia
jambolana and Tinospora cordifolia in
experimental diabetes and their effects on


47) The mechanism of action of ursolic acid as insulin secretagogue and insulinomimetic is mediated by cross-talk between calcium and kinase to regulate glucose balance

48) Author links open overlay panel Allisson Jhonatan GomesCastroMarisa Jádno SilvaFredericoLuisa HelenaCazarolliCamila PiresMendesLizandra CzermainskiBretHelenaCazarolliLuisa CarlosSchmidtZenilda LauritaBouzonVeronica Aicelesde Medeiros PintoCristianeda Fonte RamosMocair GeraldoPizzolattiFátima Regina Mena BarretoSilva


50) Z.H. Wang, C.C. Hsu, C.N. Huang, M.C. Yin Anti-glycative effects of oleanolic acid and ursolic acid in kidney of diabetic

CrossRef View Record in Scopus Google Scholar

How to cite this article:

Source of Support: Nil
Conflict of Interest: None

Your next submission with British Journal of BioMedical Research will reach you the below assets
• Quality Editorial service
• Swift Peer Review
• E-prints Service
• Manuscript Podcast for convenient understanding
• Global attainment for your research
• Manuscript accessibility in different formats
  (Pdf, E-pub, Full Text)
• Unceasing customer service
• Immediate, unrestricted online access
• Global archiving of articles

Track the below URL for one-step submission
https://bjbmr.org/manuscript-submission/