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Review Article

ANTI DIABETIC PROLIFIC DRUG DISCOVERY

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ABSTRACT

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.

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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.

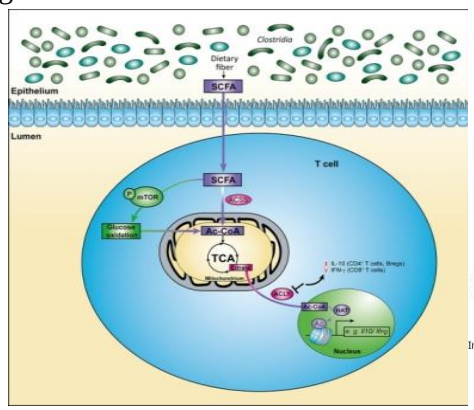
MATERIALS (Extracts)

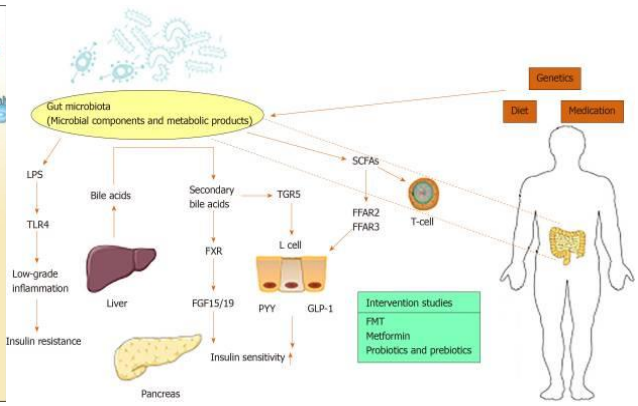
1. Withania coagulant
2. Andrographis paniculata
3. Phyllanthus emblica
4. Ashphaltum

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

ROLE OF GUT MICRIBIOME

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

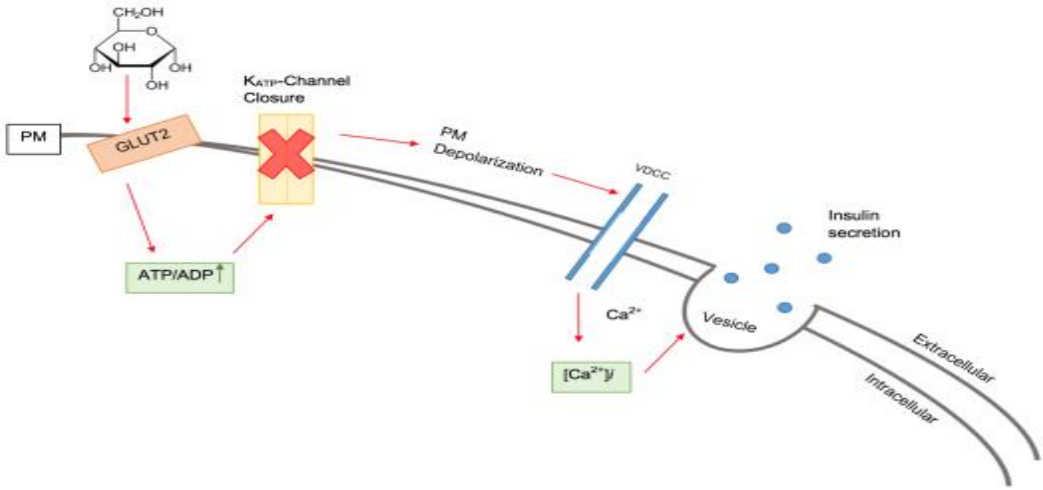
The islets of Langerhans are a cluster of cells within the pancreas that are responsible for the production and release of hormones that regulate glucose levels.

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.[3] 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.

n 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 coagulant:

10,11-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-1,2,3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-icosahydropicene-4a-carboxylic acid

Chemical Formula C30 H48 O4

THERAPEUTIC ACTIVITY

W. coagulans resulted in significantly decreased FPG, PPPG, and HbA_{1c} (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 flavanoids)

Daily treatment with aqueous *W. coagulans* at 250 mg/kg of body weight for 30 days restored plasma glucose, HbA_{1c}, 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.

***Choudhary et al.dentified 17β-hydroxywithanolide K: [(20*S*,22*R*)14α,17β,20β-trihydroxy-1-oxo-witha-2,5,24-trienolide] and 17β,20β-dihydroxy-1-oxo-witha-2,5,24-trienolide in whole plant.

Choudhary M.I., Parveen Z., Jabbar A., Ali I. Antifungal steroidal lactones from *Withania coagulance*. *Phytochemistry*. 1995; 40:1243–1246. Doi: 10.1016/0031-9422(95)00429-B. [PubMed] [CrossRef]

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- glucoside, 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 Morphometricstudy 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 b It increases biliary flow and liver weight in rat. Andrographolide produces a significant dose dependent choleretic effect, as evidence by increase in bile flow, bile salt and bile acids in conscious rats and anaesthetized guinea pigs. It shows hepatoprotective action. It improves non-specific immune response. Although both andrographis and beta glucan effective immune enhancers, Extracts of andrographis, 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)

VOULUNTARY 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.

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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.

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