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Review Article

Pharmacology for better Drug screening

Role Of Herbal Interventions In Diabetes Management

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Abstract: Diabetes mellitus is becoming a common metabolic disorder which has a serious threat to public health worldwide. Though much vigorous research is being undertaken in modern research, it is very challenging to manage diabetes and avoid complications with better quality of life. By conducting a large number of research work, numerous traditional medicines have been researched for diabetes. It is observed that the current allopathic treatment leads to numerous side effects and complications amongst the diabetic population. Thus, a new way out to avoid such complications is to adopt herbal remedies for the management of diabetes. Phytoconstituents and extracts isolated from different natural resources especially plants have always been a rich arsenal for controlling and treating diabetes and its complications. So this review helps the reader to understand the diabetes pathophysiology, possible ways in which polyherbal formulations can help management of diabetes mellitus.

Keywords: Diabetes mellitus, hyperglycaemia, insulin therapy, herbal remedies

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1. INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago. In 1936, the distinction between type I and type 2 DM was clearly made. Type 2 DM was first described as a component of metabolic syndrome in 1988. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 DM results from interaction between genetic, environmental and behavioral risk factors. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa[1,2].

1.1 Epidemiology

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors.Literature search has shown that there are a few data available on the prevalence of type 2 DM in Africa as a whole. The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM. The 2011 Centre for Disease Control and Prevention (CDC) report estimates that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM. It is predicted that the prevalence of DM in adults;type 2 DM is becoming prominent and will be increasing in the next two decades in developing countries withinpatients aged between 45 and 64 years. [3,4,5,6] According to WHO report, , approximately 285 million people worldwide (6.6%) in the 20–79 year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006, published by the International Diabetes Federation, the number of people with diabetes in India around 40.9 million was expected to rise to 69.9 million by 2025 unless urgent preventive stepsare taken. The "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. Higher prevalence of diabetes mellitus often results from in changes in dietary patterns and decreased physical activity in the urban population.[7] Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. The prevalence of diabetes is predicted to double globally from 171 million to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.[8,9,10] In developed countries, approximately 87% to 91% of the diagnosed diabetic people are estimated to have type II diabetes, 7% to 12% present type I diabetes while 1% to 3% to have other types of diabetes. In under developed and developing countries, the relative cases of type I and type II diabetes have not been studied in great detail. Nonetheless, it seems that type I diabetes is less frequent than type II diabetes, as well as it is increasing by almost 3% each year globally. It has been correlated that in most developed countries, the greater part of DM cases in toddlers and juveniles are associated with type I diabetes whereas type II diabetes is reported as a more common condition. [11] Mostly, type II diabetes presence has been elevated alongside accelerated sociocultural alterations: ageing populations, increasing number of people living in urban areas, low physical activity, increased sugar consumption as well as low fruit and vegetable intake.[12] It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases. [13] Lifestyle, Genetics, and Medical Conditions Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important for the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol.Obesity has been found to contribute to approximately 55% of cases of type 2 DM. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to the increase in type 2 DM in children and adolescents. [13] Environmental toxins may contribute to the recent increases in the rate of type 2 DM. A weak positive correlation has been found between the concentrations of bisphenol A in the urine a constituent of some plastics, and the incidence of type 2 DM. [14]There is a strong inheritable genetic connection in type 2 DM, as the risks of developing type 2 DM increases. Concordance among monozygotic twins is close to 100%, and the percent of twins with family history of DM is 25%. Recently, genes discovered to be significantly associated with developing type 2 DM, include TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX. KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and TCF7L2 (transcription factor 7-like 2) regulates proglucagon gene expression and thus the production of glucagonlike peptide-1. Moreover, obesity (which is an independent risk factor for type 2 DM) is strongly inherited. Monogenic forms like Maturity-onset diabetes of the young (MODY), constitutes up to 5% of cases. There are many medical conditions which can potentially give rise to, or exacerbate type 2 DM. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reaven's syndrome). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma,

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chronic pancreatitis, cancer. Additional factors found to increase the risk of type 2 DM include aging, high-fat diets, and a less active lifestyle.'[15,16,]

1.2 Pathophysiology

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. [17] This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM. As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal.[20] Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important gut mediators of insulin release,. Although GIP activity is impaired in those with type 2 DM, GLP1 insulino tropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. However, like GIP; GLP-1 is rapidly inactivated by DPP-IV *in vivo.* Two therapeutic approaches to this problem have been developed: GLP-1 analogues with increased half-lives, and DPP-IV inhibitors, which prevent the breakdown of endogenous GLP1 as well as GIP. Both classes of agents have shown promising potential to normalize fasting and postprandial glucose levels and also to improve beta-cell functioning. [21] Studies are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and etiology of type 2 DM. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNF alpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction).[21] A majority of individuals suffering from type 2 DM are obese, with central visceral adiposity. Therefore, the adipose tissue plays a crucial role in the pathogenesis of type 2 DM. Although the predominant theory used to explain this point is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations. The two new emerging theories are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver and pancreatic cells). These two hypotheses constitute the framework for the study of the interplay between insulin resistance and betacell dysfunction in type 2 DM as well as between our obesogenic environment and DM risk in the next decade.[18,19] Insulin resistance in type 2 diabetes patients increases the demand for insulin in insulin-targettissues. In addition to insulin resistance, the increased demand for insulin could not be met by the pancreatic β cells due to defects in the function of these cells. On the contrary, insulin secretion decreases with the increased demand for insulin by time due to the gradual destruction of β cells that could transform some of type 2 diabetes patients from being independent to become dependent on insulin. Most type 2 diabetes patients are not dependent on insulin where insulin secretion continues and insulin depletion rarely occurs. Dependence on insulin is one of the major differences from type 1 diabetes. Other differences include the absence of ketoacidosis in most patients of type 2 diabetes and autoimmune destruction of β cells does not occur. Both type 1 and type 2 diabetes have genetic predisposition, however, it is stronger in type 2 but the genes are more characterized in type 1 (the TCF7L2 gene is strongly associated with type 2 diabetes). In addition to diabetes, insulin resistance has many manifestations that include obesity, nephropathy, essential hypertension, dyslipidemia (hypertriglyceridemia, low HDL, decreased LDL particle diameter, enhanced postprandial lipemia and remnant lipoprotein accumulation), ovarian hyperandrogenism and premature adrenarche, non-alcoholic fatty liver disease and systemic inflammation. The presence of type 2 diabetes in children and adolescence who are not obese, the occasional severe dehydration and the presence of ketoacidosis in some pediatric patients with type 2 diabetes had led to the misclassification of type 2 to type 1 diabetes.[23] Some patients with many features of type 2 diabetes have some type 1 characteristics including the presence of islet cell autoantibodies or autoantibodies to GAD65 are classified as a distinct type of diabetes called latent autoimmune diabetes in adults (LADA). People diagnosed with LADA do not require insulin treatment. [23] In a recent study, reported 7.1% of European patients with type 2 diabetes with a mean age of 62 years, tested positive for GAD autoantibodies and the prevalence of LADA was higher in patients diagnosed with diabetes at a younger age. This classification of LADA as a distinct type of diabetes is still controversial.

1.3 Complications of diabetes mellitus

- Acute complications: Hypoglycemia, Hyperglycemic crises, Diabetes Ketoacidosis (DKA), Hyperglycemic hyperosmolar state (HHS)
- Chronic complications

1. Micro vascular complications: Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy
2. Macrovascular disease
3. Other complications and associated conditions: Impaired growth and development; Associated autoimmune conditions such as Hypothyroidism, Hyperthyroidism, Celiac disease,Vitiligo, Primary adrenal insufficiency (Addison's disease); Lipodystrophy (lipoatrophy and lipohypertrophy); Necrobiosislipoidicadiabeticorum; Non-alcoholic fatty liver disease; Infections seen in patients with diabetes; Limited joint mobility; Edema

1.4 Goals of management

Primary prevention is the main aim at preventing diabetes from occurring in susceptible individuals or in general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes.[2, 25]Dietary and lifestyle modifications are the main goals of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes is overweight and usually has other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidinediones. Their main goal is to restore normal

metabolic disorders such as insulin resistance and inadequate insulin secretion from pancreas. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. [24]

1.5 Treatment: Insulin and oral hypoglycemic drugs

Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycemia and preventing hypoglycemia between meals. Site of administration of insulin injection is equally important for better and safe action of insulin and can be given by intramuscular or intravenous route. Different preparations of insulin are available such as human insulin, beef insulin, pork insulin. Insulin therapy is no free from complications and adverse effects. The most important adverse effects are weight gain and hypoglycemia when inappropriate dose of insulin is taken and when there is a mismatch between meals and insulin injections. Weight gain after starting insulin therapy for uncontrolled diabetes is an inevitable consequence and is the result of increased truncal fat and muscle bulk. This is also due to reduced energy losses through glycosuria. Sulphonylureas such as glibenclamide, glipizide and biguanides such as metformin, phenformin are oral hypoglycemic drugs. Sulfonylureascausehypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind to sulfonylurea (SUR) receptors on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP)-sensitive potassium channels, leading to depolarization of the cell membrane. This in turn opens voltagegated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules. Acute administration of sulfonylureas to type 2 DM patient's increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycemic actions of sulfonylureas. Biguanides such as metformin is anti-hyperglycaemic, not hypoglycemic. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses. It has been shown to increase peripheral uptake of glucose, and to reduce hepatic glucose output by approximately 20-30% when given orally but not intravenously. Impaired absorption of glucose from the gut has also been suggested as a mechanism of action. [26,27,28]

1.6 Herbal treatment of diabetes

In the last few decades eco-friendly, bio-friendly, cost effective and relatively safe, plant-based medicines have moved from the fringe to the mainstream with the increased research in the field of traditional medicine. There are several literature reviews by different authors about anti-diabetic herbal agents, but the most informative is the review by Atta-ar-Rahman who has documented more than 300 plant species accepted for their hypoglycaemic properties. [29] The WHO has listed 21,000 plants, which are used for medicinal purposes around the world. Among these, 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world. A survey of the literature has revealed that enormous varieties of compounds acquired from numerous plant families possessed to have the hypoglycaemic action. For illustration, glycosides secluded from the families Caesalpinaceae, Compositae, Convolvulaceae, Ericaceae, Moraceae, Myrataceae, Papaveraceae, Ranunculaceae, Rhamnaceae and Scrophulaceae gave active principles which reduced blood sugars in test animals. Glycans from Ranunculaceae and Graminae demonstrated similar hypoglycaemic activity. Alkaloids from Apocynaceae, Papaveraceae, Rhamnaceae, and Zygophyllaceae were predominantly active against diabetes. Saponins from Araliaceae, glycoproteins from Malvaceae, peptides, amino acids and proteins from Papipilionaceae and Rubiaceae families also exhibited positive effects in reducing the blood sugar levels. [29] There is much research undertaken for antidiabetic activity of herbs and their actives on animals. Thus, aqueous extracts of *Bambusa dendrocalumus* leaves demonstrated significant decrease of blood sugar in both normal and alloxan-treated rabbits. [30] A glycoside obtained from the bark of *Ficus bengalensis* produced a hypoglycemic effect in in diabetic animals.[31] The alcoholic extract of the leaves of *Gymnea sylvestre* and *Tribang shill* produced insignificant reduction in blood sugar in normal rats but caused noticeable and substantial reduction in anterior pituitary-treated hyperglycemic animals.[32] Quinquefolan A, B and C (glycans) isolated from *Panax quinquefolium* roots employed significant hypoglycemic activity in mice.[33] Oryzarans A, B, C and D of *Oryza sativa* roots significantly lowered the sugar levels in normal and alloxan-induced diabetic mice. [34] Mucilages and the deacetylated product of Plantago mucilage exhibited significant hypoglycemic activity.[35] A hyperglycemic effect has been reported for the pulverized *Cuminum nigrum* seeds on blood glucose of normal and alloxan-treated rabbits. [36] *Eriobotrya japonica* leaves are found to be efficacious in reducing blood glucose levels of diabetic rabbits.[37] *Trigonella foenum-graecum* is reported to intensify peripheral utilization of glucose, upsurge hepatic and muscle glucagon contents, endorse B cells repair and regeneration and proliferate C-peptide level. It also possesses antioxidant properties and safeguards B cells from oxidative stress. It employs insulin like action by decreasing the glycated haemoglobin levels, regularizing the micro albumin urea and modifying the lipid profile. It also helps in reducing long term diabetic complications. [38] Epicatechin is a natural flavonoid found in green tea. Epicatechin proliferates the cAMP content of the islet and thus amplifies insulin secretion. [39] Bitter gourd helps in reducing the blood & urine sugar levels as it consists of number of chemical constituents like bitter glycosides, saponins, alkaloids, reducing sugars, phenolics, oils, free acids, polypeptides, sterols, 17-amino acids including methionine and a crystalline product named p-insulin. [40] Gurmar is known to reduce the intestinal absorption of sacharides in order to avoid blood sugar fluctuations. Gurmar increases insulin secretion and reduces blood sugar which is found in clinical research. [40] Many herbal drugs are used by people and various native drugs are regularly being introduced into current therapeutics. About 80% of the people, in developing countries, particularly the rural people, rely on the conventional medical remedies for health care requirements. It is very important to understand how polyherbal formulations interventions may contribute to diabetes management. The possible pathways can be modified by herbal formulations are proinflammatory pathways and cellular oxidative pathways, by altering the same can modulate insulin resistance. Insulin secretory activities, pancreatic regenerative activities and GLP like activities of the herbal formulations are very well studied by numerous researchers.[41]There are various preclinical evidences of polyherbal formulations with potential benefits in modulating

diabetic complications like cardiac and nephropathy etc. The targeted polyherbal formulation with definitive end points and its clinical validation is need of the hour to project herbal therapy in the mainstream management of diabetes. There has been a revival of interest in herbal drugs in developed countries due to a huge amount on the preference of products from natural sources.

1.7 The Future aspects of herbal remedies for diabetes mellitus

The rapidly growing occurrence of diabetes mellitus is seriousness to human physical condition all over the world. Recently, new active medicines have been extracted from plants that possess anti-diabetic activity with more effectiveness in improving the quality of life and restricting diabetic complications. Substances and extracts isolated from different natural resources play very important role to design medicine and treat hyperglycemic problem in diabetes mellitus.

2. CONCLUSION

The review summarizes that type 2 DM being a metabolic disorder can be prevented through life style modification, controlled diet, regular exercise and reducing body weight. Although new approaches for treatment and management of diabetes are explored and advanced but their adverse effects and complications makes them unfavourable for use. Thus, tailoring of herbal remedies and lifestyle modification, hand in hand, work efficiently in management of diabetes.

3. AUTHORS CONTRIBUTION STATEMENT

Ms.PriyaKhare and Dr.OmkarKulkarni conceptualized and gathered the data with regard to this work. Mr.Anuj Agarwal and Dr.Gayatri Ganu analyzed these review points and necessary inputs were given towards the designing of the review.

4. CONFLICT OF INTEREST

Conflict of interest declared none.

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