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Mini Review

An Introduction to the Pathways of Action of Herbal Products and Secondary Metabolites Required for the Management of Diabetes

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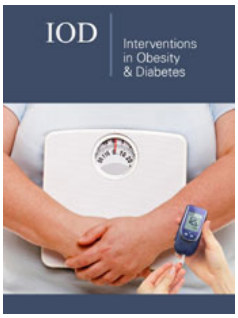

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Abstract

One of the reasons for the failures of treatments for diabetes mellitus in African medicine is the lack of knowledge of the different types of diabetes and the existence of the mechanisms of action of plant extracts or their secondary metabolites responsible for antihyperglycemic activities, called active ingredients. The different types of diabetes are not taken into account by local therapists. The present work investigates the pathways of action of herbal products and secondary metabolites necessary for the management of diabetes. To achieve this objective previous article were searching systematically using "herbal products and secondary metabolites necessary for the management of diabetes" as engine to access Google, PubMed and Google scholar databases. All the relevant articles, published in English language between 1914 and 2018 were collected for widespread review. The mechanisms of action of the active compounds like charantin, momordicoside S and its aglycones momordicosides, polypeptide-p, vicine, and momordin, in herbal medicines with relevance to their glucose-lowering identified are: inhibition of intestinal absorption of glucose, suppression key glycogenic enzymes, decreased hepatic gluconeogenesis, AMP-activated protein kinase activator, reduced expression Phosphoenolpyruvate Carboxykinase, reduced glucose and lipids and upregulation of insulin signaling pathway-associated proteins. This knowledge is of extreme importance in order to establish the best possible herbal treatments of diabetes.

Keywords: Type 1;Type 2 diabetes mellitus;Gestational diabetes;Antidiabetic activity;Herbal medicines;Previous mechanisms of action

Abbreviations: PEPCK: Phosphoenolpyruvate Carboxykinase; HCS:Human Chorionic Somatomammotropin; NAFLD: Non-Alcoholic Fatty Liver Disease; AMPK: Adenosine Monophosphate-Activated Protein Kinase

Introduction

Historical aspects

1500 years after Jesus Christ, a European doctor (Paracelsus) revealed in the urine of diabetics a substance which appeared as a white powder. 100 years after this revelation, the urine of diabetics was found to have a sweet taste. The term diabetes mellitus was used for the first time [1,2]. Improvements in medicine and technology have now made it possible to better define, diagnose, prevent, treat, classify diabetes into three large groups and identify its complications. These are type 1, type 2 and gestational diabetes. Today it globally knows that diabetes mellitus is a metabolic syndrome characterized by chronic hyperglycemia associated with impairment of either insulin secretion or the action of insulin, or both. In early time diabetes was consider as disorder of the elderly people. But now it becomes a major cause of morbidity and mortality affecting the youth and middle aged people.

Complications

As it progresses, diabetes can cause serious complications affecting the brain (Cerebrovascular damage), the heart (heart failure and ischemic heart disease), blood vessels (peripheral arterial disease), eyes (retinopathy), kidneys (diabetic nephropathy) and nerves (neuropathies). Other complications include diabetic foot, infections, bone damage and cancer. Therefore diabetes mellitus is a common consequence of uncontrolled high blood glucose and it is related with long-term destruction, dysfunction, and failure of numerous organs. Nonetheless, good disease management can meaningfully decrease the risk of these

complications [3].

Prevalence

Diabetes is reaching epidemic proportions worldwide. In 2003, the International Diabetes Federation estimated that 194 million people had diabetes worldwide. By 2025, it is expected to reach 333 million, or 6.3% of the world's population [3]. Particularly in Cameroon, the prevalence of diabetes in 2018 is 4.5% for men and 4.9% for women, for 4.7% in total.

Management

Effective prevention and controlling programs are needed; the ongoing substantial upsurge in diabetes will have severe consequences on the health and life expectancy of the global population, and also on the economy worldwide. Lower costs supplements can be used to correct nutritional insufficiencies or to maintain an adequate consumption of certain nutrients, usually used as treatments for diabetes. They are more accessible or "natural" compared to pharmaceutical products. Several vitamins, minerals, herbal medicines, and secondary metabolites have been reported to stimulate beneficial antihyperglycemic activities *in vivo* and *in vitro*. However, until now, the data remain inconsistent. Many pharmaceutical drugs generally used today are fundamentally derived from ethno pharmacological research. Medicinal plants most frequently used in Cameroon to control blood sugar level published by our research team include: *Momordica charantia Lin.* (Cucurbiataceae), *Laportea ovalifera* (Schumach. & Thonn.) Chew (Urticaceae), *Catharanthus roseaus* Lin. (Apocynaceae), *Allium cepa* Lin. (Amaryllidaceae), *Allium sativum* Lin. (Amaryllidaceae) and *Morinda lucida* Benth. (Rubiaceae). In majority of the herbal medicines and secondary metabolites used in the treatment of diabetes, the mechanisms of action involve:

Type 1 diabetes

It is an autoimmune disease which begins when the immune system destroys insulin and amylin-producing β cells, found in pancreatic islets. Why the immune system attacks the β cells remains unknown. Herbal medicines in type 1 diabetes are extra pancreatic compounds like Polypeptide-p which is sometimes referred as "plant insulin. They can inspire endogenous renewal pancreatic β cells.

Type 2 diabetes

The interface between numerous genetic and environmental factors results in a heterogeneous and progressive disorder with insulin resistance and pancreatic β cell dysfunction. Overweight and obesity are major contributors to the development of insulin resistance and impaired glucose tolerance. Herbal medicines act by rising insulin secretion, increasing glucose uptake by adipose and skeletal muscle tissues, obstructing intestinal glucose absorption (by inhibiting intestinal α-amylase and α-glucosidase), combining endogenous insulin resistance, obstructing hepatic glucose production and inspiring endogenous renewal pancreatic β cells.

Gestational diabetes

It is any abnormal carbohydrate intolerance that begins or is first demonstrated during pregnancy. Plants for this particular diabetes may react as in type 1 and type 2 diabetes. The analysis of the review of the literature on this diabetes and its complexity due to the physiology of the fetus and the physiological changes in the mother bring up 8 fundamental research questions which can help in managing gestational diabetes (Tsabang, personal communication). These fundamental hypotheses which will serve as research keys are:

a. Can plant potentially combat insulin resistant more frequent in gestational diabetes?

b. Can plant stop abnormal insulin secretion by the fetus?

c. Can plant regulate the production of HCS (human chorionic somatomammotropin) by the placenta?

d. Can plant prevent diseases in mother including obesity, preeclampsia, and the eventual need for cesarean section?

e. Can plant prevent diseases in newborns including macrosomia, birth trauma, and shoulder dystocia?

f. Can plant avoid babies at birth from developing hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia and type 2 diabetes?

g. Can plant potentially tackle the inhibition of peripheral glucose uptake in the pregnant woman?

h. Can plant potentially fight against obesity?

Other types of diabetes

Other specific types include a wide variety of relatively uncommon disorders, mostly genetically defined forms of diabetes or associated with other diseases or drugs [4].

Methodology

Two stepped methodology were used to search previous articles. A searching systematically using "pathways of action of herbal antidiabetic plants or products" as first engine and secondary metabolites necessary for the management of diabetes" as second engine to access Google, PubMed and Google scholar databases. Some relevant articles, published in English language between 1914 and 2018 were collected for extensive review.

Chemical constituents and mechanisms of action of the most studied plants: *Momordica charantia* Lin.

The main focus of this review is to describe what we know to date as mechanisms of action of the active compounds in herbal medicines. In term of chemical constitution *Momordica charantia* Lin. one the greatest used plant in Cameroon contents the following compounds: charantin, karaviloside IX, momordicoside S and its aglycones momordicosides A, B, Q, R, and T, and also polypeptide-p, vicine, and momordin [5,6]. Numerous mechanisms

of action proposed for the hypoglycemic actions of plant extracts include: inhibit intestinal absorption of glucose [7,8], suppress key glycogenic enzymes [9], and decrease hepatic gluconeogenesis [10], enhancing the activity of the AMP-activated protein kinase (AMPK) pathway (which is an important cellular regulator of lipid and glucose metabolism), and reduces expression of phosphoenolpyruvate carboxykinase (PEPCK); which results in reduced glucose levels and hypoglycemic agent [11], reduced blood glucose and blood lipids while improving glucose tolerance, upregulated the expression of several of insulin signaling pathway-associated proteins [12].

The other medicinal plant extracts and/or their bio-actives substances play antidiabetic activities that include:

a. The improvement of oxidative stress for *Annona muricata* Lin. and *Solanum torvum* Sm;

b. The enhancement of α-glucosidase action; the enlightening endothelial dysfunction for *Bidens pilosa* Lin., *Carica papaya* Lin. and *Annona muricata* Lin.);

c. The controlling cytokine expression diabetes induced damages of neural cells for *Bidens Pilosa* Lin., *Carica papaya* Lin. and *Annona muricata* Lin.);

d. The ameliorating insulin resistance, for *Momordica charantia* Lin.;

e. The suppressing hyperglycemia for *Persea americana* Mill. and *Momordica charantia* Lin.;

f. The improving hyperglycemic complications for *Carica papaya* Lin. and *Moringa oleifera* Lam.; and finally the regulating signaling pathway linking in diabetes, the enhancing immunity, the alleviating pancreatic β-cells regeneration for *Elephantopus scaber* Lin., *Momordica charantia* Lin., *Solanum torvum* Sm. and *Terminalia catappa* Lin. [13].

The mechanism of action of medicinal plants as bioactive compounds is now of significance to the worldwide diabetes epidemic [14]. The anti-aging policies ensure the preservation of appetite regulation and insulin resistance which are associated to the anti-aging genes that are blocked early in life. In both developed and developing countries nutritional interventions have become indispensable to prevent global Non Alcoholic Fatty Liver Disease and to preserve the metabolism of glucose, fatty acids, cholesterol, amyloid beta, bile acids and xenobiotics. So over food in long-lasting disease is implicated with central nervous system dysregulation of neuropeptides with atypical peripheral hormone signaling from the pancreas (insulin), adipose tissue (leptin and adiponectin) and gastrointestinal tract (neuropeptides) implicated in long-lasting diseases [15]. Nutritional and environmental epigenetics are involved in the suppression of anti-aging genes linked to the epidemic of chronic diseases. Unhealthy diets inactivate the calorie-sensitive gene Sirtuin 1 involved in epigenetic processes that promote alterations in the immune system, mitochondrial apoptosis, non-alcoholic fatty liver disease (NAFLD), diabetes, and blood loss Nitric oxide as a function of core body temperature involved in the regulation of appetite, glucose homeostasis and hepatic xenobiotic metabolism [16]. Caffeine is an appetite suppressant which may improve the adipose tissue-liver cross talk with the prevention of NAFLD in obese and Type 2 diabetic people [17]. Appetite dysregulation accelerates abnormal post-prandial lipid metabolism and non-alcoholic fatty liver disease in universal populations and early intervention is required to prevent the severity of diseases such as obesity, diabetes and neurodegenerative diseases. The anti-aging gene Sirtuin 1 is now critical for the management of diabetes and Sirtuin 1 repression leads to insulin resistance and programmed cell death. Neurons in the hypothalamus (the center of appetite) are sensitive to apoptosis and become senescent early in life, which affects global chronic diseases such as non-alcoholic fatty liver disease, obesity and diabetes [14].

Dietary components that activate anti-aging genes improve insulin therapy and should be assessed with specific amounts and doses of spices consumed that may not interfere with insulin therapy and induce mitophagy in various diseases. Food quality, appetite control and core body temperature are critical to maintain insulin therapy with unhealthy diets linked to NAFLD and diabetes. Genomic medicine and dietary activators are essential to maintain insulin therapy and prevent toxic immune reactions with relevance to NAFLD and diabetes management [18]. Appetite dysregulation involves neurons associated with the suppression of the anti-aging gene Sirtuin 1 and other anti-aging genes such as Klotho, p66Shc and FOXO1/FOXO3a that are connected to the programmed cell death (mitochondrial apoptosis) and dysregulation of glucose, lipid and amyloid beta metabolism. Nutritional intervention early in life with the consumption of very low carbohydrate diets has been recommended that allows maintenance of the autonomic innervation of the liver by the brain [14]. Nineteen [19] Sirtuin 1 activators were identified from traditional Chinese medicine. They are: ginsenoside Rg3, ginsenoside, Rb2, ginsenoside, Rb3, ginsenoside F1, and ginsenoside Rc from Panax gin-seng; ophiopogon D from *Ophiopogon japonicas*, and schisandrin A and schisandrin B from *Schisandra chinensis*. Fascinatingly, those plants involved in a traditional Chinese formula named Shengmai San, which have been clinically used for the treatment of coronary heart diseases. Some of these Sirtuin 1 activators react against mitochondrial oxidative damage in supplementary study [19].

Cameroonian antidiabetic plants review

The chemical constituents and mechanisms of action of plants such as *Momordica charantia* may include that activation of Sirtuin 1 that is critical to the treatment of insulin resistance. The leaves extract of *Gymnema sylvestre* is found to be useful for the treatment of diabetes mellitus and obesity, by inhibit the absorption of glucose in the small intestine and have inhibitory action against

glucan synthesis by glucosyltransferase. A number of gymnema products such as gymnema capsules, gymnema tea, bioshape®, and diaxinol® have been developed and using for the treatment of different diseases including diabetes [20]. The main focus of this review is to describe what we know to date as mechanisms of action of the active compounds in herbal medicines, along with their glucose-lowering mechanisms, which are either through insulin-mimicking activity or improved glucose uptake. Activators and inhibitors of Sirtuin 1 have been identified that are important to the management of diabetes. Appetite maintenance improves the endocrine and metabolic system. In-depth studies, validating of efficiencies and safeties of extracts of antidiabetic herbal medicine are needed. Also large well designed, clinical studies need to be carried out before the use of plant preparations can be recommended for treatment and/or prevention of diabetes.

Conclusion

Informed information on the pathways of action of herbal medicines and secondary metabolites and on altered diabetic patient metabolism required for the management of diabetes can be exploited for development of new herbal antidiabetic investigations. Polypeptides to proteins, all have effective antidiabetic properties. Excretions from plants that are co-secreted with insulin have demonstrated to inhibit insulin discharge and muscle glycogenesis. Amylin is thought to play a foremost role in the disturbed metabolism associated with diabetes mellitus. The search for drugs that may antagonize amylin, and consequently improve metabolic control in diabetic patients, is considered as an important investigation for innovative antidiabetic herbal agents. Medicinal plants like *Momordica charantia* L. that have been shown to improve the diabetic state without specious improvement of insulin discharge may be good sources of new Phyto drugs worldwide.

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