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Phytotherapy for Diabetes; Evidenced with the 1H NMR-Spectrometry of Local *Cnidoscolus aconitifolius* Leaf Extract: A Review

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ABSTRACT

Studies had shown that hydromethanolic leaf extract of *Cnidoscolus aconitifolius* (CA) caused dose-dependent antihyperglycaemic or hypoglycaemic effects. Its adverse effects were reportedly lesser compared to some currently used pharmaceuticals. Nuclear Magnetic Resonance (1H NMR-Spectrometry) had been used to analyze the chloroform fraction of this *CA* extract in order to identify the major and minor phytochemicals responsible for its activities. The presence of the bioactive flavonoids possibly has molecular mechanisms of lowering the diabetic glucose levels and complications. The antidiabetic compounds identified in plant extracts included: isoquercetin, eupafolin, hispidulin, oleanolic acid, β sitosterol and campesterol. These phyto-compounds work through different mechanisms, including the interference of glucose and lipid absorptions, regeneration of pancreatic islets or by increasing the insulin release by beta cells. These phyto-constituents could synergistically lower persistent hyperglycaemia and its complications. The plant leaves of CA are readily available in most residential areas as a vegetable or herb ('*Ogwu-obara*' in Igbo) with reported minimal side effects compared to more costly synthetic antidiabetic drugs. This review calls for the advancement of ethno-pharmaceutical technology in poorer African countries in order to carry out purposeful ethno-pharmacological researches and develop affordable phytotherapy for diabetes.

Keywords: NMR- Spectrometry, Phytotherapy, Diabetes, *Cnidoscolus aconitifolius*

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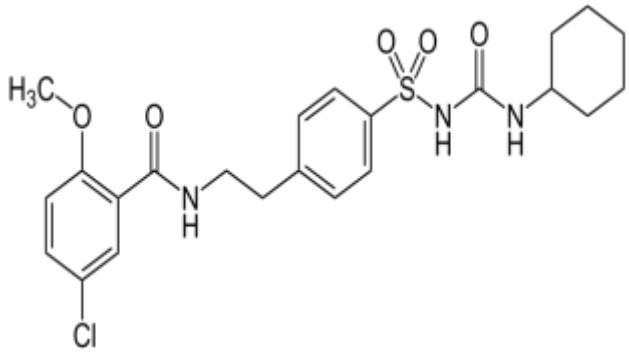
INTRODUCTION

Blood glucose is essential for normal production of energy (adenosine triphosphate, ATP) required to power metabolic activities of the human body. The homeostatic regulation of blood glucose in the body's internal environment is vital as some organs like the brain and the testes cannot function optimally without appropriate blood glucose level. However, persistently high fasting plasma glucose concentration (hyperglycaemia) above 6.9mmol/l (125mg/dl) is a disease known as Diabetes or Diabetes mellitus[1]

Diabetes is of global concern[2]. Majority of new diabetic cases are reportedly occurring in Asia and Africa due to their changing lifestyle[3], including change in diet and increased exposure to chemicals and drugs[4]. Long-term diabetes is associated with several co-morbidities, such as erectile dysfunction, blindness, poor wound healing, kidney failure, heart disease, etc as a result of considerable damage, dysfunction, and failure of various organs that develop as the disease progresses [5]. Currently, about 437 million people are suffering from diabetes and the death rate is projected to double between 2005 and 2030[6]. Apart from the expected global health care costs involved in treating and managing DM, this disease imposes additional social economic burdens from lost productivity and slow economic growth. Therefore, there is a need for the development of more appropriate preventive and therapeutic approaches that address and abolish the reduction in life expectancy and life quality imposed by DM and its complications or co-morbidities[7]. Diabetes management is complex and requires that many issues, beyond glycaemic control, be addressed[8].

The available treatments for diabetes have their own drawbacks ranging from development of resistance and adverse effects to lack of responsiveness in a large segment of patient population. Moreover, none of the glucose lowering agents adequately control the hyperlipidemia that frequently met with the disease[9]. For instance, Glibenclamide is a new generation oral antidiabetic drug



(5-chloro-*N*-(4-[*N*-(cyclohexylcarbamoyl) sulfamoyl] phenethyl)-2-methoxybenzamide)

It works by inhibiting the sulfonylurea receptor 1 (SUR1), the regulatory subunit of the ATP-sensitive potassium channels (K_{ATP})[10] in pancreatic beta cells. This inhibition causes cell membrane

depolarization opening voltage-dependent calcium channel. This results in an increase in intracellular calcium in the beta cell and subsequent stimulation of insulin release. However, glibenclamide is a major cause of drug-induced hypoglycaemia, cholestatic jaundice and associated with significantly higher annual mortality when combined with metformin than other insulin-secreting medications, after correcting for other potentially confounding patient characteristics[11].

The limitation of currently available oral anti-diabetic agents either in terms of efficacy or safety coupled with the emergence of the disease into global epidemic had encouraged alternative but appropriate therapy that can manage diabetes more efficiently and safely[12].

Medicinal plant extracts have been valuable anti-diabetic agents and may involve one or more active components responsible for blood glucose reduction [13]. Researchers are now geared toward finding appropriate nutraceutical that can obviate or minimize diabetes and its complications. The effect of several plants used as antidiabetic remedies has been confirmed, and the mechanisms of these plants are still being studied[14].

Cnidoscolus aconitifolius (CA) is an edible vegetable commonly known in traditional medicine as a blood builder ('*ogwu-obara*' in Igbo) [15]. Nuclear Magnetic Resonance (NMR) investigation of the leaf extract was used to ascertain its actual phytochemical compositions useful in extrapolating the antidiabetic mechanisms appropriate in interrupting the ravaging diabetes and its complications[16].

Phytotherapy for Diabetes: Evidenced With the 1H NMR- Spectrometry Of Local *Cnidoscolus Aconitifolius* Leaf Extract

Cnidoscolus aconitifolius (CA) is rampantly seen in most residential areas of the Southern Nigeria. The fresh leaves sample collected in one of the private residences in Owerri, Nigeria was authenticated by Dr. Mrs. M E. Bassey as *Cnidoscolus aconitifolius* and it was kept as herbarium I Samuel UUH 026113 (Port Harcourt) in the University of Uyo, Nigeria. [15].

Figure 1: *Cnidoscolus aconitifolius (CA)* obtained in Owerri, Nigeria [17].

The preparation of the extract was carried out at the Department of Pharmacognosy and Natural Medicine, University of Uyo, Akwa Ibom State, Nigeria. The fresh leaves of CA were air dried

under room temperature and extraction method was adapted from a previous report [18]. The air-dried leaves of CA were pulverized and Soxhlet-extracted with aqueous methanol (1:4, v/v). The dried leaf extract obtained was purified in chloroform and analyzed with 1H NMR- spectrometry using dimethyl sulphoxide (DMSO) solvent at the University of Cape Town with the results reported [16].

Antidiabetic Phyto-compounds

The proton NMR spectra were interpreted to indicate the presence of major phytochemicals in *CA* like flavonoids, anthranoids, saponins and alkaloids with their minor bioactive compounds. Some of the identified compounds included eupafolin, hispidulin, oleonolic acid, β-sitosterol, isoquercetin, kaempferol 3-*O*- gentiobioside, rhamnopyranosyl-(1)-glucopyranosyl-(1)-glucopyranoside, Seneciomine, Retrorsine and Seneciphylline [15, 16].

Importance of these Antidiabetic Phyto-compounds

Diabetes mellitus is a metabolic disorder found in all nations of the world. It is one of the most prevalent epidemics of the 21st century[19]. Its rapidly increasing prevalence is a significant cause for concern[20]. The projected doubling prevalence of diabetes with the associated adverse reactions of its current chemotherapeutics mandates this paper.

Current therapies seem to be insufficient to prevent diabetic complications in type2 diabetes, with a two- to four-fold likelihood for developing cardiovascular complications. Because of these limitations, there is a continuous need for the development of novel health promotion strategies and appropriate therapeutic modalities for the estimated 75% dying of diabetes- related complications from cardiovascular disease [21]. Medicinal plant extracts have been valuable anti-diabetic agents and may involve one or more active components responsible for blood glucose reduction[13].

Previous studies had shown that *Cnidoscolus aconitifolius (CA)* has a dose-dependent antihyperglycaemic potential comparable to an available antidiabetic pharmaceutical, glibenclamide. That 100mg/Kg CA extract is more than 50% antihyperglycaemic as 0.5mg/Kg b.w. Glibenclamide is therefore notable in an experimental animal study [22]. Similar effects had also been reported with plant extract when compared with Chlorpropamide[23].

Possible Mechanisms of Antidiabetic Phyto-compounds

This antihyperglycaemic activity of CA extract could be justified by the presence of flavonoids and saponins[15]. The presence of flavonoids and saponins which may be responsible for the observed antidiabetic effects of these fractions is by possibly stimulating insulin release from pancreatic beta cells [24]. These results therefore support the proposal that CA has an insulinogenic property that possibly stimulated dormant beta-cells to secrete insulin [23].

Many animal and human studies indicated the significance of pharmacological doses of standardized pure single flavonoids in improving glycaemic control, both in experimental animal models of DM and in patients with T2DM; most of the studied flavonoids act through interference with digestion of complex sugars and absorption of glucose [25, 26, 27, 28]. Inhibition of carbohydrate digestive enzymes may be of use to patients with T2DM as well as the growing pre-diabetic population around the world[29, 30].

Many *in vitro* studies suggest that the anthocyanins may decrease the intestinal absorption of glucose by retarding the release of glucose during digestion [31, 32]. Recently, it was reported that flavonoids isolated from banana flowers have the potential to activate the insulin receptor tyrosine kinase[33], and may represent an alternative choice for treatment if T2DM patients with insulin resistance [34, 35]. Flavonoids, especially quercetin have been reported to possess antidiabetic activity. It was reported that quercetin brings about the regeneration of pancreatic islets and probably increases insulin release in streptozotocin-induced diabetic[36]. Also in another study, quercetin stimulated insulin release and enhanced Ca2+ uptake from isolated islets cell which suggest a place for flavonoids in Type2 diabetes treatment[36].

There is mounting evidence that polyphenols can reduce insulin resistance in *in vitro* and animal studies [37, 38]. Currently, Metformin is a phytomedicine used safely as antidiabetic drug [39].

The results of the nutritional and electrolyte analyses of CA also indicated their antihyperglycaemic properties[40]. These showed the percentage composition of moisture, ash, crude protein, crude fat, crude fibre and nitrogen free extract i.e. carbohydrate. It also estimated the energy released by 100mg of the extract. It supported that CA is a good source of protein, vitamins, calcium, and iron; and is also a rich source of antioxidants[41]. In fact, levels of leaf nutrients are reported to be two to threefold greater than any other land-based leafy green vegetable. It is known to ameliorate anaemia and osmotic fragility induced by protein energy malnutrition [42].

CONCLUSION

Affordable local diabetes therapy is a great concern in the health care delivery of every nation. The paper reviewed the reported antidiabetic properties, including the antidiabetic phyto-constituents using 1H NMR- spectrometry and the proposed possible mechanisms of *Cnidoscolus aconitifolius* (CA) for diabetes phytotherapy. It also added the benefits, affordability and accessibility of CA as a vegetable or herbal plant in most residential areas. It therefore called for greater support of pharmaceutical science and technology in poorer countries in order to carry out advanced researches on indigenous phytotherapy and develop affordable local medicines for diabetes management.

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