

## Mechanisms of actions of some bioactive anti-diabetic principles from phytochemicals of medicinal plants: A review

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Diabetes is both an endocrine and a metabolic disease affecting large numbers of individuals worldwide. The use of natural products such as herbs in the management of diseases dates back to the prehistoric era. Herbal therapy presents a less adverse side effect when compared with the synthetic orthodox counterpart. The phytochemical components of medicinal plants have been credited for the efficacy of herbal formulations. The aim of this study is to review some common anti-diabetic plants which have been tested experimentally using recent diabetes marker parameters and to highlight the bioactive anti-diabetic principles isolated from their phytochemicals. In addition, anti-diabetic compounds isolated in the process of research in our laboratory have been cited in the review. Such keywords like anti-diabetic medicinal plants, mechanism of actions, phytochemicals, alloxan, streptozotocin, glycosylated haemoglobin, were used on different search engines to generate secondary data used in this review. Data obtained indicated that various phytochemical components of anti-diabetic herbs such as the flavonoids, saponins, tannins, alkaloids, glycosides, terpenes, were responsible for the said anti-diabetic activities of the plants. The data equally revealed that these phytochemicals acted in diverse mechanisms to bring about their activities. From the data obtained, it was concluded that phytochemicals from anti-diabetic medicinal plants/herbs are pivotal in the production of marketable novel and efficacious anti-diabetic drug in future.

**Keywords:** Anti-diabetic medicinal plants, Alloxan, Diabetes markers, Mechanism of action, Phytochemicals, Streptozotocin.

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### Introduction

Diabetes mellitus is an endocrine disease resulting from insulin deficiency, insulin inaction or both<sup>1</sup>. It is characterized by polydipsia, polyurea, ketonemia and ketonuria<sup>2</sup>. These and other clinical signs and symptoms of D. mellitus if left unattended to, will precipitate diabetic complications which on their own have been fingered as the most frequent causes of morbidity and mortality in diabetics<sup>3</sup>.

Hyperglycemia has been implicated in the development of secondary complications in D. mellitus. Aldose reductase, a very important enzyme in Polyol pathway is therefore activated in the condition of D. mellitus<sup>4</sup>.

Diabetes, “Diab” from Greek word meaning “to pass through” and “mellitus” from Latin word meaning “sweetened with honey” is a disease associated with glycosuria (presence of sugar in urine)<sup>5</sup>. World Health Organization predicts that by the year 2025, about 300 million or more people are likely going to have diabetes with the United States,

China and India leading<sup>6</sup>. D. mellitus is also one of the diseases of animals such as dogs and cats.

Traditionally, D. mellitus is classified into two-type 1 D. mellitus (insulin dependent D. mellitus) and type 2 D. mellitus (non-insulin dependent D. mellitus)<sup>7</sup>. The former is common in juveniles (thus referred to as juvenile diabetes and it is associated with the auto-immune mediated destruction of pancreatic beta cells in which case the affected individual requires exogenous administration of insulin for its management) while the latter is predominant in adults (adult onset) and it is mainly associated with peripheral insulin resistance<sup>7,8</sup>.

Management of D. mellitus employs modifications of diet, change of lifestyle, intake of oral hypoglycemic, administration of exogenous insulin and herbal remedies<sup>9</sup>. Synthetic drugs are fraught with adverse side effects<sup>10,11</sup>. Natural products such as plants and herbs have the capacity to reduce blood glucose values and ameliorate diabetes with reduced adverse side effects<sup>5</sup>. They achieve this owing to the presence of phytochemicals such as flavonoids, saponins, alkaloids, tannins, glycosides, terpenes etc<sup>8</sup>.

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The aim of this review is to highlight the importance of natural products such as herbs in the management of *D. mellitus* owing to the presence of bioactive phytochemical components. The mechanisms by which these active principles of phytochemical origin bring about their effects are also discussed.

#### Flavonoids

Flavonoids are a group of plant metabolites that constitute a family of soluble polyphenolic compounds. They are made up of two benzene rings attached by a short three carbon chain<sup>12,15</sup>. Flavonoids that occur in nature are classified into six classes namely: anthocyanidins (e.g. cyanidin, delphinidin, malvidin, peonidin, petunidin etc), flavan-3-ols (e.g. catechin, epicatechin, gallic catechin etc), flavonols (isorhamnetin, kaempferol, myricetin, quercetin), flavones (e.g. apigenin, luteolin, baicalein, chrysin), flavanones (eriodictyol, hesperetin, naringenin) and isoflavones (daidzein, genistein, glycitein, biochanin A)<sup>12,13</sup>. The anti-diabetic properties of flavonoids are attributed partly to their antioxidant potentials and partly due to their ability to modulate some cell signalling. Dietary flavonoids occur in fruits, vegetables, beverages, chocolates, herbs and plants<sup>14,15</sup>. The following flavonoids isolated from plants have been shown to possess anti-diabetic properties.

#### Diosmin

Diosmin is a flavonoid that occurs in citrus plants naturally. Experimental evidences have revealed its potent anti-diabetic activities mediated by decreases in the level of glycosylated haemoglobin, increases in the activities of glutathione peroxidases<sup>16,17</sup>, significant reductions in plasma glucose values, increases in hepatic hexokinases and glucose-6-phosphate dehydrogenases<sup>18</sup>, increasing insulin levels and ameliorating oxidative stress as evidenced by assay of superoxide dismutase, catalase and glutathione peroxidase activities. It also increased the levels of vitamins C and E<sup>19</sup>. Diosmin is isolated from *Scrophularia nodosa*, an anti-diabetic plant.

#### Fisetin

This flavonoid brings about its anti-diabetic effect by inhibiting gluconeogenesis through inhibition of mitochondrial pyruvate transport and a decrease in the cytosolic NADH/NAD redox<sup>20</sup>. Decreasing of glycogen breakdown, plasma glucose levels, glycosylated haemoglobin, mRNA and protein expression levels of gluconeogenic genes like phosphoenol pyruvate carboxykinase and by increasing plasma insulin are

among the mechanisms by which fisetin brings about its anti-diabetic actions<sup>21</sup>. Moreover, hypoglycaemic activities of fisetin flavonoids have been associated with significant decreases in nuclear factor kappa B (NF- $\kappa$ B) p65 unit, interleukin-1 $\beta$  (IL-1 $\beta$ ) and serum nitric oxide (NO)<sup>21</sup>. Fisetin, produced by *Cotinus coggygria* Scop and also found ubiquitously in strawberry, apple, grape, onions and cucumber has been advocated for use in the prevention of diabetes<sup>22,23</sup>.

#### Morin

Morin-treated diabetic rats showed anti-diabetic activities by improvement of antioxidant agents, reduction of insulin resistance, decrease in oxidative stress parameters, normalization of lipids and lipoproteins and decreases in the levels of tumour necrosis factor alpha (TNF $\alpha$ )<sup>24</sup>. Experimental evidence also suggests that morin reduced inflammatory cytokines IL-1 $\beta$  and IL-6 in diabetic animals<sup>25</sup>. Recovery of hepatic insulin and leptin sensitivity, reduction in hyperlipidaemia and liver-lipid accumulation have been fingered as mechanisms by which morin brings about its anti-diabetic actions<sup>26</sup>. Morin has been shown to reduce glucose-6-phosphatase activities, increase hexokinase, and glucose-6-phosphate dehydrogenase activities and insulin levels<sup>27</sup>. Morin is contained in many medicinal herbs such as *Prunus dulcis* (Mill), *Chlorophora tinctoria* (L), *Psidium guajava*<sup>28,29</sup>.

#### Eriodictyol

Suppression of oxidative stress, up-regulation of mRNA expression of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) and adipocyte-specific fatty acid-binding protein together with the protein levels of PPAR $\gamma$ 2 in differentiated 3T3-L1 adipocytes are key mechanisms involved in the anti-diabetic activity of eriodictyol. It has also been implicated in the reduction of retinal TNF $\alpha$ , intercellular adhesion molecule-1 (ICAM-1), vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS) and lipid peroxides<sup>30,31</sup>. Lemon fruits contain eriodictyol in abundance<sup>32</sup>.

#### Hesperidin

This flavonoid is ubiquitous in plants of the genus citrus especially *Citrus aurantium*<sup>33,34</sup>. Like eriodictyol, hesperidin exhibits anti-diabetic activity by down regulating the generation of free radicals and the release of pro-inflammatory cytokines<sup>35,37</sup>. Normalization of the lipids and adiponectin together with alterations

of the activities of glucose metabolizing enzymes decreases in the levels of thiobarbituric acid reactive substances (TBARS) and increases in the activities of lactate dehydrogenase (LDH) have been reported with hesperidin administration<sup>38,39</sup>.

#### **Naringenin**

Citrus fruits and tomatoes contain naringenin in abundance, which confers antioxidant properties to these fruits<sup>40</sup>. *Cochlospermum* also contains naringenin in large amount<sup>41</sup>. Naringenin inhibits  $\alpha$ -glucosidase activities. It also inhibits glucose uptake *in vitro* and interferes with genes associated with lipid metabolism<sup>42,43</sup>. Activation of 5'AMP-activated protein kinase (AMPK), enhancement of antioxidant activities, reduction of insulin resistance and improvement in hepatic function markers are also thought to be the mechanism of action of naringenin<sup>44-46</sup>.

#### **Apigenin**

This flavone flavonoid is ubiquitous in citrus, onions, vegetables, tea and nut<sup>47</sup>. Its mechanism of action is through the improvement of antioxidant parameters, enhancement of glucose transporter 4 (GLUT4) translocation and beta cell preservation<sup>48,49</sup>.

#### **Baicalein**

Baicalein scavenges free radicals, induces insulin production, reduces glycosylated haemoglobin, suppresses the activation of NF- $\kappa$ B, decreases the expression of inducible nitric oxide synthase (iNOS) and transforming growth factor beta (TGF- $\beta$ )<sup>50,51</sup>. Another major mechanism by which Baicalein operates is by up-regulation of AMPK<sup>44</sup>. This flavonoid is present in the roots of *Scutellaria baicalensis* and fruits of *Oroxylum indicum*<sup>52,53</sup>.

#### **Chrysin**

It is a major component of *Oroxylum indicum*. It has also been isolated from *Passiflora caerulea*, *Pelargonium peltatum*, *Tilia tomentosa*, bee pollen, honey, fruits and vegetables<sup>54-56</sup>. Treatment with chrysin has been associated with suppression of TGF- $\beta$ , fibronectin, and collagen-IV protein expression in the kidney. Serum levels of IL-1 $\beta$  and IL-6 were also reduced. With these observations, chrysin is thought to prevent nephropathy<sup>51</sup>. Chrysin administration also improves insulin levels and reduces lipid peroxidation<sup>57</sup>.

#### **Luteolin**

Luteolin is known to potentiate insulin action and increase transcriptional activation of PPAR $\gamma$ <sup>58</sup>.

Luteolin also decreases circulating levels of inflammatory molecules, Monocyte Chemoattractant Protein-1 (MCP-1), resistin and elevates adiponectin levels in obese mice<sup>59</sup>. It is also on record that luteolin improves insulin secretion<sup>60</sup>. Luteolin is found in abundance in carrots, peppers, cabbage, apple, vegetables and fruits<sup>61-63</sup>.

#### **Tangeretin**

Tangeretin administration decreased total cholesterol, leptin, resistin, IL6 and MCP-1<sup>64</sup>. It is also in the literature that its administration significantly decreased glycosylated haemoglobin, improved insulin levels, enhanced glycolytic enzymes, controlled glucose metabolism in hepatic tissues and decreased an insulin-resistant factor, MCP-1 in 3T3-L1 adipocytes<sup>65</sup>. Rinds of citrus fruits contain tangeretin.

#### **Wogonin**

This is obtained from the root of *Scutellaria baicalensis*<sup>66</sup>. Wogonin interferes with insulin sensitivity and lipid metabolism through its effect on AMPK and PPAR $\alpha$ <sup>67</sup>.

#### **Isorhamnetin**

It is an anti-diabetic principle isolated from *Hippophae rhamnoides*, *Oenanthe javanica* and *Ginkgo biloba*. Its administration reduces oxidative stress, inhibits sorbitol accumulation and interferes with lipid metabolism<sup>68-70</sup>.

#### **Kaempferol**

This flavonol is present in *Ginkgo biloba*, tea, grapefruits, edible berry and vegetables<sup>71-73</sup>. Its administration is associated with the inhibition of apoptosis, reduction of caspase-3 activity in beta cells, improvement of cAMP signalling and enhancement of insulin synthesis and secretion<sup>74</sup>. It is also associated with the enhancement of antioxidant production and reduction of IL-1 $\beta$ , TNF $\alpha$ , lipid peroxidation, nitrite and glycosylated haemoglobin<sup>75,76</sup>.

#### **Rutin**

Oranges, grapes, buckwheat, lemons, limes, berries and peaches contain rutin<sup>77,78</sup>. Rutin improves insulin secretion, restores glycogen content, decreases the level of oxidative stress, inhibits advanced glycation end products (AGEs) formation, decreases glycosylated haemoglobin and pro-inflammatory cytokines such as IL-6 and TNF $\alpha$  and restores liver antioxidant status<sup>79,80</sup>.

### Quercetin

It is a flavonol flavonoid present in onions, berries, apples, pepper and coriander<sup>81,82</sup>. Its anti-diabetic actions are exhibited by increases in anti-oxidant enzymes, decreases in lipid peroxidation, reduction in intestinal glucose absorption by inhibiting GLUT2<sup>83,84</sup>. Quercetin blocks tyrosine kinase and also the recovery of cell proliferation<sup>85</sup>.

### Genistein

This is an isoflavone flavonoid present in legumes. *Sophora subprostrata* and *Genista tinctoria* contain genistein<sup>86</sup>. Renal TBARS were reduced upon genistein administration. It also improves glucose tolerance and increases blood insulin level without affecting body weight<sup>87</sup>.

### Daidzein

Daidzein, an isoflavone flavonoid is present in nuts, soybeans and fruits. Daidzein improves lipid and glucose metabolism, improves insulin sensitivity and enhances AMPK phosphorylation in muscles<sup>88-91</sup>.

### Cyanidin

Cyanidin, an anthocyanin flavonoid exhibits its anti-diabetic actions by inhibiting  $\alpha$ -glucosidase and pancreatic  $\alpha$ -amylase<sup>92</sup>. It also prevents pancreatic apoptosis and improves antioxidant status<sup>93,94</sup>.

### Delphinidin

This is anthocyanin present in berries, tomatoes, eggplant, vegetables, carrots, sweet potatoes, red cabbage and red onions. Its anti-diabetic activity is mediated through its antioxidant effects and reductions in albumin and haemoglobin glycosylations<sup>95</sup>.

### Pelargonidin

It is present in blackberries, cranberries, ripe raspberries and blueberries<sup>96</sup>. Its administration relieves oxidative stress, nitrite levels and stimulates insulin secretion<sup>97,98</sup>.

### Saponins

Saponins are major plant metabolites that naturally occur as surface-active glycosides<sup>99</sup>. They are composed of sugar moieties linked to a hydrophobic aglycone known as sapogenin which could also be a triterpenoid or a steroid<sup>100</sup>. Several anti-diabetic medicinal plants owe their activities to saponins. The anti-diabetic properties of *Anabasis articulata* are as a result of saponin present in it<sup>101</sup>. The saponin induces insulin production. Amelioration of oxidative stress and AGES formation effects of *Astragalus membranaceus* is attributed to its saponin<sup>102</sup>.

Diosgenin, a saponin from *Dioscorea rotundata* is noted for increasing the activity of glucose-6-phosphate<sup>103</sup>. Saponins from *Enteda phaseoloides* have the ability to elevate serum insulin levels, alleviate hyperglycemia and decrease lipid levels<sup>104</sup>.

Administration of saponin from *Garcinia kola* to alloxan-induced diabetic rats reduced significantly, the plasma glucose levels consequent upon insulin release from the pancreas<sup>105</sup>. *Helicteres isora* saponin is known to reduce serum lipid, plasma glucose, expression of the fatty acid binding protein and glucose-6-phosphatase and at the same time increases GLUT 4<sup>106</sup>. Saponin from the fruit of *Mormodica charantia* has been reported to have anti-diabetic property. It does this by inhibiting disaccharidase activity<sup>107</sup>. Triterpene saponins isolated from this plant activated AMPK greater than that achieved by troglitazone<sup>108</sup>.

Geinoside is a saponin isolated from *Panax notoginseng* and it is known to inhibit gluconeogenesis<sup>109</sup>.

*Platycodi radix* produces platyconic acid, a saponin which is involved in insulin-stimulated glucose uptake in the 3T3-L1 adipocyte. The saponin is known to increase glycogen accumulation and decrease triacylglycerol storage in the liver. It also enhanced the expression of adiponectin and PPAR $\gamma$  in adipose tissues, improve insulin signalling and increases GLUT 4<sup>110</sup>.

The saponin-rich fraction of *Polygonatum adoratatum* alleviated signs of diabetes and enhanced glucose uptake. Increases in superoxide dismutase activity and decreases in malondialdehyde levels were observed upon the administration of the saponin<sup>111</sup>.

*Solanum anguivi* saponin is used in the management of diabetes and hypertension. It also has the potentials to induce antioxidant enzymes and decrease glucose levels in alloxanized rats<sup>112</sup>.

Arjunolic acid, a triterpene saponin from *Terminalia arjuna* exhibits anti-diabetic activity by the inhibition of excessive reactive oxygen species' formation. It also inhibits  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors<sup>113</sup>. Saponin isolated from *Trigonella toenum-graecum* significantly inhibited triglyceride accumulation, reduced the triglyceride content and mRNA expression levels of lipogenic genes and as a result, inhibits lipid accumulation in HepG2 cells of obese diabetic rats<sup>114</sup>.

### Alkaloids

Alkaloids are secondary plant metabolites and are found also in bacteria, fungi and other animals. An

alkaloid is a true naturally occurring compound that contains basic nitrogen atoms. Some researchers regard alkaloids as a special case of amines<sup>115</sup>.

Alkaloids are classified as true alkaloids e.g. nicotine, atropine, morphine; protoalkaloids e.g. mescaline, adrenaline, ephedrine; polyamine alkaloids e.g. putrescine, spermidine and spermine; pseudoalkaloids e.g. caffeine, theobromine, theophylline etc, peptide and cyclopeptide alkaloids<sup>115</sup>.

Alkaloids have been implicated as the active principles in some anti-diabetic medicinal plants. Sharma *et al.*<sup>116</sup> reported anti-diabetic potential of an alkaloid from *Capparis deciduas* in diabetic mice. The anti-diabetic mechanism of the alkaloid was reported as a significant improvement of GLUT 4, glucokinase activity and peroxisome PPAR $\gamma$ . Other mechanisms observed include reductions in total cholesterol, triglyceride, attenuation of glucose-6-phosphatase activity and improvement in the hepatic glycogen content. Significant reductions in phosphoenol pyruvate carboxykinase and aldose reductase activities were also observed.

Naturally occurring carbazole alkaloids isolated from *Murraya koenigii* have also been fingered as the anti-diabetic principles of that plant. Patel *et al.*<sup>117</sup> reported that koenidine increased insulin sensitivity, aided glucose uptake and GLUT 4 translocation in L6-GLUT4 myc myotubules. They further concluded that koenidine may be useful in managing insulin resistance and diabetes.

In yet another study, Punitha *et al.*<sup>118</sup> reported that benzyl tetra isoquinoline alkaloid-berberine exhibited anti-diabetic activity in streptozotocin-nicotinamide induced type 2 diabetic rats. Administration of the alkaloid in diabetic rats mitigated oxidative stress parameters, reduced elevated lipids, ameliorated glycosylation of haemoglobin and improved the antioxidant status while there were reductions in the activities of gluconeogenic enzymes.

Alkaloids from *Catharanthus roseus* have also been reported by Tiong *et al.*<sup>119</sup> as potent anti-diabetic and antioxidant compounds. The four alkaloids-Vindoline I, Vindolidine II, Vindocine III and Vindolinine IV, isolated from dichloromethane extract of *C.roseus* induced relatively high glucose uptake in pancreatic beta TC6 or myoblast C2C12 cells with vindocine showing the highest activity. The compounds-Vindolidine II, Vindocine III and Vindolinine IV, inhibited protein tyrosinase phosphatase-1B (PTP-1B) while vindocine alleviated oxidative damage induced by hydrogen peroxide<sup>119</sup>.

Moreover, alkaloids of *Aerva lanata* roots ameliorated diabetes in streptozotocin-nicotinamide induced type 2 diabetes in rats<sup>120</sup>. The authors reported that a partially purified alkaloid from the plant caused significant reductions in the serum glucose level 20 hrs post administration. The alkaloid was further identified as Canthin-6-one derivative<sup>120</sup>.

Another alkaloid whose anti-diabetic potential has been reported is Fenugreek alkaloid. Abou El-Soud *et al.*<sup>121</sup> submitted that administration of the alkaloid-containing extract to streptozotocin-induced diabetic rats resulted in significant elevation of plasma insulin, decrease in serum lipids and lipid peroxide formation.

#### Tannins

Tannin is a polyphenolic biomolecule present in natural products such as berries, nuts, legumes, chocolate, spices and herbs<sup>122-124</sup>. Three major classes of tannins are distinguished viz: Hydrolyzable tannins e.g. gallic acid, Non-hydrolyzable or condensed tannins e.g. flavones and Phlorotannins e.g. phloroglucinol. Tannins have been reported as the bioactive anti-diabetic principles of some medicinal plants.

Hypoglycaemic *Stachytarpheta indica* has 6.4 % tannins as opposed to 2.5 % flavonoids<sup>125</sup>. Condensed tannins isolated from various food items such as cereals, legumes, oilseeds and vegetables have shown significant anti-diabetic and antioxidant properties. According to Kunyanga *et al.*<sup>126</sup>, condensed tannins extracted from  $\alpha$ -amaranth grain, finger millet, field bean, sunflower seed, drumstick and amaranth leaves exhibited anti-diabetic effects mainly by inhibiting the activation of  $\alpha$ -amylase and  $\alpha$ -glucosidase activities.

It has also been reported that tannic acid stimulates transportation of glucose and inhibition of differentiation in 3T3-L1 adipocytes<sup>127</sup>. This, according to them was achieved by phosphorylation of insulin receptor and translocation of glucose transporter 4 (GLUT 4). Tannic acid also inhibited the important genes for adipogenesis.

#### Terpenes

Terpenoid, andrographolide-lipoic acid conjugate has demonstrated hypoglycaemic potentials<sup>128</sup>. Benzofuran-2-carboxaldehyde is a hypoglycaemic diterpene isolated from *Globba pendula*<sup>129</sup>. Glucose lowering activities of diterpenoids of clerodane have also been reported<sup>130</sup>. Huang *et al.*<sup>131</sup> demonstrated the anti-diabetic activities of stevioside and rebaudioside, diterpenes isolated from *Stevia rebaudiana*. Translocation of Glut 4 has been implicated

as the mechanism of its action. Hypoglycaemic and hypolipidaemic potentials of the diterpene, trans-dehydrocrotonin (t-DCTN), from *Croton cajucara* has been demonstrated in alloxanized rats<sup>132</sup>. In the same vein, dehydroabietic acid has been found to suppress and increase pro-inflammatory (TNF $\alpha$ ) and anti-inflammatory (adiponectin) agents respectively<sup>133</sup>. Salvicin, Salvin and Salvifolin are bicyclic diterpenoids that have shown potentials as anti-diabetic agents<sup>134</sup>. Salacinol and Kotalanol are diterpenes isolated from *Salaci oblonga* and they have demonstrated anti-diabetic activities by inhibiting  $\alpha$ -glucosidase activities<sup>135</sup>. Kotalegenin inhibits aldose reductase<sup>135</sup>. Salvipholin has demonstrated anti-diabetic activity through stability of insulin secretion<sup>136</sup>.

In an earlier diterpenes- Icacenone, Icacinol, Humirianthenolide, 17-hydroxy-icacinol observed to be were responsible for the anti-diabetic activities exhibited by *I. trichanta* extract<sup>137</sup>. The extract was hypoglycaemic and hypolipidaemic in action. Potentiation of insulin action amongst other possible mechanisms was suggested as the mode of action of the extract.

Triterpenes are a class of hydrocarbon compounds composed of three terpenes and consist of six isoprene units e.g. squalene. They are classified based on the number of rings they contain e.g. pentacyclic triterpenes (5 rings). Functionalized triterpenes are called triterpenoids. Other examples of triterpenes include polypodatetraene, malabaricane, lanostane, hopane, oleanane etc<sup>138,139,127</sup>. Triterpenoid saponins are triterpenes that belong to the saponin group of compounds. Plants produce them and they include eleutherosides, ginsenosides<sup>140</sup>.

Some anti-diabetic plants have been reported to possess triterpenes as their bioactive principles. Tan *et al.*<sup>141</sup> reported that triterpenoids isolated from bitter melon demonstrated anti-diabetic potentials by activation of the AMPK pathway. They further concluded that bitter melon (*Momordica charantia*) may be beneficial in the development of therapeutics for obesity and diabetes.

Triterpenoid isolated from the root bark of *Cussonia arborea* also demonstrated potent anti-diabetic properties in alloxan-induced diabetic rats<sup>142</sup>.

#### Glycosides

The anti-diabetic activity of *Gymnema Sylvester* was linked to the presence of glycoside contained therein<sup>143</sup>.

Bioactive flavonoid glycosides isolated from *Jatropa curcus* has also been shown to possess anti-

diabetic activity in streptozotocin-induced diabetic rats<sup>144</sup>. The active principle acted by decreasing the serum  $\alpha$ -amylase and lactate dehydrogenase activities. The extract also modulates oxidative stress parameters such as malondialdehyde. Cardiac glycoside isolated from the seed of *Securigera securidaca* (Fabaceae), a plant used in Iranian folk medicine as an anti-diabetic agent, mediate its hypoglycaemic activity by increasing insulin secretion<sup>145</sup>. Kaempferol is a glycoside-rich fraction obtained from unripe soybean leaves. Its anti-diabetic activity is linked to its ability to reduce glycosylated haemoglobin. The liver fatty acid synthase was also decreased in the experiment following treatment with kaempferol<sup>146</sup>. Quercetin and quercetin 3-o-glycoside isolated from *Vaccinium vitis* crude berry extract showed hypoglycaemic activities by mediation through AMPK<sup>147</sup>.

#### Others

Other compounds with anti-diabetic activities such as polyunsaturated fatty acids and glycols have also been reported. In another study of ours entitled "Bioassay-guided isolation and structural elucidation of the anti-diabetic principle of methanol leaf extract of *Newbouldia leavis* (P. Beauv)", we isolated 9-(4-nonyl-phenyl)-non-8-enoic acid, a long chain unsaturated fatty acid from *Newbouldia laevis* as the anti-diabetic principle of the plant<sup>148</sup>. The polyunsaturated fatty acid exhibited hypoglycemic activities comparable to that achieved by the reference drug, glibenclamide, in the alloxan-induced diabetic rat. Pinitol, a sugar alcohol isolated from *Sutherlandia frutescens* leaves has shown great anti-diabetic activities. The anti-diabetic activities of pinitol were likened to that of insulin<sup>149</sup>. Asuzu and Nwaehujor<sup>150</sup> reported the anti-diabetic activities of D-3-O-methylchiroinositol. Here we submitted not only the anti-diabetic but hypolipidaemic and antioxidant activities of D-3-O-methylchiroinositol isolated from the stem bark of *Piliostigma thonningii*. The structure of D-3-O-methylchiroinositol is given in Fig. 1.

#### Discussion and Conclusion

Diabetes mellitus is a metabolic and an endocrine disease affecting humans and animals with fatal consequences when left unmanaged. Management of this ailment can be in the form of modification of lifestyle, diet and use of anti-diabetic drugs such as oral hypoglycemics and insulin therapy. Synthetic anti-diabetic drugs are fraught with adverse side effects and are also expensive.

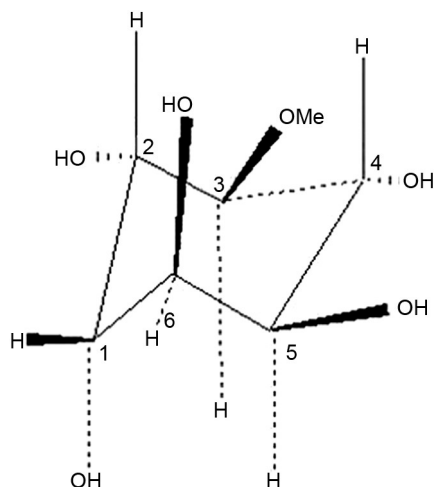


Fig.1 — D-3-O-methylchiroinositol.

Research into *D. mellitus* and its management in recent times has been geared towards isolation of efficacious active anti-diabetic agents of natural origin. A lot of studies have been carried out in various medicinal plants in this regard. Results have not only indicated that many medicinal plants possess anti-diabetic potentials but have demonstrated specific bioactive anti-diabetic principles and various mechanisms of actions of these agents.

Bioactive anti-diabetic principles of plant origin are mainly phytochemicals which include but not limited to flavonoids, saponins, alkaloids, tannins, terpenes, and glycosides. These phytochemicals act in a number of diverse mechanisms to bring about their anti-diabetic effects. Some of the mechanisms involved include increase in insulin secretion, decreases in hepatic glucose output, regulation of certain enzymes involved in carbohydrate metabolism such as  $\alpha$ -glucosidase inhibitors, modulation of certain regulation molecules such as PPAR $\gamma$ , hypolipidaemic activities, antioxidant effects, interference with the activities of some glycolytic enzymes such as phosphoenolpyruvate carboxykinase activities, amelioration of glycosylated haemoglobin, enhancement of the expression of glucose transporters and others.

Flavonoids were observed to be the most popular anti-diabetic principle among the phytochemicals reviewed. These naturally occurring secondary plant metabolites (Phytochemicals) hold great potential for production of marketable, novel and effective anti-diabetic drugs in near future. In general, bioactive anti-diabetic agents of plant origin constitute a group of natural products that have recently gained popularity in the health sector for management of

various ailments such as diabetes mellitus. Satisfactory management of *D. mellitus* in future is pivotal on medicinal plants.

### Conflict of interest

Authors declare no conflict of interest

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