A systematic analysis of anti-diabetic medicinal plants from cells to clinical trials.

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Background. Diabetes is one of the fastest-growing health emergencies of the 21st century placing a severe economic burden on many countries. Current management approaches have improved diabetic care, but several limitations still exist, such as decreased efficacy, adverse effects, and the high cost of treatment, particularly for developing nations. There is, therefore, a need for more cost-effective therapies for diabetes management. The evidence-based application of phytochemicals from plants in the management of diseases is gaining traction. **Methodology**. Various plants and plant parts have been investigated as antidiabetic agents. This review sought to collate and discuss published data on the cellular and molecular effects of medicinal plants and phytochemicals on insulin signaling pathways to better understand the current trend in using plant products in the management of diabetes. Furthermore, we explored available information on medicinal plants that consistently produced hypoglycemic effects from isolated cells to animal studies and clinical trials. **Results.** There is a substantial literature describing effects of a range of plant extracts on insulin action and insulin signaling, revealing a depth in knowledge of molecular detail. Our exploration also reveals effective antidiabetic actions in animal studies, and clear translational potential evidenced by clinical trials. **Conclusion.** We suggest that this area of research should be further exploited in the search for novel therapeutics for diabetes.

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12 **Abstract**

13 **Background.** Diabetes is one of the fastest-growing health emergencies of the 21st century placing

14 a severe economic burden on many countries. Current management approaches have improved

15 diabetic care, but several limitations still exist, such as decreased efficacy, adverse effects, and the

16 high cost of treatment, particularly for developing nations. There is, therefore, a need for more

17 cost-effective therapies for diabetes management. The evidence-based application of

18 phytochemicals from plants in the management of diseases is gaining traction. **Methodology**.

19 Various plants and plant parts have been investigated as antidiabetic agents. This review sought to

20 collate and discuss published data on the cellular and molecular effects of medicinal plants and

21 phytochemicals on insulin signaling pathways to better understand the current trend in using plant

22 products in the management of diabetes. Furthermore, we explored available information on

23 medicinal plants that consistently produced hypoglycemic effects from isolated cells to animal

24 studies and clinical trials. **Results.** There is a substantial literature describing effects of a range of

25 plant extracts on insulin action and insulin signaling, revealing a depth in knowledge of molecular

26 detail. Our exploration also reveals effective antidiabetic actions in animal studies, and clear

27 translational potential evidenced by clinical trials. **Conclusion.** We suggest that this area of

28 research should be further exploited in the search for novel therapeutics for diabetes.

29 **List of Abbreviations**

30   ACC: Acetyl-CoA carboxylase
31   Akt: Protein kinase B
32   AMPK: Adenosine monophosphate-activated protein kinase
33   AS160: Akt substrate 160 kDa
34   ATPase: Adenosine triphosphatase
35   CI : Confidence interval
36   GCK: Glucokinase
37   GLP-1: Glucagon-like peptides-1
38   GLUT: Glucose transporter
39   GSK-3: Glycogen synthase kinase 3
40   GSV: Glucose storage vesicle
41   HbA1c: Hemoglobin A1c
42   HDL: High-density lipoprotein
43   HSC: Hematopoietic stem cell
44   IFN: Interferon
45   IR: Insulin receptor
46   IRS: Insulin receptor substrate
47   LDL: Low-density lipoprotein
48   LPS: Lipopolysaccharide
49   PEPCK: Phosphoenolpyruvate carboxykinase
50   PI3K: Phosphoinositide-3 kinase
51   PPARγ: Peroxisome proliferator-activated receptor gamma
52   PTP1B: Protein tyrosine phosphate 1B
53   SGLT1: Sodium-glucose linked transporter1
54   T1DM: Typ1 diabetes mellitus
55   T2DM: Type 2 diabetes mellitus
56

58 **INTRODUCTION**

59 *Statement of the problem.*

60 Diabetes mellitus is a metabolic disorder characterized by sustained hyperglycemia with numerous

61 macrovascular and microvascular complications [1-3]. Depending on the etiology, diabetes has

62 been classified broadly into Type 1 diabetes mellitus (T1DM), resulting from a deficiency in

63 insulin production, and Type 2 diabetes mellitus (T2DM), a defect in insulin action [1]. T1DM

64 accounts for around 10% of cases, while T2DM accounts for about 90%. T2DM and its

65 complications have contributed to a significant decrease in life expectancy [3-4]. The latest data

66 suggests that 1 in 10 adults are living with diabetes, of which almost half are undiagnosed [3],

67 representing around 537 million citizens, and diabetes contributes to 1 in 9 deaths [2]. These

68 figures are projected to continue to rise. It is estimated that most countries devote 5–20 % of
69 healthcare expenditure to diabetes [5]. The global spending to treat diabetes and its complications
70 was US$760 billion in 2019, projected to increase to US$825 billion by 2030 [2,8]. The disturbing
71 increase in the prevalence of diabetes is a call for an augmented approach to the management of
72 T2DM [2].
73
74 The conventional management of diabetes involves lifestyle modifications to control contributing
75 factors such as obesity, hypertension and hyperlipidemia, based on the patient's awareness [9-12],
76 and the use of hypoglycemic agents by healthcare providers [13-15]. Approaches to using
77 antihyperglycemic agents to control hyperglycemia in diabetic patients involve different targets.
78 For example, the sulfonylureas (e.g., chlorpropamide) and newer secretagogues (e.g., glipizide)
79 increase insulin output by blocking the K^+-ATPase channel of the pancreatic β-cell [13,16-17].
80 The biguanides (e.g., metformin) act through inhibition of hepatic gluconeogenesis and promoting
81 glycogenesis with increased insulin sensitivity [13,15,17]. Insulin sensitizers (e.g.,
82 thiazolidinediones) potentiate insulin action on muscle, adipocytes, liver and other tissues by
83 selectively binding to peroxisome proliferator-activated receptor gamma (PPARγ) [13,18]. Others
84 include α-glucosidase inhibitors (e.g., acarbose), which competitively inhibits intestinal α-
85 glucosidase and pancreatic α- amylase with a resulting decrease in postprandial plasma glucose
86 [13,19-20]. Incretin mimetics (e.g., exenatide) control postprandial insulin secretion by binding to
87 the pancreatic glucagon-like peptides-1(GLP-1) receptors leading to increased glucose-dependent
88 insulin secretion from the β-cells [14, 20-21]. Exenatide also restores first-phase insulin secretion
89 in patients with T2DM and promotes β-cells proliferation and islet neogenesis [21-22]. The use of
90 insulin for immediate glycemic control has been reserved for emergency situations [14, 23].
91 Undoubtedly, these approaches have improved diabetic care over time, but several limitations still
92 exist, such as decreased efficacy, adverse effects, and high cost of treatment [24-25].
93
94 *Medicinal plants as medicines in diabetes treatment.*
95 The global worsening of morbidity and mortality from diabetes [3,7-8,26-28] justifies the need for
96 more diversified research for new therapies. Throughout human history, medicinal plants have
97 been used for the prevention and treatment of both human and animal diseases [31-34]. Medicinal

98 plants have been recognized as a stable source for drug discovery since ancient times [29,36-38]

99 and The World Health Organization has reported an increased patronage of natural and medicinal

100 plant drug products [29]. Many modern drugs are obtained from medicinal plants and further

101 purified or optimized using structure-activity relationship-driven drug design and pharmacokinetic

102 parameters [36,39].

103 Evidence-based application of phytochemicals from plants in the management of diseases has

104 received wide acceptability [35,37]. For example, several reports of medicinal plants with

105 anticancer activities have been published [40-42]. Ethnopharmacological surveys of plants and

106 phytochemicals with antihypertensive activities [43-45] have been well documented. There is also

107 substantial literature of their utility in treatment of other chronic diseases such as Alzheimer's [46-

108 47], depressive disorders [48-49], Parkinson's disease [40] and diabetes [17,51-52].

109 Various plants and plant parts have been investigated for their hypoglycemic activities as potential

110 medicine in the treatment of diabetes mellitus [11]. By way of examples, phytocompounds from

111 the fruit of *Momordica charantia* (bitter lemon) have been extensively studies for antidiabetic

112 effects [53-55]. The roots of *Zingiber officinale* (ginger) exert antidiabetic and hypolipidemic

113 effects on streptozotocin-induced diabetic rats [58-60]. *Bidens pilosa* has been shown to reduce

114 fasting blood glucose level and hemoglobin A1c (HbA1c) in clinical trials [48]; three variants of

115 *B. pilosa* were shown to possess anti-diabetic properties [49]. The hydroethanolic extract of the

116 seed of *Parinari curatellifolia* reduces plasma glucose levels and low-density lipoproteins in

117 diabetic rats [63-64]. The blood sugar reducing effects of *Gymnema* sylvestre popularly known as

118 'gurmar' ('sugar destroyer') has been widely studied [52- 53]. Phytochemical constituents of

119 *Glycyrriza uralensis* (licorice) have been found to exhibit profound antidiabetic properties in

120 experimental animals [54]. While some studies do consider the potential molecular or cellular

121 mechanisms of the antidiabetic effects [4,66], others focus on potential properties such as

122 antioxidant [60, 64] and anti-obesity [67-68] effects without direct discussion of mechanism.

123 This review aims to collate, discuss, and present published data on the cellular and molecular

124 effects of medicinal plants and phytochemicals on insulin signaling pathways to better understand

125 the current trend in the use of plant products in the management of T2DM (Figure 1). Furthermore,

126 we have explored available information on the cell-biology of these medicinal plants that

127 consistently produced hypoglycemic effects, with the intention of providing a reference point for

128 the molecular basis of some of the more commonly used anti-diabetic plant extracts. We explored

129 how these plant products might affect known insulin signaling systems and insulin effectors, and

130 then extended our review into known effects on animal models and explored clinical trials of these

131 compounds with the intention of providing a summary-view of related studies and a holistic

132 overview of their use in rodent models or clinical trials. We conclude that plant products should

133 be considered a vital tool in the armory for development of low-cost, effective anti-diabetic

134 therapies.

135   *Figure 1 here.*

136

137

138 **Fig 1 Schematic Representation of Antidiabetic Development from Plant to Clinical Trial**

139 The pathway from plant extract to effective therapy involves many steps. Plants, often identified from local

140 knowledge/use, are a source of extract prepared using a range of approaches and the extracts screened using simple

141 cell-based models such as Caco-2 cells or L6 skeletal myotubes for *in vitro* effects. Signaling pathways and effectors

142 are used as surrogate assays for potential antidiabetic effects (e.g., glucose transport). Further work involves an

143 examination of effects using rodent models of diabetes and clinical trials.

144

145 **Methodology.**

146 We used a range of search terms to scan Google Scholar, PubMed, Science Direct, NIH National

147 Library of Medicine and Scopus to retrieve published literature on medicinal plants and

148 phytochemical effects on insulin signaling and effector pathways. Search terms focused on known

149 signaling systems involved in propagating insulin signals (e.g., Protein kinase-B/Akt (hereafter

150 referred to as Akt); Phosphoinositide-3 kinase (PI3K); Glycogen synthase kinase-3(GSK-3);

151 AMP-activated protein kinase (AMPK); Protein tyrosine phosphatase 1 B (PTP1B); known

152 effector molecules or processes (e.g., Glucose transporters (GLUT) and GLUT4 storage vesicles

153 (GSVs; also known as GSC – GLUT4 storage compartment); Glucokinase (GCK); Glucagon

154 secretion; Lipolysis; Lipogenesis; Hepatic glucose output; and other molecules implicated in

155 insulin action of insulin sensitivity, such as Peroxisome proliferator-activated receptor gamma

156 (PPARγ). Searches were performed between December 2021 and April 2022. We excluded papers

157   not in English and not freely available via our institution (in this case the University of Strathclyde;
158   <0.2% of articles retrieved) and no time limitation for publication date was employed. Our
159   searches aimed to capture papers which described a potential effect on either signaling systems
160   (e.g., PI3K, Akt etc.) or a biological output (e.g. glucose transport, GLUT4 mRNA). This was
161   subsequently extended into whole animal studies and clinical trials.

162   Throughout we use the scientific and common names of the medicinal plants, and describe the
163   chemistry used in the extraction process – a key consideration for studies of this type. In all tables,
164   extracts are alphabetized by species unless multiple different species were used in the same study,
165   in which case these are placed arbitrarily at the top of each table for clarity.

166   **Results**

167   ***Studies using cell lines.***

168   *Effects of Medicinal Plants and Phytochemicals on Glucose Transport and Glucose Transporters.*

169   Defective insulin-stimulated glucose transport is hallmark of T2DM [4,70-72]. Glucose
170   transporters (GLUT) of the facilitative diffusion type are a multi-gene family of proteins which
171   function to move glucose across cell membranes [4, 29, 36]. Among the facilitative GLUT
172   isoforms, GLUT4 is particularly important as it is expressed predominantly in skeletal and adipose
173   tissues and accounts for post-prandial glucose disposal in these tissues [29, 70]. Skeletal muscle
174   contribute largely to a greater part of the total body mass in humans and it regulates several
175   physiological processes including up to 85% of insulin- mediated glucose up-take through GLUT4
176   [60]. Many studies have utilized this for therapeutic management of diabetes and in particular the
177   role of extracellular matrix [60]. Skeletal muscle contraction during exercise improves GLUT4
178   translocation to the cell membrane for glucose uptake and insulin-sensitivity [61]. Also, altered
179   muscle glycogen synthesis play a major role in insulin resistance, and glycogen synthase,
180   hexokinase, and GLUT4 are the major culprit involved in the skeletal muscle pathogenesis of type
181   2 dibetes [62][63]. GLUT2 and GLUT5 are responsible for intestinal glucose and fructose uptake
182   [27], while GLUT1 is present ubiquitously in all the body tissues [64]. The dominant glucose
183   transporters found in the small intestine are sodium-glucose linked transporter 1 (SGLT1) which
184   accumulates glucose into adsorptive epithelial cells against its concentration gradient and GLUT2
185   which mediates movement of glucose from the epithelial cells into the blood [27]; inhibition

186   reduces the amount of glucose absorbed into the body. The hemodynamic activities of the glucose

187   transporters have been extensively researched [4, 29, 36,70]. Medicinal plants' products and

188   phytochemicals that modify the action of the glucose transporters could significantly contribute to

189   the search for effective drugs in the management of diabetes. Table 1 is a collation of studies of

190   medicinal plants known to modulate glucose transport in cell lines. Some notable highlights of this

191   extensive literature are discussed briefly below.

192   ***Table 1 here***

193   In one of the most comprehensive studies, Schreck and Meizig used Caco-2 cells exposed to a

194   range of plant extracts to identify potential inhibitors of glucose transport. They reported between

195   40 % to 80 % reduction using the methanolic extracts of a range of plants including the fruits of

196   *Aronia melanocarpa, Cornus officinalis, Crataegus pinnatifida, Lycium chinense,* and *Vaccinium*

197   *myrtillus;* the leaves of *Brassica oleracea, Juglans regia, Peumus boldus*, and the roots of

198   *Adenophora triphylla*. The authors also reported 50% to70 % reduction by aqueous extract from

199   the bark of *Eucommia ulmoides* and fruit skin of *Malus domestica* [27]. These effects are likely

200   acting via inhibition of GLUT1, the predominant transporter in these cells.

201   One of the key facets of insulin action is to drive the delivery of GLUT4 molecules from

202   intracellular stores to the surface of fat and muscle cells, a process called 'translocation'.

203   Stadlbauer et al. [2] used CHO-K1 cells expressing GLUT4 and total internal reflection

204   microscopy to identify GLUT4 translocation-inducing effects of some thirty plant extracts.

205   Though the taxonomy of some of the plants were not fully defined, they included *Hoodia*, *Sapindus*

206   *mukorossi*, *Quillaja saponaria*, *Papaver*, *Castanea*, Bitter orange (genus and species not

207   specified), Oregon grape (genus and species not specified), Common daisy flowers, Rosebay

208   willowherb leaves and Goldenrod flower as potential compounds that could be exploited as

209   potential anti-hyperglycemic agents in the treatment of T2DM via effects on GLUT4

210   redistribution.

211   While the above study used a non-classical insulin target tissue (for good experimental reasons),

212   others have focused upon more 'physiological' cell systems. Through bioassay-guided

213   fractionation, Kanaujia and colleagues [65] reported two chebulinic acid derivatives from

214   *Capparis moonii* with significant stimulatory effects on glucose uptake effects concomitant with

215   increased IR-β, Insulin receptor substrate-1 (IRS-1) phosphorylation, and mRNA expression of

216   GLUT4 and PI3K in L6 muscle cells. Carnosol from Rosemary extract stimulated AMPK-
217   dependent GLUT4 translocation with no effect on Akt phosphorylation in L6 myotubes [66].
218   Methanolic extract of *Gundelia tournefortii* potentiated insulin-stimulated GLUT4 translocation
219   to the plasma membrane in skeletal muscle L6 cells [67]. An aqueous extract of *Cassia abbreviata*
220   induced a two-fold increase in GLUT4 translocation in C_2C_{12} [mouse] skeletal muscle cells
221   probably via activation of the canonical PI3K/Akt pathway [68].

222   Naowaboot and colleagues reported the mechanism of antihyperglycemic effects of *Morus alba*
223   leaf extract, including increasing glucose uptake via activation of the PI3K pathway and the plasma
224   membrane translocation of GLUT4 in rat adipocytes [69]. Ethyl acetate extract and 3β-taraxerol
225   isolated from *Mangifera indica* promoted increased GLUT4 translocation and glycogen synthesis
226   in 3T3-L1 adipocytes [70]. The study also noted the effect on glycogen synthesis was due to PI3K-
227   dependent activation of Akt (with subsequent inactivation of glycogen synthase kinase 3B
228   (GSK3β) phosphorylation (discussed further below). The fruit of *Citrullus colocynthis* enhanced
229   insulin-induced GLUT4 translocation and Akt phosphorylation in 3T3-L1 adipocytes [71].

230   Stadlbauer et al. screened further natural products as alternatives to insulin through quantitation of
231   GLUT4 translocation in insulin-sensitive CHO-K1 and importantly extended their remarkable
232   study into commercial adipocyte cells. Of the seven medicinal plants tested, *Portulaca oleracea*
233   and *Coccinia grandis* were found to induce GLUT4 translocation together with increased glucose
234   concentration uptake likely mediated by PI3K/Akt pathway in adipocytes [72].

235   Such findings, together with the many others noted in Table 1 and which space preclude detailed
236   discussion of here, suggest natural products can drive re-distribution of GLUT4 to the plasma
237   membrane in an insulin-mimetic manner. But effects are not confined to GLUT4. For example,
238   Kang and colleagues reported upregulation of GLUT2 in the liver (and up-regulated GLUT4 in
239   muscle) as the possible mechanism of the antidiabetic effects of *Panax ginseng* (black ginseng).
240   Manzano and Williamson investigated the glucose uptake inhibition of polyphenols, phenolic acid,
241   and tannins from strawberry (*var*. Abion) and apple (*var*. golden delicious) in Caco-2 intestinal
242   cell monolayers and reported increased inhibition of GLUT2 and SGLT1 and reduced glucose
243   intestinal bilayer transport [73]. Enhancement of glucose uptake by *mitragyna speciosa* and
244   mitragynine in rat L6 myotubes is associated with increased GLUT1 protein content [74]. And the
245   glucose uptake (GLUT4) enhancement activity of *G. sylvestre* in L6 myotubes alongside the

246 amelioration of insulin resistance in the 3T3-L1 adipocytes cells have been reported [75]. One

247 further study of note is the report that the methanol extract of the aerial part of *Selaginella*

248 *tamariscina* enhanced glucose uptake in 3T3-L1 adipocytes, possibly by inhibition of PTP1B [166-

249 167]. Collectively, these studies reveal that medicinal plants have a range of action on glucose

250 transport across multiple tissues of relevance to the treatment of diabetes.

251

252 *Medicinal Plants and Phytochemical Effects on PI3K and Akt activity.*

253 In the canonical insulin signaling pathway controlling glucose homeostasis, insulin receptor

254 substrates are phosphorylated on tyrosine residues which then act as docking sites for downstream

255 signaling molecules. Of particular note, IRS-1 recruits phosphoinositide 3-kinase (PI3K) [78].

256 PI3K phosphorylates phosphatidylinositol 4,5-biphosphate to form phosphatidyl-inositol 3,4,5-

257 trisphosphate that in turn promotes Akt phosphorylation and activation [29,102]. Akt is an

258 important nexus on the insulin signaling cascade because of its multi-substrate activities [69-70].

259 Phosphorylation of Akt initiates a cascade of downstream events through many substrates,

260 including phosphorylation of Akt substrate of 160 kDa (AS160), a RabGAP (GTPase activating

261 protein); this in turn leads to GLUT4 translocation in muscle and adipose cells [98-99]. Defects in

262 Akt phosphorylation, as seen in impaired insulin activation, are associated with development of

263 muscle and adipose insulin resistance in obesity and T2DM [69,101-102]. The insulin PI3K/Akt

264 pathway has been widely targeted in T2DM pharmacotherapy [29, 69,102] and is important in the

265 pathophysiology and therapy of other diseases [83]. Evidence of medicinal plants and

266 phytochemicals modifying PI3K/Akt actions have been documented and are presented in Table 2.

267 Some examples are briefly outlined below.

268   ***Table 2 here***

269 An ethyl acetate extract and 3β-taraxerol of *Mangifera indica* significantly activate GLUT4

270 translocation via a PI3K dependent pathway in 3T3-L1 adipocytes [70]. Polysaccharides from corn

271 silk (*Maydis stigma*) increased phosphorylation of Akt in a dose-dependent manner in L6 skeletal

272 muscle myotubes [84]. Similarly, phosphorylation of Akt in response to an extract of *Folium*

273 *sennae* was described, together with a significant enhancement of GLUT4 translocation [85].

274 Antidiabetic effect of alkaloids from the seeds of *Nigella glandulifera* increased the activity of the

275 PI3K/Akt pathway in L6 myotubes with a concomitant increase in glycogen synthesis and

276 hexokinase activity [86]. Four C21 steroidal glycosides A-D from *G.sylvestre* promoted GLUT4

277 translocation to the plasma membrane in L6 cells via activation of PI3K/ AKT [87]. These and

278 other studies (Table 2) point to a significant number of useful PI3K/Akt modulators within

279 medicinal plants.

280 Many studies have examined effects of medicinal plants in hepatoma cells, as liver is a key site of

281 post-prandial glucose disposal with a notable emphasis on PI3K/Akt signaling (Table 2).

282 Heteropolysaccharides of *Grifola frondosa* (edible mushroom) increased IRS1/PI3K mRNA levels

283 and enhanced insulin sensitivity [88]. Polysaccharides of *Dendrobium officinale* increased the

284 activity of PI3K and Akt and partially ameliorated symptoms in diabetic mice, pointing to a clear

285 effect in a complex organism rather than simply in cell culture models. [89]. Inhibition of

286 phosphorylated insulin receptor substrate-1(IRS-1), but activation of PI3K/Akt in insulin-resistant

287 HepG2 cells by polyphenol-rich extract of Zhenjiang aromatic vinegar has been documented [90].

288 Homogeneous polysaccharides from *Sargassum pallidum* ameliorate insulin resistance by

289 upregulation of PI3K, Glycogen synthase (GS), and IRS-1 expression in insulin-resistant HepG2

290 cells [91]. Monosaccharides from *Anemarrhena asphodeloides Bunge* exhibited hypoglycemic

291 effects by activating PI3K/Akt, IRS-1signaling pathway, and inhibiting α-glucosidase activities in

292 insulin-resistant-HepG2 cells [92]. A natural flavonocoumarin (α-Methylartoflavonocoumarin)

293 isolated from *Juniperus chinensis* was reported to activate PI3K/Akt pathway in insulin-resistant

294 HepG2 cells [93]. Thus, effects are evident both at the level of gene expression and activity

295 mediated by a range of extracts.

296

297 *Activity of Medicinal Plants and Phytochemicals on Glucokinase.*

298 Glucokinase (GCK) is important in the regulation of glucose metabolism in liver and pancreas.

299 GCK is essential for pancreatic insulin secretion and hepatic insulin action via phosphorylation of

300 glucose to glucose 6- phosphate [69, 112]. Low GCK levels have been observed in T2DM and

301 could serve as a potential drug target for therapeutic intervention [113-114]. GCK is currently

302 being targeted as therapeutic for T2DM [95]. Glucokinase activators have been advocated as an

303 alternative approach to restoring and improving glycemic control in T2DM [116-117]. Several

304 medicinal plants and phytochemicals with glucokinase activities have been recognized [99]. We

305   have focused on the cellular and molecular glucokinase activities of medicinal plants in tissue
306   culture models (Table 3).

307   ***Table 3 here***

308   Glucokinase activation by the leaf extract of *Costus igneus* (known in India as the 'insulin plant'
309   for its purported anti-diabetic action) was examined in differentiated human hematopoietic stem
310   cell (HSCs) as a model of β-cells. The extract increased GCK and inhibited of glucose-6-
311   phosphatase activity by *C. igneus*, thereby improving glucose sensing, insulin production, and
312   decreased gluconeogenesis [100]. It was also reported that *C. igneus* profoundly increased insulin
313   receptor and GLUT2 gene expression (Table 1). Insulin-like proteins (ILP) purified from *C. igneus*
314   also showed hypoglycemic activity in insulin-responsive cell line RIN 5f cells [101]. Activation
315   of free fatty acid-receptor1 (FFAR1) and GCK by anthocyanin-rich extract from the pericarp of
316   purple corn was demonstrated in HepG2 cells [102]. Significant elevations in glucokinase gene
317   expression in response to ethanol, ethyl acetate, and n-hexane fruit extract of *Momordica*
318   *balsamina,* were reported in RIN-m5F cells [103].

319

320   *Medicinal Plants Modifying Activity of Glycogen Synthase Kinase-3 (GSK-3)*

321   GSK-3 inhibits glycogen synthase activity. Insulin phosphorylates GSK-3 and prevents glycogen
322   synthase inactivation [104]. This role of GSK-3 in the insulin signaling pathway provides a
323   mechanistic approach to the use of GSK-3 inhibitors in the treatment of insulin-resistant diabetes.
324   Two studies are worthy of comment. Ethanolic extract of Shilianhua (*Sinocrassula indica Berge*)
325   was found to induce GSK-3β phosphorylation similarly to insulin in 3T3-L1 preadipocytes and rat
326   skeletal L6 myoblasts, indicating a possible mechanism of antidiabetic activity [105]. This extract
327   also enhanced insulin-stimulated glucose consumption in L6 myotubes and H4IIE hepatocytes,
328   and insulin-independent glucose uptake in 3T3-L1 adipocytes. The result also showed increased
329   GLUT1 protein expression in 3T3-L1 and GLUT4 protein expression in L6 myotubes cells [105].
330   Hot water reduction from the root of *Sarcopoterium spinosum* increased glycogen synthesis via
331   induction of GSK-3 β phosphorylation in L6 myotubes [106]. *S. spinosum* also enhanced basal
332   insulin secretion in the pancreatic β-cells and inhibited isoproterenol-induced lipolysis in 3T3-L1
333   adipocytes [106].

334

335   *Peroxisome Proliferator-activated Receptor-gamma (PPARγ) and Medicinal Plants.*

336   Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the nuclear receptor

337   super-family which play integral roles in glucose and lipid metabolism [107]. These receptors are

338   targets for diabetes therapy and also for the treatment of cardiovascular disease, cancer, and

339   inflammation [107]. We present the effects of various medicinal plants on PPARγ activity and

340   gene expression (Table 4).

341   ***Table 4 here***

342   Chloroform extract of the fruit of *Momordica charantia* has been reported to significantly increase

343   PPARγ gene expression 2.8-fold, comparable to the insulin sensitizer rosiglitazone (2.4-fold) in

344   L6 myotube skeletal muscle cells [108]. Huang et al. demonstrated that *Punica granatum* flower

345   extract and ethyl acetate fractions enhanced PPARγ gene expression and protein levels in a

346   macrophage cell line [109]. Increased mRNA of PPARγ (and GLUT4) by *Nymphaea nouchali*

347   seed extract in 3T3-L1 adipocytes as the possible mechanism of its anti-hyperglycemic effect was

348   reported [110]. Exposure of 3T3-L1 adipocytes to an ethanol extract of *Miconia* increased mRNA

349   of PPARγ by 1.4-fold and inhibited α-amylase and α-glucosidase. The extract also increased lipid

350   accumulation by around 30% as a possible anti-diabetic mechanism of action [111]. Upregulation

351   of PPARγ together with GLUT4, SREBP and FAS expression was observed in 3T3-L1 adipocytes

352   treated with the leaf extract of *Moringa concanensis* [112]. Effects in muscle models have also

353   been reported: Kim et al. reported increased transcription activity and mRNA levels of PPARγ in

354   C_2C_{12} myotubes by *Boehmeria nivea* ethanol leaf extract [113] and Korean red peppers

355   (*Yeongyang korea*) increased glucose uptake in C_2C_{12} via increased transcriptional activity of

356   PPARγ [114].

357

358   *AMP-activated Protein Kinase (AMPK)*

359   AMP-activated protein kinase (AMPK) is a known energy sensor for metabolic homeostasis [115]

360   which plays a central role in regulating lipid and protein metabolism together with fatty acid

361   oxidation and muscle glucose uptake [135]. AMPK plays a crucial role in insulin sensitivity, which

362   explains its place as a potential drug candidate for T2DM therapy [138-139]. AMPK systems have

363   been said to be partly responsible for the health benefits of exercise and AMPK is an important

364 downstream effector of metformin. It has also been proposed as a possible target for novel drugs

365 in managing obesity, type 2 diabetes, and metabolic syndrome [140-141]. Ethnopharmacological

366 investigators have reported that several medicinal plants modulate the activity of AMPK in cell

367 models, and we have summarized these reports in Table 5, and highlight a few notable studies

368 below.

369   ***Table 5 here***

370 Ethanolic extract and phytochemical compounds from *Cimicifuga racemosa* mediate increased

371 AMPK activity in fully differentiated HepaRG cells and is a possible mechanism of antidiabetic

372 activity [119]. Yuan and Piao reported activation of AMPK by the petroleum ether fraction of

373 *Artemisia sacrorum* in HepG2 cells [120]. They showed increased phosphorylation of AMPK (on

374 T172), acetyl-CoA carboxylase (ACC; reside S79), and GSK-3β and reported concomitant

375 downregulation of phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-phosphatase

376 (G6Pase). Similarly, Zheng et al., exploring the anti T2DM activity of *Entada phaseoloides* in

377 primary mouse hepatocytes and HepG2 cells, reported suppression of hepatic gluconeogenesis via

378 activation of the AMPK signaling pathway and Akt/GSK-3β [121]. Extract of *Rosmarinus*

379 *officinalis* significantly increased glucose consumption in HepG2 cells via increased

380 phosphorylation of AMPK and ACC and potentially increased liver glycolysis and fatty acid

381 oxidation [122]. Thus, numerous examples of medicinal plants exerting effects via AMPK in

382 hepatoma cell lines have been described (Table 5).

383 Effects mediated via AMPK have been reported in other cell types. These include an alcoholic

384 extract of *Artemisia dracunculus* enhanced insulin release from β-cells isolated from mouse and

385 human islets via activation of AMPK and suppressed LPS/IFNγ-induced inflammation [123].

386 Effects on glucose transport in muscle lines include an extract of *Crocus sativus* (saffron) which

387 increased glucose uptake and insulin sensitivity in C_2C_{12} myotubes by increased phosphorylation

388 of AMPK in a dose and time-dependent manner [124] and compounds isolated from the seed of

389 *Iris sanguinea* was reported to be via AMPK and ACC phosphorylation in the same cell type [125].

390 Ethanolic extract and isolated compound (β-sitosterol) from *Malva verticillata* seed significantly

391 increased activation of AMPK as the molecular mechanism for glucose uptake in L6 myotubes

392 [126]. Triterpenoids from the stem of *Momordica charantia* have been reported to overcome

393   insulin resistance in FL83B and C2C12 via AMPK activation [127]. Hence, the effects of such
394   compounds on AMPK is an active and vigorous area of research.

395

396   ***Studies in animal models.***

397   The process of drug development encompasses pre-clinical experimentation (*in vitro*, *in silico*, and
398   *in vivo*) leading ultimately to clinical trials in humans. To understand if there is ongoing vertical
399   research towards developing antidiabetic agents from these medicinal plants, we reviewed their
400   exploitation in experimental animal models as summarized in Table 6. Some highlights are
401   discussed below.

402   ***Table 6 here***

403   *Aronia melanocarpa* fruit juice was found to mediate a dose-dependent decrease in plasma glucose
404   and triglyceride levels in streptozotocin-induced hyperglycemic rats [168-169], corresponding to
405   the observations on glucose transport in Caco-2 cells alluded to above (Table 1) [27]. Similarly,
406   the antidiabetic and hyperlipidemic effects of *Crataegus pinnatifida* were investigated in high fat-
407   fed mice. The results showed decreased glucose production and triglyceride synthesis via induction
408   of AMPK phosphorylation [130], compared with inhibition of SGLT1 and GLUT2 in Caco-2 cells
409   [27]. These provide a good example of studies in cell lines being translated into animal models.

410   The fruit of *Vaccinium myrtillus* was reported to significantly reduce serum glucose, total
411   cholesterol, low density lipoprotein cholesterol, and very low density lipoprotein cholesterol, and
412   triglycerides in alloxan-induced hyperglycemic adult male Wistar rats [131].

413   *Juglans regia* extracts reduce blood glucose levels in diabetic mice [132], ameliorated
414   streptozotocin-induced diabetic peripheral neuropathy in rats [133], and significantly decreased
415   blood glucose, glycosylated hemoglobin, LDL, triglycerides, and total cholesterol in Wistar rats
416   [134]. An aqueous extract of the seeds of *Momordica charantia* reduced blood glucose level,
417   glycosylated hemoglobin, lactate dehydrogenase, glucose-6-phosphatase, fructose-1,6-
418   biphosphatase, and glycogen phosphorylase but increased the activities of glycogen synthase and
419   hexokinase in streptozotocin-induced diabetic rats, providing clear evidence of a systematic and
420   programmed action on key metabolic activities [135]. Similarly, polysaccharides of *Dendrobium*

421 *officinale* reduced blood glucose level, glycated serum protein, total cholesterol, LDL-C, and

422 increased HDL-C in type 2 diabetic rats [136]. *Cimicifuga racemosa* extracts from rhizomes and

423 roots reduced body weight, plasma glucose, improved glucose metabolism, and increased insulin

424 sensitivity in obese diabetic mice [119]. Tarralin™, an ethanolic extract of *Artemisia dracunculus,*

425 significantly lowered blood glucose concentrations and PEPCK in diabetic KK-A^y mice [137].

426 Yumeng and partners described the effects of Gymnemic acid isolated from *G. sylvestre* on insulin

427 signalling pathways in the type 2 diabetic rats as activation of PI3K/AKT together with AMPK

428 phosphorylation [87]. Such studies exemplify the power of medicinal plants in the amelioration of

429 metabolic disturbances, and Table 5 summarizes the wide array of studies relevant to diabetes

430 research.

431

432 ***Medicinal Plants in Clinical Trials.***

433 The process of drug discovery necessitates that a drug molecule or product that has successively

434 passed through the preclinical stage of drug development is carefully tested in clinical trials. We

435 reviewed those plants that progressed to clinical trials and present our findings in Table 7. As this

436 area is particularly important, we have provided some detail of key studies in the sections below.

437   ***Table 7 here***

438 Prospective open-label clinical trials of Alixir 400 PROTECT® (standardized extract of *Aronia*

439 *melanocarpa*) in 143 patients demonstrated controlled glycemia, blood pressure improvement, and

440 beneficial effects on LDL-C, triglycerides and total cholesterol, and was of significant (*p<0.05*)

441 overall benefit in diabetic hypertensive patients [138]. Similarly, a meta-analysis of controlled

442 clinical trials carried out on *Aronia melanocarpa* daily supplementation revealed significant

443 (*p<0.05*) decreases in total cholesterol, blood pressure and a reduction in cardiovascular and

444 diabetic risk factors, clearly supporting a useful role in therapy [139].

445 Lipid lowering effects are also a common feature of clinical trials with medicinal plants. Hu et al.

446 demonstrated the beneficial effects of a multi-herb formula containing *Crataegus pinnatifida* for

447 dyslipidemia in a randomized double-blind, placebo-controlled trial, reporting decreased plasma

448 lipids, glucose levels, HbA1c, and LDL-C at 95% CI [140]. A randomized, double-blind placebo-

449 controlled trial of *Juglans regia* leaf extract resulted in a significant decrease (*p<0.05*) in fasting

450   blood glucose levels, triglycerides, total cholesterol and HbA1c compared with placebo [141].

451   Similar beneficial effects were reported in further trials [142] including beneficial effects in

452   patients with coronary artery disease with significant decreases ($p=0.04$) in total cholesterol, BMI,

453   and LDL [143]. A clinical investigation of oral administration of *Portulaca oleracea* seeds in 30

454   T2DM subjects revealed a significant decrease ($p<0.001$) in serum levels of triglycerides, total

455   cholesterol, LDL-C, and liver enzymes, but increased ($p>0.001$) levels of HDL-C and albumin

456   [144]. Purslane (*Portulaca oleracea* capsule) also drove a significant difference ($p>0.01$) in the

457   triglycerides, liver enzymesand fasting blood glucose in 74 people with T2DM in a randomized

458   double-blind, placebo-controlled clinical trial. An improvement in both insulin resistance, and

459   LDL-C levels was also reported [145].

460   Decreased blood glucose levels are often used as a key outcome. A 14-day clinical investigation

461   involving 26 people with T2DM on a low (0.5 g/kg) and high (1 g/kg) doses of aqueous and

462   alcoholic extract of the powdered leaves of *Mangifera indica* showed a significant decrease in

463   blood glucose levels in all groups [146]. Similarly, both raw and processed seeds of *Ocimum*

464   *basilicum* in patients with diabetes and dyslipidemia revealed beneficial effects including

465   decreased blood glucose, a reduction in body mass index, triglycerides, LDL-C, and decreased

466   HDL-C at 5% and 1% levels of significant [147]. A significant decrease ($p<0.05$) in the fasting

467   blood glucose and HbA1c levels were observed in people with T2DM after 2 month treatment with

468   the fruit capsule of *Citrullus colocynthis* [148].

469   In a randomized, double-blind, crossover study of 60 diabetic subjects receiving *Salacia oblonga*

470   extract, William and colleagues reported significant decrease ($p<0.05$) in glyceamia and

471   insulinemia in patients after high carbohydrate meal [149]. A four-week randomized double-blind,

472   placebo-controlled clinical trial of fermented red ginseng (*Panax ginseng*) involving 42 patients

473   with impaired fasting glucose or T2DM also showed significant decrease ($p<0.01$) in postprandial

474   glucose levels and increased postprandial insulin levels compared to the placebo group [150]. A

475   further study supported these conclusions [151].

476   Many other studies, highlighted in Table 7, have shown pronounced and beneficial effects.

477   Not all data are conclusive. The results of a 60-day randomized-placebo clinical trial by Hasanzade

478   and colleagues using *Cinnamomum cassia* in 70 people with T2D revealed no significant

479   difference ($p>0.05$) between the test and placebo [152]. On the other hand, Hoehn and Stockert in

480 a smaller trial reported significant decrease in blood sugar levels of the patients taking 1000 mg

481 *Cinnamomum cassia* capsule for 12 weeks [153]. An aqueous extract of *G. sylvestre* (GS4)

482 400mg/day used over 18 to 20 months supplementation drove significant decreases (*p<0.001*) in

483 blood glucose, glycosylated haemoglobin and glycosylated plasma protein in 22 patients [154]. It

484 should also be clearly noted that many of the clinical studies performed to date include relatively

485 small numbers of patients. Larger studies will provide impetus for more work in this area.

486

487

488 **CONCLUSION AND FUTURE PERSPECTIVES**

489 Diabetes mellitus-related morbidity and mortality continues to increase globally and necessitates

490 urgent action to identify and drive novel therapies which can be widely used in under-developed

491 economies. Our review reveals that antidiabetic drugs of herbal origin can play a modulatory role

492 in insulin signaling pathways and drive metabolically relevant changes in insulin action, such as

493 elevated glucose transport. Tissue culture systems have provided key insight into the molecular

494 mechanisms of the phytochemicals beneficial to diabetic patients and have contributed both

495 mechanistic insight and facilitated the development of more clinically-facing treatments. Among

496 the plants we reviewed in tissue culture systems, close to half (45%) have been investigated for

497 their antidiabetic activities in mammals (rats, mice, and rabbits) and 4% have been tested in human

498 clinical trials. The positive outcomes reported in these clinical trials should be recognized as

499 providing a new impetus to phytobiology research as an effective treatment for insulin resistance

500 and diabetes. In future, larger-scale clinical trials are clearly warranted given the largely positive

501 effects of many of these natural products. There is aneed to screen larger numbers and citizens of

502 different genetic backgrounds to identify potential population-specific benefits. Similarly, the

503 coupling of phytochemical studies to genomic data may offer a powerful means to develop

504 combination therapies and more personalized medicine approaches.

505

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Figure 1

Figure 1

Fig 1 Schematic Representation of Antidiabetic Development from Plant to Clinical Trial The pathway from plant extract to effective therapy involves many steps. Plants, often identified from local knowledge/use, are a source of extract prepared using a range of approaches and the extracts screened using simple cell-based models such as Caco-2 cells or L6 skeletal myotubes for *in vitro* effects. Signaling pathways and effectors are used as surrogate assays for potential antidiabetic effects (e.g., glucose transport). Further work involves an examination of effects using rodent models of diabetes and clinical trials.
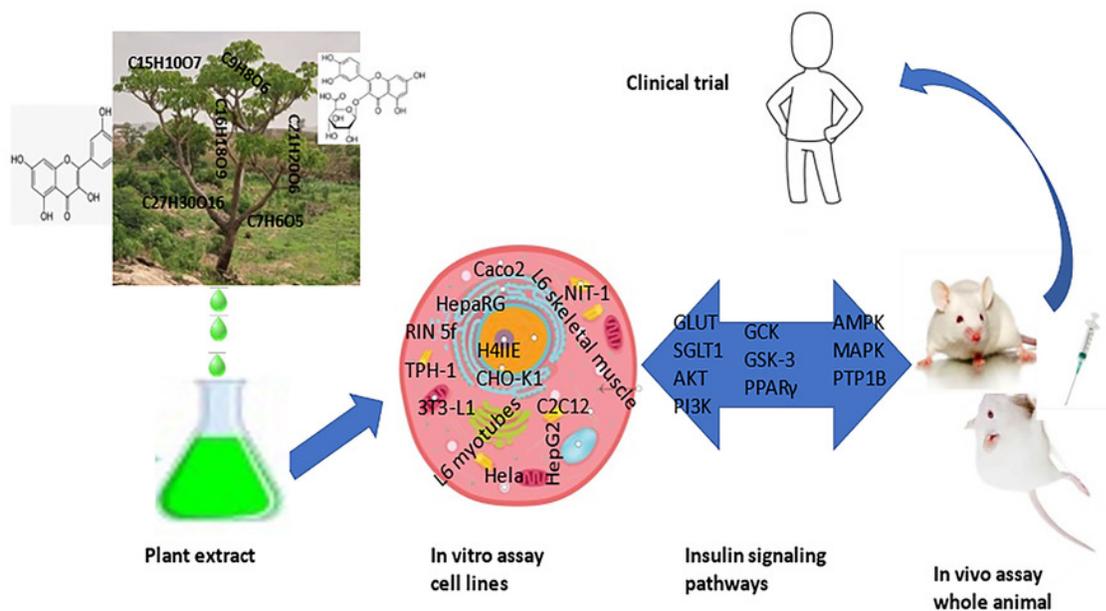
Table 1: Medicinal Plant Active on Glucose Transporters

Shown are studies in which the indicated plants have been shown to drive a change in glucose transport. Where possible these have been alphabetized, but studies in which multiple plant species or extracts were used in a single study are shown at the top of the table.

1 **Table 1: Medicinal Plant Active on Glucose Transporters**

2 Shown are studies in which the indicated plants have been shown to drive a change in glucose transport. Where possible these have

3 been alphabetized, but studies in which multiple plant species or extracts were used in a single study are shown at the top of the table.

Medicinal plant	Phytochemistry	Key effectors	Summary	References
Aronia melanocarpa, Cornus officinalis, Crataegus pinnatifida, Lycium chinense, Vaccinium myrtillus, Brassica oleracea, Juglans regia, Peumus boldus, Adenophora triphylla, Eucommia ulmoides, and *Malus domestica*	Methanolic extract of the leaves, roots, aqueous extract from the bark, and fruit skin.	SGLT 1 and GLUT2.	Inhibition of intestinal SGLT1 and GLUT2 in Caco-2 cells.	[27]
Hoodia, Sapindus mukorossi, Quillaja saponaria, Papaver, Castanea, Bitter orange, Oregon grape, *Saposhnikovia divaricata,* Sponge gourd, Black radish, *Asparagus,* Neem, Uzara, Reetha B, *Chelidonium majus,* Teasel, *Tetradium ruticarpum,* Southern wax myrtle, Bistort, Indian tobacco, Figwort, Rangoon creeper, *Peruvian rhatany,* Chinese rhubarb, Poppy capsule and flowers, Ivy, Common daisy leaves and flowers, Rosebay willowherb, and Goldenrod.	Plant extracts.	GLUT4	Stimulation of GLUT4 translocation in CHO-K1 and 3T3-L1 cells and plasma membrane insertion of GLUT4 in Hela cells.	[2]
Trigonella foenumgraecum, Urtica dioica, Atriplex halimus, and Cinnamomum verum	50 % ethanol extract of the various parts.	GLUT4	Increased translocation of GLUT4 to the plasma membrane in L6-GLUT4myc rat muscle cells.	[155]
Rhododendron groenlandicum, Alnus incana, Sarracenia purpurea	Leaf, bark, and whole plant, respectively.	GLUT4	Increased total membrane expression of GLUT4 and	[156]

			phosphorylation of AKT and AMP in C2C12 and H4IIE cell lines.	
Strawberry and Apple	Polyphenols, phenolic acid, and tannins.	GLUT2, SGLT1	Inhibition of GLUT2 and SGLT1 in human intestinal Caco-2 cells.	[73]
Annona stenophylla	Aqueous root extract.	GLUT4	Enhanced GLUT4 and gene expression in C2C12 muscle cell lines.	[157]
Apios americana	Glycosides from the leaves.	MAPK and glucose uptake	Restores glucose uptake, glucose consumption, and glycogen content in HepG2 cells via MAPK and Nrf2 pathways.	[158]
Capparis moonii	Gallotannins from hydro-alcoholic fruit extract.	GLUT4	Increased phosphorylation of IR-β, IRS-1, and GLUT4, PI3K mRNA expression in L6 myotube cells.	[65]
Cassia abbreviate	Aqueous leaf, seed, and bark extract.	GLUT4	Enhanced GLUT4 translocation and gene expression in C2C12 mouse skeletal muscle cells.	[68]
Cinnamomum burmannii	Water extract and polyphenols.	GLUT4 GLUT1	Increased expression of mRNA GLUT4, IR, GLUT1in mouse 3T3- adipocytes.	[159] [160]
Cinnamomum cassia	Cinnamic acid from a hydroalcoholic bark extract.	GLUT4	Increased GLUT4 mRNA and inhibition of PTP1B activity in L6 myotubes.	[161]
Citrullus colocynthis	Fruit and seed extracts and solvent fractions.	GLUT4	Enhancement of insulin-induced GLUT4 translocation in	[71]

			adipocytes.	
Costus igneus [insulin plant]	Leaf extract	Glucokinase/ GLUT2	Increased glucokinase activity, insulin, and GLUT2 gene expression but inhibition of glucose-6-phosphatase activity in human hematopoietic stem cells [HSCs] showing β-like cells action. *C. igneus* contained insulin-like proteins [ILP] with hypoglycemic activities in insulin-responsive cell line RIN 5f.	[100] [101]
Dandelion powder	Chloroform extract.	GLUT4	Increased GLUT4 expression and membrane translocation via the AMPK pathway in L6 cells.	[162]
Folium sennae	Ethanol extract.	GLUT4	Promotes membrane translocation and mRNA of GLUT4 via AMPK, AKT, and G protein-PLC-PKT pathways and internalization of C^{2+} in L6 cells.	[85]
Gundelia tournefortii	Hexane and methanol extract of the aerial part.	GLUT4	Enhanced translocation of GLUT4 to the plasma membrane by the methanol extract than the hexane extract in L6 myotube cells.	[67]
Kigelia pinnata	Isolated phytochemicals from ethanol extract of *K. pinnata* twigs.	GLUT4	Increased GLUT4 translocation to the skeletal muscle cell surface in skeletal muscle cells.	[163]
Mangifera indica	Ethylacetate extract and 3β-	GLUT4	GLUT4 translocation and	[70]

	taraxerol.		glycogen synthesis in 3T3-L1 adipocytes.	
Maydis stigma [corn silk]	Extracted polysaccharides.	GLUT4	Membrane translocation of GLUT4 in rats L6 skeletal muscle and regulation of PI3K/AKT pathways.	[84]
Mitragyna speciosa	Water, methanol extract, and mitragynine [a principal constituent].	GLUT1	Increased GLUT1 content in rat L6 myotubes.	[74]
Momordica balsamina	ethanol, ethyl acetate, and n-hexane fruit extract	GLUT2	Increased GLUT2 gene expression	[103]
Momordica charantia	Aqueous and chloroform extract of the fruit.	GLUT4	Increased glucose uptake with GLUT4, PPARγ, and PI3K mRNA gene expression in L6 myotube cells.	[108]
Moringa concanensis	Leaf extract	GLUT4 via PPARγ effects	3T3-L1 adipocytes, enhanced GLUT4 gene expression	[112]
Morus alba	Ethanol leaf extract.	GLUT4	Stimulation of glucose uptake and GLUT4 translocation to the plasma membrane via activation of PI3K in rat adipocytes.	[69]
Nymphaea nouchali	Seed extracts	GLUT4 via PPARγ effects	Increased GLUT4 mRNA expression	[110]
Ocimum basilicum	Methanol, hexane, and dichloromethane are extracts of the stem, leaf, and flowers.	GLUT4	Elevated GLUT4 translocation to the plasma membrane HepG2 and rat L6 muscle cells.	[164]
Panax ginseng [black ginseng]	Ethanolic extract of black ginseng.	GLUT4	Increased phosphorylation of AMPK, increased upregulation of	[165]

			GLUT2 in the liver and GLUT4 in the muscle.	
Pinus pinea [pine]	Bark extract	MAPK and glucose uptake	Activation of p38MAPK, which in turn activates SGLT1 and GLUT2 in Caco-2 cells.	[166]
Portulaca oleracea and *Coccinia grandis*	Plant extract.	GLUT4	PI3K mediated GLUT4 translocation in insulin-sensitive CHO-K 1 cells and adipocytes.	[72]
Rosemary	Carnosol [diterpene] found in Rosemary.	GLUT4	AMP-dependent increase GLUT4 translocation in L6 skeletal muscle cells.	[66]
Salacia oblonga	Hot water extract of the root, stem, and mangiferin, the bioactive compound.	GLUT4	GLUT4 and concomitant phosphorylation of 5'AMP-activated protein kinase in L6 myotubes and 3T3- adipocytes.	[167]
Selaginella tamariscina	Selaginellins and bioflavonoids from methanol extract.	PTP1B and glucose uptake	Glucose uptake and inhibition of PTP1B in 3T3-L1 adipocytes	[166,167]
Sinocrassula indica Berge	Ethanolic extract	GLUT1, GLUT4	Increased glucose uptake in L6 myotubes and H4IIE hepatoma cells	[105]
Gymnema sylvestre	Methanolic leaf extract	GLUT4	Enhanced glucose uptake in L6 myotubes cells	[75]

Table 2: Medicinal Plants Modifying PI3K/Akt activity

Shown are studies in which the indicated plants have been shown to drive activation of the canonical insulin signalling molecules PI3K and Akt. Table is constructed in alphabetical order of plant species.

1 **Table 2: Medicinal Plants Modifying PI3K/Akt**

2 Shown are studies in which the indicated plants have been shown to drive activation of the canonical insulin signalling molecules
3 PI3K and Akt. Table is constructed in alphabetical order of plant species.

Medicinal plant	Phytochemistry	Target	Summary	References
Anemarrhena asphodeloides Bunge	Monosaccharides	PI3K	Activation of PI3K/Akt, IRS-1 signaling pathway, and inhibition of α-glucosidase activity in HepG2 cells.	[92]
Broussonetia kazinoki	A flavan [Kazinol B] purified the root.	Akt	Improved insulin sensitivity via Akt and AMPK activation in 3T3-L1 adipocytes.	[168]
Dendrobium officinale	Polysaccharide	PI3K	Increased PI3K/Akt phosphorylation in insulin-resistant HepG2 cells.	[89]
Folium sennae	Ethanol extract.	Akt	Increased AMPK, Akt, and PKC phosphorylation in L6 rat skeletal muscle.	[85]
Grifola frondosa	Heteropolysaccharide of the fruiting body.	PI3K	Increased mRNA of IRS1/PI3K, and downregulation of JNK1 signaling in HepG2 cells.	[88]
Juniperus chinensis	α- Methyl artoflavano coumarin from *Juniperus chinensis*.	Akt	PI3K/Akt and inhibition of PTP1B in HepG2 cells.	[93]
Mangifera indica	Ethyl acetate extract [EAE] and 3β-taraxerol phytochemistry.	PI3K	Increased PI3K level and GLUT4 translocation in 3T3-L1 adipocytes.	[70]
Maydis stigma [corn silk]	*Maydis stigma* [corn silk] extract.	Akt	A dose-dependent increase in expression of p-Akt/Akt in L6 skeletal	[84]

			muscle myotubes.	
Nigella glandulifera	Alkaloids from the seeds.	PI3K	Increased PI3K/Akt pathway together with inhibition of PTP1B.	[86]
Nigella glandulifera	Norditerpenoid alkaloids of the seeds.	Akt	PI3K/Akt pathway, inhibition of PTP1B, increased glycogen synthesis with hexokinase activity in L6 myotubes	[86]
Sargassum pallidum	Homogeneous polysaccharides.	PI3K	Upregulation of PI3K, GS, and IRS-1 gene expression in insulin-resistant HepG2 cells.	[91]
Zhenjiang aromatic vinegar	Polyphenol-rich extract.	PI3K	Activation of PI3K/Akt pathway in IR-HepG2 cells.	[90]

Table 3: Medicinal Plants with Activities on Glucokinase [GCK]

Table 3: Medicinal Plants with Activities on Glucokinase [GCK] Shown are studies in which the indicated plants have been shown to drive changes in glucokinase activity or expression. Table is constructed in alphabetical order of plant species.

1 **Table 3: Medicinal Plants with Activities on Glucokinase [GCK]**

2 Shown are studies in which the indicated plants have been shown to drive changes in glucokinase activity or expression. Table is
3 constructed in alphabetical order of plant species.

Medicinal plant	Phytochemistry	Summary	References
Costus igneus [insulin plant]	Leaf extract.	Increased glucokinase activity, insulin, and GLUT2 gene expression but inhibition of glucose-6-phosphatase activity in human hematopoietic stem cells [HSCs] showing β-like cells action. *C. igneus* contained insulin-like proteins [ILP] with hypoglycemic activities in insulin-responsive cell line RIN 5f.	[100] [101]
Momordica balsamina	Ethanol, ethyl acetate, and n-hexane fruit extract.	Increased GCK and GLUT2 mRNA gene expression in RIN-m5F cells.	[103]
Zea mays [Purple corn]	Anthocyanins from the pericarp.	Activation of GCK in HepG2 cells decreased glucose uptake in Caco-2 cells and increased glucose-stimulated insulin secretion in iNS-1E in the pancreas.	[102]

Table 4: Medicinal Plants Modifying Activities of Peroxisome Proliferator-activated Receptor-gamma [PPARγ]

Shown are studies in which the indicated plants have been shown to mediate effects probably via PPRγ. Table is constructed in alphabetical order of plant species. Where possible these have been alphabetized, but studies in which multiple plant species or extracts were used in a single study are shown at the top of the table.

1 **Table 4: Medicinal Plants Modifying Activities of Peroxisome Proliferator-activated Receptor-gamma [PPARγ]**

2 Shown are studies in which the indicated plants have been shown to mediate effects probably via PPRγ. Table is constructed in
3 alphabetical order of plant species. Where possible these have been alphabetized, but studies in which multiple plant species or
4 extracts were used in a single study are shown at the top of the table.

Medicinal plant	Phytochemistry	Summary	References
Yeongyang korea [Korea red pepper], *Capsicum annuum*	Ethanol extract.	Increased PPARγ and AMPK phosphorylation in C2C12 myotubes.	[114]
Boehmeria nivea	Ethanol leaf extract.	Increased mRNA levels of PPARγ in C2C12 myotubes cells.	[113]
Miconia sp.	Ethanol extract of the aerial part.	Increased PPARγ mRNA and GLUT4 in 3T3-L1 adipocytes.	[111]
Momordica charantia	Chloroform extract of the fruit.	Increased mRNA gene expression of PPARγ in L6 myotube skeletal muscle cells, as well as GLUT4 and PI3K.	[108]
Moringa concanensis	Leaf extract.	Upregulation of mRNA of PPARγ, GLUT4, FAS, Tsrebp, DAG, and Akt signaling in 3T3-L1 adipocytes.	[112]
Nymphaea nouchali	Seed extract.	Increased mRNA of PPARγ and GLUT4 in 3T3-L1 adipocytes.	[110]
Punica granatum	Flower aqueous extract and ethyl acetate fraction.	Increased mRNA PPARγ gene and protein expression in TPH-1-derived macrophage cell line.	[109]

Table 5: Medicinal Plants Regulating AMP-activated Protein Kinase [AMPK]

Shown are studies in which the indicated plants have been shown to mediate effects via AMPK activity. Table is constructed in alphabetical order of plant species.

1 **Table 5: Medicinal Plants Regulating AMP-activated Protein Kinase [AMPK]**

2 Shown are studies in which the indicated plants have been shown to mediate effects via AMPK activity. Table is constructed in
3 alphabetical order of plant species.

Medicinal plant	Phytochemistry	Summary	References
Artemisia dracunculus	Alcoholic extract [PMI-5011].	Increased insulin secretion through AMPK activation in NIT-1 cells.	[123]
Artemisia sacrorum	Petroleum ether fraction.	Decreased glucose production via the AMPK-GSK-CREB pathway in HepG2 cells.	[120]
Aspalathus linearis	80 % ethanol extract.	Amelioration of insulin resistance in C2C12 via activation of AMPK and Akt pathway.	[169]
Cimicifuga racemosa	Ethanol extract and Phyto-compounds.	Increased AMPK activity in HepaRG cells.	[119]
Crocus sativus [Saffron]	Methanol extract.	Increased glucose uptake and insulin sensitivity via AMPK phosphorylation in C2C12 mouse myotubes cells.	[124]
Entada phaseoloides	Total saponin extract.	Suppression of hepatic gluconeogenesis via AMPK and Akt/GSK3β in Primary hepatocytes and HepG2 cells.	[121]
Iris sanguinea	Isolated compounds from methanol extract of the seeds.	Increased glucose uptake via activation of ACC and AMPK in mouse C2C12 skeletal myoblast.	[125]
Malva verticillata	Ethanol extract and compound isolate [β-sitosterol].	Increased glucose uptake via AMPK phosphorylation in L6 myotubes.	[126]
Momordica charantia	Triterpenoids from the stem.	Overcome insulin resistance via AMPK activation in FL83B and C2C12 cells.	[127]
Psidium guajava	Flavonoids from the	AMPK phosphorylation in rat L6 myotubes and L02	[170]

	leaves.	human hepatic cells.	
Rhodiola crenulata	Methanol extract.	Inhibition of gluconeogenesis in human hepatic HepG2 cell via activation of AMPK.	[171]
Rosmarinus officinalis	Dichloromethane-methanol extract.	Regulate glucose and lipid metabolism through activation of AMPK and PPAR pathways in HepG2 cells.	[122]
Sechium edule	Water and polyphenol extract of the shoot.	Inhibition of lipogenesis and stimulation of lipolysis via AMPK activation and decreased lipogenic enzymes in HepG2 cells.	[172]
Stauntonia chinensis	Triterpenoid saponins.	Increased glucose uptake in HepG2 insulin-resistant cells via AMPK phosphorylation and IR, IRS-1, PI3K/Akt pathways	[173]
Toona sinensis	Leaf extract.	Increased glucose uptake in C2C12 myotubes due to AMPK activation.	[174]
Vigna angularis [Azuki bean]	Extract	Increased phosphorylation of AMPK and Akt in HepG2 cells.	[175]

Table 6: Medicinal Plants Having Antidiabetic Activity in Tissue Culture and Whole Animal Biology

Studies of medicinal plants with demonstrated anti-diabetic properties are listed. Plants are arranged in alphabetical order. The animal model studies are cross-referenced to cellular studies of the same extract/plant wherever possible.

1 **Table 6: Medicinal Plants Having Antidiabetic Activity in Tissue Culture and Whole Animal Biology**

2 Studies of medicinal plants with demonstrated anti-diabetic properties are listed. Plants are arranged in alphabetical order. The animal

3 model studies are cross-referenced to cellular studies of the same extract/plant wherever possible.

Medicinal plants	Phytochemistry	Animal model	Summary	Animal Study	Cell Study
Yeongyang korea [korea red pepper], *Capsicum annuum*	Seed extract.	Mice	Improved glycemic control, decreased hepatic gluconeogenesis, and increased FOXO1 and AMPK phosphorylation.	[176]	[114]
Anemarrhena asphodeloides	Glycosides	Mice	Inhibition of hepatic gluconeogenesis/glycogenolysis.	[177]	[83]
Annona stenophylla	Aqueous root extract.	Rats	Decreased glucose level.	[178]	[157]
Apios americana	Flower or methanolic extract of the flower.	Mice	Decreased plasma glucose level.	[179]	[158]
Aronia melanocarpa	Fruit juice.	Rats	Decreased plasma glucose and triglycerides in diabetic rats.	[168,169]	[27]
Artemisia dracunculus	Ethanolic extract.	Mice	Lowered glucose and PEPCK concentrations.	[137]	[123]
Aspalathus linearis	Tea extract.	Mice	Improved impaired glucose tolerance.	[180]	[169]
Boehmeria nivea	Methanol extract of the root.	Wistar rats	Restore normal glucose, lipids, and antioxidants level.	[181]	[113]

Brassica oleracea	Raw sprouts.	Rats	Decreased blood glucose, glycated hemoglobin, and hepatoprotection.	[182]	[27]
Cimicifuga racemosa	Rhizomes and root extract.	Mice	Reduced body weight, plasma, glucose, and increased insulin sensitivity.	[119]	[119]
Cinnamomum cassia	Bark extract.	Diabetic mice	Decreased blood glucose and triglycerides levels.	[183]	[161]
Citrullus colocynthis	Fruit ethanol extract.	Albino rats	Reduced blood glucose and improved pathology.	[184]	[71]
Costus igneus [insulin plant]	Powdered leaves.	Rats	Decreased fasting and postprandial glucose level	[185]	[100]
Crataegus pinnatifida	Fruit extract.	Mice	Decreased glucose production and triglyceride synthesis via AMPK phosphorylation.	[130]	[27]
Crocus sativus	Hydroethanolic extract of aerial parts.	Rats	Reduced blood glucose and improved diabetic complications.	[186]	[124]
Curcuma longa	Curcuminoids and sesquiterpenoids from rhizome solvent fractions.	Mice	Decreased blood glucose levels and stimulation of adipocyte differentiation.	[187]	[188]
Dendrobium officinale	Stem extract.	Rats	Reduced blood glucose, total cholesterol, triglycerides, and LDLP-C.	[136]	[89]
Entada phaseoloides	Entagenic acid from seed kernel.	Mice	Improved blood glucose, insulin resistance, and changes in pancreatic islets.	[189]	[121]

Eucommia ulmoides	Leaves	Rats and Mice	Hypoglycemia and hypolipidemic effects in streptozotocin-induced hyperglycemia.	[177,178]	[27]
Gundelia tournefortii	Water extract.	Mice	Decreased blood glucose level, body weight, triglycerides, and cholesterol, but increased renal protection.	[181,182]	[67]
Juglans regia	Leaves and ridges.	Mice Rats	Decreased blood glucose, hepatic phosphoenolpyruvate carboxykinase, glycogen phosphorylase activity, glycosylated hemoglobin, LDL, triglycerides, and total cholesterol.	[132] [174,175]	[27]
Juniperus chinensis	Berries ethanol extract.	Rats	Improved blood glucose level and other diabetic parameters.	[194]	[93]
Kigelia pinnata	Methanolic extract of the flower.	Rats	Decreased blood glucose, serum cholesterol, and triglycerides.	[195]	[163]
Malva verticulata	Tea	Mice	Decreased blood glucose, LDL-C, and total cholesterol and increased HDL-C and leptin.	[196]	[126]
Mangifera indica	Aqueous extract of the leaves.	Rats	Decreased fasting blood glucose level.	[197]	[70]
Momordica charantia	Aqueous seed extract.	Rats	Reduced blood glucose, glycosylated hemoglobin, lactate dehydrogenase, glucose-	[135]	[108]

			6-phosphatase, fructose-1,6-biphosphatase, and glycogen phosphorylase, but increases the activities of glycogen synthase and hexokinase.		
Momordica charantia	Saponins	Rats	Decreased fasting blood glucose, triglycerides, total cholesterol, and increased insulin content and sensitivity.	[198]	[127]
Morus alba	Polysaccharides from fruit.	Rats	Reduced blood glucose and lipid levels.	[199]	[69]
Ocimum basilicum	Aerial parts.	Rats	Inhibition of glycogenolysis.	[200]	[164]
Opuntia ficus-indica	Powder or water extract of the stem.	Rats	It inhibits α-glucosidase and reduces blood glucose levels.	[201]	[202]
Panax ginseng	Ethanol extract of the seed.	Obese diabetic mice	Increased insulin-stimulated glucose disposal, energy expenditure, and reduced cholesterol levels.	[203]	[165]
Peumus boldus	Boldine alkaloid from the leaves and bark.	Rats	Dose-dependent decrease in oxidative markers and mitochondrial protection	[204]	[27]
Portulaca oleracea	Aqueous extract.	Male Wistar rats	Decreased Hb A1C, serum glucose level, TNF-α, and IL-6.	[205]	[72]
Psidium guajava	Leaf extract.	Rats	Antidiabetic	[206]	[170]
Punica granatum	Fruit aqueous extract.	Wistar rats	Reduces fasting blood glucose and lipid levels.	[207]	[109]
Rhodiola crenulata	Methanol root	Mice	Decreased postprandial blood	[208]	[171]

	extract.		glucose.		
Rosmarinus officinalis	Water extract.	Rats	Decreased blood sugar level and oxidative stress markers.	[209]	[66]
Salacia oblonga	Water extract of the root.	Obese Zucker rats	Improved interstitial and perivascular fibrosis and inhibition of postprandial hyperglycemia.	[210]	[167]
Sapindus mukorossi	Fruit	Rats	Decreased glucose and lipid levels.	[211]	[2]
Sarcopoterium spinosum	Aqueous extract.	Mice	Prevents diabetes progression.	[212]	[213]
Sechium edule	Methanol and ethyl acetate fraction.	Rats	Antidiabetic and antioxidant.	[214]	[172]
Selaginella tamariscina	Total flavonoids	Rats	Decreased plasma FBG, HbA1c, triglycerides, total cholesterol, FFA with increased insulin, HDL-C, and C-peptides.	[215]	[77]
Stauntonia chinensis	Total saponins from the stem.	Mice	Hypoglycemic and hypolipidemic.	[216]	[173]
Toona sinensis	Quercetin from the leaves.	Mice	Antidiabetic and antioxidant.	[217]	[174]
Trigonella foenum-graecum	Seed powder.	Female Albino rats	Reduced elevated fasting blood glucose and enzyme levels.	[218]	[92]
Urtica dioica	Aqueous extract of the aerial parts.	Wistar rats and Swiss mice	Decreased glucose level in oral glucose tolerant test [OGTT].	[220]	[92]
Vaccinium myrtillus	Fruit	Rats	Decreased total cholesterol,	[131]	[27]

			LDL-C, VLDL-C, and triglycerides in alloxan-induced hyperglycemic rats.		
Vigna angularis	Hot water extract and polysaccharides from the leaves.	Mice and Rats	Reduced FBG, an triglycerides, but increased HDL-C, and reduction in diabetes progression.	[215,216]	[175]
Zea mays [Purple corn]	Extract	Mice	Decreased fasting blood glucose, HbA1c, and PEPCK, increased insulin secretion, AMPK and GLUT4 in diabetic mice.	[223]	[102]
Gymnema sylvestre	Phytoconstituents	Rats	Reduced hyperglycemia via through PI3K/AKT activation	[87]	[224]

Table 7: Medicinal Plant Antidiabetics From Cell-biology to Clinical Trial

Shown are studies in which the indicated plants have been examined in clinical trials.

1 **Table 7: Medicinal Plant Antidiabetics From Cell-biology to Clinical Trial**

2 Shown are studies in which the indicated plants have been examined in clinical trials.

Medicinal plants	Phytochemistry Product	Clinical trial	References
Aronia melanocarpa	Alixir 400 PROTECT® [Standardized extract]	Prospective open-label trial of 148 patients.	[138]
Cinnamomum cassia	Extract and 1000 mg capsule.	Randomized-placebo control of 70 patients and another study of 19 subjects.	[239,240]
Citrullus colocynthis	Fruit capsule.	Randomized clinical trial of 50 T2D patients.	[148]
Crataegus pinnatifida	Multi-herb	Randomized double-blind, placebo-controlled trial of 40 patients.	[140]
Curcuma longa	500 mg/ day	Randomized double blind, placebo-controlled trial of 71 patients	[225]
Gundelia tournefortii	250 mg of hydroalcoholic extract of the aerial parts.	Randomized double-blind, placebo-controlled trial of 38 patients.	[143]
Juglans regia	Leaf extract 100 mg twice daily and a hydroalcoholic leaf extract.	Randomized double-blind, placebo-controlled trial of 61 and 50 patients.	[227,228]
Mangifera indica	Low dose[0.5 g/kg] and high dose [1 g/kg] of the leaf extract.	Clinical investigation of 26 T2DM patients.	[146]
Momordica charantia	2000 mg/day of dried powder of fruit.	Randomized, double-blind, placebo-controlled trial of 24 patients.	[226]
Morus alba	300 mg extract.	Randomized clinical trial of 60 type 2 diabetic patient [T2DM].	[227]
Ocimum basilicum	Raw and processed seeds.	45 days clinical trial using convenient sampling.	[147]
Opuntia ficus-indica	Nopal [*Opuntia ficus-indica*	Clinical study.	[228]

	preparation].		
Panax ginseng	Extract of fermented root and Korean red ginseng preparation.	Randomized clinical trial of 42 subjects and double-blind randomized crossover design of 19 subjects.	[237,238]
Portulaca oleracea	Seeds	Clinical study of 30 patients and randomized trial of 74 subjects.	[234,235]
Punica granatum	Dried flower mouth wash.	Randomized trial of 80 diabetes patients with gingivitis.	[229]
Salacia oblonga	Extract [240, 480 mg/kg]	Randomized double-blind crossover trial of 60 patients.	[149]
Trigonella foenum-graecum	Seed capsule.	Multicenter randomized, placebo-controlled, double-blind, add-on clinical trial of 154 T2D patients. Another 12 weeks trial of 12 patients.	[241,242]
Urtica dioica	Ethanolic extract.	Double-blind, randomized trial of 50 diabetic women.	[232]
Gymnema sylvestre	Leaf water extract	22 non-insulin dependent diabetic patients	[154]