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A review on upregulation of glucokinase expression by selected plants and their phytoconstituents

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***Abstract*---**Glucokinase is, an allosteric enzyme involved in glycolysis, is rapidly regulated in the liver through glucokinase regulatory protein and remains essential for blood glucose homeostasis. The present review provides brief information about the effects of a few selected plants and phytochemicals on human glucokinase activation and gene modulation. A thorough and relevant literature search from several scientific databases, comprising Google Scholar, Web of Science, Scopus and PubMed, was carried out. We highlighted the seven plants (Acorus tatariowii Schott, Allium hirtifolium Boiss, Apache red maize, Mulberry species, Pterocarpus marsupium, Sapium ellepticum, Mangifera indica) and their phytoconstituents (Tatanans A-C, alliogenin , gitogenin , kaempferol , quercetin and shallomin,1-deoxynojirimycin,cyanidin-3-rutinoside,resveratrol,cyanidin-3-glucoside,oxyresveratrol, lupeol, alpha-tocopherol, uteolin-7-glucoside, amentoflavone, and Mangiferin) on human glucokinase

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enzyme activation and gene modulation. This review concluded that investigation of glucokinase activators of plant origin is the major research focus in the management of type 2 diabetes.

***Keywords*---**glucokinase, diabetes, glucose homeostasis, medicinal plants, phytochemicals.

Introduction

Diabetes is a metabolic disease that comprises a heterogeneous group of disorders characterised by hyperglycaemia, which occurs because impaired insulin secretion and sensitivity lead to derangements of carbohydrate, fat, and protein metabolism. Diabetes afflicted around 537 million people in 2021, as per the International Diabetes Federation, and by 2045, the number of individuals with diabetes is anticipated to rise to 783 million [IDF Diabetes Atlas10th edition 2021]. Several drugs are available to treat type-2 diabetes, including sulfonylureas, glinides, metformin (a biguanide), thiazolidinedione's (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, alpha-glucosidase inhibitors, dopamine agonists, bile acid sequestrants, oral glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose transport protein 2 (SGLT2) inhibitors [Tahrani, A. A *et al* 2016]. However, these therapies have their limitations and drawbacks. Currently, more and a wide range of new therapeutic investigations focusing on enhancing postprandial and fasting glycaemic balance are under development.

The glucokinase (GCK) (Hexokinase type IV) exhibits distinctive properties in comparison to pervasively expressed hexokinase isoforms type I-III [K Dementhon *et al* 2019]. Most glucose-sensing organs express it, particularly pancreatic α- and β-cells, liver hepatocytes, ventromedial hypothalamic neurons, gastrointestinal K and L cells, and pituitary gonadotrophs. Glucokinase distribution in human body shown in the Figure 1. In the pancreas' β-cell, GCK acts as a glucostat, modulating the rate at which glucose reaches the glycolytic pathway (glucose phosphorylation) and is metabolised [MA Magnuson et al 2006]. Its function in pancreatic α -cells is unclear, however it might be engaged in the regulation of glucagon secretion [Mithieux, G. *et al* 1998].

GCK controls the rate of hepatic glucose uptake in hepatocytes and is implicated in glycogen synthesis and hepatic glucose production (HGP) regulation [Agius, L. *et al.*, 2009]. Interaction with glucokinase regulatory protein (GKRP) regulates GCK activity in the liver [Stehouwer,C. D *et al.,* 2018]. In hypoglycaemic situations, GKRP binds to the inactive conformation of glucokinase and sequesters it to the nucleus. In hyperglycaemic circumstances, GKRP causes glucokinase to be released into the cytoplasm, where it can be transformed into its active form by binding to glucose. GCK is also found in glucose-sensing neurons in the ventromedial hypothalamus, where it controls the hypoglycaemic counter-regulation response (CRR) [Levin, B. E. *et al.,* 2002]. In addition to some pituitary cells [Golson, M. L *et al.*, 2006]. GCK can also be found in the K and L cells of the gut's endocrine system [Magnuson, M. A. *et al* 1994 & Hattersley, A. T. *et al.,*2009]. Its functions are unknown, but it may be involved in detecting nutrition. Mutations in the GCK gene produce two types of diabetes: maturity-

onset diabetes of the young (GCK-MODY) and persistent neonatal diabetes (PND), a severe type of diabetes that appears at birth [Froguel, P *et al.,* 1993]. PND is a recessive condition that is caused by homozygous or compound heterozygous inactivating GCK mutations and necessitates insulin therapy within the first month of life [De León DD & Stanley CA, *et al.,* 2008.]. GCK-MODY diabetes is an autosomal dominant subtype with an early onset and modest persistent hyperglycaemia [Byrne, M. M. *et al.,* 1994]. On the other hand, heterozygous activating GCK mutations cause hyperinsulinemia and hypoglycaemia [Glaser, B *et al.,* 1998]. These activating mutations cause GCK activation at lower-than-normal glucose concentrations, leading to improper insulin secretion and hypoglycaemia. Loss of function mutations in the GKRP, leads to pseudo-activation of hepatic glucokinase, have also been linked to lower blood glucose levels, as well as higher plasma triglyceride and free fatty acid levels [Beer, N. L., *et al.,* 2009]. Taken collectively, the phenotypes show the enzyme's critical physiological involvement in glucose metabolism regulation.

The discovery of GCK activators has opened a new era of drug research in the search for new diabetic therapies. These small-molecule drugs attach to an allosteric region on the enzyme and probably promote a high-affinity conformation, increasing the enzyme's apparent affinity for glucose. Several GCK activators, including Piragliatin, AZD1656, AZD6370, AMG151, and MK-0941, have progressed to phase II clinical trials; significant glucose lowering activity has been observed, as well as potential side effects such as hypoglycaemia and elevated triglyceride levels [Matschinsky, F. M *et al.,* 2010]. In the present situation, everyone is looking forward to natural products, particularly those produced from plants, as natural sources are generally considered to be much safer than synthetic sources, with fewer side effects. Hence, in this review, we discuss plants and their Phytochemicals activities on the human glucokinase enzyme.

Methods

The literature search for the present study was carried out using several scientific databases, including Google, Scopus, PubMed, Google Scholar, Web of Science, and Science Direct. The focus of the study was on medical plants and their phytoconstituents that increase GCK activity for diabetes management. Chemical structures of phytochemicals shown in the Figure 2.

Glucokinase activation by plants and their phytochemicals: *in-vivo* and *in-vitro* studies

From the thorough and relevant literature search, we examined the effects of a few medicinal plants and their phytochemicals on human glucokinase activation and gene modulation. The GCK activators from plants and phytochemicals are discussed below (Table 1).

Table 1
The GCK activators from plants and their phytochemicals

Name of plant	**Phytochemicals**	**Dosage**	**Cellular & molecular effects**	***In vitro/ in vivo* studies**	**References**
Acorus tatariowii schott	Tatanans A-C	1.85μM 0.52 μM 0.16 μM	↑Glucokinase (GCK)	GCK Enzymatic assay	(19)
Allium hirtifolium	Alliogenin, Gitogenin, Kaempferol, Quercetin and Shallomin	200mg/kg	↑Hepatic glucokinase (GCK) ↑Hepatic glucokinase gene	Diabetic rats	(21)
Apache Red *Zea mays*	Phenolic-rich water extract from	43.4μg/ml	↑Hepatic glucokinase (GCK)	Liver HepG2 cells	(22)
Mulberry	Resveratrol, Oxyresveratrol, 1-Deoxynojirimycin Cyanidin-3-glucoside and Cyanidin-3-rutinoside	15−50 Mm 25−50 μM	↑ glucokinase (GCK)	liver HepG2 cells	(28)
Pterocarpus marsupium	Aqueous extract	1g/kg	↑Glucokinase (GCK) ↑Hexokinase (HK) ↑Phosphofructokinase (PFK)	Diabetic rats	(30)
Sapium ellepticum	Lupeol, α-tocopherol, amentoflavone and luteolin-7-glucoside Leaf extract	400 mg/kg	↑ Glucokinase (GCK) ↑Glucose-6-phosphatase	Diabetic rats	(32,33)
Mangifera indica	Mangiferin	0–1 mM for 24 hours 200 mg/kg for 8 weeks	↑ Glucokinase (GCK)	HepG2 cell and mouse C2C12 myoblast Cell db/db mice	(24)

Acorus tatarinowii Schott

Acorus tatariowii schott ("Chang Pu") is a Chinese medicinal herb that has been used for thousands of years, belonging to the *Acoraceae* family. Its rhizome is a well-known conventional Chinese medicine, and it has been included as the top-grade medication in "Shen Nong's Herbal Classic," the oldest Chinese Materia medica book. In China, a water-dipped solution is administered to treat forgetfulness, dementia, and apoplexy [Zheng, X. *et al.,* 2020.]. Three new activators from the rhizomes of Acorus tatarinowii Schott have been identified as Tatanans A(1), B(2), and C(3) (sesquinlignans). With EC1.5 values ranging from 0.16-1.85 M, Tatanans A-C dominantly boosted GCK metabolic activity. Tatanans A-C were shown to be more potent than GKA22, a synthetic activator. Tatanans are interesting precedents for anti-hyperglycaemic medication research and

development due to their high GCK activity and unique structural characteristics [Yu, D. Q. *et al.,* 2011].

Allium hirtifolium Boiss

The Persian Shallot (*Allium hirtifolium Boiss*) is a *Liliaceae* family member. It is also known as Moosir and is a natural plant that grows in various places in Iran. Its bulbs and blossoms are used in the diet as nutrition and also as medical therapy [Fathi, B *et al.,* 2011]. It is observed that GCK expression and its activities are increased with its regular usage. In a dose-dependent way, GCK activity was significantly increased with Persian shallot (P 0.05) in STZ-induced diabetic rats. The steroidal and flavonoidal derivatives of alliogenin (4), gitogenin (5), shallomin (6), kaempferol (7) and quercetin (8) of Persian shallot. These phytochemicals have a high binding free energy and have a lot of interactions with GAK's allosteric site residues [Singh, S. *et al.,*2020].

ApacheRed Zea mays L.

In-vitro results of a phenolic-rich aqueous extract from the pericarp of Apache red maize (RPE) enhanced genotype activates the type-2 diabetes marker glucokinase (GCK). The major components of this extract are phenolic acids, anthocyanins, and some flavonoids. GCK, which has an EC50 of 43.4 g/mL and is activated by RPE in pancreatic INS-1E cells and liver HepG2 cells, which may be because of allosteric changes [De Mejia, E. G. *et al.,*2019].

Mangiferin

Mangiferin (2-D-glucopyranosyl-1,3, 6,7-tetrahydroxy-9H-xanthen-9-one) is derived from the leaves and bark of *Mangifera indica*. It can be isolated using mango peels and kernels, *Iris unguicularis*, *Anemarrhena asphodeloides* rhizomes, and *Bombax ceiba* leaves. It has antibacterial, antidiabetic, anti-oxidative, anti-allergic, hypocholesterolaemia, anticancer, and immunomodulatory properties [Faizi, S *et al.,* 2005]. In structured-based virtual ligand screening, Mangiferin (9) was identified as a possible glucokinase activator. In in-vitro and in-vivo investigations, this compound regulates blood glucose levels by activating GCK without inducing hypoglycaemia [Chen, J. *et al.,* 2017].

Mulberry

Mulberry (Morus) belongs to the family Moraceae, a traditional Chinese plant that has been reported to possess many pharmacological effects [Xiumei, G. *et al.,* 2010] [25]. The mulberry resources have potential effects on hyperglycaemia, mainly due to the presence of 1-deoxynojirimycin (DNJ)(10), resveratrol (RES)(11), oxyresveratrol (OXY) (12), cyanidin-3-glucoside (C3G)(13), and cyanidin-3-rutinoside (C3R)(14). DNJ, an alkaloid constituent, remains the principal hypoglycaemic agent of the mulberry leaf [Asano, N. *et al.,* 2008 & Ji, D. F., *et al.,* 2013]. At 12.5 M, only resveratrol (RES), 1-deoxynojirimycin (DNJ), cyanidin-3-rutinoside (C3R), and cyanidin-3-glucoside (C3G), improved glucose utilisation and enhanced GCK activity within the cell. At 12.5 M, NJ and RES increased GCK translocation significantly, but other components had only minor effects. GCK's

intramolecular hydrogen bonds can be ruptured by DNJ, C3G, and C3R, accelerating allosteric activation at an early stage. In the last phase, RES and OXY may bind to the "hydrophobic pocket" on the GCK to stabilise the active GCK. Otherwise, GKRP can interact with RES, OXY, C3G, and C3R at the F1P binding site to stimulate GCK translocation and dissociation. The enzymatic assessment revealed that RES (1550 M) and OXY (2550 M) considerably increased GCK activities, owing to their GCK binding characteristics. Furthermore, C3G and C3R have the greatest over-expression effects on GCK expression [Lu, Y. H. *et al.,* 2016].

Pterocarpus marsupium

Pterocarpus marsupium, a plant in the Fabaceae family, has been used for thousands of years in India and its neighbouring countries due to its various biological activities. All parts of P. marsupium are used in several human diseases. It has been widely used in the homoeopathic, Ayurvedic and Unani systems of medicine [Devgun, M., *et al.,* 2009]. The large tree, *Pterocarpus marsupium Roxb* (family *Leguminoceae*), is found in India's central, western, and southern parks. An aqueous extract of *Pterocarpus marsupium* (PM) (1 g/kg PO) activates glucokinase (GCK), hexokinase (HK), and phosphofructokinase (PFK) [Grover, J. K., et al., 2002].

Sapium ellepticum

Sapium ellepticum (*S. ellipticum*) (Hochst) has been used in the treatment of diabetes by locals (ethno-botanical Survey). It belongs to the family *Euphorbiaceae* and is commonly called a jumping seed tree. This plant is widely distributed in the south-west parts of Nigeria and in eastern and tropical Africa [Lewis, W.H. *et al.,* 1986]. *Sapium ellepticum leaf extract activates and also inhibits key enzymes of the glycolytic and glycogenolytic pathways in diabetes [*Ighodaro, O. M., *et al.,* 2017*], including pancreatic-amylase, intestinal-glucosidase [*Ighodaro, O. M., *et al.,* 2016*] , glucokinase, and glucose-6-phosphatase.* The *in-vitro* GCK assessment of *S. ellipticum* extract is supported by the presence of luteol (15), alpha-tocopherol (16), amentoflavone (17), and luteolin-7-glucoside (18), which have decent binding affinities and substantial binding complexations with allosteric site residues of GCK enzyme[Singh, S. *et al.,* 2019].

Conclusion

Glucokinase is a significant glucose phosphorylating enzyme that regulates glucose levels in the body, and the subsequent hypoglycaemic effect of its activation as a therapeutic target for diabetes mellitus has attracted a lot of attention. Since 2003, a number of glucokinase activators (GCKAs) have been discovered, and their ability to lower blood glucose has been demonstrated in a number of animal models of type 2 diabetes. However, recent phase II trials have revealed that GCKAs lose their efficacy after a few months of treatment and are linked with a significant incidence of hypoglycaemia. Also, individuals treated with GCKAs usually develop dyslipidaemia. Pharmaceutical companies and researchers are re-evaluating new GCKAs and the development of newer GCKAs derived from plants. The above-mentioned phytochemicals have shown significant

improvement in the gene expression, modulating and activity of glucokinase. Overall, natural products of plant origin have the potential to activate the human glucokinase enzymes.

Conflict of Interest

The authors declare that there is no conflict of interest

Acknowledgement

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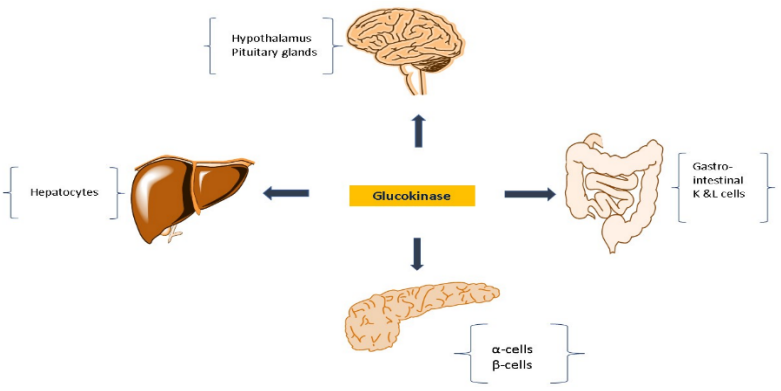

Figure 1. Glucokinase distribution in human body

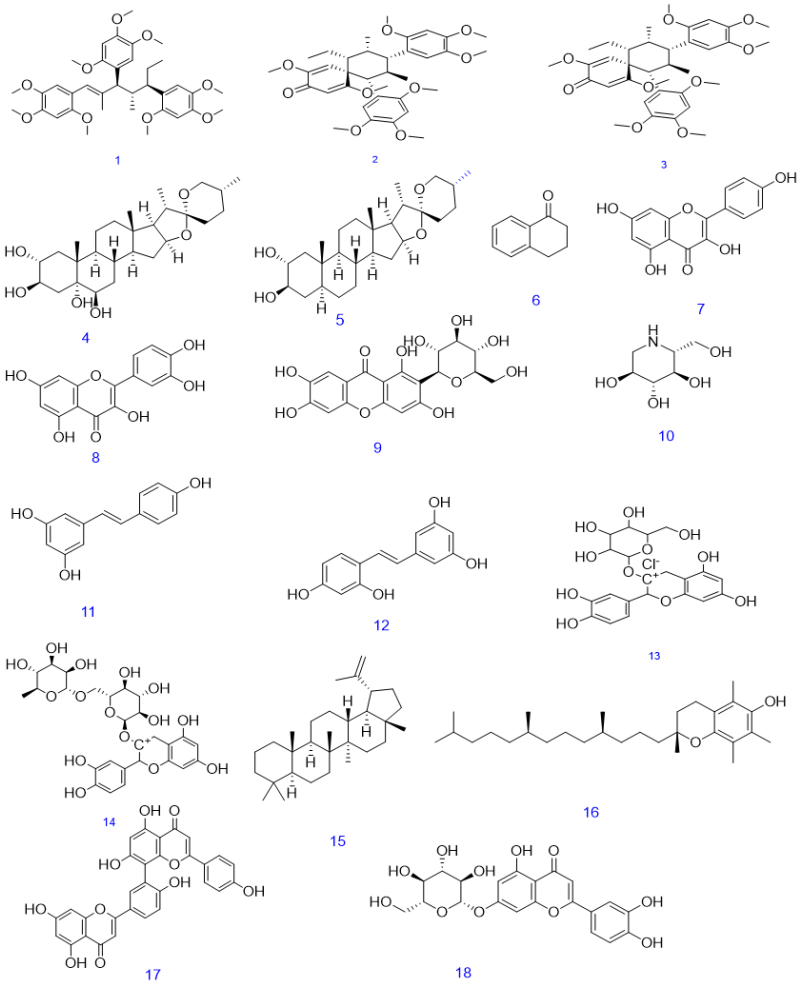

Figure 2. Chemical structures of Phytochemicals