MEDWIN PUBLISHERS
Committed to create value for Researchers

Diabetes and Obesity International Journal
ISSN: 2574-7770

The K_{ATP} Channel is a Potential Target for Natural Plant Products in Type 2 Diabetes Mellitus

AL Kury L.T[1]* and Abdoh A[2]

[1]Department of Health Sciences, Zayed University, UAE

[2]School of Medicine, Royal College of Surgeons in Ireland, Bahrain

***Corresponding author:** Lina T. Al Kury, Department of Health Sciences, College of Natural and Health Sciences, Zayed University, Abu Dhabi, UAE, Tel: 00971506623975; Email: Lina.AlKury@zu.ac.ae

Review Article

Volume 5 Issue 1

Received Date: December 12, 2019

Published Date: January 16, 2020

DOI: 10.23880/doij-16000219

Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder affecting a vast number of people all around the world. Diabetes is mainly characterized by chronic hyperglycemia, resulting from defects in insulin secretion or insulin action, or both. To date, several glucose-lowering drugs have been used clinically. These drugs exert their anti-diabetic effect by stimulating insulin secretion, increasing peripheral absorption of glucose, delaying the absorption of carbohydrates from the intestine and reducing hepatic gluconeogenesis. The concern over effectiveness and side effects of currently available therapies in the treatment of Type 2 DM (T2DM) has promoted interest in discovery and development of natural antidiabetic drugs. Plants used in folk medicine to treat DM represent a viable alternative for the control of this disease. Several plants with antidiabetic properties exert their effects by inhibiting ATP-sensitive potassium (K_{ATP}) channels in the β-cell plasma membrane, resulting in membrane depolarization and stimulation of insulin release from insulin stores by exocytosis. In this article, we examined the results of earlier studies on the actions of natural compounds on pancreatic K_{ATP} channels. It is likely that these natural compounds can be employed as lead structures for the synthesis of therapeutic agents to treat T2DM in future clinical studies.

Keywords: Diabetes Mellitus; Natural Plant Products; K_{ATP} channels.

Abbreviations: DM: Diabetes Mellitus; SUR: Sulfonylurea Receptor 1; DCM; Dichloromethane; GK: Goto-Kakizaki; ROS: Reactive Oxygen Species; AGE: Advanced Glycation End.

Introduction

Diabetes mellitus is a chronic metabolic disorder affecting a vast number of people worldwide. It is expected that the total number of people with diabetes will rise from 171 million in 2000 to 366 million in 2030 [1]. Diabetes is mainly characterized by chronic hyperglycemia, resulting from defects in insulin secretion or insulin action, or both. Diabetes is classified into two main types: Type I Diabetes Mellitus (T1DM) and Type II Diabetes Mellitus (T2DM) with T2DM comprising about 85% of diabetes cases. In T1DM, there is a decreased in insulin secretion due to the damage in β-

cells of the pancreas, resulting in individuals with this condition relying essentially on exogenous insulin administration for survival [2]. In contrast, T2DM is characterized by decreased peripheral resistance to insulin, resulting in reduced insulin sensitivity to the skeletal muscles, adipose tissues and liver. The major complications associated with diabetes mellitus are classified as microvascular (including retinopathy, neuropathy and nephropathy) and macrovascular (including cardiovascular myopathy and cerebrovascular diseases) [2,3]. Hyperglycemia plays an important role in the onset and development of these complications, mainly by generating reactive oxygen species (ROS) which causes lipid peroxidation and membrane damage. Furthermore, hyperglycemia results in excessive non-enzymatic glycation of proteins and formation of advanced glycation end products (AGE). The glycation modifications can further deteriorate the pathology of diabetes [4,5].

Currently, there are a number of effective medications for the treatment of T2DM; however, many of these medications are associated with side effects. In addition, long term medication is very costly. Therefore, natural products can be a good alternative to replace or at least supplement the use of conventional drugs.

Current Pharmacological Agents in the Treatment of T2DM

To date, several glucose-lowering drugs have been used clinically. These drugs exert their anti-diabetic effect by 1) stimulating insulin secretion (sulfonylureas and meglitinides), 2) increasing peripheral absorption of glucose (biguanides and thiazolidinediones), 3) delaying the absorption of carbohydrates from the intestine (alpha glucosidase), and 4) reducing hepatic gluconeogenesis (biguanides). For example, metformin, from the biguanide family, is a potent antihyperglycemic agent now recommended as the first line oral therapy for T2DM. The generally accepted mechanism for metformin action is the inhibition of hepatic gluconeogenesis [6]. The main effect of this drug is to acutely decrease hepatic glucose production, mostly through a mild and transient inhibition of the mitochondrial respiratory-chain complex 1 [7]. As a consequence, the resulting transient decrease in cellular energy status promotes activation of AMP-activated protein kinase (AMPK), a well-known cellular energetic sensor. Consequently, metformin-induced AMPK activation is believed to promote transcriptional inhibition of hepatic gluconeogenic program [8]. Sulphonylurea drugs have been used for over 60 years to treat T2DM [9] and they are commonly used as a second line class of antidiabetic drugs [10]. Sulphonylureas stimulate insulin secretion from pancreatic β-cells primarily by closing ATP-sensitive potassium (K_{ATP}) channels in the β-cell plasma membrane [11,12]. As direct inhibitors of channel activity, sulphonylureas act only as partial antagonists at therapeutic concentrations. However, they also exert an additional indirect inhibitory effect via modulation of nucleotide-dependent channel gating [13]. Sulphonylureas are largely used due to their potency, fewer drug interactions and less severe adverse reactions. However, sulfonylureas lose their effectiveness after 6 years of treatment in 44% of patients [14].

Role of Pancreatic K_{ATP}

Pancreatic β-cells express ATP-sensitive potassium (K_{ATP}) channels that are needed for normal insulin secretion and are considered as a potential target for the development of drugs for the treatment of diabetes. Pancreatic K_{ATP} is a metabolic sensor that is influenced by the metabolic state of the cell and responsible for initiating the ionic events that precede insulin exocytosis by converting the intracellular ATP/ADP ratio into membrane excitability in pancreatic β cells [15,16]. The intracellular ATP formed by oxidative phosphorylation inhibits K_{ATP} channels, reducing K^+ efflux. This causes membrane depolarization of β-cells resulting in Ca^{2+} influx through voltage- dependent L-type calcium channels and stimulation of insulin release from insulin stores by exocytosis [17]. In addition to this pathway, other K_{ATP} channels -independent pathway involves second messengers such as cyclic AMP (cAMP) and diacylglycerol, and exerts its stimulatory effect on insulin exocytosis [18,19].

The K_{ATP} channel is composed of hetero-octameric protein complex of four inward-rectifying potassium channel 6 (Kir6) pore-forming subunits and four sulfonylurea receptor 1 (SUR) regulatory subunits. Specifically, pancreatic K_{ATP} channels consist of Kir6.2 and SUR1 subunits, which have high-affinity binding sites for inhibitory sulfonylureas and glinides [15]. K_{ATP} channels have a rich and diverse pharmacology with a number of agents acting as specific inhibitors and activators.

Effect of Natural Products on Pancreatic K_{ATP} Channel

Nearly 60-80% of the world's population uses traditional medicines derived from medicinal plants for

various diseases including diabetes [20]. The concern over effectiveness and side effects of currently available therapies in the treatment of T2DM has promoted interest in discovery and development of natural antidiabetic drugs. Plants used in folk medicine to treat diabetes mellitus represent a viable alternative for the control of this disease. Several herbs with antidiabetic properties exert their effects by stimulating insulin secretion, decreasing intestinal glucose absorption, increasing glucose uptake by adipose and skeletal muscle tissues, increasing glycogenesis or inhibiting hepatic glucose glycogenolysis [21-23]. Plants containing natural antioxidants such as tannins, flavonoids, vitamin C and E can preserve β-cell function by free radical scavenging and prevention of diabetes-induced ROS formation [24]. Several plants exert their antidiabetic effects by inhibiting ATP-sensitive potassium (K_{ATP}) channels in the β-cells of the pancreas, resulting in increased insulin secretion. The plants mentioned below have been commonly used in traditional medicine and were examined for their hypoglycemic effects in earlier studies.

Enicostemma Littorale

Enicostemma littorale Blume, a small herb of family Gentianaceae, is commonly used in India for its anti-cancer [25] and anti-inflammatory effects [26]. Experimentally, the herb has also been reported for its blood-glucose lowering potential in alloxan-induced diabetic rats [27,28]. Maroo, et al. [28] has shown that a single dose of aqueous extract of *E. littorale* (15 g dry plant equivalent extract per kg) causes a significant increase in the serum insulin levels in alloxan-induced diabetic rats at 8 hours, whereas glybenclamide showed increase in serum insulin levels both at 4 and 8 hours. Using rat pancreatic islets, the extract enhanced glucose-induced insulin release and was partially able to reverse the effect of diazoxide (K_{ATP} channel opener). Incubation with Ca^{2+} chelator (EGTA) and Ca^{2+} channel blocker (nimodipine) did not affect the glucose-induced insulin release augmented by the extract. Therefore, the results suggested that the glucose lowering effect of the aqueous extract of *E. littorale* is associated with potentiation of glucose-induced insulin release through the K_{ATP} channel-dependent pathway, but did not require Ca^{2+} influx [28].

Ocimum Sanctum

Ocimum sanctum Linn. (Labiatae), commonly known as holy basil, is a herbaceous plant found throughout the South Asian region and is widely used as an anti-stress medication and to treat conditions such as bronchitis, skin diseases, chronic fever, and hemorrhage. *O. sanctum* leaves were found to possess hypoglycemic effects in experimental animals [29,30]. For example, the ethanol extract of *O. sanctum* leaves has been shown to cause a significant reduction in blood glucose levels in normal, glucose-fed hyperglycemic and streptozotocin-treated diabetic rats. Furthermore, a diet containing leaf powder fed to normal and diabetic rats for 1 month significantly reduced fasting blood glucose [30]. In a randomized, placebo-controlled, crossover, single blind clinical trial, leaf extract of *O. sanctum* caused a significant decrease in fasting and post-prandial glucose [31]. A more recent study on alloxan-treated diabetic rats has also shown that an ethanol extract of *O. sanctum* reduces hyperglycemia in both acute and long-term feeding studies [32]. In an attempt to understand the mechanism of hypoglycemic effect of *O. sanctum* leaves, ethanol extracts and partition fractions of *O. sanctum* leaves were evaluated for their effects on insulin secretion using isolated perfused rat pancreas, isolated islets and clonal BRIN-BD11 cells [33]. In all of the three preparations, ethanol extract and partition fractions were able to stimulate insulin secretion in a concentration-dependent manner. Involvement of the K_{ATP} channel in the stimulatory action of *O. sanctum* was evident in β -cells. Diazoxide inhibited the insulin-releasing effects of the extract, suggesting that the closure of K_{ATP} channels participates in the overall mechanism of action of *O. sanctum* [33].

Psacalium Decompositum

An earlier study has investigated the mechanism of the hypoglycemic effect of root and rhizome aqueous decoctions of the medicinal herb *Psacalium decompositum* (Asteraceae) [34,35]. *P. decompositum,* commonly known as "matarique", is a widely used remedy in folk medicine in Mexico for the treatment of diabetes, ulcers, pain, rheumatic disorders, hepatic and renal colic, and neuralgia. The study has identified three hypoglycemic sesquiterpenoids; cacalol, cacalone epimer mixture, and cacalol acetate. All compounds were able to block K_{ATP} channels in aortic smooth muscle rings in a similar way to glibenclamide. However, the sesquiterpenoids were less effective than glibenclamide in lowering plasma glucose levels, suggesting that they may display a higher affinity to SUR2 subunit of K_{ATP} channels in aortic smooth muscle than to SUR1 subunit in pancreatic beta-cells [34].

Teucrium Polium

One of the medicinal plants that has been used in folk medicine for the treatment of diabetes in Iran is *Teucrium*

polium L. Studies have reported a number of therapeutic effects for this plant including antioxidant [36], anti-inflammatory, [37] and hypolipidemic [38] effects. Mirghazanfari, et al. [39] tested the effect of a *T. polium* extract on insulin secretion in isolated rat pancreas. Interestingly, only the Methanolic extract but not the aqueous extract of *T. polium* caused a significant increase in insulin release. Furthermore, diazoxide (K_{ATP} channel opener) and verapamil (Cav channel blocker) were used to assess the mechanism of insulin secretion by *T. polium.* The results of this study showed *T. polium* extract had an insulinotropic effect that was inhibited by both diazoxide and verapamil. These findings indicate that the extract-stimulated insulin secretion is mediated through the inhibition of K_{ATP} channels, activation of Ca_v channels, or both. Furthermore, it was concluded that the insulinotropic effect of *T. polium* extract can be attributed to the presence of the compound apigenin only in methanolic extract but not in aqueous extract [39].

Nelumbo Nucifera

Nelumbo nucifera is an aquatic perennial and national flower of India and Vietnam. Its leaves, rhizomes, and seeds are all used in Asian cuisine. In addition, the plant has been used in traditional Vietnamese medicine to treat diabetes. Nguyen, et al. [40] found that Nuciferine, extracted from *N. nucifera*, stimulated insulin secretion in isolated islets and in INS-1E cells at both 3.3 and 16.7 mM glucose concentrations. Nuciferine acted primarily by closing K_{ATP} channels. In addition, the effect of nuciferine was abolished by diazoxide, nimodipine, protein kinase A, and protein kinase C inhibition. Nuciferine had a weaker affinity for binding to the sulfonylurea receptor, a stronger effect on insulin secretion, and less cytotoxicity than glibenclamide [40].

Kalanchoe Pinnata

Kalanchoe pinnata Lam. (Crassulaceae) is used as a traditional medicine worldwide to treat several illnesses. The major reported pharmacological effects are immunosuppression [41], hepatoprotection [42], antitumor [43], and hypoglycemic activity [44]. Patil, et al. [45] evaluated *Kalanchoe pinnata* Lam. (Crassulaceae) for its antihyperglycemic and insulin secretagogue potential through *in vivo* and *in vitro* studies. The dichloromethane (DCM) fraction of the plant demonstrated glucose-independent insulin secretagogue action similar to the currently used drug glibenclamide. In streptozotocin-induced diabetic rats, fasting blood glucose values were significantly reduced on treatment with 10mg/kg body weight of DCM fraction. In addition, the insulin level and lipid profile values were close to normal values. Glycated hemoglobin was also improved to 8.4% compared with 12.9% in diabetic controls. *In vitro* studies demonstrated a dose-dependent insulin secretagogue action. Insulin secretion was 3.29-fold higher compared to the positive control. Most importantly, the insulin secretagogue activity was found to be K_{ATP} channel-dependent [45]. Similarly, another species of Kalanchoe, *K. crenata* (Crassulaceae), was also shown in an earlier study to possess antihyperglycemic activity. Its antihyperglycemic mechanism was proposed to be due to modulation in insulin sensitivity [46].

Leonurus Sibiricus

The plant *Leonurus sibiricus* L. has been used to treat T2DM in traditional medicine of many Asian countries. Many pharmacological effects of *L. sibiricus* were reported in the literature. For example, the plant was shown to exert an anti-inflammatory activity in rats [47] and humans [48] and to possess a potent antioxidant activity [49]. Treatment with a *L. sibiricus* herb extract has been shown to affect the atherogenic process in animals. For example, C57BL/6 mice displayed decreased plasma cholesterol levels, reduced plasma triglyceride levels, and an increased HDL-cholesterol concentration when given atherogenic diet supplemented with a *L. sibiricus* herb extract compared to animals receiving the atherogenic diet alone [49]. The effect of extracts from the plant *L. sibiricus* on insulin secretion, electrophysiological properties, intracellular calcium concentration and cell proliferation of INS-1E insulinoma cells were investigated by Schmidt, et al. [50]. Insulin secretion of rat INS-1E cells was significantly increased in the presence of aqueous and methanolic *L. sibiricus* extracts. Acute application of the aqueous extract resulted in K_{ATP} inhibition, membrane depolarization, and an increase in intracellular Ca^{2+} concentration. Interestingly, the electrophysiological effects were comparable to those of tolbutamide. Furthermore, treatment with the aqueous extract stimulated INS 1-E cell proliferation. The findings of this study support the use of *L. sibiricus* in the treatment of DM and related disorders in traditional medicine [50]. A more recent study investigated the short- and long-term effects of the flavonoid quercetin and its glycoside rutin, which are constituents of *L.* sibiricus extract, on beta cells. Although both constituents are known to exert insulinotropic properties *in vivo* and *in vitro*, rutin did not alter insulin secretion or the electrophysiological behavior of rat INS-1 cells. In contrast, quercetin acutely stimulated insulin release, presumably by transient K_{ATP} channel inhibition and intracellular Ca^{2+} stimulation.

Diazoxide caused a significant hyperpolarization and completely prevented quercetin and tolbutamide - induced membrane depolarization, suggesting that K_{ATP} channels are direct targets of quercetin. Long term application of quercetin inhibited cell proliferation and induced apoptosis, most likely due to the inhibition of PI3K/Akt signaling [51].

Gynostemma Pentaphyllum

The pharmacological effects of the herbal plant *Gynostemma pentaphyllum*, commonly known as Jiaogulan, have been proven in many studies. The plant was previously reported to have high radical scavenging capacity [52], anti- inflammatory [53], hypoglycemic [54] and anticancer effects [55]. Earlier study has investigated the mechanism of antidiabetic effect of *G. pentaphyllum* water extract on blood glucose and serum insulin levels in Goto-Kakizaki (GK) rat, an animal model T2DM [56]. The results of this study have shown that *G. pentaphyllum* extract improved glucose tolerance, increased plasma insulin levels, and increased insulin secretion from islets isolated from the treated rats. *In vitro* results show that the *G. pentaphyllum* extract stimulated insulin release from the isolated rat islets at high glucose only. In addition, extract-induced insulin release was partly mediated via K_{ATP}, L-type Ca^{2+} channels, and protein kinase A system, and partly dependent on pertussis toxin sensitive G_e-protein at high glucose [56].

Lupinus Mutabilis

Lupinus mutabilis, commonly named Tarwi [57], is a legume usually consumed as cooked seeds , and is traditionally used to reduce glycemia after the meal [58]. Clinical trials showed that *L. mutabilis* reduces blood sugar in slightly hyperglycemic subjects, and cooked *L. mutabilis* seeds reduce glycemia in patients with type 2 diabetes, an effect related to its alkaloid content [58,59]. A recent study evaluated the anti-diabetic effect of *L. mutabilis* in the spontaneously diabetic Goto-Kakizaki (GK). The mechanism of insulin release was tested in pancreatic islets isolated from both GK and Wistar rats as healthy controls. The hydroethanolic extract of *L. mutabilis* seeds improved glucose tolerance in both GK and Wistar rats by enhancing insulin release. This effect was mainly mediated by L-type calcium channel, the PKC and PKA systems and G protein-coupled insulin exocytosis and partially mediated by K_{ATP} channels of the beta cells [60].

Swietenia Humilis

Recently, some active components from the seeds of *Swietenia humilis*, commonly used to treat T2DM in Mexico, were isolated and identified; these compounds were tetranortriterpenoids of the mexicanolide class and exhibited not only antidiabetic but also antihyperalgesic effects in hyperglycemic mice [61,62]. In an attempt to evaluate the mechanism of antihyperglycemic effect of *S. humilis*, Ovalle-Magallanes, et al. [63] tested the effects of selected mexicanoloides *in vivo* (Using streptozotocin-treated mice) and *in vitro* (using INSE1, H4IIE and C2C12 cells). The findings of this study showed that *S. humilis* mexicanolides interact with multiple pharmacological targets including pancreas (K_{ATP} channels), liver (glucose-6-phosphatase), and skeletal muscle (mitochondria and possibly glucose transporters) to modulate glucose homeostasis, indicating that these compounds could be a promising resource to treat T2DM [63].

Conclusion

DM is a chronic metabolic disorder affecting a vast number of people worldwide. Although conventional antidiabetic drugs are effective in treating DM; nonetheless, they are associated with unavoidable side effects. On the other hand, medicinal plants may act as an alternative source of antidiabetic agents. However, lack of understanding of the precise mechanism impedes their use. K_{ATP} channels are metabolic sensors needed for normal insulin secretion and are considered a potential target for the development of drugs for the treatment of DM. It is likely that natural compounds can be employed as lead structures for the synthesis of therapeutic agents that target K_{ATP} channels to treat T2DM in future clinical studies.

References

1. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27(5): 1047-1053.

2. Forbes JM, Cooper ME (2013) Mechanisms of diabetic complications. Physiol Rev 93(1): 137-188.

3. Patel DK, Kumar R, Laloo D, Hemalatha S (2012) Diabetes mellitus: an overview on its pharmacological aspects and reported medicinal plants having

antidiabetic activity. Asian Pac J Trop Biomed 2(5): 411-420.

4. Sekhon-Loodu S, Rupasinghe HPV (2019) Evaluation of Antioxidant, Antidiabetic and Antiobesity Potential of Selected Traditional Medicinal Plants. Front Nutr 6: 53.

5. Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, et al. (2018) An update on natural compounds in the remedy of diabetes mellitus: A systematic review. J Tradit Complement Med 8(3): 361-376.

6. Hundal RS, Krssak M, Dufour S, Laurent D, Lebon V, et al. (2000) Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 49(12): 2063-2069.

7. El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, et al. (2000) Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 275(1): 223-228.

8. Zhou G, Myers R, Li Y, Chen Y, Shen X, et al. (2001) Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 108(8): 1167-1174.

9. Thulé PM, Umpierrez G (2014) Sulfonylureas: a new look at old therapy. Curr Diab Rep 14(4): 473.

10. Wang Z, Wang J, Chan P (2013) Treating type 2 diabetes mellitus with traditional chinese and Indian medicinal herbs. Evid Based Complement Alternat Med 343594.

11. Hales CN, Milner RD (1968) The role of sodium and potassium in insulin secretion from rabbit pancreas. J Physiol 194(3): 725-743.

12. Ashcroft FM, Rorsman P (1989) Electrophysiology of the pancreatic beta-cell. Prog Biophys Mol Biol 54(2): 87-143.

13. Proks P, Reimann F, Green N, Gribble F, Ashcroft F (2002) Sulfonylurea stimulation of insulin secretion. Diabetes 51(S3): S368-S376.

14. Holman RR (2006) Long-term efficacy of sulfonylureas: a United Kingdom Prospective Diabetes Study perspective. Metabolism 55(5-S1): S2-S5.

15. Bryan J, Crane A, Vila-Carriles WH, Babenko AP, Aguilar-Bryan L (2005) Insulin secretagogues, sulfonylurea receptors and K_{ATP} channels. Curr Pharm Des 11(21): 2699-2716.

16. Hibino H, Inanobe A, Furutani K, Murakami S, Findlay I, et al. (2010) Inwardly rectifying potassium channels: their structure, function, and physiological roles. Physiol Rev 90(1): 291-366.

17. Quan Y, Barszczyk A, Feng ZP, Sun HS (2011) Current understanding of K_{ATP} channels in neonatal diseases: focus on insulin secretion disorders. Acta Pharmacol Sin 32(6): 765-780.

18. Bratanova-Tochkova TK, Cheng H, Daniel S, Gunawardana S, Liu YJ, et al. (2002) Triggering and augmentation mechanisms, granule pools, and biphasic insulin secretion. Diabetes 51(S1): S83-S90.

19. Zawalich WS, Zawalich KC (2001) Effects of protein kinase C inhibitors on insulin secretory responses from rodent pancreatic islets. Mol Cell Endocrinol 177(1-2): 95-105.

20. Shrestha PM, Dhillion SS (2003) Medicinal plant diversity and use in the highlands of Dolakha district, Nepal. J Ethnopharmacol 86(1): 81-96.

21. Li WL, Zheng HC, Bukuru J, De Kimpe N (2004) Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J Ethnopharmacol 92(1): 1-21.

22. Prabhakar PK, Doble M (2011) Mechanism of action of natural products used in the treatment of diabetes mellitus. Chin J Integr Med 17(8): 563-574.

23. Bhat M, Zinjarde SS, Bhargava SY, Kumar AR, Joshi BN (2011) Antidiabetic Indian plants: a good source of potent amylase inhibitors. Evid Based Complement Alternat Med 2011: 810207.

24. Aslan M, Orhan N, Orhan DD, Ergun F (2010) Hypoglycemic activity and antioxidant potential of some medicinal plants traditionally used in Turkey for diabetes. J Ethnopharmacol 128(2): 384-389.

25. Kavimani S, Manisenthlkumar KT (2000) Effect of methanolic extract of Enicostemma littorale on Dalton's ascitic lymphoma. J Ethnopharmacol 71(1-2): 349-352.

26. Sadique J, Chandra T, Thenmozhi V, Elango V (1987) The anti-inflammatory activity of Enicostemma littorale and Mollugo cerviana. Biochem Med Metab Biol 37(2): 167-176.

27. Vijayvargia R, Kumar M, Gupta S (2000) Hypoglycemic effect of aqueous extract of Enicostemma littorale Blume (chhota chirayata) on alloxan induced diabetes mellitus in rats. Indian J Exp Biol 38(8): 781-784.

28. Maroo J, Vasu VT, Aalinkeel R, Gupta S (2002) Glucose lowering effect of aqueous extract of Enicostemma littorale Blume in diabetes: a possible mechanism of action. J Ethnopharmacol 81(3): 317-320.

29. Chattopadhyay RR (1993) Hypoglycemic effect of Ocimum sanctum leaf extract in normal and streptozotocin diabetic rats. Indian J Exp Biol 31(11): 891-893.

30. Rai V, Iyer U, Mani UV (1997) Effect of Tulasi (Ocimum sanctum) leaf powder supplementation on blood sugar levels, serum lipids and tissue lipids in diabetic rats. Plant Foods Hum Nutr 50(1): 9-16.

31. Agrawal P, Rai V, Singh RB (1996) Randomized placebo-controlled, single blind trial of holy basil leaves in patients with noninsulin-dependent diabetes mellitus. Int J Clin Pharmacol Ther 34(9): 406-409.

32. Vats V, Grover JK, Rathi SS (2002) Evaluation of anti-hyperglycemic and hypoglycemic effect of Trigonella foenum-graecum Linn, Ocimum sanctum Linn and Pterocarpus marsupium Linn in normal and alloxanized diabetic rats. J Ethnopharmacol 79(1): 95-100.

33. Hannan JM, Marenah L, Ali L, Rokeya B, Flatt PR, et al. (2006) *Ocimum sanctum* leaf extracts stimulate insulin secretion from perfused pancreas, isolated islets and clonal pancreatic beta-cells. J Endocrinol 189(1): 127-136.

34. Campos MG, Oropeza M, Torres-Sosa C, Jiménez-Estrada M, Reyes-Chilpa R, et al. (2009) Sesquiterpenoids from antidiabetic *Psacalium decompositum* block ATP sensitive potassium channels. J Ethnopharmacol 123(3): 489-493.

35. Jimenez-Estrada M, Chilpa RR, Apan TR, Lledias F, Hansberg W, et al. (2006) Anti-inflammatory activity of cacalol and cacalone sesquiterpenes isolated from *Psacalium decompositum*. J Ethnopharmacol 105(1-2): 34-38.

36. Esmaeili MA, Zohari F, Sadeghi H (2009) Antioxidant and protective effects of major flavonoids from *Teucrium polium* on beta-cell destruction in a model of streptozotocin-induced diabetes. Planta Med 75(13): 1418-1420.

37. Tariq M, Ageel AM, al-Yahya MA, Mossa JS, al-Said MS (1989) Anti-inflammatory activity of *Teucrium polium*. Int J Tissue React 11(4): 185-188.

38. Rasekh HR, Khoshnood-Mansourkhani MJ, Kamalinejad M (2001) Hypolipidemic effects of *Teucrium polium* in rats. Fitoterapia 72(8): 937-939.

39. Mirghazanfari SM, Keshavarz M, Nabavizadeh F, Soltani N, Kamalinejad M (2010) The effect of "*Teucrium polium* L." extracts on insulin release from in situ isolated perfused rat pancreas in a newly modified isolation method: the role of Ca^{2+} and K^{+} channels. Iran Biomed J 14(4): 178-185.

40. Nguyen KH, Ta TN, Pham TH, Nguyen QT, Pham HD, et al. (2012) Nuciferine stimulates insulin secretion from beta cells-an in vitro comparison with glibenclamide. J Ethnopharmacol 142(2): 488-495.

41. Cruz EA, Da-Silva SA, Muzitano MF, Silva PM, Costa SS, et al. (2008) Immunomodulatory pretreatment with *Kalanchoe pinnata* extract and its quercitrin flavonoid effectively protects mice against fatal anaphylactic shock. Int Immunopharmacol 8(12): 1616-1621.

42. Yadav NP, Dixit VK (2003) Hepatoprotective activity of leaves of *Kalanchoe pinnata* Pers. J Ethnopharmacol 86(2-3): 197-202.

43. Supratman U, Fujita T, Akiyama K, Hayashi H, Murakami A, et al. (2001) Anti-tumor promoting activity of bufadienolides from *Kalanchoe pinnata* and *K. daigremontiana x tubiflora.* Biosci Biotechnol Biochem 65(4): 947-949.

44. Ojewole JA (2005) Antinociceptive, anti-inflammatory and antidiabetic effects of *Bryophyllum pinnatum* (Crassulaceae) leaf aqueous extract. J Ethnopharmacol 99(1): 13-19.

45. Patil SB, Dongare VR, Kulkarni CR, Joglekar MM, Arvindekar AU (2013) Antidiabetic activity of *Kalanchoe pinnata* in streptozotocin-induced diabetic rats by glucose independent insulin secretagogue action. Pharm Biol 51(11): 1411-1418.

46. Kamgang R, Mboumi RY, Fondjo AF, Tagne MA, N'dillé GP, et al. (2008) Antihyperglycaemic potential of the water-ethanol extract of *Kalanchoe crenata* (Crassulaceae). J Nat Med 62(1): 34-40.

47. Islam MA, Ahmed F, Das AK, Bachar SC (2005) Analgesic and anti-inflammatory activity of *Leonurus sibiricus.* Fitoterapia 76(3-4): 359-362.

48. Shin HY, Kim SH, Kang SM, Chang IJ, Kim SY, et al. (2009) Anti-inflammatory activity of Motherwort (*Leonurus sibiricus* L.). Immunopharmacol Immunotoxicol 31(2): 209-213.

49. Lee MJ, Lee HS, Park SD, Moon HI, Park WH (2010) Leonurus sibiricus herb extract suppresses oxidative stress and ameliorates hypercholesterolemia in C57BL/6 mice and TNF-alpha induced expression of adhesion molecules and lectin-like oxidized LDL receptor-1 in human umbilical vein endothelial cells. Biosci Biotechnol Biochem 74(2): 279-284.

50. Schmidt S, Jakab M, Jav S, Streif D, Pitschmann A, et al. (2013) Extracts from *Leonurus sibiricus* L. increase insulin secretion and proliferation of rat INS-1E insulinoma cells. J Ethnopharmacol 150(1): 85-94.

51. Kittl M, Beyreis M, Tumurkhuu M, Fürst J, Helm K, et al. (2016) Quercetin Stimulates Insulin Secretion and Reduces the Viability of Rat INS-1 Beta-Cells. Cell Physiol Biochem 39(1): 278-293.

52. Xie Z, Liu W, Huang H, Slavin M, Zhao Y, et al. (2010) Chemical composition of five commercial *Gynostemma pentaphyllum* samples and their radical scavenging, antiproliferative, and anti-inflammatory properties. J Agric Food Chem 58(21): 11243-11249.

53. Yang F, Shi H, Zhang X, Yu LL (2013) Two novel anti-inflammatory 21-nordammarane saponins from tetraploid Jiaogulan (*Gynostemma pentaphyllum*) . J Agric Food Chem 61(51): 12646-12652.

54. Yeo J, Kang YJ, Jeon SM, Jung UJ, Lee MK, et al. (2008) Potential hypoglycemic effect of an ethanol extract of *Gynostemma pentaphyllum* in C57BL/KsJ-db/db mice. J Med Food 11(4): 709-716.

55. Lu KW, Tsai ML, Chen JC, Hsu SC, Hsia TC, et al. (2008) Gypenosides inhibited invasion and migration of human tongue cancer SCC4 cells through down-regulation of NFkappaB and matrix metalloproteinase-9. Anticancer Res 28(2A): 1093-1099.

56. Lokman EF, Gu HF, Wan Mohamud WN, Ostenson CG (2015) Evaluation of Antidiabetic Effects of the Traditional Medicinal Plant *Gynostemma pentaphyllum* and the Possible Mechanisms of Insulin Release. Evid Based Complement Alternat Med 2015: 120572.

57. Atchison GW, Nevado B, Eastwood RJ, Contreras-Ortiz N, Reynel C, et al. (2016) Lost crops of the Incas: Origins of domestication of the Andean pulse crop tarwi, *Lupinus mutabilis*. Am J Bot 103(9): 1592-606.

58. Fornasini M, Castro J, Villacrés E, Narváez L, Villamar MP, et al. (2012) Hypoglycemic effect of *Lupinus mutabilis* in healthy volunteers and subjects with dysglycemia. Nutr Hosp 27(2): 425-433.

59. Baldeón ME, Castro J, Villacrés E, Narváez L, Fornasini M (2012) Hypoglycemic effect of cooked *Lupinus mutabilis* and its purified alkaloids in subjects with type-2 diabetes. Nutr Hosp 27(4): 1261-1266.

60. Zambrana S, Lundqvist LCE, Mamani O, Catrina SB, Gonzales E, et al. (2018) *Lupinus mutabilis* Extract Exerts an Anti-Diabetic Effect by Improving Insulin Release in Type 2 Diabetic Goto-Kakizaki Rats. Nutrients 10(7).

61. Ovalle-Magallanes B, Medina-Campos ON, Pedraza-Chaverri J, Mata R (2015) Hypoglycemic and antihyperglycemic effects of phytopreparations and limonoids from Swietenia humilis. Phytochemistry 110: 111-119.

62. Ovalle-Magallanes B, Déciga-Campos M, Mata R (2017) Antihyperalgesic activity of a mexicanolide isolated from *Swietenia humilis* extract in nicotinamide-streptozotocin hyperglycemic mice. Biomed Pharmacother 92: 324-330.

63. Ovalle-Magallanes B, Navarrete A, Haddad PS, Tovar AR, Noriega LG, et al. (2019) Multi-target antidiabetic mechanisms of mexicanolides from *Swietenia humilis*. Phytomedicine 58: 152891.