Review Article

Antidiabetic Activity of Medicinal Plants

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ABSTRACT

Diabetes mellitus is a metabolic issue at first recognized by lost glucose homeostasis, because of disturbances of carbohydrate, fat and protein digestion, coming from imperfections in insulin generation, emission, insulin activity. Diabetes comprises in two types; Type I and Type II. Most hypoglycemic plant constituents, such as alkaloids, phenolic acids and amino acids, inhibit insulinase *in vitro* and are hypoglycemic *in vivo* in normal rats. The wide kind of chemical classes indicates that a variety of mechanisms might be involved in the lowering of the blood glucose level.

Keywords: Diabetes mellitus, medicinal plant, antidiabetic activity.

INTRODUCTION

Medicinal plants continue to be an essential therapeutic guide for reducing sicknesses of human. Upon the last 2500 years, there have been highly strong traditional regulations of medicinal care such as Chinese and the Unani, born and practiced, more in the eastern landmass. These conventions are as yet flourishing, since; about 80% of the general population in the creating nations depends on these frameworks of prescription for their essential health care needs[1]. These plants contain substances that can be utilized for medicinal purposes, of which are forerunners for the manufacture of drugs[2].

A great deal of research work has been completed on some therapeutic herbs and they have been found to have definite action on the nervous, circulatory, respiratory, digestive and urinary systems; in addition the sexual organs, the skin, vision, hearing and taste[3]. The nature has a finger print on drug discovery sciences and chemist role arises in the isolation, chemical structure determination of the bioactive molecules [4-17].

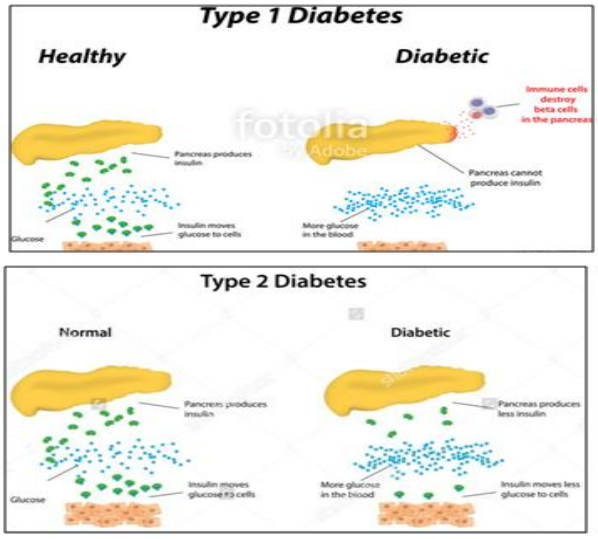
Diabetes mellitus is a metabolic issue at first recognized by lost glucose homeostasis, because of disturbances of carbohydrate, fat and protein digestion, coming from imperfections in insulin generation, emission, insulin activity[18]. This can bring about in long-term damage for organs, such as, kidneys, liver, eyes, nerves, heart and veins. Disturbance in some of these organs can lead to death[19]. However, a strong increase of physical inactivity, obesity, and type-2 diabetic patients has been recently observed. The fact indicates that the bad habit of obesity and physical inactivity may constitute the main reasons for the increasing load of diabetes in the developed contries[20]. Diet is one of the main factors that related to a wide range of ailments including diabetes. Diet constitutes a pivotal hand of the overall control of diabetes, which may include diet alone, diet with oral hypoglycemic drugs, or diet with insulin[21].

The well-known symptoms of diabetes are polyuria, polydipsia, polyphagia and loss of body weight[22].

Diabetes mellitus types

Diabetes comprises in two types; Type I and Type II; Type I diabetes frequently alluded to as phenomenon diabetes, is insulin dependent (IDDM) and known to influence just 5% of the diabetic population; it is a result of cell intermediated immune system destruction of the insulin delivering and secreting *β*-cells of the pancreas, which brings about a deficiency of insulin for the body[23]. The Type II diabetes, which is non-insulin dependent

(NIDDM), for the most part creates in adults beyond 40 years old[24]; it is an aftereffect of a decreased capacity of insulin to animate glucose take-up in peripheral tissues, insulin resistance, and the defficiency of the pancreatic *β*-cell to secrete insulin enough hence, *β*-cell failure[25]. It is right now affecting around 143 million individuals[26] and the quantity of those affecting is expanding day by day, by 2030 it is predicted to achieve 366 million populace overall[26]. Currently accessible treatment for diabetes, for example, sulfonylureas, metformin, glucosidase inhibitors, troglitazone, and so on; among them metformin is secretagogues which have a plant origin[27]. However, these are reported accompanied by several side effects, such as, liver debates and diarrhea[28]. In the most recent years, there has been a growing interest in the herbal medicine in care and management of diabetes both in developing and developed countries, because of their natural origin and also showed of fewer side effects[29-31]. Biological activities and positive effects of the plants are attrebuted to its chemical composition; that are rich in phenolics, flavonoids, terpenoids, alkaloids coumarins and glycosides.



Diabetes mellitus types

Antidiabetic medicinal plants constituents and mechanism of action

To understand how plant constituents can be hypoglycemic in animals, it is advantageous to consider the reasons why compounds with hypoglycemic activity present in plants. Generally, investigations of medicinal agents from plants fixate on plant secondary metabolites. It has been hypothesized that bioactive plant secondary metabolites may assume a part in chemical defense mechanisms[32,33]. While the exact mechanisms that may be included in chemically interceded coevolution amongst plants and herbivores or pathogenic living beings are disputable[34,35], it has been recommended that natural selection would guarantee the survival for reproduction of those individuals of a varieties having the gene coding for generation of a toxin, while individuals without the toxin would be expended[36]. Glucose is the metabolic vitality source and most vital biosynthetic portents in plants, so glucose undergoes stockpiling and mobilization under hormonal control in plants as it does in animals. Now the questions at our mind for natural products chemists are; which biological species offered these compounds, what is the molecule structure and how potent are they as medicinal agents?

Most hypoglycemic plant constituents, such as alkaloids, phenolic acids and amino acids, inhibit insulinase *in vitro* and are hypoglycemic *in vivo* in normal rats[37,38]. The wide kind of chemical classes indicates that a variety of mechanisms might be involved in the lowering of the blood glucose level. Moreover some of these constituents may have therapeutic potential, while others may produce hypoglycemia as a side-effect of their toxicity.

Toxicity of hypoglycemic medicinal plants

Whether almost hypoglycemic plant constituents have arisen through headway as chemical defense compounds, hence it mieght be perceived that for the source plant's survival, the best methodology is a non-selective toxin which will hinder herbivory incautions of the species of herbivore assaulting it. Frequently the improvement of new drugs from plants does not include rising the potency of the lead natural product due to this has been streamlined by millions of years of coevolution. Or maybe the task is to accomplish ideal selectivity and minimize general toxicity. Quantitative structure-activity relationship investigation is a basic instrument for accomplishing this goal. While a long history of traditional classical use may propose that a plant is relatively non-toxic, this should be confirmed by in-depth literature review and appropriately controlled test bioassays. Nearly of the reports of toxicity for antidiabetic plants are gotten from case investigations or Poison Control Center reports of human poisoning or damage. Species known to contain toxic compounds, such as pyrrolizidine alkaloids, were recorded in the database as toxic, even though the actual concentration in the plant may not be known. So complete information was also included from acute toxicity studies and determination of LD_{50} value, to solve the poisoning problems[39].

Discoveries of antidiabetic phytochemicals

All of the medicinal plants discussed mentioned this point is well known, commercially available drugs that have been used clinically for many decades around the world. Moreover, in the past near years, scientists have isolated and identified many phytochemicals that exhibited promise as potential antidiabetic drugs.

However the antidiabetic activity of medicinal plants is the focal point of this state of art, plants provide a multiblicity of medicines for several types of illness and diabetic disease. The antidiabetic activity of the major known phytochemicals will be summarized herin. The mechanism of action antidiabetic activity of the phytochemicals will be qualified. The most common antidiabetic bioassay methods will be assigned as well.

Pre-clinical trials

Traditional medicine is practices based on concept that to provide health care using plants[40]. A clinical trial is any research study that tentatively refers human participants to assess the effects on health outcomes[41]. Herbs trial on people starts with pre-clinical (initial test in humans) stage which is additionally named as nonclinical studies and it is very important stage and critical of the test, and during that stage critical practicality, iterative testing and plant safety data is collected. Clinical trials including new drug from medicinal plant are commonly classified into five phases. Each phase of the procedure is considered as a separate clinical trial. The plant-improvement process will typically continue through all five phases over numerous years. If the plant successfully goes through Phases 0, 1, 2, 3 and 4, it will usually be approved by the ministry of health. Each phase has an alternate reason and enables researchers to answer an alternate question:

1- Phase 0, trials is called pre-clinical phase and is the first-in-human trials. Single sub therapeutic doses of the plant examination as drug are given to a few number of subjects, humans or animals (10 to 15) to accumulate preparatory information on the plant's pharmacodynamics (what the plant does to the body) pharmacokinetics (what the body does to the plant) and toxicity testing.
2- Phase 1, trials researchers test an experimental plant treatment in a little group of people (20-80) for the first time to assess its safety, determine a safe dosage extend, and identify its side effects.
3- Phase 2, trials the test plant treatment is applied to a bigger group of people (100-300) to check whether it is successful and to additionally assess its safety.
4- Phase 3, trials the treatment is applied to large groups of people (1,000-3,000) to confirm its viabelity, screen side effects and reactions, compare it to commonly used treatments, and gaher information that will permit to be used safely.
5- Phase 4, trials post marketing studies design extra information, including the treatment's dangers, benefits and ideal use[42].

Screening assay for medicinal plants

A screen test: It is a biological assay that gives a device that can be utilized to test for or choose the presence and level of a target activity (for example; antidiabetic activity) in a specific sample (plant). Bioassays in a screening program should be fast, easy to direct, applicable, capable of being automated, cost effectiveness, and of the power to present high throughput.

i. Isolation and purification of medicinal plants secondary metabollites:
Numerous higher plants contain novel metabolites with antidiabetic activities. The compounds discovered in medicinal plants may avoid synthetic drugs side effects, due to the fact that, they must accumulate within living cells.

ii. Compounds structure identification of the medicinal plants:
Upon using different spectroscopic methods and chemical analysis.

iii. In case of performance for targeted results (antidiabetic activity), other pharmaceutical steps (Phases 0, 1, 2, 3 and 4) are overcome before starting clinical trials which summarized previously.

Medicinal plants with antidiabetic activity

Saponins

Saponins are secondary metabolites amphipathic glycosides which manufactured by many different plant species, characterized by having high molecular weight, consisting of a sugar moiety or moieties united to a triterpenoid (C-30) or steroid (C-27) sapogenins[43]. The oligosaccharide in saponin molecule is attached at the C3 position but in some saponins, additional sugars are attached at C-26 or C-28 positions[44].

Saponin has gotten various attentions due to their numerous biological activities that including the anti-diabetic property and is promising compounds with potential to be produced into new drugs for anti-diabetes[45,46].

Triterpenoidal saponins

Antidiabetic activity of triterpenoid saponin (TTS), (3-O[*β*-D-xylopyranosyl-(1→2)-*β*-D-glucopyranosyl-(1→4)-α-L-arabinopyranosyl-oxy]-16 α-hydroxy-13 *β*,28-epoxyolean-30-al) (**1**) (Figure **1**), isolated from *Primula denticulate* at a dose of 200 mg/kg body weight and ethanol extract at a dose of 1000 mg/kg body weight safely normalized the elevated blood-glucose level and restored serum towards normal values. Triterpenoids can reduce blood glucose through increased insulin secretion, which is able to improving pancreatic secretion and therefore making insulin secretion from pancreatic *β*-cells[47].

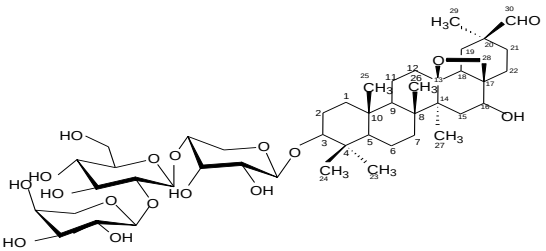
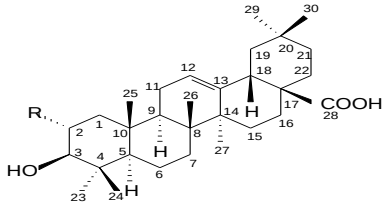


Figure 1: The structure of compound **1**.

In addition, oleanolic acid (**2**) and maslinic acid (**3**) (Figure **2**), were isolated as saponins from *Lagerstroema speciosa*. Both compounds showed significant α-glucosidase inhibatory activity at IC_{50} value of 6.29 and

5.52 µg/mL, respectively because their C-2 was a methylene group[48].



(2) R=H

(3) R=OH

Figure 2: The structure of compounds **2** and **3**.

The saponin extract of *Cochlosperum vitifolium* causes blood glucose level depression by 35.98 % as compared to the metformin group after 3 and 7 days treatment. The capabelity of the saponin extract to decrease elevated blood glucose levels to normal levels is an essential for the liver to come back to its typical homeostasis in test diabetic rats. Besides, this reality indirectly indicates that the anti-diabetic effect of saponin from the leaves of *Cochlosperum vitifolium* is mostly due to insulin release from the existing pancreas cells[49].

Steroidal saponins

A new steroid, withanolide (**4**) (Figure **3**), was confined from the acetone extract of *Elephantopus scaber* L. (Asteraceae), also known as elephant's foot. Oral administration of the compound (2 mg kg^{-1} bw) significantly reduced hyperglycemia in STZ-induced diabetic rats. A greatest reduction of serum glucose level (156.8 mg d^{-1} l^{-1}), about 69 % decrease in the blood sugar levels compared to the diabetic control (glibenclamide 0.6 mg kg^{-1}), was showed[50].

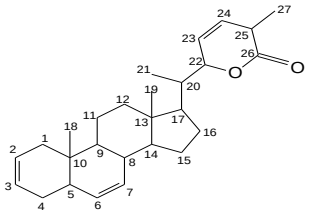


Figure 3: The structure of compound **4**.

An antidiabetic beta sitosterol (**5**) (Figure **4**), was isolated from *Solanum surattense* showed significant increase in the pancreatic protein content of diabetic rats and exerts protective effects on serum and pancreatic tissue. That is clearly shows that it neutralizing free radicals and ROS, mieght is effective in prohebiting protein damage caused by oxidative stress, which is reasoning to be involved in the degeneration of *β*-cells[51].

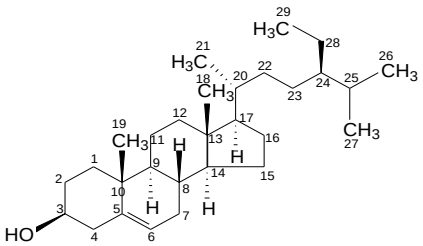


Figure 4: The structure of compound **5**.

Nasution *et al*., suggested that the isolate *β*-sitosterol propionate (**6**) (Figure **5**), isolated from *Artocarpus camansi* (Kulu) leaves showed, a great ability to reduce blood glucose, that is, 30 minutes after the administration; it can reduce blood glucose of mice 87.67 mg/dL; after 60 minutes reduce the blood sugar as much as 89 mg /dL; and after 90 minute, reduce blood sugar 22 mg/dL, in male mice[52].

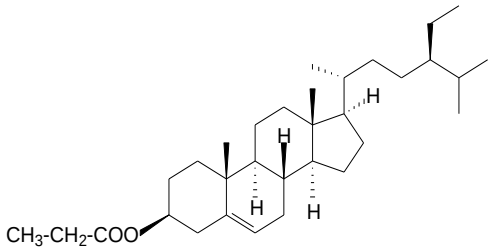
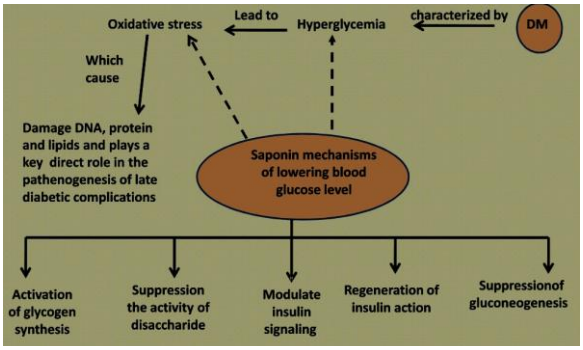


Figure 5: The structure of compound **6**.

Mechanism of action of saponins in diabetes

Diabetes mellitus (DM) is a serious chronic disturbance that is regularly accompanied by distinct complications such as retinopathy, neuropathy, nephropathy and cardiovascular disease[53]. Oxidative stress plays a fundamental role in the development of DM which increases complications with increased free radical formation[54]. Reactive oxygen species produces from oxidative stress, which consequant toxic effect on cell development, growth and survival[55]. Oxidative stress is made with the production of advanced glycation which has a strong association with the diabetic complications[56]. Free radicals which resulted from oxidative stress interceded and advanced modified *β*-cell kill[57]. Additionally, oxidative stress reacts with polyunsaturated fatty acids at the membrane of lipid and cause lipid peroxidation[58]. Moreover saponin can reduce the increase in blood glucose by inhibiting the enzymes that break down and devided disaccharides into monosaccharides due to their antioxidant activity[59].



Polyphenols

The word phenol mentions to a chemical structure formed by attaching between an aromatic benzenoid (phenyl) ring and a hydroxyl (-OH) group; most polyphenols contain repeating phenolic moieties. They are one of the most important and

certainly the most numerous among the groups of phytochemicals present in the plant kingdom such as cinnamic acids (C6-C3), stilbenes (C6-C2-C6), flavonoids (C6-C3-C6), coumarins (C6-C3) and anthocyanidines (C6-C3-C6).

Oral administration of the *Terminalia chebula*, *Terminalia belerica*, *Emblica officinalis* extracts (100 mg/kg body weight) diminished the blood sugar level in normal and in alloxan (120 mg/kg) diabetic rats significantly within 4 h. Proceeded with, daily administration of the drug created a supported effect[60]. Infact, it was found that customary pharmaceuticals used as a part of human diabetes furthermore have a critical cell reinforcement development. It may be possible that these concentrates may diminish the effect of blazing cytokine release in the midst of diabetes which may be one of the causative administrators for the tissue diversion and insulin resistance[61].

Flavonoids

Flavonoids are polyphenolic molecules and poorly soluble in water represent a large class of at least 6000 phenolic compounds phytonutrients (plant chemicals) found in almost fruits, vegetables, tea, nuts, cocoa, grain seeds, chocolate and responsible for the vivid colors in fruits and vegetables. Given the hypothesized that; it is biologically plausible that consumption of flavonoids or flavonoid-rich foods may reduce the risk of diabetes[62,63]. Structurally, flavonoids composed of two aromatic rings (A and B) linked by a 3-carbon chain that forms an oxygenated heterocyclic ring (C). There are six subclasses of flavonoids including flavones, flavonols, flavanones, flavonols, isoflavones and anthocyanidins. New concepts have showed up with this pattern, such as nutraceuticals, nutritional therapy, phytonutrients and phytotherapy. This functional foods and phytomedicines play important positive roles in keeping up blood glucose levels, glucose uptake, insulin secretion and modulating immune function to prevent particular DM[64, 65].

Recently, Ganugapati *et al.*, reported that flavonoids separated from banana flowers have the power to activate the insulin receptor tyrosine kinase, and may represent an option choice for treatment if (type 2 diabetes mellitus) T2DM patients with insulin resistance[66, 67].

Quercetin (**7**) (Figure **6**), is a flavonoid has been reported to possess antidiabetic activity. Vessal *et al.*, revealed that quercetin service about the recovery of pancreatic islets and probably raise insulin release in streptozotocin-induced diabetic[68].

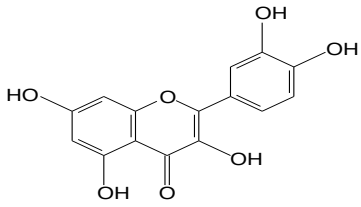


Figure 6: The structure of compound **7**.

Flavanone compound; 5,7,4'-trihydroxy-3',5'-dimethoxyflavanone (**8**) (Figure **7**), isolated from *Jatropha gossypifolia* L. stimulated glucose uptake in insulin-resistant cells in a concentration-dependent manner, up to 27 % at 50 µg/ml[69].

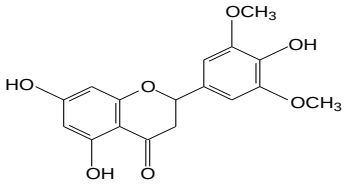


Figure 7: The structure of compound **8**.

Moreover, Ginseng polypeptides (**9**) (GPP) (amino acids series) isolated from the root of *Panax ginseng* Mey, when injected subcutaneously under the skin at daily doses of 50 and 100 mg/kg for 7 successive days in mice causes suppression in blood glucose and increase liver glycon level and motivate insulin secretion[70].

Isorhamnetin (**10**) (Figure **8**), is a bioactive compound found in therapeutic plant, *Salicornia herbacea*, when administered orally at 25 mg/kg in STZ-induced diabetic rats caused not only a significant inhibition of serum glucose concentration but also sorbitol collection in the lenses, red blood cells, and sciatic nerves[71]. Recently, *Rodríguez-Rodríguez et al.;* were suggesting that isorhamnetin glycosides may have the antidiabetic effect and their effect on lipid content[72].

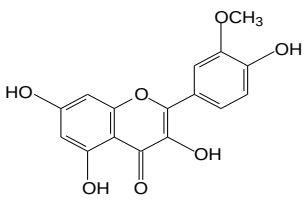


Figure 8: The structure of compound **10**.

Kaempferol glycoside-rich fraction was optained from the leaves of unripe Jindai soybean (edamame) (*Glycine max* (L.) Merr., Fabaceae). The major flavonoid is identified as kaempferol 3-*O*-*β*-D-glucopyranosyl-(1→2)-*O*-[α-L-rhamnopyranosyl-(1→6)]-*β*-D-galactopyranoside (**11**) (Figure **9**). Feding of mice with kaempferol glycoside-rich fraction resulted in; liver triglyceride level and fatty acid synthase (FAS) activity were both decreased in mice. Results suggest that it would be benifet to improve the diabetes condition and this compound may be heedful with the modulation of diabetes[73].

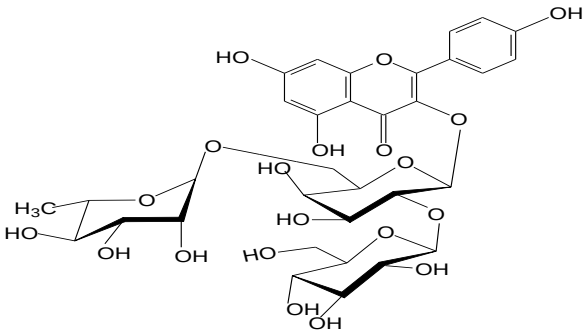


Figure 9: The structure of compound **11**.

Anthocyanins

The primary anthocyanin contained in the anthocyanin enriched extract of *Vaccinium angustifolium* Aiton, malvidin-3-*O*-glucoside (**12**) (Figure **10**), was an active hypoglycemic agent when administered as a pure compound. Therefore, in conclusion that the hypoglycemic activity of the blueberry fruite extract was largely anthocyanin specific compared to the phenolic-rich extract which showed lower hypoglycemic activity. Malvidin-3-*O*-glucoside treatment (300 mg/kg) lowered blood glucose levels in the mice by 34 %, was comparable to the metformin positive control at 300 mg/kg[74].

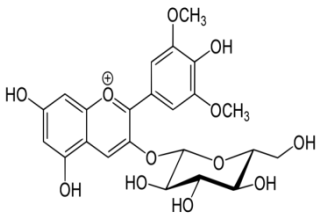


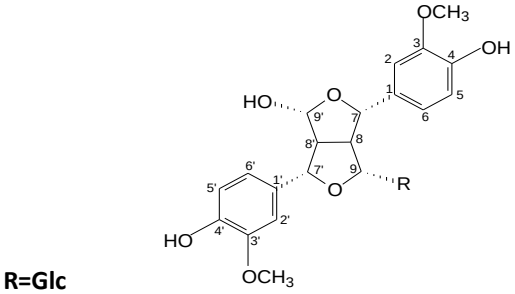
Figure 10: The structure of compound **12**.

Mechanism of action of flavonoids in diabetes

Flavonoids animate glucose uptake in peripheral tissues, managed the activity and/or expression of the rate-restricting enzymes in the carbohydrate metabolism pathway and act as insulin secretagogues or insulin mimetics, presumably, by impacting the pleiotropic systems of insulin signaling, to enhance the diabetes status[75].

Lignans

A new furofuran lignan, 9'α-hydroxy-9α-*O*-*β*-D glucopyranosylpinoresinol named lactucaside (**13**) (Figure **11**), were isolated from *Lactuca indica* showed a significant antidiabetic activity with lowering of plasma glucose at a dose of 1 mM/kg. Furthermore in a preliminary test, the aqueous acetone extract of fresh *L. indica* was also found to be exhibeted significant antidiabetic activity[76].



R=Glc

Figure 11: The structure of compound **13**.

Phenolic acids

Phenolic acids are ubiquitous in edible vegetable, fruits, and nuts, and it is estimated that an average of 1-2 g/day of these components may be consumed in a human diet, which have demonstrated potential antidiabetic effects[77]. Oral administration of gallic acid (GA) (**14**) (Figure **12**), isolated from *Terminalia bellerica* Roxb. causes a dose-dependent decrease in blood glucose levels. At 20 mg/kg body weight (BW), GA induced significantly fall blood glucose (81.8 mg/dL), total cholesterol, triglyceride, low-density lipoprotein cholesterol, urea, uric acid, and creatinine and at the same time markedly increased plasma insulin (16.3 µU/mL), C-peptide, and glucose tolerance levels[78].

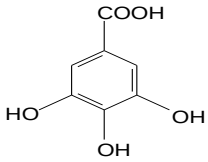


Figure 12: The structure of compound **14**.

Phellinus linteus present in Asian countries used in folk medicinal for the treatment of various illnesses. *P. linteus* acts as an antidiabetic agent and protects *β*-cells from the toxic effects of ROS in diabetes[79], which is a royalty attributed to ellagic acid (EA) (**15**) (Figure **13**).

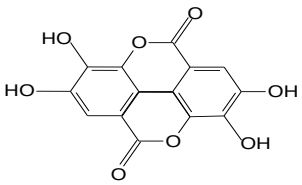


Figure 13: The structure of compound **15**.

Another pleasant study exhibeted that syringic acid (SA) (**16**) (Figure **14**) isolated from *Herba dendrobii*, significantly prohibited diabetic cataract in rat lenses by inhibiting aldose reductase (AR) activity (IC_{50} value of inhibition by SA towards AR was, 213.17 µg/mL) and gene

expression, which has the potential to be advanced into a new drug for medical management of diabetic cataract[80].

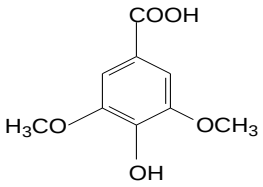


Figure 14: The structure of compound **16**.

Administration of caffeic acid (CA) (**17**) (Figure **15**), decreased the elevation of plasma glucose level in insulin-resistant rats accepting a glucose challenge test. CA also increases the glucose uptake into the isolated adipocytes. Increased glucose employment by CA appears to be responsible for the lowering of plasma glucose[81].

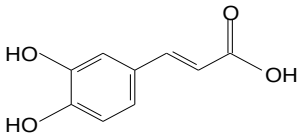


Figure 15: The structure of compound **17**.

The consuming of whole-grain wheat recovers the metabolic diseases, indicating the quality of sinapic acid (**18**) (Figure **16**), in diabetic disorders[82].

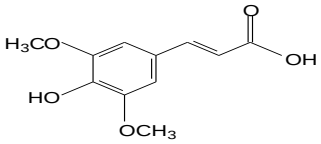


Figure 16: The structure of compound **18**.

Cinnamic acid (**19**) (Figure **17**), isolated from *Cinnamomum cassia* activates insulin-mediated glucose transport through the involvement of GLUT4, but via a PI3K-independent pathway, in L6 myotubes[83].

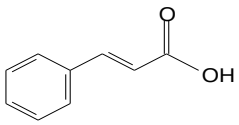


Figure 17: The structure of compound **19**.

Alkaloids

They are a group of naturally occurring chemical compounds that predominantly contain basic nitrogen atoms; a number of alkaloids have been isolated from several medicinal plants and explored for their probable antidiabetic activity in various animal models.

Tecomine alkaloid (**20**) (Figure **18**), was separated from the *Tecoma stans* L. (Bignoniaceae) at Egypt. It was showed a potent stimulating effect on the basal glucose uptake rate in rat adipocytes from normoglycemic rats with an EC_{50} value of $6.79X10^{-9}$ M[84].

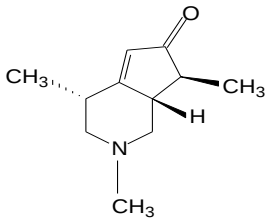


Figure 18: The structure of compound **20**.

Vindolicine alkaloid (**21**) (Figure **19**), isolated from Catharanthus roseus (L.) G. Don; reported to possess the most potent activity in PTP-1B (PTP-1B is an enzyme that belongs to the protein tyrosine phosphatase family and a negative controller of the insulin signaling pathway) inhibition, which supports further development of this compound as a novel PTP-1B suppressor that may serve as "insulin sensitizer" in the management of type 2 diabetes; refers to its high antioxidant and PTP-1B inhibition activities[85].

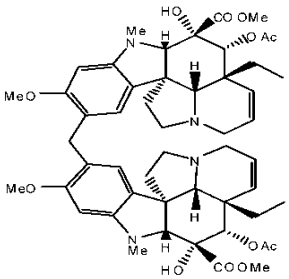


Figure 19: The structure of compound **21**.

Mahanimbine (**22**) (Figure **20**), is a carbazole alkaloid isolated is from *Murraya koenigii* (L.) Spreng. (Rutaceae) leaves showed anti-diabetic activity in streptozotocin-induced diabetic rats and appreciable α amylase inhibitor and weak α glucosidase inhibitory effects after administration of 50 mg/kg and 100 mg/kg of mahanimbine for 30 days once a week[86].

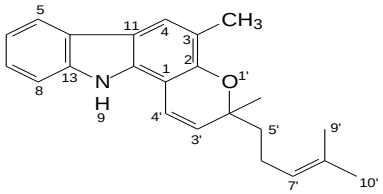


Figure 20: The structure of compound **22**.

Metformin (1,1-Dimethylbiguanide) (**23**) (Figure **21**), is an antidiabetic drug marketed under the commerce name Glucophage and originated from the French lilac or goat's rue (*Galega officinalis*), which is a plant used in traditional medicine for several centuries[87]. Metformin's main effect is to decrease liver glucose production[88] and increases insulin sensitivity, which increases peripheral glucose uptake. In addition outcomes observed to be sustained even in those with some degree of kidney disease, heart failure, or liver problems[89]. The American Diabetes Association recommends metformin as a first-line agent to treat type 2 diabetes[90].

Galega officinalis

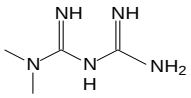


Figure 21: The structure of compound **23**.

Coumarins

Coumarin is an odorous organic chemical compound belongs to the benzopyrone chemical class, which is a colorless crystalline material in its standard state. It is a natural compound found in many plants and used in certain perfumes and fabric conditioners.

A coumarin compound, 7- methoxy coumarin (**24**) (Figure **22**), isolated from *Rhizophora mucronata* bark part; cause a worthy decreases in blood glucose level in diabetic mice when the compound administrated with (500 $mg.kg^{-1}$ and 1000 $mg.kg^{-1}$) for 1 day, in *in vivo* animal modal[91].

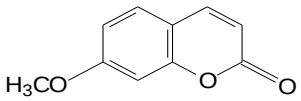


Figure 22: The structure of compound **24**.

Peucedanol 7-*O*-*β*-D-glucopyranoside (**25**) (Figure **23**), isolated from *Peucedanum japonicum* revealed 39 % inhibition of postprandial hyperglycemia at 5.8 mg/kg dose[92].

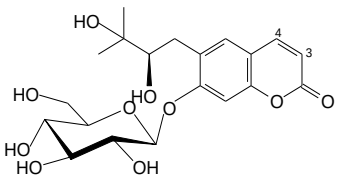


Figure 23: The structure of compound **25**.

Tannins

Kobayashi *et al*., showed that a tannin compound, epigallocatechin gallate (**26**) (Figure **24**) from green tea, was found to inhibit the intestinal glucose uptake by a sodium dependent glucose transporter[93].

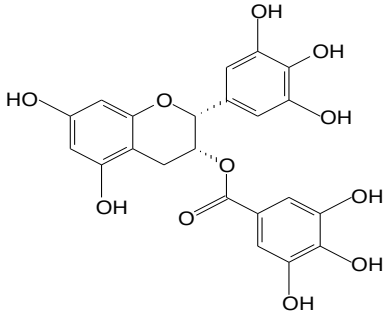


Figure 24: The structure of compound **26**.

The polyphenols of green tea was found to increased serum glucose levels from 77.39/13.8 to 176.49/20.5 at 60 min but returned to normal at 240 min when administrated of 2 g glucose/kg b.wt. to normal rats. At dose level of 100 mg/kg b.wt., a significant reduction in blood glucose was seen from 12th day by 25.5 % and at 18th day after alloxan treatment the percent reduction in serum glucose was 44.1 %. Blood glucose levels in the control (alloxan treated) and normal (alloxan non-treated) group was remained unchanged over this period[94].

Other green tea extract (GTE) and black tea extract (BTE) were also studied by Tang *et al*., which found that, both BTE and GTE were highly effective in lowering blood glucose to levels of the normal group studed. Interestingly, GTE could decrease insulin resistance (IR); while for BTE was mainly through stimulating insulin secretion and protecting *β* cell function by its antioxidant action against nitrosative stress which may explain its hypoglycemic activity. This can be explained by the existance of catechins in the chemical analysis, which is 71.5 % in GTE, while in BTE presented by 15.3 %[95].

(+)–catechin or (2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol (**27**) (Figure **25**), an active compound isolated from the leaves of *Quercus gilva* Blume by methanol; showed potent α-glucosidase inhibitory activity with IC_{50} value of 168.60 ± 5.15 µmol/L.

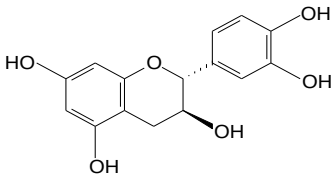


Figure 25: The structure of compound **27**.

Essential oils

The antidiabetic activity of essential oils extracted by n-hexane, petroleum ether, dichloromethane from *Carthamus tinctorius* L. (safflower) was assayed *in vitro* against protein tyrosine phosphatase 1B (PTP1B). The results showed that the n-hexane extract exhibited *in vitro* inhibitory enzyme activity against PTP1B (IC_{50} value of 36.1 µg mL^{-1}), which holds a good potential for treating diabetes[96].

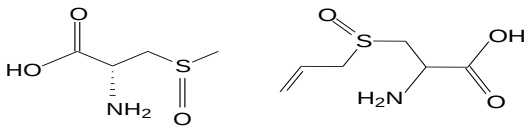
Al Jamal and Ibrahim showed that daily consumption of olive oil had positive effect on fast blood glucose (FBG) and lipid profiles of healthy controls. In addition, the positive effect of olive oil consumption was much more strenuous in the diabetic group as levels of FBG, low density lipoprotein (LDL), triglyceride (TG) and total cholesterol (Ch) decreasing by 16-32 % in both asymptomatic participants and type 2 diabetes that were improved[97].

Plant foods in the management of diabetes mellitus

Diet has been famous as a corner stone in the management of diabetes mellitus. Spices are the common

dietary that provides the taste and flavour of foods. Besides, spices are also known to extend several useful physiological infeluence including the antidiabetic activity[98].

Allium cepa, a spice plant is commonly known as onion and (family liliaceae). Since the last decades until now, it has been used traditionally for the treatment of different diseases. Among numerous activities of *Allium cepa*, hypoglycemic activity is considered as one of its significant activity in diabetes mellitus. For example, different experimental studies on animals showed that the anti-diabetic effects of *Allium cepa* is attributed to the sulphur containing compounds isolated from onion such as S-methly cysteine sulfoxide (**28**)[99] and S-allyl cysteine sulfoxide (**29**) (Figure **26**)[100], which can increase the level of insulin in blood due to it is directly act on pancreas organ.



(28) **(29)**

Figure 26: The structure of compounds **28** and **29**.

Garlic (*Allium sativum*), which is a common cooking spice and has a very long history as a tradition remedy, has been reported to have antidiabetic activity. Breifly, it is commenly believed that hypoglycemic agents should focus on two mechanisms: insulin secretagogue and insulin-sensitizing influences. Some studies suggest that garlic may exert its hypoglycemic effect via both last mechanisms. Evidence suggests that garlic's antioxidative, antiinflammatory and antiglycative activities are responsible for garlic's role in preventing diabetes improvement and the development of diabetes-related complications. Also it has been shown that two major volatile sulfur compounds of garlic oil are diallyl sulfide (**30**) and diallyl disulfide (**31**) (Figure **27**), responsible for its antidiabetic activity[101]. Both garlic and garlic extracts exhibeted effective effect in reducing insulin resistance. Daily usage of garlic is strongly benifecial in controlling diabetes and diabetes-associated pathologies.

(30) **(31)**

Figure 27: The structure of compounds **30** and **31**.

Turmeric (*Curcuma longa* Linn) is widely used as a spice; it has been used in folk medicine as a remedy for numerous diseases including cough, diabetes and hepatic disorders. Since ancient times, a hug works have been done to establish the pharmacological properties of Turmeric.

Curcumin is the main chemical constituent of Turmeric and confirmed for its antidiabetic activity through increasing the postprandial serum insulin levels[102].

Cumin (*Cuminum cyminum*) is a flavor spice in food; its seeds are used in the cooking of many various cultures, in both whole and ground forms. It also has many uses as a folk medicinal plant. Ahmed *et al*., report the anti-hyperglycaemic influence of black cumin (*Cuminum nigrum*), and attributing the antidiabetic effect to the flavonoid compounds containing in cumin[103]. A suppressor of insulin secretion with potent *β*-cell protective action was also isolated from the petroleum ether fraction. The authors concluded that *Cuminum cyminum* was able to lower blood glucose without causing hypoglycaemia or *β*-cell burn out[104].

Ginger (*Zingiber officinale*) is a flowering plant whose rhizome, ginger root or, is extensively used as a spice and proved to be active in folk medicine. Ginger and their constituents showed essential role in the control of diabetes and its complications via anti hyperglycemic activity. The actual mechanism of action of ginger in diabetes desease control is might be due to the inhibition of oxidative stress[98].

Curry leaf (*Murraya koenigii*), has strong spicy and seasoning type flavor; its leaves are used in numerous dishes in India, and other countries and it is used as an herb in traditional medicine. Moreover, curry leaf has been found to have anti-hyperglycemic and hypoglycemic effects[105].

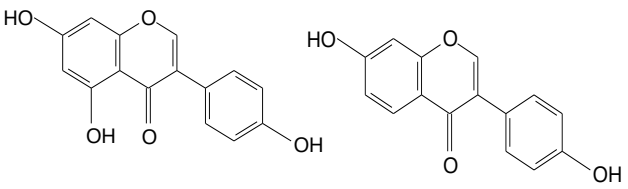
Mustard (*Brassica nigra*) is generaly used as a spice. Studies in rats showed a hypoglycemic activity in normal animals, as well as effects (decreased serum glucose and increased insulin response) on postprandial glucose in diabetic-induced animals, upon testing both the whole plant and extracts. Sugested mechanisms include modulation of gluconeogenic and glucolytic enzymes[106].

Coriander (*Coriandrum sativum*), its all parts are edible, but the fresh leaves and the dried seeds are the most parts traditionally used in cooking for several countries; the roots are highly intense flavor than the leaves.

Coriandrum sativum has been reprted as a traditional remedy for diabetes by lowered the blood sugar when added to the diet of diabetic mice; its antihyperglycemic action is associated with stimulation of insulin secretion and enhancement of glucose uptake and metabolism by muscle, reflecting the effects of more than one active constituent[107].


Leguminous plants mostly pulses or soybeans ought to be made the principle source of dietary needs in the advancement of healthy lifestyles in terms of functional food. Legumes are protein rich containing a lot of soluble nutritious fiber, polyunsaturated fatty acids, vitamins, minerals, and bioactive substances which have antioxidant activity. These possess α-glycosidase inhibitors which can distinctly diminish glucose utilization if added to the daily meals.

Leguminous plants possess genistein (**32**) which is a plant estrogen, belongs to isoflavones class and daidzein (**33**) (Figure **28**); they were α-amylase inhibitors, and α-glucosidase inhibitors which have possessed very high antidiabetic activities. Their high amount of bioactive compounds interferes with the metabolism of glucose. The most significant consumption of vegetables and legumes is directely associated with prevention of T2D risk[108].



(32) **(33)**

Figure 28: The structure of compounds **32** and **33**.

Methods adopted for antidiabetic activity of medicinal plants

Antidiabetic study in alloxan-induced diabetes rats

Induction of Diabetes Mellitus Male Wistar rats weighting from (180-200 g) were housed in standard conditions and fed with normal diet and water ad libitum. Diabetes was induced by intraperitonel injection of alloxan at a dose of 150 mg/kg body weight. Alloxan was dissolved in 0,9 % sodium chloride. After the injection, they had free access of food and water. The rats were given 5 % glucose solution after 6 h from alloxan injection to drink overnight to counter any hypoglycemic shock. The diabetic state was assessed by measuring the fasting plasma glucose concentration 72 h after alloxan treatment in fasting rats. The rats with a plasma glucose level above 250 mg/dl were selected for the experiment and considered as diabetic[109].

Antidiabetic study in Streptozotocin (STZ)-induced diabetes rats

The antidiabetic study was carried out in STZ-induced diabetic rats. The study was carried out for 21 d. The animals were fasted for 18 h before the experiment and blood-glucose levels were checked. It was considered as the day zero reading. The dose of extract was given orally daily to animals for 21 d. The blood-glucose levels were checked at 0, 7, 14, and 21 d period. The blood was collected by snipping the rats' tail with a sharp razor. The collected blood was centrifuge at 2000 rpm for 15 min and determination of blood-glucose levels were carried out using a GOD-POD assay method by semi-autoanalyser[77].

Biochemical factors evaluation

Glucose diffusion inhibitory assay

An aqueous extract of the plant was prepared by maceration at 37°C. 1 ml of the extract was then placed in a dialysis membrane along with glucose solution (0.22 mM in 0.15 M sodium chloride). It was then tied at both ends using thread and it was immersed in a beaker containing 40 ml of 0.15 M sodium chloride and 10 ml of distilled water. The control contained 1 ml of 0.15 M sodium chloride containing 22 mM glucose and 1ml of distilled water. The beakers were then placed on orbital shaker and kept at room temperature. The movement of glucose into the external solution was monitored every half hour. Three replications of this were done for 3 hours[110].

Inhibition assay for α-amylase activity (DNSA)

Four concentrations of plant extract were prepared by dissolving in double distilled water. These were 25 mg/ml, 50 mg/ml, 75 mg/ml and 100 mg/ml. A total of 500 µl of plant extract and 500 µl of 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M sodium chloride) containing α-amylase solution (0.5 mg/ml) were incubated for 10 minutes at 25 °C. After pre-incubation, 500 µl of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9 with 0.006 M sodium chloride) was added to each tube at 5 s intervals. This reaction mixture was then incubated for 10 minutes at 25 °C. 1 ml of DNSA (3,5-dinitrosalicylic acid) colour reagent was added to stop the reaction. These test tubes were then incubated in a boiling water bath for 5 minutes and cooled to room temperature. Finally this reaction mixture was again diluted by adding 10 ml distilled water following which absorbance was measured at 540 nm[111].

Inhibition of alpha-glucosidase enzyme

The inhibitory activity was determined by incubating a solution of starch substrate (2 % w/v maltose or sucrose) 1 ml with 0.2 M Tris buffer of pH 8.0 and various concentrations of plant extract for 5 min at 37 °C. The reaction was initiated by adding 1 ml of alpha-glucosidase enzyme (1 U/ml) to it followed by incubation for 40 min at 35 °C. Then the reaction was terminated by the addition of 2 ml of 6 N HCl. Then the intensity of the colour was measured at 540 nm[112].

Calculation of 50 % Inhibitory Concentration (IC_{50}):

The concentration of the plant extract required to inhibit 50 % of alpha glucosidase activity (IC_{50}) was calculated. Percentage inhibition (I %) was calculated by I % = (Ac-As)/Ac X 100, where Ac is the absorbance of the control and As is the absorbance of the sample[113].

Cell assay

MIN6 *β*-cells were grown at 37 °C with 5 % CO_2 in DMEM (Dulbecco's Modified Eagle's Medium) media with 15 % fetal bovine serum, 1 % penicillin/streptomycin, 1:200 gentamicin, and 1 % basel medium eagle. Cells were trypsinized off the plate, split, and replated into 6-well plates and grown until confluent. The extract and isolated compounds were re-suspended in 100 % DMSO to make a stock solution of 125 mg/ml. The assay was performed similarly to a previously described method[114]. Cells were incubated with Kreb's Ringer buffer (KRB) for 60 min on the plate. Cells were then rinsed with fresh KRB twice, and an aliquot of the second wash was saved as a base line insulin measurement. Cells were then incubated for 60 min with KRB (negative control), 50 µM glipizide with 27 mM glucose in KRB (positive control), or 0.1 % DMSO in KRB (vehicle control). The extract was tested at 25, 75, and 125 µg/ml concentrations, while compounds were tested at 5, 10, and 25 µg/ml. Treatment solutions were collected at 60 min, and insulin concentrations were determined by ELISA.

Measurement of glucose uptake using radiolabeled 3-O-methylglucose (3MG)

For this assay, the rate of 3MG transport is quantified using a modified version of the L-arabinose uptake method described by[115]. As 3MG is nonphosphorylatable glucose analog it can be used to accurately measure the initial rate of glucose transport. However, use of 3MG necessitates a very short incubation time because of the rapid equilibration of the analog across plasma membranes. The assay also requires either a rapid separation of cells from incubation medium, usually by centrifugation through a suitable oil cushion, or the prevention of 3MG efflux by washing with a mercuric chloride solution. In the protocol detailed 3MG efflux is prevented by rinsing the cells quickly with ice-cold buffer instead of mercuric chloride solution.

3T3-L1 adipocyte culture and glucose consumption assay

Equal amounts (5×10^5 cells) of 3T3-L1 pre-adipocytes were seeded and cultured in normal D-glucose (100 mg/dL) Dulbecco's modified Eagle medium with 10 % fetal bovine serum, 1% penicillin–streptomycin in a humidified atmosphere of 95 % air and 5 % CO_2 at 37 °C. When the cells reached 100 % confluence, 3T3-L1 preadipocytes were induced to be differentiated by treating the culture with 450 mg/dL D-glucose, 0.32 µM insulin, 0.5 mM 3-isobutyl-1-methylxanthine and 1 µM dexamethasone for 2 days. Then, the culture medium of the differentiated adipocytes was changed to Dulbecco's modified Eagle medium containing 450 mg/dL D-glucose with or without the administration of the tested compounds. After 24 hours, the glucose consumption activity was determined by measuring the medium glucose concentration. The coefficient of variation of the analyzer was 0.62-0.92 % within-run and 1.1-1.2 % between days. To confirm whether our *in vitro* model was sufficient to measure the glucose-lowering effect, insulin was used as the positive control. The insulin powder was dissolved in 0.01 M acetic acid (pH 3.0) to provide a 10^{-2} M stock solution and then diluted in distilled water. EO samples were dissolved in dimethyl sulfoxide (DMSO) to make 60 µL/mL stock solutions and then diluted in DMSO; the final concentration of DMSO in the medium was 0.1%[116,117]. All samples test their bioactivity in 60 µ/L concentration.

Evaluation of Protein Tyrosine Phosphates 1B (PTP1B) activity

The *in vitro* PTP1B activity assay was conducted based on a protocol previously described by Taghibiglou *et al*. During the assay, p-NPP was used as substrate. *p*-nitrophenyl phosphate (p-NPP) was diluted in the assay buffer (50 mM HEPES, pH 7.3, 100 mM NaCl, 0.1 % bovine serum albumin (BSA), and 1 mM Dithiothreitol (DTT)). In the evaluation of PTP1B inhibitor, different concentrations of extract was incubated with GST-PTP1B1-321, and the enzyme activities were detected in a 96-well microplate spectrophotometer at 30 °C. The enzyme activities were determined by measuring the absorbance at 405 nm generated by the formation of product p-NPP. The PTP1B inhibition was expressed as percentage of inhibition and calculated by the following equations:

Reaction rate (%) = $([PTP1B]_{test}/[PTP1B]_{control}) \times 100$ (1)
Inhibition rate (%) = 100 − reaction rate (%) (2)

Extract concentration providing 50 % inhibition (IC_{50}) was calculated from the plot of inhibition percentage against extract concentration. All determinations were carried out in triplicate, and the results were averaged[118].

Future perspective

This symmetrical state of art evaluates the effects of medicinal plants as antidiabetic agents. A huge number of Egyptian plants were always used as traditional herbs and give recipe for different illnesses. Among many disease or disorders of carbohydrate and fat; diabetes mellitus is a serious disorder effecting large population over the world and it is clear that; there is an increase in the number of patients suffering from diabetes in every age through the last decades until now. The plants often extend a distinguishing effect for some diseases including diabetes mellitus. Natural drugs from traditional Egyptian medicine are of popularity from aristocrats to common people, due to numerous advantages such as fewer side-effects, less toxic, better patient tolerance, relatively less expensive and favor due to a long history of use to protect their health and

to avoid the serious problems associated with synthetic drugs such as; insulin, troglitazone, tolbutamide and repaglinide. In addition, the medicinal plants effective for both the control of blood glucose and the modification of the course of diabetic complications without side-effects.

Plant derived compounds such as:

1. 1,1-Dimethylbiguanide, metformin, came from the traditional approach of using *Galenga officinalis*, widely used hypoglycemic drug having the ability to decrease liver glucose production and increases insulin sensitivity, which increases peripheral glucose uptake and sustained even in those with some degree of kidney disease, heart failure, or liver problems. Such plant derived compound need to be commercialized and made available at low costs. To demonstrate having the least side effects in the long run; it can furthermore be used in a combination with other known potent antidiabetic molecules and drugs to cure this awful disease. Hence the American Diabetes Association recommends metformin as a first-line agent to treat type 2 diabetes.

2. S-methly cysteine sulfoxide, S-allyl cysteine sulfoxide and diallyl sulfide which are gained from onion and garlic can increase the level of insulin in blood, so the diabetic patients should be clinically realized about the pharmacological benefits of these cheap and available plants and should also be advised to increase its dietary supplementation for the management of diabetes mellitus. For the Egyptian medicines must be the scientists focusing on finding active compounds and develop new drugs to treatment diabetes from these available plants at lower cost and can be awarded by developing countries as well.

3. A new steroid, withanolide and Vindolicine alkaloid may represent a novel antidiabetic drugs; while the latter reported as a most potent and novel PTP-1B suppressor.

4. Syringic acid significantly has the potential to be developed into a new drug for therapeutic management of diabetic cataract.

5. Instantly, diabetic patient involve modifications for the lifestyle, for example, increased physical activity, weight control by reducing caloric capacity and increasingly, the dietary recommendations for plant food products, which are economic and easily available such as whole grains, berries, fruits, and vegetables, all known to be excellent sources of dietary fibre and phenolic products that of great benefit for diabetic patients and its complications.

6. The requirement for sufficient standards of herbal preparations to guarantee quality, safety and true therapeutic efficacy has been highlighted since the utilization of plant medication and phytotherapy. It is consequently vital that chronic toxicity studies be performed before recommending a plant-derived drug for antidiabetic treatment and their in vitro and in vivo pharmacological evaluation.

Discover a new active component from Egyptian medicinal plants with affirmed hypoglycemic activity must be continued which may become instead of synthetic drugs which having a harmful side effects and high coasted. It is a significant effort to isolate and clarify their pharmacological mechanism, and lastly, to create traditional dosage forms which controls and developed diabetes as well as takes care of associated complications. Recent technology could be benefit equipment for determine the potential polyphenolic plant origin compounds against diabetic chronic disease.

Moreover the utilization of the novel nanotechnology technique for drug discovery in the improvement of the drug efficacy within fewer doses; that is will be economically beneficial.

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