International Journal of Chemical and Biomolecular Science
Vol. 1, No. 3, 2015, pp. 167-178
http://www.aiscience.org/journal/ijcbs

Evaluation of the Effects and Mechanisms of Bioactive Components Present in Hypoglycemic Plants

Marisa F. Mendes[1, *], I. David L. Bogle[2]

[1]Chemical Engineering Department, Technology Institute, Universidade Federal Rural Do Rio de Janeiro (UFRRJ), Seropédica, Rio de Janeiro, Brazil
[2]Chemical Engineering Department, University College London (UCL), London, United Kingdom

Abstract

Diabetes mellitus is a disease that is becoming increasingly prevalent worldwide. In many cases, people do not have access to synthetic drugs and make use of teas of different plants present in different countries, in order to reduce the symptoms. The plant extracts may contain bioactive compounds and may also contain toxic substances harmful to the human body. Much has been published about plants with antidiabetic activity, identifying their bioactive compounds, but there is no work in the literature that identifies the mechanisms of action of the extracts or isolated compounds of the extracts for a better understanding of the chemical reactions that occur in patients with diabetes. Therefore, this study aims to review published works that have tried to show some active mechanism of the different compounds (flavonoids, saponins, polyphenols, vitamins, etc.), to explore these mechanisms through mathematical models that can predict the benefits of these extracts to, in the future, facilitate the application of these natural products into less expensive drugs. It can be concluded that many of the extracts and isolated compounds from different hypoglycemic plants have as main mechanisms the induction of the insulin secretion, the enhancement of the number of beta cells of pancreatic islets, and have antioxidant properties.

Keywords

Diabetes, Flavones, Hypoglycemic Activity, Antioxidant Property

Received: July 28, 2015 / Accepted: August 22, 2015 / Published online: September 2, 2015

1. Introduction

Type 2 diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia as a result of reduced sensitivity to the hormone insulin, predominantly present in the liver, adipose tissues and skeletal muscles. It is also characterized by either deficiency of insulin production due to destructive lesions of pancreatic β-cells or by cellular resistance to insulin (Li et al., 2015; Bahmani et al., 2014; Sharma et al., 2014; Manosroi et al., 2011).

According to Sharma et al. (2014), the number of people suffering from the disease worldwide is estimated to be over 173 million and this figure is likely to be increased to 300 million or more by the year of 2025. According also to Diabetes International Federation, the country with the higher number of people with diabetes is China, with 92.3 million, followed by India (63 million) and USA (24.1 million).

The pharmacological treatment of diabetes includes oral hypoglycemic and insulin. Today, inhibiting carbohydrate-hydrolyzing enzymes (α-amylase and α – glucosidase) is one of the therapeutic approaches for decreasing postgrandial hyperglycemia (Tiwari and Rao, 2002 cited by Huang et al.,

* Corresponding author
E-mail address: marisamendes@globo.com (M. F. Mendes), d.bogle@ucl.ac.uk (I. D. L. Bogle)

2015). Before the discovery of anti-diabetic drugs and insulin, diabetic patients used medicinal plants and traditional medicine (Ovalle-Magallanes et al., 2015; Bahmani et al., 2014) and evidence has shown that the use of plants is a viable alternative for the treatment of diabetes (Vasconcelos et al., 2011). There are large portions of the worldwide population that have no access to commercial medicines which motivate them to use plants as an alternative for the treatment. Moreover, current synthetic agents and insulin used effectively for the treatment of diabetes are scarce especially in rural areas, are expensive, and have prominent adverse effects. Complementary and alternative approaches to diabetes management such as isolation of phytochemicals with anti-hyperglycemic activities from medicinal plants are therefore imperative (Elekofehinti, 2015).

Due to the extensive use of folk medicine for various diseases, there are in the literature many reviews dealing with the use of different plants. For diabetes, Grover et al. (2002) have reported about 800 plants with bioactive compounds. These may act through different mechanisms, including the inhibition or stimulation of enzymatic activity and/or protein expression. Marles and Farnsworth (1995) listed 1200 species that have been used to treat diabetes worldwide, and after twenty years Ovalle-Magallanes et al. (2015) affirmed that there are nearly 3500 species medicinally used in Mexico folk medicine, of which up to 383 species are employed for the treatment of type 2 diabetes mellitus. According to Arumugam et al. (2013), out of an estimated 250000 higher plants, and less than 1% have been screened pharmacologically and very few with regard to diabetes mellitus. Other plants, such as the one studied by Aragão et al. (2010), have also been observed to have hypoglycemic and insulin-release stimulatory effects (Gupta et al., 1984; Twai and Al-Badr, 1998). Trojan-Rodrigues et al. (2012) also cited more than 81 species of the southern Brazil that have hypoglycemic effects, but no mechanisms of action were evaluated. Another review published by Mukherjee et al. (2006) was based on the Indian medicinal plants with hypoglycemic potential showing their bioactive compounds (alkaloids, imidazoline, polysaccharides, flavonoids, saponins and ferulic acid) and some strategies of mechanisms.

For example, plants of the genus *Bauhinia* (Leguminosae) are widely distributed in most tropical countries and have frequently been used in folk medicine to treat several ailments, especially diabetes. Some of them are extensively used such as *B. manca*, *B. rufences*, *B. forficata*, *B. cheitantha* and *B. splendens* as tea in the diabetes treatment (Silva and Filho, 2002; Trojan-Rodrigues et al., 2012). Bahmani et al. (2014) cited some effective herbs for diabetes. Marles and Farnsworth (1995) also cited plants of the Fabaceae, Asteraceae and Lamiaceae families.

All of these plants, cited by the authors, may operate through different mechanisms that effect blood sugar. Some of them may increase the insulin kinase, some of them may inhibit insulinase activity and others may increase reconstruction of pancreatic β cells. For example, according to Aslan et al. (2010), antioxidants (tannins, flavonoids, vitamins C and E, etc.) have been shown to prevent the destruction of β cells by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes. Antidiabetic activity of tannins (epicatechin and catechin derivatives) (Perez et al., 1998), coumarins, flavonoids, terpenoids, arginine and glutamic acid has been confirmed by some studies based on experimental animal models (Marles and Farnsworth, 1995; Ojewole, 2002; Aslan et al., 2010). Moreover, fibers of plants may also interfere in the absorption of carbohydrates and thus have an effect on blood glucose (Bahmani et al., 2014). However, it is difficult to draw any logical conclusion on the mechanism of the hypoglycemic effect of such a diverse mixture of chemical compounds contained in the plant extracts.

There are exceptions, such as plants that have a major active component that is responsible for the treatment of a specific disease. An example is berberine that is the major active component (5.2-7.7%) of *Rhizoma coptidis*, a popular traditional Chinese herb for the treatment of diabetes and inflammation. In 1988, the hypoglycemic effect of berberine was first reported when it was prescribed to treat diarrhoea in diabetic patients. Since then, the component has been used as an anti-diabetic agent in folk medicine in China. It has been widely studied and evidenced in patients and various animal models (Yin et al., 2012).

Due to this, knowledge about medicinal plants could encourage the production of phytotherapeutics from different plants or the isolation of the bioactive molecules with known action mechanism. Although there are already many reviews published involving medicinal plants from many countries, they did not show the action mechanism of the extract against the diseases. The difficulty in understanding the mechanism relies on the fact that there is no homogeneity in the way that the studies with antidiabetic plants are conducted, which complicates the interpretation of the results (Frode and Medeiros, 2008 cited by Trojan-Rodrigues et al., 2012).

Because of this, in the literature there are not many published works dealing with in vivo experiments and mathematical modelling of diabetes with the objective to better understand the effects of the drugs and the teas obtained from the medicinal plants and, moreover, to know the exact bioactive components responsible for the hypoglycemic activities.

In order to compile all the action mechanisms, this review

aims to assemble different published works dealing with hypoglycemic plants, trying to specify the main mechanism to model the diabetes chemical reactions in order to understand the influence of the bioactive compounds and improve the use of natural products as medicines for diabetes.

The study is divided into sections showing the active mechanisms of the extracts, of the bioactive compounds, their effect on glucose, on lipid metabolism, as AMPK activators and on liver morphology.

2. Total Extracts as Hypoglycemic Agents

There are already many studies published involving hypoglycemic plants originating from different parts of the world but in this review only the works where active mechanism explanation was cited are discussed. This highlights the importance of phytochemical and preclinical studies with these plants, identifying the extracts and their potential.

Some of the most important extracts from the plants and their effects are given in Table 1 and are discussed below.

Table 1. Biologically active extracts from plants with anti-diabetes activity.

Extracts	Plants (Scientific names)	Components	Effects	References
Aqueous and methanolic stem barks extract	*Anarcadium occidentale*	Terpenoids, coumarin	Hypoglycemic activities	Ojewole (2003)
Decoction extracts	*Bauhinia divaricata* *Bauhinia forficata* *Bauhinia monandra* *Bauhinia megalandra*	Alkaloids, flavonoids	Improve of carbohydrate metabolism; inhibition of glucose-6-phosphatase	Silva and Filho (2002)
80% aqueous ethanol extract	*Cydonia oblonga* *Helianthus tuberosus* *Alium porrum*	Coumarins, fructans, lectins, tannins, flavonoids, carotenoids, saponnins, fatty acids	Inhibitory effects on kidney tissue; lipid peroxidation level	Aslan *et al*. (2010)
Aqueous extracts	*Anogeissus acuminata* *Catunaregam tormentosa* *Diocrescis erythroclada* *Rauwolfia serpentine* *Mimosa pudica*	Glycosides, Xanthones, Tannins, alkaloids	Free radical scavenging activity; Strong antioxidant activities	Monosroi et al. (2012)
Aqueous extracts	*Octomeles sumatrana*	Vitamins C and E	Increase of Slc2a2 mRNA level and reduction of mRNA levels of G6 phase	Azahar et al. (2012)
Alcoholic extract	*Cassia occidentalis*	Achrosin, emodin, anthraquinones, anthrones, apigenin, cassiolin, campesterol, chrysophanic acid, chrysoriol	Antibacterial, antifungal, antidiabetic, anti-inflammatory, anti-mutagenic and anti-hepatoprotective activities	Lin et al. (2012) and Sharma et al. (2014)

Ojewole (2003) cited that it is difficult to draw any logical conclusion on the mechanism of the hypoglycemic effect due to the fact that the extracts of the majority of the plants contain many chemical compounds present as a diverse group. Specifically, the author evaluated the hypoglycemic effect of stem-bark extracts of cashew in normal and streptozotocin-treated rats. The aqueous and methanolic extracts significantly reduced the mean basal blood glucose concentrations of normal and diabetic rats, but the methanolic one was found to be more pronounced. They concluded that it is difficult to definite biological activities via different mechanisms, but it is possible that the effects may be due, in part, to their terpenoid and coumarin contents. According to the author, the mechanism remains largely speculative and it is unlikely to be due to the stimulation of pancreatic beta-cells and subsequent secretion of insulin. It could be observed that an aqueous or methanolic extract is less potent than insulin as an antidiabetic agent, but as the experimental results indicate that it possesses hypoglycemic activity, this observation lends credence to the popular use of the plant.

Babiaka et al. (2015) also cited that the presence of coumarin scopoletin, along with betulinic acid and acacetin as the three most active components of the ethanol extract of *Artemisia afra*, used in the treatment of diabetes. The same components were found in the acetone fraction of *Senna singueana* stem bark from South Africa, that have demonstrated anti-diabetic effects in a rat model against type-2 diabetes.

In 2002, Silva and Filho made a review of the chemical composition of plants of the *Bauhinia* family, because they are famous to have hypoglycemic effects and a large number of citations. One of the plants studied was *B. divaricata*, whose infusion at 20% reduced glycemia by 39% and the authors attributed this effect to the presence of the alkaloid trigoneline. However there is no application to an animal

model to confirm this. Another famous plant is the *B. forficata* that presents the major number of publications involving hypoglycemic activity. Pepato et al. (1998), cited by Silva and Filho (2002), analysed the plant decoction (150 g/L) and orally administrated the extract to diabetic rats. The animals showed an improvement in the carbohydrate metabolism verified by the lower levels of glycaemia and glycosuria. A hypoglycemic effect, higher than insulin, was observed by the alcoholic extracts (500 mg/Kg) of *B. monandra*, reducing the glycaemic level in mice. The inhibition of glucose-6-phosphatase was observed by the aqueous extract of *B. megalandra* and this effect seemed to be related by the presence of some flavonoids.

Three plants from Turkey were studied by Aslan et al. (2010), *Cydonia oblonga* (CO), *Helianthus tuberosus* (HT) and *Allium porrum* (AP), because of their special composition, like coumarins, fructans, lectins, tannins, flavonoids, carotenoids, saponins and fatty acids. Extracts with 80% aqueous ethanol were administrated to diabetes induced rats and CO and AP extracts resulted in remarkable hypoglycemic effect, reducing the blood glucose concentration although HT extracts increased blood glucose level. Diabetic rats showed a marked increase in lipid peroxidation in kidney, liver and heart tissues compared to the non-diabetic control group. The rats treated with the extracts showed a significant reduction in the level of lipid peroxidation. HT and AP extracts also showed an inhibitory effect on kidney tissue lipid peroxidation level. However, all of the extracts were found inactive for non-protein sulphlydryl groups (GSH) levels on kidney, liver, and heart tissues of diabetic rats. The authors commented that the reason this situation might arise is from the short time of the experiments. It is possible therefore to say that the extracts are insufficient for cellular antioxidant defense but might possess another mechanism of antioxidant action along with antilipidperoxidative activity. Further studies are necessary to determine the exact nature of the active principles and the active mechanism of the plant extracts.

The same lipid peroxidation activity studied by Aslan et al. (2010) was observed by Monosroi et al. (2011) who tested various Thai plants (*Anogeissus acuminata* AA; *Catunaregam tormentosa* CT; *Dioecrescis erythroclada* DE; *Rauwolfia serpentine* RS; *Mimosa pudica* MP). Aqueous extracts of the plants revealed high contents of glycosides, xanthones, tannins and alkaloids. The AA extract showed the highest free radical scavenging activity which was 4 times that of ascorbic acid (control). All of the extracts reduced the blood glucose level compared with the standard drugs used in the experiments, insulin and glibenclamide, although AA caused the following reduction: 78.98%, RS 66.60%, CT 59.00%, DE 55.51% and MP 50.36%. The better performance of AA extract could be explained by the evidence that strong antioxidant activities of some plants may be responsible for many biological properties (Saghizadeh et al., 1996). However the quantity of AA extract used was higher than the other drugs, which emphasizes that the potency and reaction mechanism was lower and different. The AA extract may have aided glucose reduction by improved receptor responsiveness of insulin glucose uptake by the tissue in diabetic mice. It may have mimicked thiazolidiendiones in its reaction mechanism, as observed by other studies (Ojewole, 2006). Ullah et al. (2015) made a review based on the oxidative stress describing the benefit effects of vitamins and other antioxidants in diabetes mellitus, confirming the experimental observations of Aslan et al. (2010) and Monoroi et al. (2011).

Although *Octomeles sumatrana* is a plant commonly used as tonic in Malaysia, Azahar et al. (2012) studied its hypoglycemic effect and its molecular mechanisms administering the aqueous extract in diabetic induced mice. Treatment with the extract caused a significant increase in the expression of Slc2a2 mRNA level (essential for glucose secretion) at doses of 0.3 and 0.5 g/Kg, compared to diabetic rats in the control sample. mRNA levels of G6Pase was significantly reduced in extract treated groups at doses of 0.3 and 0.5 g/Kg by 53 and 63%, respectively, compared to the diabetic untreated group. As the insulin level was not measured in this work, the authors made some hypothetical suggestions that the plasma glucose lowering effect in the absence of plasma insulin concentration suggests that the plant extract may involve an insulin independent mechanism.

Lin et al. (2012) and Sharma et al. (2014) studied the hypoglycemic potential of alcoholic root extract of *Cassia occidentalis*, a common weed from South India, Burma and Sri Lanka. It is known to possess antibacterial, antifungal, antidiabetic, anti-inflammatory, anti-mutagenic and hepatoprotective activity. A wide range of chemical compounds have been isolated from this plant (Yadav et al., 2010). The results showed that the animals treated with the extract of the plant have increased their body weight compared to diabetic control and recovered the body weight significantly toward normal level which may be due to the lipid lowering activity of the extract. Moreover, the extracts showed hypoglycemic activity because the total β-cell mass reflects the balance between the renewal and loss of these cells. Because of this, the decrease in blood glucose level may be due to potentiation of insulin effect either by increase in pancreatic secretion of insulin from beta cells or by increase in peripheral glucose uptake.

Among all of the plants cited by many authors, *Malmea depressa* is widely used in southeast Mexico and was studied by Andrade-Cetto et al. (2008). They identified 2

phenylbutane derivatives and 1 phenylpropane derivative, but they did not prove the effect of these substances, only the effects of the butanolic extracts of the plant. Although the oral administration of the extract to rats led to a reduction in the blood glucose and triglyceride levels and increased the plasma insulin levels compared to the control group and to the group administrated by a synthetic drug, there is no suggestion about the mechanism action of the extract. Research like this is common in the literature, showing some evidence of hypoglycemic activity, but not explaining the probable chemical reactions that cause the effects. Another example is the work of Vargas et al. (2010) on abajeru (*Chrysobalanus icaco*) extracts obtained using supercritical fluid at different conditions of temperature and pressure. The authors did not prove the effect of the extracts because there were no experimental models, but the composition of the extracts (sterols, vitamins, triterpenes and flavones) revealed why the plant is widely used in folk medicine as a tea to treat diabetics.

3. Bioactive Compounds Affecting Glucose and Lipid Metabolism

Table 2. The most biologically active natural compounds with proven anti-diabetes activity.

Plants (Scientific names)	Natural compounds class	Effects	References
Camelia sinensis	catechins	Inhibition of lipid peroxidation Inhibition of intestinal glucose uptake Improve of beta cell function and stimulation of insulin secretion Increased expression level of GLUT4 transporter	Sabu et al. (2002) Kobayashi et al. (2000) Tang et al. (2013)
Penthorum chinense	polyphenols	Regulation of insulin secretion and DPPH free radical scavenging ability	Huang et al. (2015)
Stevia rebaudiana Bertoni	polyphenols Vitamin C and E	Antioxidant and antidiabetic properties / increase the number of beta cells Synergic effects that reduce the production of reactive oxygen species	Shivanna et al. (2013)
Acacia Arabica, Gentiana olivieri, Biophytum sensitivum, Caelsalpinia bonducella, Catharanthus roseus, Ficus bengalensis, Ceropia obtusifolia	Chlorogenic acid Isoorientin	Potent antioxidant activity Stimulation of pancreatic beta cell to release insulin	Andrade-Cetto and Heirich (2005) Andrade-Cetto and Wiedenfeld (2000) Revilla-Monsalve et al. (2007)
Plants (Scientific names)	Natural compounds class	Effects	References
Cecropia pachystachya	Chlorogenic acid	Inhibitor of the glucose-6-phosphate translocase component	Schwab et al. (2001)
Anarcadium occidentale	Stigmast-4-en-3-ol and stigmast-4-en-3-one	Hypoglycemic effect	Alexander-Lindo et al. (2004)
Anoda cristata	flavonoids	Inhibitory activity against α-glycosidade	Juarez-Reyes et al. (2015)
Morus multicaulis Perr.	Deoxynojirimycin polysaccharide	Increase the conversion of glucose-6-phosphatase in glycogen Restore the damaged pancreas to normalcy	Li et al. (2015)
Astragalus membranaceus *Discorea polygonoids* *Trigonella foenumgraecum*	saponins	Enhancement of antioxidant activity Increase of expression of Glut4	Elekofehinti (2015)
Swietenia humilis Swietenia macrophylla	limonoids	Activation of glycogen synthesis Triglycerides reduction in blood	Ovalle-Magallanes et al. (2015) Dwanjee et al. (2009)

The previous section mentioned works which evaluated the behaviour of the total extract of the plant. This section shows the compounds found in the extracts that are reported to be responsible for hypoglycemic effects. Many studies can be found involving flavonoids, polyphenols, polysaccharides, limonoids and saponins as the major important components that have direct relationship with the reduced glucose level in the blood.

Although there is a list of natural anti-diabetes possible drugs, citing all natural antidiabetic plants and their components is out of the scope of this paper. So, we have summarized in Table 2 only the most biologically active metabolites with proven anti-diabetes activity.

3.1. Catechins

Various polyphenols were found in different plants such as the catechins (for example, gallocatechin, epigallocatechin, epicatechin, epigallocatechin gallate and epicatechin gallate) present in many different teas. In 2002, Sabu et al. studied the effect of the polyphenols present in the aqueous extract of *Camellia sinensis* in diabetic mice induced by alloxan. They

concluded that an aqueous solution of green tea polyphenols was found to inhibit lipid peroxidation because the glutathione content in the liver of the rats increased and consequently reduced glucose level in the rats was observed. The same behaviour was demonstrated by Gomes et al. (1995) who had studied the anti-hyperglycemic effect of black tea. Kobayashi et al. (2000) showed that epigallocatechin gallate was found to inhibit intestinal glucose uptake by a sodium dependent glucose transporter.

Other green (GTE) and black (BTE) tea extracts were also studied by Tang et al. (2013), because of their anti-diabetic activities applied to an animal model and the mechanisms were explored by a homeostatic model assessment (HOMA). They used five weeks old mice and the tests were conducted for 12 weeks. Generally, both BTE and GTE were highly effective in lowering blood glucose to levels of the normal group. Moreover, insulin resistance (IR) and β cell function (B%) were evaluated using the HOMA model based on the assumption that the relationship between glucose and insulin in the basal state reflects the balance between hepatic glucose output and insulin secretion. From the results, IR increased in the diabetic group, and GTE could supress the increase but BTE could not. β cell function was significantly elevated by BTE treatment and was raised to three times higher than the diabetic group. For the group treated with GTE, it was also higher but not significantly different.

GTE and BTE exerted their hypoglycemic effects by different mechanisms and according to the authors the difference in the composition of the two teas accounts for the discrepancy in their mechanistic pathway. GTE could decrease IR while for BTE was mainly through stimulating insulin secretion and maintaining β cell function. This can be explained by the presence of catechins in the chemical analysis, which is 71.5% in GTE, while in BTE only 15.3%.

Also, pancreatic sections of diabetic mice fed with BTE showed regeneration of β cells. Thus, the authors concluded that the BTE helps in regeneration of a damaged pancreas and protects pancreatic β cells by its antioxidant action against nitrosative stress. BTE has been found to quench reactive oxygen species such as singlet oxygen, superoxide and hydroxyl radicals, which may explain its hypoglycemic activity.

Wu et al. (2004), cited by Tang et al. (2013) concluded that the alleviation of IR by GTE is associated with the increased expression level of GLUT4 transporter in a fructose-fed rat model and similar results were found in a dog model (Serisier et al., 2008 cited by Tang et al., 2013).

3.2. Chlorogenic Acid

Another polyphenol with hypoglycemic effect is chlorogenic acid, whose effect was tested by Ivorra et al. (1989), and demonstrated in diabetic rats. It is identified as an inhibitor of the glucose-6-phosphate translocase component, and this behaviour results in a reduction of hepatic glucose production (Schwab et al., 2001). According to the authors, flavonoids and other polyphenols are also able to act as antioxidants as they have the ability to scavenge free radicals. Other evidence of the chlorogenic acid effect was observed by Aragão et al. (2010) who studied a plant from Central and South America and widely used in Brazil, *Cecropia pachystachya*. In alloxan-induced diabetic rats, the methanolic extract caused a significant effect reducing the glycemic levels after 12 hours with a blood glucose reduction of 68%. The same extract had no effect on blood glucose in normal rats. As alloxan causes a reduction in insulin release by the destruction of the β-cells, inducing hyperglycemia, the authors suggested that the action of the extract is an extrapancreatic mechanism. However there were no insulin measurements.

Chlorogenic acid was also cited by Andrade-Cetto and Heirich (2005) who presented a review of Mexican plants with hypoglycemic effect, showing the main bioactive compounds. The possible mechanism of action was attributed to the presence of chlorogenic acid and also isoorientin. The second molecule was isolated by Andrade-Cetto and Wiedenfeld (2000). The hypoglycemic effect of the plant would have been caused by the liver not providing glucose due to the action of the acid during the fasting of the animals. In relation to the isoorientin, Deliorman-Orhan et al. (2003), cited by Andrade-Cetto and Heinrich (2005), tested the hepatoprotective activity of *Gentiana olivieri* and concluded that the effect might possibly be due to the potent antioxidant activity of the compound. Among all the plants presented in the study, seven of them stimulate pancreatic beta cells to release insulin (*Acacia arabica*, *Aloe vera*, *Biophytum sensitivum*, *Caelsalpinia bonducella*, *Catharanthus roseus*, *Ficus bengalensis* L., *Hibiscus rosa* sinensis). Moreover, Revilla-Monsalve et al. (2007) tested the hypoglycemic effect of *Ceropia obtusifolia* Bertol and concluded that isoorientin and chlorogenic acid were also responsible for the main effects.

3.3. Saponins

Saponins were well studied by Elekofehinti (2015) who published a review showing various saponins and their origin as significant effects on glucose metabolism. Astragaloside, present in *Astragalus membranaceus*, inhibits hepatic glucogen phosphorylase and glucose 6 phosphatase activities and expression of their genes and improves insulin resistance. Diosgenin, present in two different plants, *Discorea polygonoids* and *Trigonella foenum-graecum*, has

two different effects on glucose metabolism. When it is present in the first plant, it increases pyruvate kinase activity and inhibits glucose 6 phosphatase activity, but when it is present in the extract of the second plant, it decreases insulin resistance and inhibits carbohydrate digestion/absorption. *Terminalia arjuna* contains in its extract arjunolic acid, which inhibits α-amylase and α-glucosidade activity. Platyconic acid, present in *Platycodi radix*, enhances insulin sensitivity, increases glucogen accumulation and increases Glut4 translocation into membranes.

In general, the hypoglycemic action of saponins is through restoration of insulin response, improvement in insulin signalling, increased plasma insulin levels and induction of insulin release from the pancreas, inhibition of disaccharide activity, activation of glycogen synthesis, inhibition of gluconeogenesis, inhibition of α-glucosidase activity, inhibition of mRNA expression of glycogen phosphorylase and glucose 6 phosphatase and the increase of expression of Glut4. Moreover, as saponins contain in its structure many -OH groups, they are responsible for enhancement of antioxidant activity and this property is responsible for the prevention of reactive oxygen species formation in diabetes. This is important because many works have shown a direct consequence of hyperglycemia in diabetes (Elekofehinti; Li & Gong, 2015).

3.4. Other Polyphenols

Three polyphenols can be isolated from *Penthorum chinense*, a plant widely distributed in eastern Asia, such as China, Japan, Korea, and eastern Russia (Huang et al., 2015). The extracts were administrated to diabetic rats in order to compare with a control. All of the results referring to α-amylase inhibition and blood glucose levels were better than the control. A dose of 300 mg/Kg of the extract was sufficient to decrease the blood glucose from the first week to the second in comparison to the diabetic control animals. Moreover, a significant increase of insulin was observed after the administration of the extract, suggesting that the regulation of insulin secretion might be one of the factors responsible for the anti-diabetic activity of the plant. Two of the polyphenols showed a remarkable DPPH free radical scavenging ability which also indicates the anti-diabetic activity of the extract due to the anti-oxidative stress effect (Nimse & Pal, 2015).

Other polyphenols and compounds such as dicaffeoylquinic acid, chlorogenic acid, quercetin 3-O-xyloside, apigenin-7-O-glucoside, 3,4-dimethoxycinnamic acid, luteolin 7-O-rutinoside, caffeic acid were isolated from a plant called *Stevia rebaudiana* Bertoni, extensively used in diabetes treatment. Due to this Shivanna et al. (2013) studied the potential of the ethanol extract in relation to the antioxidant and antidiabetic properties. Wheeler et al. (2008) found two other polyphenols in the same plant, rebaudioside A and stevioside, present in leaf extract and the hypoglycemic effect was attributed to them. However, these components were not present in the Shivanna's et al. (2013) study. Although peroxidation was reduced significantly in rats fed with stevia leaves powder and polyphenols compared to diabetic group, it reduced the elevated levels of blood glucose by 36.64% compared to the untreated diabetic control.

The mechanism involved in the lowering of blood glucose levels by stevia could be due to modulation of glucose transport, or glucose disposal, or better insulin secretion. The results of the study showed an increase in the serum insulin level in the stevia and polyphenols extract groups. Perhaps stevia could enhance the number of beta cells of pancreatic islets in diabetic treated rats. The increase in insulin levels suggested that stevia would enhance the secretion of insulin from beta cells.

Other compounds like vitamin E and vitamin C have been demonstrated to be antioxidants that scavenge the free radicals generated in cell membranes. According to other authors cited by Shivanna et al. (2013), the synergic effects between these two vitamins are particularly efficient for reducing production of reactive oxygen species. As cited by the author, tissue antioxidant concentrations such as vitamin E decreased due to its mobilization to blood in control diabetic rats.

3.5. Flavonoids

Flavonoids have proved to be potential antidiabetic agents by Pereira et al. (2011) because they exert multiple actions that are both hypoglycemic (insulinomimetic action) and antihyperglycemic (insulin secretagogue). Despite this, flavonoid action is dependent on the number, type, and position of glycosyl residues on the natural compounds. The actions of kaempferitrin and kaempferol-3-neohesperidoside were shown, providing strong evidence of stabilizing glucose homeostasis in diabetic rats. Quercetin and rutin actions were also investigated. Quercetin activates hexokinase and glucokinase and inhibits both glycogen phosphorylase and hepatic glucose-6-phosphatase. Shimizu et al. (2000) demonstrated a marked reduction in glucose absorption, after in vivo treatment by oral gavage. According to Pereira et al. (2011), other works reported that the inhibitory effect of quercetin on glucose absorption is due to the competitive inhibition of the sodium-dependent glucose transporter. Among the properties of rutin, an increase in insulin and C-peptide serum levels is reported providing a protective effect on pancreatic β-cells, restoration of glycogen content and hexokinase activity, and decreased glucose-6-phosphatase and fructose-1, 6-biphosphatase activities.

Two flavonoids (acacetin and diosmetin) were isolated from an infusion of the plant *Anoda cristata* from Juarez-Reyes et al. (2015). The results demonstrated that the extracts and compounds were effective for reducing blood glucose levels, causing significant hypoglycemic effect and possess antioxidant capacity. This can be attributed to acacetin and its glycosides that exhibited also significant inhibitory activity against α-glycosidases which reduces the impact of carbohydrates on blood sugar. Babiaka et al. (2015) also observed with tests in vivo that flavonoids inhibit the carbohydrate hydrolysing enzyme α-glucosidase, confirming their hypoglycemic activities.

Different components were extracted from mulberry leaves by Li et al. (2015), deoxynojirimycin (DNJ) and polysaccharide (P), to show their anti-hyperglycemic effect. They tested the components alone, but the results indicated that better results were obtained with a combination. The components were administrated in diabetic rats and the results were compared to a control group. The mixture decreased blood glucose after oral administration to diabetic mice for 90 d. The same treatment resulted in remarkable up-regulation of the expression of the glycolysis enzymes (glucokinase, phosphofructokinase and pyruvate kinase) that were measured in the liver. Also, mice treated with the mixture presented significant reduction in pyruvate carboxylase, fructose-1, 6-biphosphatase and phosphoenolpyruvate carboxykinase levels, such as glucose-6-phosphatase. This suggests that glucose-6-phosphatase is converted to glycogen, which results in attenuation of hepatic glucose outputs with the mixture treatment.

Moreover, the decrease in blood glucose may be due to increased insulin secretion and peripheral glucose metabolism. To verify this hypothesis, the authors measured protein levels in pancreas and insulin resistance in tissues of the liver and muscle. As upregulation in protein level was observed and blood insulin concentrations were increased, they concluded that the mixture is able to restore the damaged pancreas to normalcy and DNJ increases β-cell proliferation.

3.6. Other Components

In addition to the common compounds already cited with hypoglycemic effect, there are two different classes known as limonoids and saponins that have been proved to be effective in hypoglycemic applications. Ovalle-Magallanes et al. (2015) isolated eight limonoids of the mexicanolide type from the hexane extract of *Swietenia humilis* to be evaluated in relation to their hypoglycemic and antihyperglycemic effects. The daily administration of the extract (100 mg/Kg) to rats during a week provoked a significant hypoglycemic effect, reducing serum triglycerides and uric acid without any changes in insulin levels suggesting that the mechanism involved an insulin sensitizing. An increase on glycogen content was also observed and a reduction in the abdominal fat in the rats. The reduction in blood triglycerides is compatible with an increase in glucose uptake in adipose tissue. The opposite behaviour was mentioned by De et al. (2011), who reported the effect of the oral administration of methanol extract of *S. mahagoni*, over 21 days, where it lowered the glycogen levels in diabetic rats. Dewanjee et al. (2009) also cited the effect of another limonoid, swietenine (25 and 50 mg/Kg), isolated from *S. macrophylla*, that showed a moderate hypoglycemic action in a diabetic rat model.

It is important to notice that the compounds could act synergistically on different molecular targets to produce antidiabetic and hypolipidemic effects. Moreover, a mixture with other components present in the extract of the plant could enhance the bioavailability of one or several compounds in the extract, thus improving their pharmacological action. This is why some mechanisms were difficult to prove and are absent in the literature. Better understanding of the effects of the compounds can promote their use as natural products with the prospects of an increase in the quality of life of people suffering from diabetes.

Flavones, sterols and terpenes are also important compounds for the hypoglycemic effect (Silva and Filho, 2002). Alexander-Lindo et al. (2004) isolated two compounds from the hexane extract of the bark of *Anarcadium occidentale* (cashew), stigmast-4-en-3-ol and stigmast-4-en-3-one. Both compounds produced significant hypoglycemic activity after intravenous administration at a dose of 1.3 mg/Kg body weight of dogs. Also, the intravenous administration of the hexane extract to normal healthy dogs produced a significant lowering of the blood glucose levels. The bark of the cashew plant exhibited a hypoglycemic effect probably due to the presence of these compounds.

4. Bioactive Compounds Activates AMP-Activated Protein Kinase (AMPK)

One of the most important mechanisms to stimulate insulin secretion is AMPK activation. This is known because AMPK is a key energy-sensing/signalling system in the cells and acts as a fuel gauge by monitoring cellular energy levels (Yin et al., 2012). It is so important because the activation of AMPK is well known to increase insulin sensitivity and regulate mitochondrial function (Kahn et al., 2005).

Barnes et al. (2004) have reported that AMPK plays a key role in regulating carbohydrate and fat metabolism, serving

as a metabolic master switch in response to alterations in cellular energy charge. Yin et al. (2012) also reported that one of the mechanisms found in hypoglycemic activity components is AMP-activated protein kinase (AMPK) activation.

There are few results that relate the AMPK activation to specific bioactive components. Catechins and berberine were investigated and their biological effect was proved. Tang et al. (2013) also concluded that GTE and BTE, because of the catechins present in GTE and theaflavins present in BTE, significantly attenuated the high glucose-induced insulin, reduced lipid accumulation, supressed fatty acid synthesis and stimulated fatty acid oxidation through the AMPK pathway in cultured cells (Murase et al., 2009).

The presence of catechins was also evaluated by Vasconcelos et al. (2011) in the bark extract of *Caesalpinia ferrea* Martius and the molecular mechanisms that exert hypoglycemic action. The first mechanism is Akt activation that acts on glycogen synthase. Moreover Daisy et al. (2010) have shown that animals treated with catechins isolated from another plant (*Cassia fistula*) exhibited increased expression of GLUT4 even in the absence of regeneration of pancreatic β cells.

Beyond all the active mechanisms of catechins, they still have a hepatoprotective effect against the increase of hepatic up take of amino acids. This behaviour was also cited by Tsuchiya et al. (2001) who proved that catechins improve the permeability of the hepatocyte membrane. Another mechanism, also cited by Zhou et al. (2001), is the reduced activation of AMPK and the increased activation of acetyl-CoA carboxylase (ACC), which allow the oxidation of fatty acids in the skeletal muscle and in the liver of extract treated animals which suggests a restoration of the energy balance. This is explained by the low levels of total cholesterol, triglycerides and epididymal adipose tissue mass found in extract treated animals.

Moreover, Babiaka et al. (2015) cited that epicatechin has some ability to lower glucose levels.

Recently berberine was cited as a hypoglycemic compound due to its effect in the inhibition of mitochondrial function by stimulation of glycolysis and activation of AMPK pathway. It is able to lower blood insulin level via enhancing insulin sensitivity. However, in patients with poor β cell function, berberine may improve insulin secretion via resuscitating exhausted islets. It is said that it has many extra beneficial effects like cholesterol-lowering, as well as anti-arrhythmic and nitric oxide inducing properties (Yin et al., 2012).

5. Effect of Bioactive Components in Liver

Although the liver plays a central role in glucose metabolism, there are only two reported results showing the positive behaviour of the bioactive compounds on liver morphology.

Tang et al. (2013) evaluated the liver morphology and compared the hypoglycemic effects of GTE and BTE for diabetic and normal mice. Liver histology revealed many accumulated lipid droplets in the cytoplasm of hepatocytes in diabetic mice, but very few in the control ones. GTE and BTE treatments ameliorated the damage to hepatocytes to different degrees. Their microphotograph of the liver from diabetic mice treated with GTE resembles a normal liver, probably due to the presence of catechins. The results from BTE improved from the diabetic group, however there were still considerable number of lipid droplets in the liver.

Li et al. (2015) also evaluated the influence of the bioactive compounds in the liver and in hepatic cells. When observed under a microscope, normal hepatic cells have an irregular polygonal shape and form clusters adhering to the liver plate wall. The treatment with DNJ and P separately did not affect cell morphology. The cells incubated with streptozotocin significantly decreased in number and exhibit pathological changes such as a dark appearance and black spots. Treatment with the mixture of DNJ and P restored the shape and structural integrity of the damaged cells, confirming all of the works mentioned above that concluded that the main mechanism is the increase in the number of beta cells.

6. Conclusions

In summary, a considerable number of plants are traditionally used for the treatment of diabetes. Many of the mechanisms of the bioactive compounds are not known and therefore the use of natural products as drugs is still difficult.

According to this review, it could be possible to find promising candidates for the treatment of diabetes mellitus that could be achieved through evaluation of the anti-diabetic properties of different extracts of the medicinal plants, their fractions and the isolated compounds.

Alkaloids, saponins, vitamins, polyphenols, flavonoids, and limonoids could be isolated from the plant extracts and, based on this review, are promising oral hypoglycemic agents. The mechanism for regulating blood glucose and lipids has been presented and various animal models were presented. The major mechanisms are related to the activation of the AMPK pathway, insulin secretion and increase of number of beta cells of pancreatic islets (Figure 1). A more detailed explanation of the mechanisms for each

bioactive compound is summarized in Figure 2. It is possible to observe that the main effects are the stimulation of insulin secretion and protective effect or regeneration of β-cell function.

The knowledge of the main active mechanisms of the bioactive compounds present in hypoglycemic plants will allow representation of chemical reactions that occurred in diabetic and non-diabetic patients through mathematical modelling. The models will help with the prediction of the behaviour of bioactive compounds reducing the need for experimental animal models.

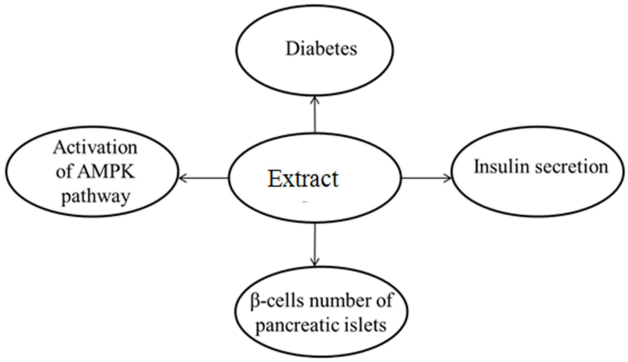

Figure 1. Therapeutic effects of the extracts present in hypoglycemic plants.

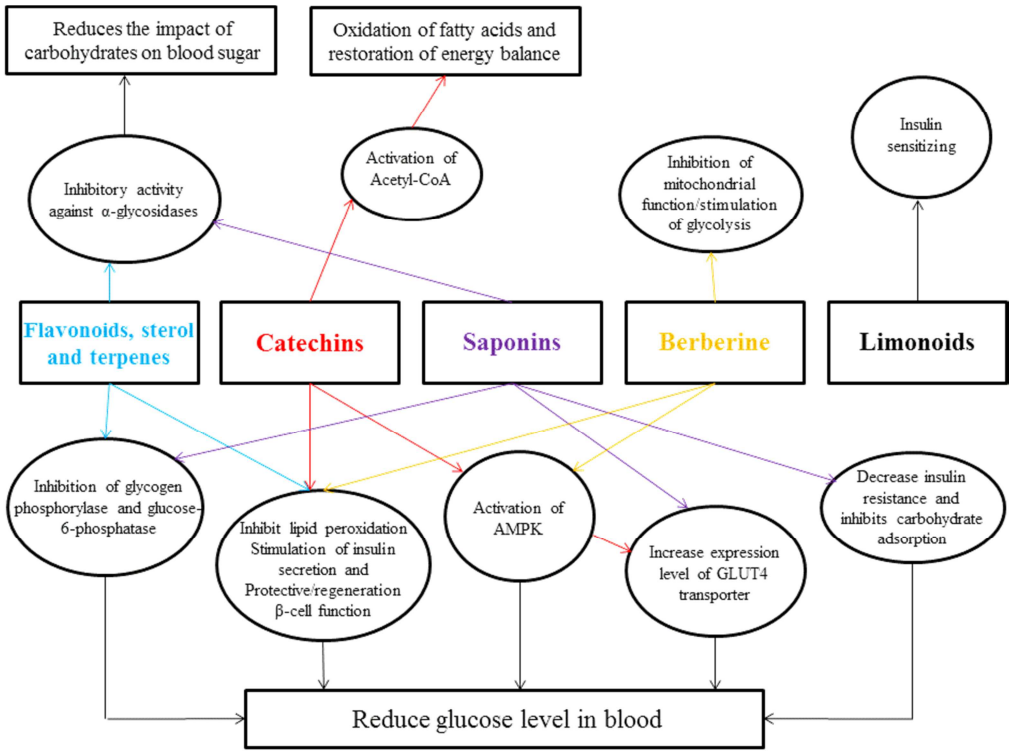

Figure 2. Possible active mechanisms of the bioactive compounds present in the medicinal plants.

The identification of the mechanisms together with the bioactive components stimulate further investigations using mathematical modelling. Bioactive components that are responsible for the hypoglycemic effects can further develop modern anti-diabetic drugs.

If we are able to ascertain the active mechanism of bioactive compounds present in hypoglycemic plants we can develop mathematical models to aid system understanding and help predict medical effects.

Acknowledgments

To CNPq, for the financial support.

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