Pharmacogn. Mag.
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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ORIGINAL ARTICLE

Influence of Flavonoids on Mechanism of Modulation of Insulin Secretion

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Submitted: 07-03-2017 Revised: 31-07-2017 Published: 13-11-2017

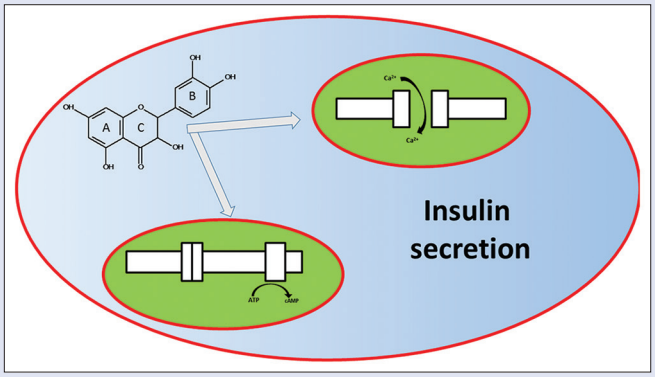
ABSTRACT

Background: The development of alternatives for insulin secretion control *in vivo* or *in vitro* represents an important aspect to be investigated. In this direction, natural products have been progressively explored with this aim. In particular, flavonoids are potential candidates to act as insulin secretagogue. **Objective:** To study the influence of flavonoid on overall modulation mechanisms of insulin secretion. **Methods:** The research was conducted in the following databases and platforms: PubMed, Scopus, ISI Web of Knowledge, SciELO, LILACS, and ScienceDirect, and the MeSH terms used for the search were flavonoids, flavones, islets of Langerhans, and insulin-secreting cells. **Results:** Twelve articles were included and represent the basis of discussion on mechanisms of insulin secretion of flavonoids. Papers in ISI Web of Knowledge were in number of 1, Scopus 44, PubMed 264, ScienceDirect 511, and no papers from LILACS and SciELO databases. **Conclusion:** According to the literature, the majority of flavonoid subclasses can modulate insulin secretion through several pathways, in an indication that corresponding molecule is a potential candidate for active materials to be applied in the treatment of diabetes.

Key words: Diabetes, flavones, flavonoids, insulin, insulin-secreting cells, islets of Langerhans

SUMMARY

- The action of natural products on insulin secretion represents an important investigation topic due to their importance in the diabetes control
- In addition to their typical antioxidant properties, flavonoids contribute to the insulin secretion
- The modulation of insulin secretion is induced by flavonoids according to different mechanisms.



Abbreviations used: K_{ATP} channels: ATP-sensitive K^+ channels, GLUT4: Glucose transporter 4, ERK1/2: Extracellular signal-regulated protein kinases 1 and 2, L-VDCCs: L-type voltage-dependent Ca^{+2} channels, GLUT1: Glucose transporter 1, AMPK: Adenosine monophosphate-activated protein kinase, PTP1B: Protein tyrosine phosphatase 1B, GLUT2: Glucose transporter 2, cAMP: Cyclic adenosine monophosphate, PKA: Protein kinase A, PTK: Protein tyrosine kinase, CaMK II: Ca^{2+}/calmodulin-dependent protein kinase II, GSIS: Glucose-stimulated insulin secretion, Insig-1: Insulin-induced gene 1, IRS-2: Insulin receptor substrate 2, PDX-1: Pancreatic and duodenal homeobox 1, SREBP-1c: Sterol regulatory element binding protein-1c, DMC: Dihydroxy-6′-methoxy-3′,5′-dimethylchalcone, GLP-1: Glucagon-like peptide-1, GLP-1R: Glucagon-like peptide 1 receptor.

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DOI: 10.4103/pm.pm_87_17

Access this article online
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INTRODUCTION

Insulin is produced in β-cells being considered as a key metabolic hormone[1] and essential for maintaining glucose homeostasis. Insulin circulates in the blood and acts at skeletal myocytes and adipocytes to facilitate glucose uptake through membrane insertion of the insulin-sensitive glucose transporter 4 (GLUT4), stimulating fuel storage in liver, fat, and skeletal muscle.[2]

Insulin secretion is extremely sensitive to changes in blood glucose.[3] The stimulus for insulin secretion by glucose takes place with increase in the intracellular ATP levels. In the intracellular medium, the increase of ATP levels leads to closure of ATP-sensitive K^+ channels (K_{ATP}) resulting in the membrane depolarization capable of opening the voltage-dependent Ca^{2+} channels, which promote influx of extracellular Ca^{2+}, inducing insulin secretion.[4-7]

Cite this article as: Dias Soares JM, Pereira Leal AE, Silva JC, Almeida JR, de Oliveira HP. Influence of flavonoids on mechanism of modulation of insulin secretion. Phcog Mag 2017;13:639-46.

The glucose is the most potent stimulator of insulin secretion and can achieve acute and long-term regulation of insulin secretion.[8] However, other nutrients also are capable of triggering insulin release or amplify glucose-stimulated insulin secretions (GSISs)[9] such as hormones,[10] proteins,[11,12] and pharmacological agents.[13]

In recent years, different therapeutic strategies to increasing or improving insulin secretion *in vivo* or *in vitro* by the use of natural products have been explored. Scheen reported that new insulin secretagogues should offer advantages over sulfonylureas in the near feature.[14] Most of the plants contain substances that have antidiabetic effect and insulin secretagogue as plant extracts, functional foods,[15-18] and some isolated as triterpenes and derivatives,[19,20] phytosterols,[21,22] stilbene,[23] and iridoid glycoside[24] have shown activity which stimulates or potentiates insulin secretion in pancreatic islets.

Flavonoids represent a class of phenolic compounds (benzopyran heterocycle linked to a benzene ring) divided into subclasses based on the degree of oxidation of the C4 position, hydroxylation pattern, and substitution of the C3 position.[25] The basic flavonoid skeleton offers numerous substituents that can subdivide into major subclasses as flavonols, flavones, flavan-3-ols, anthocyanidins, flavanones, and isoflavones and into smaller subclasses as dihydroflavonols, flavan-3,4-diols, coumarins, chalcones, dihydrochalcones, and aurones.[26]

Studies indicate several benefits of flavonoids due to their antioxidant properties.[27-29] Furthermore, the plant extracts and/or its fractions containing flavonoids can act on insulin secretagogue.[30] Thus, in this review, we focus on findings related to the insulin secretion due to the flavonoids action, highlighting the mechanism of modulation of insulin secretion.

METHODS

Search strategy and databases

The internet bibliographic search on flavonoids and their insulin secretion mechanisms was conducted in 2016. The following databases and platforms were consulted: PubMed, Scopus, ISI Web of Knowledge, SciELO, LILACS, and ScienceDirect on April 8, 2016. The MeSH terms used for the search were flavonoids, flavones, islets of Langerhans, and insulin-secreting cells. Different combinations of these keywords were used. This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA statement).[31]

Selection of papers

Complete articles were included in the review by observing the following inclusion criteria: studies that show the mechanism of insulin secretion of isolated flavonoids. Studies were excluded according to the following exclusion criteria: studies which reported the insulin secretion mechanism of the extracts or fractions containing flavonoids or their metabolites and/or derivatives, studies that no explain the mechanism of insulin secretion, and those articles related to review articles, meta-analysis, abstracts, conference proceedings, editorials/letters, and others.

Discrepancies on the study inclusion/exclusion were decided with the reach of a consensus. All electronic search titles, selected abstracts, and full-text articles were reviewed by a minimum of two reviewers.

Data extraction

Data were extracted employing standardized forms. Extracted information included data regarding type of flavonoid, doses, concentration or quantity utilized, animal used, parameters assessed, and results and mechanisms of action of insulin secretion.

RESULTS

Corresponding literature was in the order of 820 productions/scientific papers, including original articles, reviews, and book chapters. Papers in ISI Web of Knowledge were in number of 1, Scopus 44, PubMed 264, ScienceDirect 511, and no papers from LILACS and SciELO databases.

Reviews, book chapters, and posters were excluded, and it was performed after a screening for relevant titles and full papers and also removed all repeated. Twelve articles met the inclusion and exclusion criteria established. All of the checked steps and article description are described in the following flow chart [Figure 1].

From these documents, it was observed the increasing interest in the application of flavonoids to treatment of diabetes. The development of new medications from natural compounds offers potential for the management of diabetes through therapies with products of natural sources solely or by association with synthetic drugs, which can avoid the side effects of antidiabetic drugs, such as insulin and oral hypoglycemic agents.[32,33]

In general, flavonoids or its fractions have shown that their hypoglycemic activities are due to the inhibition of glucose transport, upregulatory

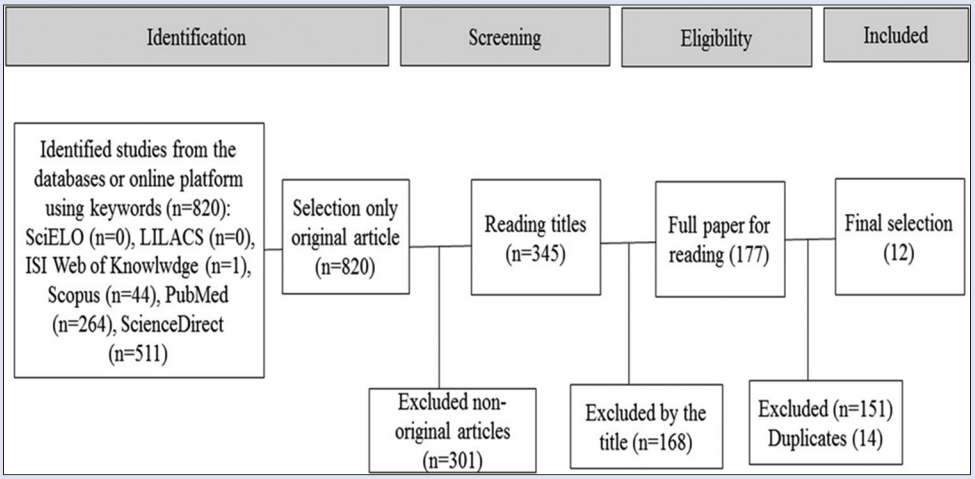

Figure 1: Flowchart of the selection of the articles included

activities of glucose uptake, improved GSIS, and/or restoration of insulin secretion capacity;[34] besides that, it plays a protective role on osmotic fragility of cells, resembling the insulin. Table 1 summarizes the insulin secretion mechanism described by the papers included in this study.

DISCUSSION

All of the types of flavonoids have an important antioxidant activity, which explain some of its beneficial effects. They can exhibit antiviral,[47-49]

Table 1: Insulin secretion mechanism of flavonoids

Authors, year, country	Flavonoids	Doses, concentration, or quantity	*In vitro* or *in vivo* model	Mechanisms
Hii and Howell, 1985, England[35]	Epicatechin and quercetin	0.01 and 0.8 mmol/L 0.01 mmol and 0.1 mmol/L	Islets from male Wistar rats	Epicatechin and quercetin act by alterations in Ca^{2+} fluxes
Ohno *et al.*, 1993, Japan[36]	Genistein	1, 5, 10, 20, 50 μg/mL	MIN6 cells	Genistein acts through calcium influx extracellular and elevation the concentration of cAMP
Liu *et al.*, 2006, USA[37]	Genistein	0.01, 0.1, 1, 5, 10 and 100 μM	INS-1, mouse MIN6 cells and isolated mouse islets	Genistein stimulates intracellular cAMP accumulation and activates PKA via PTK independent and estrogen receptor independent
Lee *et al.*, 2009, Korea[38]	Genistein	1 μM, 5 μM, 25 μM, 50 μM, 100 μM, e200 μM	INS-1 rat insulinoma cells and Sprague-Dawley (SD) islet cells	Genistein acts by stimulation of ATP-generating nutrients mainly leucine/glutamine and its effect potential effect on insulin secretion resulted from the activation of CaMK II. Besides, PKA and PKC activation was not involved in potentiation effect
Fu and Liu, 2009, USA[39]	Genistein	1, 5, 10 μM	INS-1E cells, mouse islets were isolated from male C57BL/6J mice and human islets	Genistein enhances GSIS in long-term activity and on cAMP/PKA-mediated one with elevation in the intracellular Ca^{2+} concentration and new protein synthesis. Moreover, the effect of genistein on insulin secretion is not due to a modulation of insulin synthesis or an adverse effect on the cells, not mediated through modification in glucose metabolism or K_{ATP} channel activity and PTK independent.
Youl *et al.*, 2010, France[40]	Quercetin	0.2, 2, 20, 200 μmol/L	INS-1 cells and rat pancreatic islets	Quercetin might act through an increase in basal (Ca^{2+}_i) and subsequent ERK1/2 activation
Zhang and Liu, 2011, China[41]	Kaempferol	0.01, 0.1, 1 and 10 μM	INS-1E beta-cells or human islets	Kaempferol might improve ATP generation in beta-cells and provide increase in the transcriptional activation of insulin mediated by cAMP signaling
Bardy *et al.*, 2013, France[42]	Quercetin	2 to 20 mmol/L	INS-1 cells and rat isolated pancreatic islets	Quercetin promotes the entry of extracellular Ca^{2+} rather than to the mobilization of intracellular Ca^{2+} from the endoplasmic reticulum activating of L-type Ca^{2+} channels
Kappel *et al.*, 2013, Brazil[43]	Rutin	50 mg/kg (0.04 M)	Male Wistar rats and islets isolated	Rutin increase the insulin secretion by modulates Ca^{+2} uptake in pancreatic islets by opening L-VDCC, PLC, and PKC signaling pathways, characterizing K_{ATP} channel-independent pathways
Chen *et al.*, 2014[44]	Silibinin	30 μM	Rat insulinoma INS-1 cells	Silibinin may upregulate expression of Insig-1, IRS-2, PDX-1 and insulin mRNA and downregulate SREBP-1c transcription and thus increase insulin secretion
Hu *et al.*, 2014, China[45]	2′,4′-Dihydroxy-6′-methoxy-3′,5′-dime thylchalcone (DMC)	2 and 20 μM	RIN-5F cells derived from rat pancreatic β-cells	DMC may mimic GLP-1 to enhance the expression of GLP-1R mediating PDX-1 translocation and to promote the expression of GLUT2 and GCK
Balamurugan *et al.*, 2015, India[46]	2R, 3R taxifolin 3-O-rhamnoside	50 mg/kg	Male Wistar rats	2R, 3R taxifolin 3-O-rhamnoside acts through closure of K_{ATP} channels and the opening of cell-surface Ca^{2+} channels signaling pathway

cAMP: Cyclic adenosine monophosphate; K_{ATP}: ATP-sensitive K^+ channels; GCK: GLUT2 and glucokinase; GLUT2: Glucose transporter 2; PDX-1: Pancreatic and duodenal homeobox 1; GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide 1 receptor; SREBP-1c: Sterol regulatory element binding protein-1c; IRS-2: Insulin receptor substrate 2; L-VDCCs: L-type voltage-dependent Ca^{+2} channels; PLC: Phospholipase C; PKC: Protein kinase C; *ERK1/2*: Extracellular signal-regulated protein kinases 1 and 2; GSIS: Glucose-stimulated insulin secretion; ATP: Adenosine triphosphate

anti-inflammatory,[50-53] anticancer,[54-56] and hypoglycemic activity,[57-62] among others.[63,64] Thus, to better comment on the major classes of flavonoids and corresponding characteristics, we discuss the insulin secretion mechanism by subgroups of flavonoids.

Flavonol

The flavonols comprise one of the major groups of flavonoids. Usually, flavonols are found in woody angiosperms.[65] The main flavonols are most commonly found as O-glycosides.[26] Different disposition of phenolic OH groups on 3 hydroxyflavone molecule can be explored for production of new compounds.

Quercetin is the most abundant of the flavonol. It is found in a variety of food and medicinal botanicals.[66,67] Studies reported that quercetin can improve glucose uptake in peripheral insulin,[68] providing reduction in the blood glucose level of diabetic rats to normal values, which is attributed to its ability to regenerate pancreatic β-cells and to increase insulin release.[69] Furthermore, quercetin may be considered as a partially useful supplement for the treatment of diabetic depression.[70] However, the oral bioavailability of quercetin is poor which hinders wide applications,[71] which are directed to the determination of improved bioavailability from the incorporation in nanomaterials.[72,73]

Kaempferol is a flavonol present in a variety of plants and fruits showing several antioxidants effects. Kaempferol may act as α-glucosidase inhibitor,[74] improving the insulin resistance[75] and glucose homeostasis.[76] Concerning rutin, it is chemically a flavonol glycoside compound of quercetin and disaccharide rutinose that present multiple pharmacological activities.[77] Rutin showed antidiabetic activity.[78-81]

In terms of insulin secretion mechanisms (described in the literature), until now, there are five studies describing such modulation mechanisms of insulin secretion by flavonol. Reports that used the flavonol quercetin involve the modulation of Ca^{+2}, either through influx or increase basal or by intracellular mobilization from the endoplasmic reticulum activating of L-type Ca^{2+} channels.[35,40,42] The rutin has a similar activity in comparison with calcium uptake in pancreatic islets through L-type voltage-dependent Ca^{+2} channels (L-VDCCs).[43] Kaempferol might improve ATP generation in β-cells and provide an increase in the transcriptional activation of insulin mediated by cyclic adenosine monophosphate (cAMP) signaling.[41] These processes are integrated by Ca^{2+} signals in the insulin granule exocytosis.[82]

The increased level of Ca^{2+} stimulates processes to trigger many different cellular pathways[83] and into β-cells since calcium is crucial to insulin secretion. Thus, the flavonols may directly or indirectly act on the calcium modulation and thus can be an alternative to available hypoglycemic drugs. However, more studies are necessary to validate the bioavailability and adverse effects of these flavonols.

Flavan-3-ol

Catechin is a phytonutrient member of flavan family such as epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate, and epigallocatechin-3-gallate.[84] Studies indicate that flavan-3-ol can exert both inhibitory activities[85,86] as stimulus for insulin secretion.[87] EC is found in large amounts in grape pomace[88] and has been considered a strong antioxidant. Typical mechanism of insulin secretion was described in 1985 by Hii and Howell, who showed that EC and quercetin (as above) may act by alterations in Ca^{2+} fluxes to enhance insulin secretion.[35] Indeed, the increase in intracellular calcium concentration promotes the insulin secretion.

Isoflavones

Isoflavone aglycones are two aromatic rings linked by a heterocyclic pyrane ring. They are present mainly in plants of *Leguminosae* family and generally found in soybeans, red clover, and kudzu root in highest concentrations.[89] The main isoflavones in soybean are genistein and daidzein.

Genistein is a phytoestrogen characterized by a wide variety of health benefits,[90] considered a pluripotent and promising therapeutic agent to diabetes, with activity in inhibition of glucose uptake in mature adipocyte, enhancement in the GSIS, improvement in insulin resistance state, and reduction in the reactive oxygen species-induced β cell damage.[91]

El-Kordya EA, Alshahrani AM recently reported that genistein has a protective effect on pancreatic β-cells damage, and in high dosage, it possesses the ability to regenerate β-cells and consequently improves serum levels and decreases high serum glucose in diabetic rats.[92] Furthermore, the study of Lee *et al.* showed that genistein derivatives stimulates glucose uptake and the mechanism can be established by adenosine monophosphate-activated protein kinase activation, GLUT4 and GLUT1 expressions, and protein tyrosine phosphatase 1B inhibition.[93]

Until now, a few studies described the corresponding mechanism, in which genistein is able to improve or increase insulin secretion. In 1993, Ohno *et al.* demonstrated that genistein increases insulin secretion in a dose-dependent manner up to 20 μg/mL and this should be through calcium influx extracellular and elevation the concentration of cAMP.[36] Liu *et al.* showed that genistein stimulates insulin secretion in a dose of 0.01–5 μM stimulating intracellular cAMP accumulation, which subsequently activates protein kinase A (PKA) via protein tyrosine kinase (PTK) independent and estrogen receptor independent.[37]

In 2009, Lee *et al.* reported that the concentration of 50 μM of genistein exhibit improved effect on insulin secretion stimulated by ATP-generating nutrients mainly leucine/glutamine activating of Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) and PKA and PKC independent.[38] Fu and Liu showed that genistein at 5 μM has the maximal increase in the insulin secretion in long-term acting in the cAMP/PKA and the elevation of intracellular Ca^{2+} concentration is independent on K_{ATP} channel activity and PTK.[39]

Based on this information, genistein has the potential to improve and increase insulin secretion by increasing the calcium concentration into intracellular medium which characterizes the primary signal in the regulation of insulin secretion and cAMP, an important molecule that acts as a type of cellular secondary messenger. When activated, the cAMP exerts a regulatory effect in multiple peripheral tissues, enhances insulin sensitivity, stimulates glucose uptake, and promotes gene expression.[94,95] It might also generate ATP into cells and activate CaMK II. CaMKII participates in GSIS in several steps of this process, such as the modulation of cytoplasmic content of ATP and the synthesis of insulin granules.[96] Furthermore, all possible mechanisms are independent of PKC.

Flavonolignans

Flavonolignan has in its composition a portion of flavonoid and other of lignan. Silibinin is the major pharmacologically active compound of Silymarin, an isomeric mixture from the *Silybum marianum* that containing at least six flavonolignans.[97-100] Extracts and flavonoids from *S. marianum* have been reported in the literature as hypoglycemiant and applied for pancreas recovery for diabetics.[101,102] This activity can be associated to Silibinin. According to Chen *et al.*, Silibinin protects β-cells from glucotoxicity and can improve GSIS and upregulate expression of insulin-induced gene 1 (Insig-1), insulin receptor substrate 2 (IRS-2), pancreatic and duodenal homeobox 1 (PDX-1), and insulin mRNA and downregulate sterol regulatory element binding protein-1c (SREBP-1c) transcription.[44]

PDX-1 is involved in the regulation factor in the cascade regulating insulin secretion, regulating the transcription of insulin and other insulin secretion-related genes,[103] IRS-2 mediates effects of insulin and insulin-like growth factor 1, and Insig-1 negatively regulates SREBPs. Therefore, this transcription factors and genes contribute to insulin secretion, as well as some studies have showed.[104-106]

Chalcone

Chalcones are aromatic ketone with two phenyl rings that are precursors of flavonoids and isoflavonoids and exert several of biological and pharmacological activities.[107,108] Generally, natural chalcones occur as petal pigments and have been found in the heartwood, bark, leaf, fruit, and root.[109] Different studies have showed that chalcones present antihyperglycemic properties, while chalcone with iodine substitution showed great potential in reducing glucose medium concentration,[110] increasing insulin secretion,[111] and increasing glucose uptake.[112]

In a study published Hu *et al.*, it was reported that 2',4'-dihydroxy-6'-methoxy-3',5'-dimethyl chalcone may increase insulin secretion under the condition of elevated glucose by mimicking glucagon-like peptide-1 (GLP-1) to enhance the expression of glucagon-like peptide 1 receptor (GLP-1R)-mediated PDX-1 translocation and to promote the expression of GLUT2 and glucokinase (GCK).[45] GLP-1 promotes insulin secretion, maintains a blood sugar balance, and improves pancreatic islet cell function.[113,114] Besides, it has been used as alternative to conventional hypoglycemic agents and insulin injectable therapies since it has a lower risk of causing hypoglycemia[115] because the GLP-1 has alternative mechanisms may act as negative feedback pathway for insulin secretion, activating the K_{ATP} channels through phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-dependent pathway.[10]

The different mechanisms of activity of GLP-1 are regulated by the GLP-1R. The GLP-1R induces in the cytosol PKA activity that regulates the insulin gene transcription factor of pancreatic duodenal homeobox-1 (PDX-1) by increasing its expression and its nuclear translocation[116,117] and this activation leads to insulin secretion. On the other hand, the 2',6'-dihydroxy-4'-methoxy-3',5'-dimethyl chalcone might stimulate the secretion of insulin by increasing the GLUT2 and GCK. The GLUT 2 facilitates transport of glucose and thus initiates the GSIS by the uptake of glucose.[118] After, glucose is then phosphorylated by glucokinase and further metabolized through the glycolytic route. Thereby, this process increases the production of ATP into the cell that increases calcium influx and leads to insulin secretion.

Flavanone

Flavanones are flavonoids that have generally a disaccharide glycosylated at position seven. This derivative is characterized by a wide variety of biological activities[119] with antihyperglycemic activity.[120-122] However, there are few reports on flavanone with antidiabetic activity. In 2015, Balamurugan *et al.* isolated an flavanone: 2R, 3R taxifolin 3-O-rhamnosid, and tested its action as insulin secretagogue, which showed action through closure of K_{ATP} channels and the opening of cell surface Ca^{2+} channels signaling pathway.[46] This mechanism is similar to the mechanism of sulfonylureas.[123] Thus, further studies are needed to confirm effective and low side effects that sulfonylureas to be a more effective alternative.

CONCLUSIONS

Emerging evidence indicates that flavonoids can be an alternative in the treatment diabetes. Insulin secretagogues' effects may be due to different mechanisms. Flavonoids can modulate insulin secretion through alterations in Ca^{2+} fluxes by L-type Ca^{2+} channels or L-VDCCs or by others mechanisms, intracellular cAMP accumulation, sometimes PKA-mediated, activation of CaMK II, or by the transcription factors or its products (genes), as PDX-1, GLP-1, IRS-2, Insig-1, and so on. The subclasses flavonol and isoflavones show the better activities of modulation and evidence that can be promising to treatment of diabetes. Despite of these findings, more studies are needed to prove the long-term effects of flavonoids in insulin secretion and to ensure its applicability in diabetic patients.

Financial support and sponsorship

This work was supported by Brazilian Funding Agency FACEPE, CAPES, FINEP, CNPq, and FAPESB.

Conflicts of interest

There are no conflicts of interest.

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