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Antidiabetic effect of Tryptophan, Nuciferin, and isoquercetin in Lotus rhizome

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ABSTRACT: The antidiabetic property of *Nelumbo nucifera* rhizome, a medicinal food used to manage diabetes mellitus in Sri Lankan, a native medicine has not been scientifically explained yet. The lotus rhizome is found to compose several medicinally active compounds with anti-diabetic properties, including Betulinic acid, Tryptophan, Nuciferin, isoquercetin, Rutin, β- Sitosterol, Stigmasterol, and Fibre. A narrator review was conducted to identify the scientific basis of the antidiabetic property with the explanation of the molecular level mechanisms of glucose homeostasis of these medicinally active components. This article reviews the bio-physiological mechanisms of glucose homeostasis by Tryptophan, Nuciferin, and isoquercetin. A literature search was done in PubMed and Google Scholar databases using different combinations of the search terms "Nelumbo nucifera rhizome", "Lotus rhizome", "phytochemicals", "antidiabetic effect", "hypoglycaemic effect", "Tryptophan", "Nuciferin", "isoquercetin" and "molecular mechanism". Tryptophan is found to reduce blood glucose levels via five identified mechanisms, namely, inhibiting intestinal glucose absorption, inhibiting liver gluconeogenesis, improving insulin resistance, increasing insulin secretion in the pancreas, and enhancing glucose uptake in adipocytes. Nuciferin can improve blood glucose by stimulating the closure of Adenosine Triphosphate dependent potassium (K-ATP) channels and triggering insulin release. Isoquercetin can inhibit α-glucosidase in the small intestine and regulate the expression of mRNA which codes insulin resulting in increased insulin release. This review explains to the medical practitioners of various medical practices the scientific basis of the antidiabetic effect of lotus rhizome allowing them to utilize it as a medicinal food for the benefit of diabetic patients under their care.

Keywords: *Nelumbo nucifera* root; Medicinal food; Bioactive compounds; Hypoglycemic effect; Molecular mechanism

1. INTRODUCTION

Nelumbo nucifera rhizome has been used as a medicinal food for many communicable and non-communicable diseases in Sri Lankan traditional medical system(Samarakoon, 2019),(Weragoda, 1980). Especially, the native Sri Lankan medical practice 'Deshiya Chikithsa', has been successfully using the medicinal effect of lotus rhizome for the management of Diabetes mellitus since very far in its history. Consumption of healthy food with medicinal properties in the routine diet is very important for the smooth management of diabetes mellitus (Katulanda *et al.*, 2008),(Illangasekera, Nugegoda, and Perera, 1993). Even though the Sri Lankan native medicine explains the medicinal property of many foods for many noncommunicable diseases including diabetes mellitus, the lack of scientific evidence for them has restricted Western medical

practitioners from using this native medical knowledge in managing patients under Western medical care. This review is planned to compose a comprehensive document explaining the scientific basis of the antidiabetic effect of nelumbo nucifera rhizome, utilizing the scattered scientific knowledge in PubMed and google scholar databases.

2. MATERIALS AND METHODS

The methodological approach for this narrative review on the antidiabetic effect of medicinally active components in lotus rhizome was conducted using google scholar and PubMed databases on the articles published until 30th September 2022. Initial search terms were "Nelumbo nucifera rhizome" AND "phytochemicals" AND "antidiabetic effect", "Nelumbo nucifera rhizome" AND "phytochemicals" AND "hypoglycaemic effect", "Lotus rhizome" AND "phytochemicals" AND "antidiabetic effect", "Lotus rhizome" AND "phytochemicals" AND "hypoglycaemic effect". After the initial scrutiny, with each identified medicinally active compound another search was conducted to identify the bio-physiological mechanisms of the antidiabetic effect. For this article, the three functional components - Tryptophan, Nuciferin, and isoquercetin - were separately searched, combined with the key terms "hypoglycaemic effect" AND "molecular mechanism", "antidiabetic effect" AND "molecular mechanism". The reference list of each selected article was searched to ensure the inclusion of all important articles and all the relevant full-text articles in the English language were studied for this narrative review. Only the google scholar database was searched for identifying the articles to describe the molecular-level mechanisms of insulin secretion using the search term "molecular mechanism of insulin secretion". Only the first two relevant full texts in the English language were referred to this.3. Results

Lotus rhizome is found to have nine bioactive compounds with an antidiabetic effect namely, Betulinic acid, Tryptophan, Nuciferin, isoquercetin, Rutin, β- Sitosterol, Stigmasterol, Neferin, and Fibre. This article discusses only the bio-physiological mechanisms of the hypoglycaemic activity of Tryptophan, Nuciferin, and isoquercetin. Tryptophan and its metabolites are found to reduce blood glucose levels via five identified mechanisms, namely, inhibiting intestinal glucose absorption, inhibiting liver gluconeogenesis by suppressing phosphoenolpyruvate formation by holding back the phosphoenolpyruvate carboxykinase, improving insulin resistance, increasing insulin secretion in the pancreas and enhancing glucose uptake in adipocytes. Nuciferin can improve blood glucose by stimulating the closure of K-ATP channels and triggering insulin release. Isoquercetin can reduce intestinal glucose absorption by inhibiting the α-glucosidase enzyme while it is also found to regulate the expression of mRNA which codes insulin resulting in an increased insulin release. For a comprehensive understanding of these mechanisms, it is mandatory to have a deep knowledge of the molecular mechanism of insulin biosynthesis in the β cells of the pancreas and the following chapter discusses it describing the relevant stimulatory and inhibitory effects of the three studied medicinally active compounds - Tryptophan, Nuciferin, and isoquercetin.

4. Discussion

4.1. Tryptophan

Scientific studies have shown that a low-carbohydrate diet with high protein content improves blood glycemia and is useful in the management of type 2 diabetes mellitus (Figure 1). Several combinations of amino acids have been studied on this. Isoleucine and serine combination is found to improve insulin sensitivity while L-glutamine, threonine, and glycine are delivering a combination effect to decrease the maximal responsiveness of insulin in the glucose transport system of adipocytes. The most important amino acid, L-tryptophan is shown to deliver the glucose homeostasis effect directly and via its metabolites through several bio-physiological mechanisms(Inubushi *et al.*, 2012a)·(Goodarzi *et al.*, 2021).

4.1.1. Tryptophan inhibits gut glucose absorption

Tryptophan can reduce the intestinal absorption of dietary glucose resulting in a reduction of post-prandial blood glucose levels (Inubushi et al., 2012b). One described mechanism is by modulating gut motility and delaying gastric emptying (Hajishafiee et al., 2021)

4.1.2. Tryptophan is effective in upregulating liver gluconeogenesis

Tryptophan is found to inhibit liver gluconeogenesis by suppressing phosphoenolpyruvate formation by holding back the phosphoenolpyruvate carboxykinase which is a key regulatory enzyme in phosphoenolpyruvate synthesis (Inubushi et al., 2012a), (Pogson, Crisp and Smith, 1975).

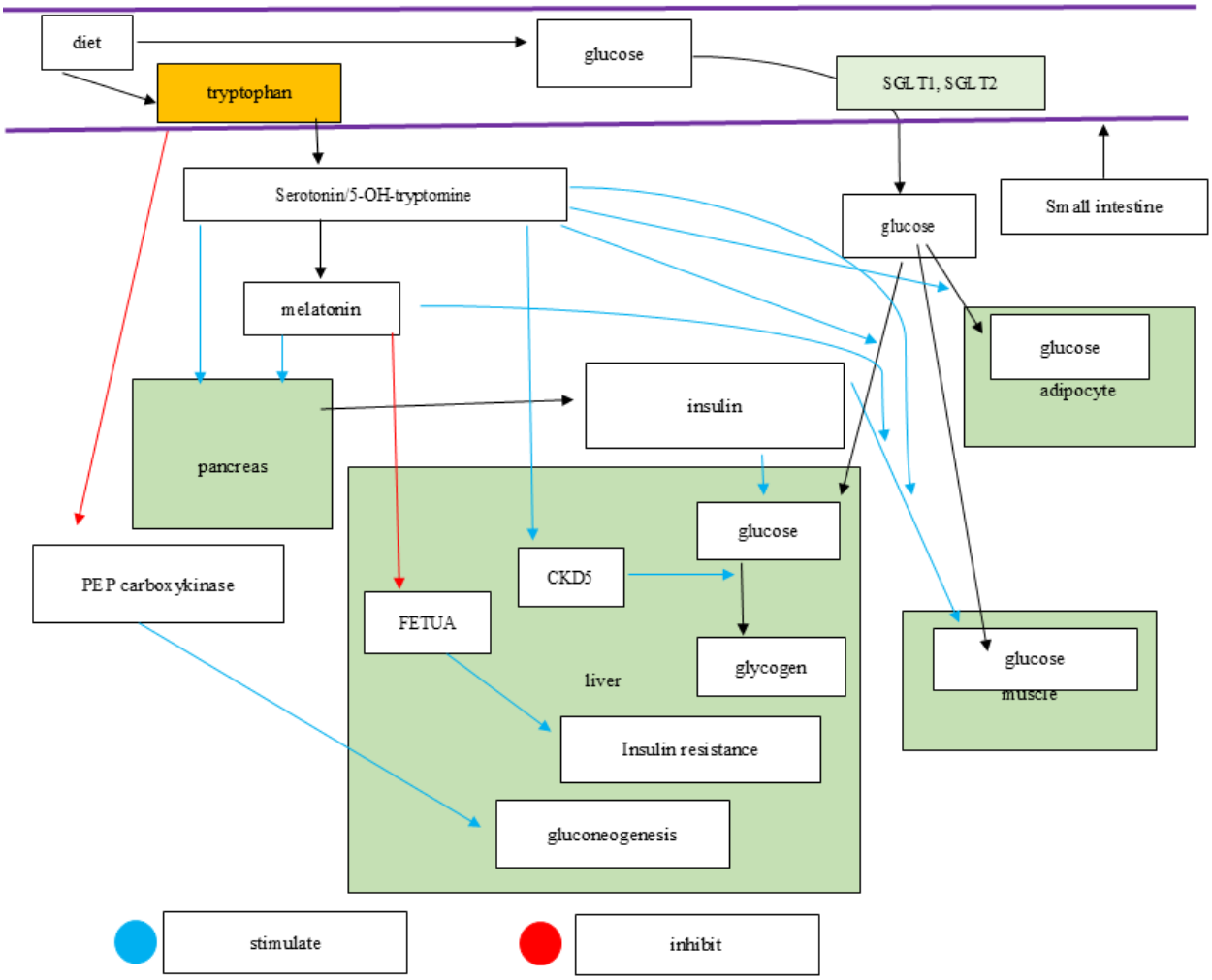

Figure 1. Tryptophan in blood glucose regulation. FETUA, fetuin-A; CKD5, cyclin-dependent kinase 5; PEP, phosphoenolpyruvate; SGLT1, Sodium-Glucose Cotransporters 1; SGLT2 Sodium-Glucose Cotransporters 2

4.1.3. Serotonin is effective in insulin secretion

Tryptophan is converted to serotonin which is found in the gastrointestinal mucosal cells, platelets, and central nervous system while serotonin becomes the precursor for melatonin, the hormone that regulates the sleep-wake cycle. Tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase (5-HTP-decarboxylase) convert tryptophan to serotonin (5-hydroxy tryptamine / 5HT) in two steps while serotonin N transferase and hydroxy indole O-methyl transferase produce melatonin from serotonin (Inubushi et al., 2012a). 5-HT is found to stimulate insulin secretion from the beta cells of the pancreas, further strengthening its antidiabetic effect and modulating glucose uptake into skeletal muscles (Goodarzi et al., 2021), (Robinson, 2009).

4.1.4. Melatonin improves insulin resistance and insulin secretion in the pancreas

Insulin resistance is known to be associated with the hepatokine, fetuin-A (FETUA), a protein coded by the α2-HS-glycoprotein gene. Melatonin is found to improve insulin resistance by downregulating FETUA in the liver (Heo et al., 2018). The stimulatory effect of melatonin on pancreatic beta cells further enhances its anti-diabetic property by increasing insulin secretion from pancreatic beta cells (Inubushi et al., 2012a), (Heo et al., 2018).

4.1.5. Serotonin enhances glucose uptake in adipocytes

5-hydroxy tryptamine (serotonin) is found to increase insulin-mediated glucose uptake in adipocytes and the liver, enhancing hepatic glycogen synthesis. It increases glycogen

synthesis by stimulating cyclin-dependent kinase 5 (CDK 5). The effective level of tryptamine is dependent on the dietary availability of tryptophan. Therefore, a tryptophan-rich diet increases blood tryptamine levels under physiological conditions resulting in improving glucose homeostasis (Inubushi et al., 2012a), (Goodarzi et al., 2021).

4. 2. Nuciferin

Nuciferin is found to deliver its antidiabetic effect by stimulating insulin release by the pancreatic beta cells (Figure 2).

4.2.1. Molecular mechanism of insulin biosynthesis in the β cells of the pancreas

Insulin which is synthesized in the pancreatic beta cells is transcribed from mRNA as a single polypeptide precursor, proinsulin, which is composed of a B chain with an amino-terminal, a chain with a carboxy-terminal and a connecting peptide called C peptide. Within the endoplasmic reticulum, it is undergone several endopeptidase reactions, and mature insulin is formed with two separate peptides, peptide A and B. Mature insulin molecule and peptide C are packed in secretary vesicles and transported to the cytoplasm (Eliasson *et al.*, 2008).

When the plasma glucose concentration is increased after meals, they enter into the beta cells via the GLUT2 transporter increasing the intracellular metabolism of glucose in the beta cells. This leads to an increase in the ATP/ADP ratio in the beta cells resulting in an increased closure of ATP-sensitive potassium channels (K-ATP channels) that causes beta cell membrane depolarization and opening of the voltage-sensitive membrane calcium channels. With the opening of these channels, calcium enters the cytoplasm and triggers the insulin-containing vesicles to express insulin to the plasma. In addition to this, the K-ATP independent pathway of insulin release, mediated by cyclic adenosine monophosphate (cAMP) and diacylglycerol has been explained (Bataille, 2002). Nuciferin is found to stimulate the closure of K-ATP channels and trigger insulin release (Nguyen *et al.*, 2012). (Figure 2).

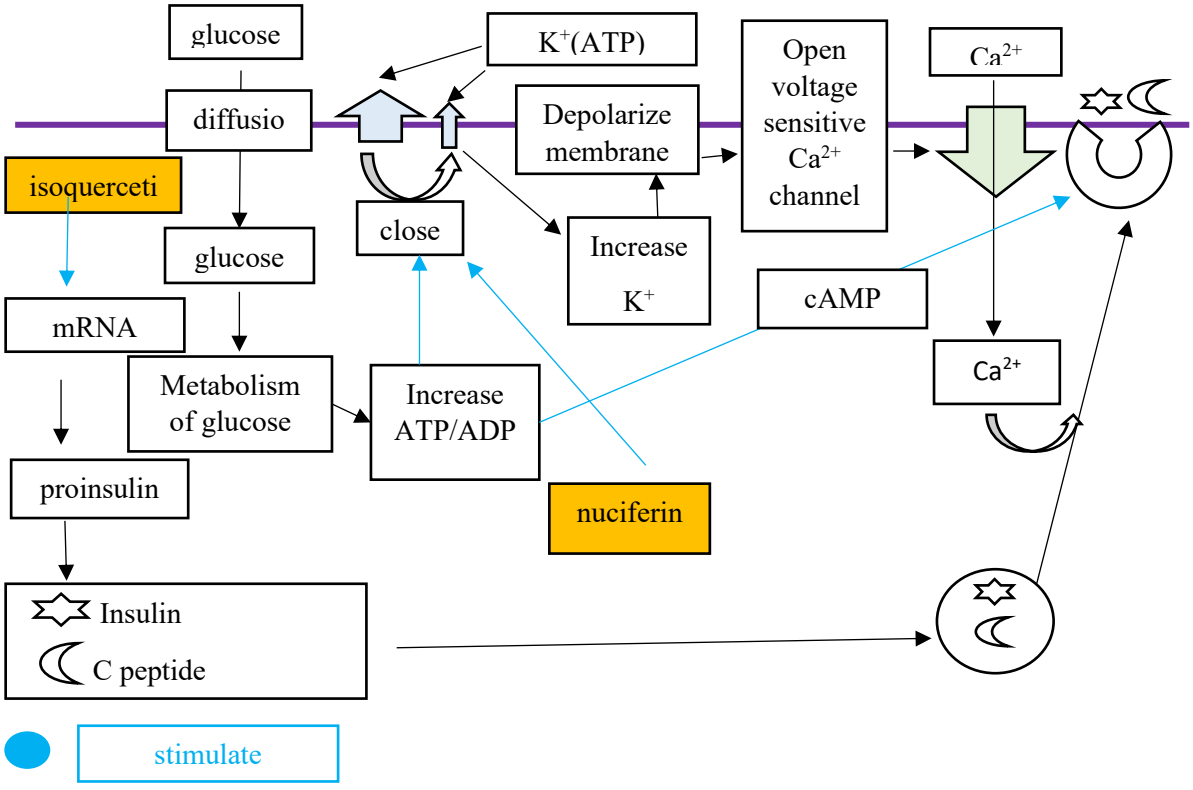

Figure 2. Nuciferine and Isoquercetin in the regulation of insulin biosynthesis in the β cells of the pancreas. K+(ATP), Adenosine triphosphate-sensitive potassium channel; ATP, Adenosine triphosphate ADP, Adenosine diphosphate; cAMP, Cyclic adenosine monophosphate

4.3. Isoquercetin

Isoquercetin is a flavonoid and contained in nelumbo nucifera rhizome in good quantity. Isoquercetin is found to inhibit α-glucosidase which is a key regulatory enzyme of glucose absorption in the small intestine, resulting in a reduction of carbohydrate digestion and absorption, lowering the post-prandial blood glycemia (Zhang *et al.*, 2011). This is also believed to regulate the insulin signaling pathway, but the exact molecular pathway is not clearly understood yet. However, studies show that the introduction of isoquercetin regulated the expression of mRNA which codes insulin and carbohydrate metabolizing enzyme α-glucosidase (Jayachandran *et al.*, 2018). (Figure 3).

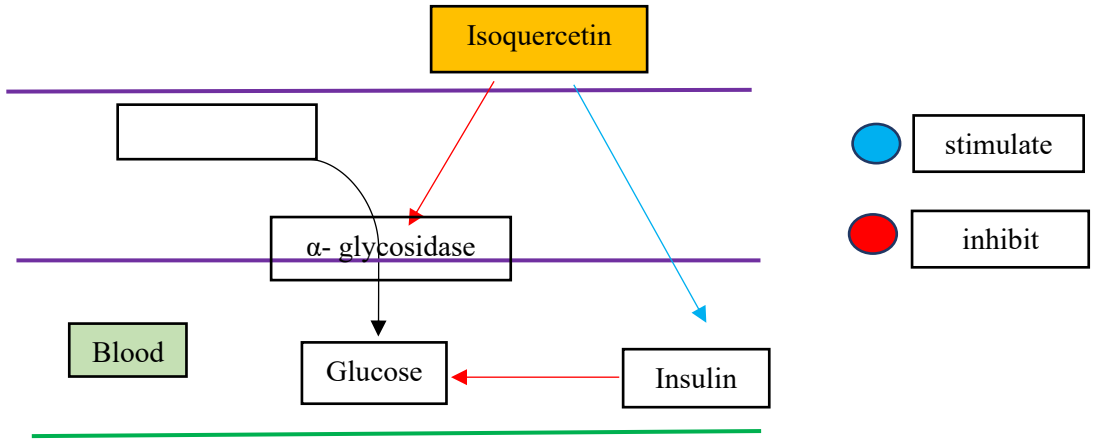

Figure 3. Isoquercetin in the regulation of intestinal glucose absorption

5. CONCLUSIONS/FUTURE DIRECTIONS

Nelumbo nucifera rhizome is composed of many bioactive components with antidiabetic effects namely, Betulinic acid, Tryptophan, Nuciferin, Isoquercetin, Rutin, β- Sitosterol, Stigmasterol, Neferin, and Fibre. Of these components, Tryptophan, Nuciferin, and isoquercetin exert their antidiabetic effect via many molecular-level mechanisms including inhibiting gut glucose absorption by reducing gut motility, inhibiting liver gluconeogenesis, stimulating insulin secretion from the beta cells of the pancreas, improving insulin resistance, enhancing hepatic glycogen synthesis, stimulating the closure of K-ATP channels and triggering insulin release and, reducing gut glucose absorption by inhibiting α-glucosidase. Composing a single document with the existing scattered scientific knowledge on the antidiabetic effect of lotus rhizome allows the medical practitioners of various medical practices to understand the scientific basis of the medicinal value of lotus rhizome for diabetes mellitus and to conduct clinical trials to prove it scientifically. Even though the knowledge of the antidiabetic property of Nelumbo nucifera rhizome is originally gained from Sri Lankan native medicine, as the current scientific knowledge can explain its antidiabetic property with scientific evidence, even the Western medical practitioners can use this knowledge for the management of diabetic patients under their care.

List of abbreviations

K-ATP: Potassium- Adenosine Triphosphate
mRNA: messenger Ribonucleic acid
5-HTP: *5-hydroxytryptophan*
5HT: 5-hydroxy tryptamine
FETUA: fetuin-A
CDK 5: cyclin-dependent kinase 5
GLUT2: Glucose transporter type 2
ADP: Adenosine diphosphate
cAMP: Cyclic adenosine monophosphate

Author Contributions: Damean De Silva, the principal investigator, conceptualized and designed the study, led the data collection, conducted the data analysis and interpretation prepared the draft of the manuscript, and reviewed the manuscript. Upul Senarath advised the data analysis and interpretation and reviewed the manuscript. Pathirage Kamal Perera advised the data analysis and interpretation and reviewed the manuscript.

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