The Mechanism of Natural Active Substances in Chicory for Treating Diabetes

Peigeng Song *

College of Environmental and Safety Engineering, Shenyang University of Chemical Technology, Shenyang, China, 110142

* Corresponding Author Email: 2319020314@stu.syuct.edu.cn

Abstract. Diabetes mellitus is a prevalent and frequent chronic metabolic disease characterized by hyperglycemia. While conventional drugs are available, their use is limited due to side effects. Natural products of medicinal plants are gradually recognized by countries all over the world because of their good curative effect and small side effects. The aims of this article are to discuss the hypoglycemic effects of chicory's natural active substances and their mechanisms in diabetes treatment. The results show that natural active substances in chicory exhibit significant hypoglycemic effects. Chicory natural active substances can play a certain hypoglycemic role in diabetes through different ways. The results of data analysis indicate that that the existence of natural active substances in chicory includes three mechanisms of action: promoting insulin secretion, affecting insulin signaling pathway and promoting glucose uptake and other anti-diabetic activities. This article can provide insights for further pharmacological research on chicory's natural active substances in diabetes treatment.

Keywords: Chicory Acid, Hypoglycemic, Diabetes, Insulin, Mechanism Analysis.

1. Introduction

Diabetes shows the serious threat to human health, which is one of the main causes of premature death, blindness, kidney failure, cardiovascular and cerebrovascular accidents and disability, and is closely related to cancer and cognitive dysfunction, posing a serious threat to national health [1]. There are more than 100 million people with diabetes in China, and the incidence of diabetes is trending younger. The cause of diabetes is related to many factors, such as genetics, diet, exercise, aging and environment. Its slow development is not easy to detect and difficult to cure after onset, which has become a major global public health problem. At present, the treatment of diabetes is mainly divided into two types, including drugs therapy and non-drugs therapy. The medication is still a very common and effective form of treatment. In Western medicine, common hypoglycemic drugs mainly include biguanides, sulfonylureas, α-glycosidase inhibitors, insulin sensitizers and insulin secretors. Although these hypoglycemic drugs can control blood sugar levels to a certain extent, they are often accompanied by some side effects, such as nausea and vomiting. The side effects for sulfonylureas and insulin secretors also include hypoglycemia, liver damage and gastrointestinal discomfort [2]. Therefore, the search for an effective natural hypoglycemic substance has become one of the hot spots in the field of diabetes research.

Chicory is renowned for its diverse bioactive compounds, which are readily extractable from the plant. Its distinctive chemical composition and biological properties have piqued the interest of numerous researchers in the field. Polysaccharides play an important role in regulating immune function, anti-oxidation, lowering blood sugar and blood lipids, and affecting intestinal flora. Chicory polysaccharide also has potential application value for diabetes treatment. The results of plasma LDL-C were determined by standard diet control group, diabetes group and diet group supplemented with 10% chicory. No obvious difference between the chicory group and normal or diabetic controls was observed in the short time. After 10 days, chicory had significantly higher effects on LDL-C than normal controls. The chicory herb significantly reduced LDL-C after 50 days compared to normal controls and diabetic controls [3]. It can be seen that chicory can be used as a hypoglycemic drug for diabetic animals. Although chicory has been shown to be useful in the treatment of diabetes, the

specific hypoglycemic mechanism that exists is unclear. Therefore, it is necessary to analyze the hypoglycemic mechanism of chicory.

This article provides a systematically analysis of the impact of chicory active components on type 2 diabetes mellitus (T2DM) and elucidates their mechanism of action. The findings offer valuable insights for future studies focusing on chicory's potential as a therapeutic agent. Data from animal and clinical trials indicate that the active ingredients in chicory regulate the pathological and physiological processes of metabolic diseases. For example, chicory acid (CRA) can promote insulin secretion, affect insulin signaling pathway, promote glucose uptake and other anti-diabetic activities.

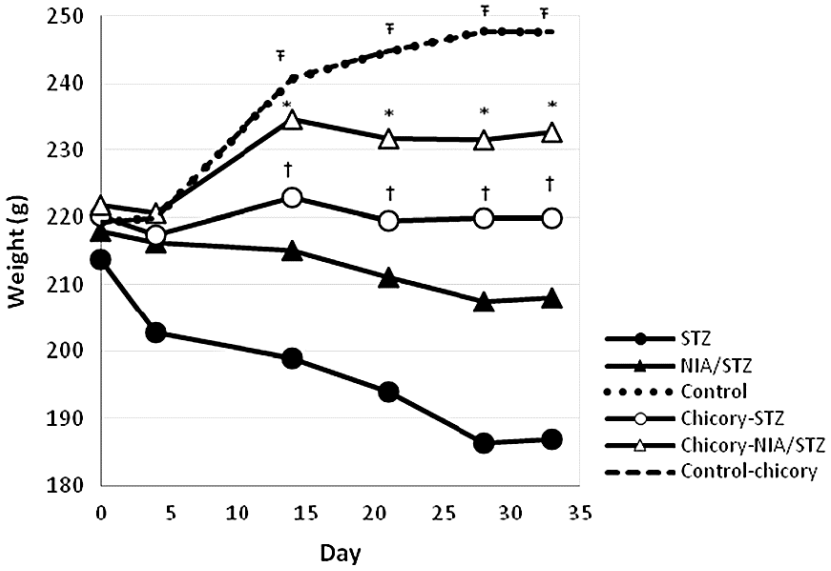


Figure 1. The average daily weight of each group [4].

2. Analysis of hypoglycemic ability

After 4 weeks of treatment with chicory, the average body weight of rats in STZ group decreased significantly, with a proportion of 12.5% [4]. The average body weight of rats in NIA/STZ group did not change significantly, with a proportion of 4.5%, while the value in chicory -STZ group remained almost unchanged, with a proportion of 1.6% (Figure 1). It can be seen that chicory prevents excessive weight loss in both early and advanced diabetic patients and does not cause weight gain in diabetic patients [4].

The results show that FBS values of rats in the control group and the chicory control group remained basically unchanged, FBS values of rats in the STZ group increased significantly, and FBS values of rats in the NIA/STZ group increased moderately but not significantly. However, the FBS value of the rats in the chicory STZ group and the chicory NIA/STZ group decreased appropriately (Figure 2), so it can be seen that the chicory treatment group can resist the excessive increase of FBS value [4]. This data showed that chicory was able to reduce blood sugar levels in rats with advanced and early diabetes.

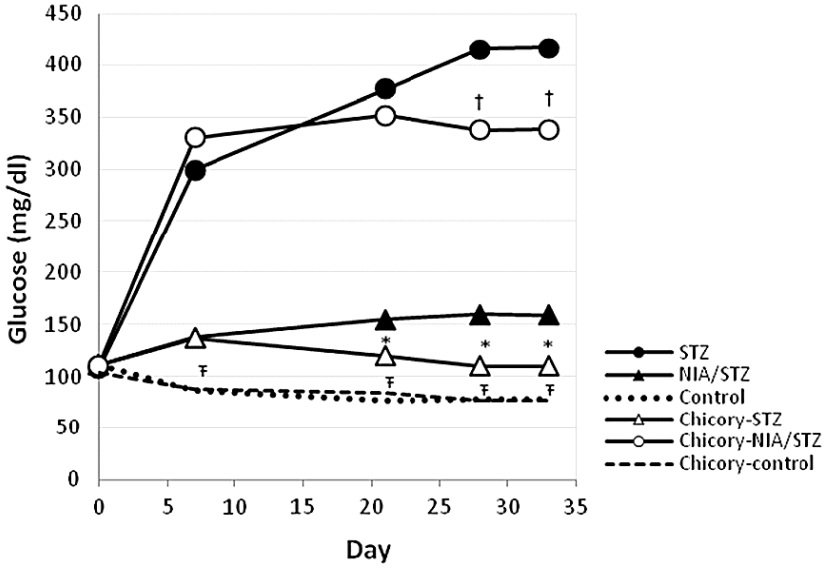


Figure 2. Average daily FBS in each group [4].

3. Mechanism analysis

3.1. Promoting insulin secretion based on CRA

The effects of CRA and chlorogenic acid (CGA) on insulin secretion was also analyzed [5]. When glucose content was 2.8 mM, CGA could significantly increase insulin secretion, up to 2.2 times that of the control group, while CRA had no effect on insulin secretion. When the glucose content was 8.3 mM, both CRA and CGA could increase insulin secretion, which was 1.4 times and 1.6 times of the control group, respectively (Figure 3). This suggests that CRA and CGA can stimulate the secretion of insulin by islet beta cells. CRA and CGA also enhance glucose uptake by muscle cells, thereby improving insulin sensitivity [5].

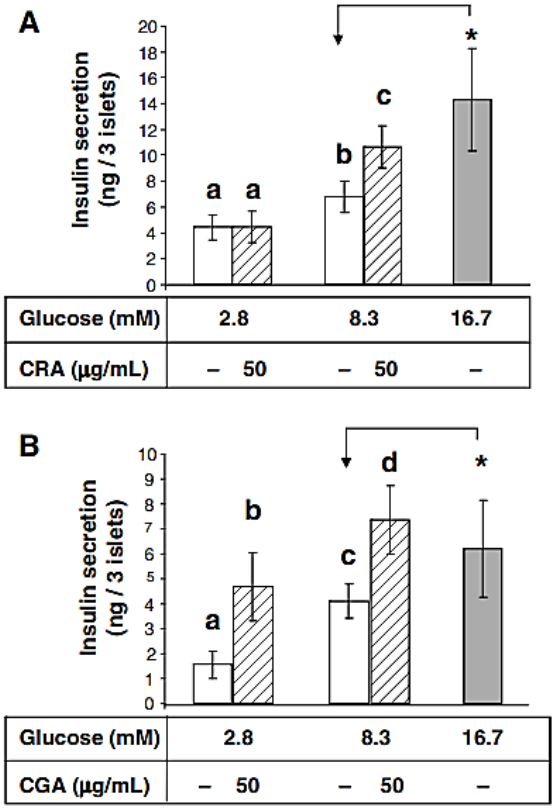


Figure 3. Effect of CRA and CGA on insulin secretion [5].

Compared with STZ group, CRA inhibited the increase of glucagon secretion and the decrease of insulin secretion (Figure 4A). Moreover, the expression of pancreatic endocrine-related genes such as pancreaticoduodenal homeobox 1 (*Pdx1*), insulin 1 *(Isl1*), neurogenin 3 (*Ngn3*), glucose transporter 2 (*GLUT2*) and neurogenic differentiation 1 (Neurod1) was detected. CRA can activate pancreatic endocrine-related genes, significantly prevent STZ-induced damage during pancreatic differentiation, inhibit pancreatic cell apoptosis and regulate the expression of pancreatic endocrine-related genes (Figure 4B), thereby increasing insulin secretion [6].

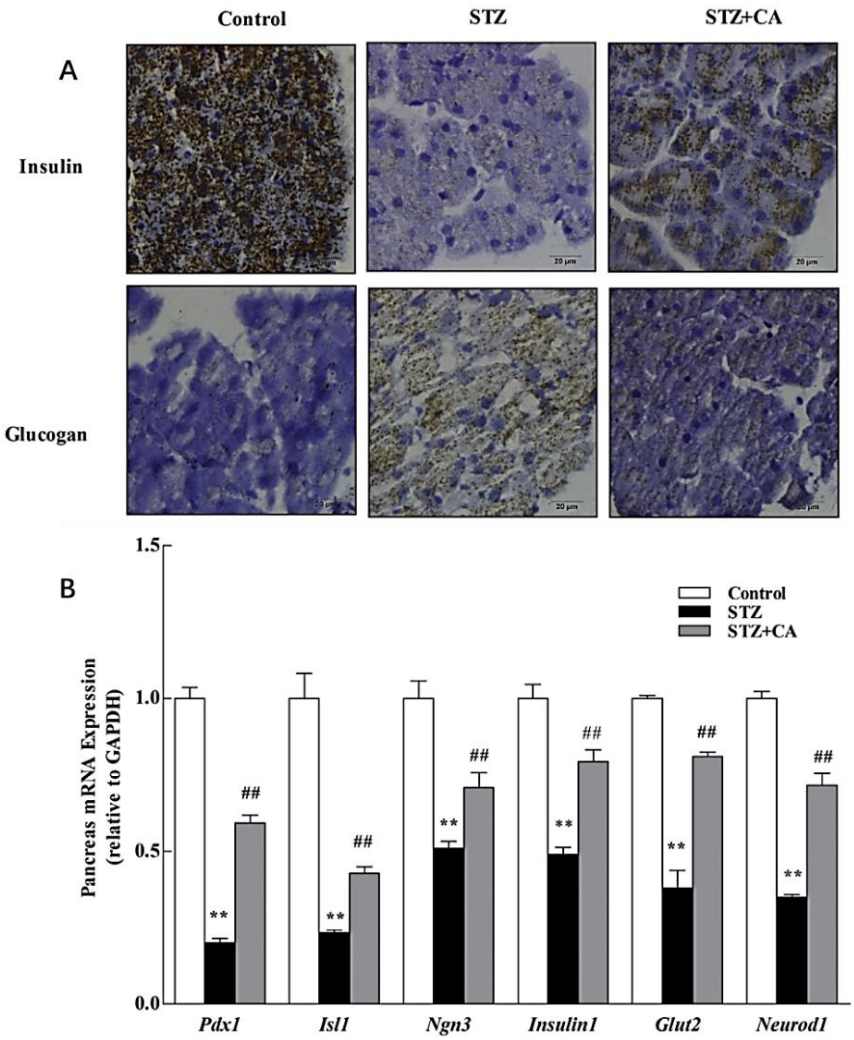


Figure 4. CRA role in the prevention of pancreatic insufficiency and decreased insulin secretion [6].

3.2. Effects of chicory on insulin signaling pathway

The results show that the feeding the rats chicory extract for 2 weeks may be sufficient to fully restore insulin sensitivity [7]. The CME has the potential to treat metabolic diseases by inhibiting PTP1B and regulating key insulin signaling pathway proteins, thereby improving insulin sensitivity and glucose metabolism. The inhibition of S1P signaling pathway can be considered as a potential therapeutic target for T2DM. The effects of palmitic acid and CRA on S1P signaling pathways in PBMCs was investigated [8]. Palmitic acid significantly increased the expression of SPHK1 and S1PR1 genes, as well as S1PR1 protein levels. However, CRA can improve palmitic acid-induced up-regulation of SPHK1, S1PR1 gene and S1PR1 protein (Figure 5). These findings suggest that CRA may be a novel inhibitor of the S1P signaling pathway and shows a significant role in the pathogenesis of T2DM [8].

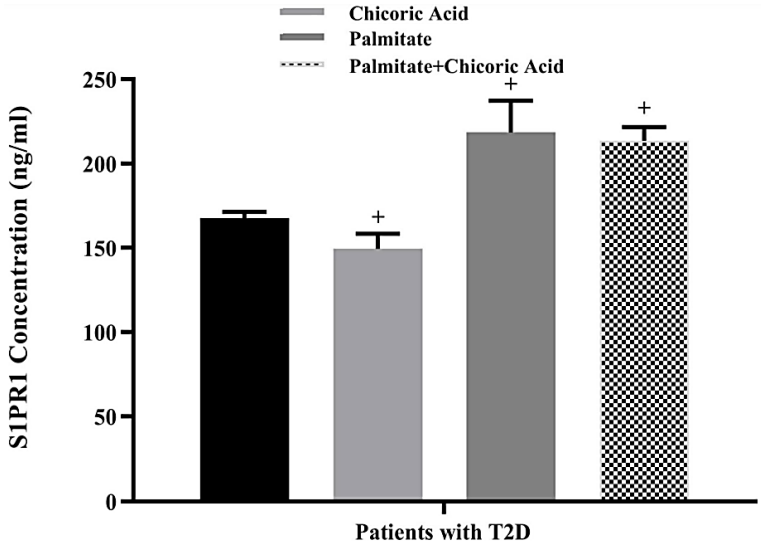


Figure 5. Effect of palmitate and CRA on S1PR1 concentration in peripheral blood [8].

The role and molecular mechanisms of glucose metabolism disorders through CRA was analyzed [9]. CRA promoted the expression of GLUT4 and membrane translocation by regulating insulin signaling pathway, inhibited the expression of PTP1B, thus promoting glucose uptake and improved insulin resistance in adipocytes. By inhibiting the serine phosphorylation of IRS-1, stimulating the tyrosine phosphorylation of IRS-1 and activating the phosphorylation of downstream Akt, CRA activates the insulin signaling process and improves insulin sensitivity. In HepG2 hepatocytes induced by high glucose concentration, CRA promotes tyrosine phosphorylation of IRS-1 and phosphorylation of Akt, activates insulin signaling pathway, stimulates translocation of GLUT2 from cytoplasm to cell membrane, and increases glucose transport capacity. At the same time, CRA inhibits serine phosphorylation of IRS-1, thereby improving insulin resistance [9].

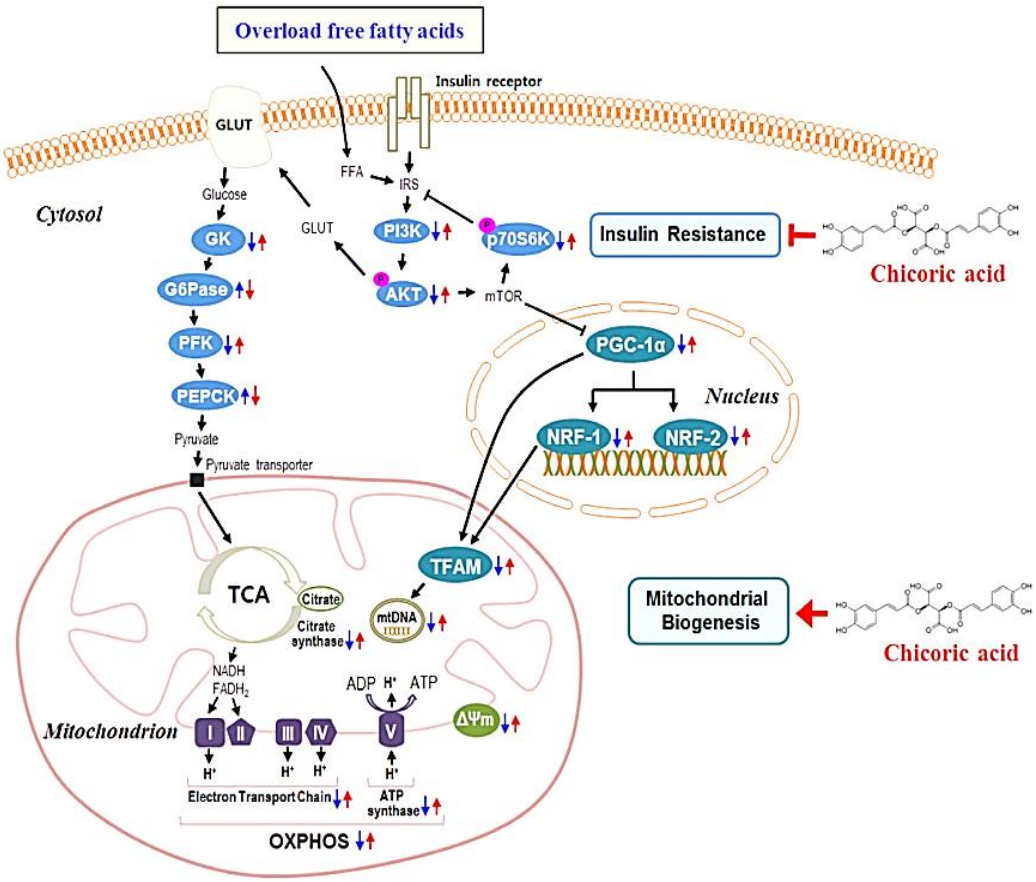


Figure 6. A review of the beneficial effects of CRA [10].

CRA was found to improve insulin resistance by regulating insulin signaling pathways [10]. CRA enhances insulin stimulated glucose uptake and activation of the insulin signaling pathway (IRS/PI3K/AKT). CRA also inhibits key factors that lead to insulin resistance, such as fatty acid-induced inflammation and mitochondrial dysfunction. CRA increased mitochondrial membrane potential and oxygen consumption in muscle cells and liver, and enhanced mitochondrial function. CRA also upregulates key genes related to glucose metabolism, thereby inhibiting gluconeogenesis and promoting glucose utilization [10].

For the specific action mechanism of insulin, it uses IRS/PI3K/AKT signal to achieve the regulation of nutrition and metabolic homeostasis. Activated AKT utilizes mTOR and its downstream effectors to synthesize glycogen and protein. Insulin can translocate GLUT4 to stimulate muscle to obtain glucose. FFA inhibits glucose transport associated with the reduction of IRS-PI3K and causes insulin resistance. The decrease of AKT can induce insulin resistance. CRA treatment can be used to regulate glucose uptake in FFA-induced insulin resistance C2C12 myoblasts, thereby altering the expression levels of PI3K, p-AKT, and p-p70S6K. This phenomenon was confirmed by the experimental analysis of IPGTT and IPITT, and CRA treatment significantly reduced fasting blood glucose and insulin levels, thus effectively regulating insulin resistance.

In addition, the introduction of CRA can also be used to regulate the expression levels of GK, PFK, G6Pase and PEPCK genes in the liver. GK uses blood sugar to control glucose uptake by the liver. G6Pase works by catalyzing dephosphorylation of glucose 6-phosphate, which is the final step in glycogenolysis and gluconeogenesis. PEPCK is an important enzyme in gluconeogenesis. Therefore, the reduction of liver G6Pase and PEPCK can regulate gluconeogenesis, while the alteration of GK and PFK can achieve glucose activation and regulate its use, which may be related to the improvement of liver insulin sensitivity in CRA-treated mice.

ATP can be obtained by combining TCA cycle with OXPHOS. Acetyl-coa, produced by glycolysis and fatty acid beta-oxidation, enters the TCA cycle in the mitochondrial matrix, thereby reducing NADH and FADH. The electrons received by NADH and FADH are transferred to the electron transport chain. After CRA treatment, mitochondrial content increased and mitochondrial enzyme activity changed. CRA can not only regulate the activity of PGC-1α, NRF-1, NRF-2 and TFAM to change mitochondrial content, so as to control the number of mitochondrial complexes. The treatment of CRA can be used to regulate mitochondrial function as well as insulin resistance. As shown in Figure 6, improvements in mitochondrial function controlled by CRA treatment can be used to regulate FFA-induced insulin resistance, and CRA may be useful for diet-induced insulin resistance.

The role of CRA and SOCS3 in insulin resistance was investigated [11]. It was found that overexpressed SOCS3 affected insulin signaling mainly by inhibiting the phosphorylation of insulin receptor substrate and promoting ubiquitination degradation of insulin receptor substrate. The study found that chicory acid can inhibit the expression of SOCS3 in a dose-dependent and time-dependent manner, and the mechanism may be caused by inhibiting the transcription level of SOCS3 [11].

3.3. Promoting glucose uptake based on CRA

The effect of CRA and CGA on glucose uptake was explored [5]. In the case of insulin stimulation of L6 muscle cells, CRA and CGA could significantly increase glucose uptake by 16.4% and 16.1%, respectively (Figure 7). In the absence of insulin stimulation of L6 muscle cells, CRA and CGA also increased glucose intake, but did not change much [5], indicating that CRA and CGA can improve the glucose uptake.

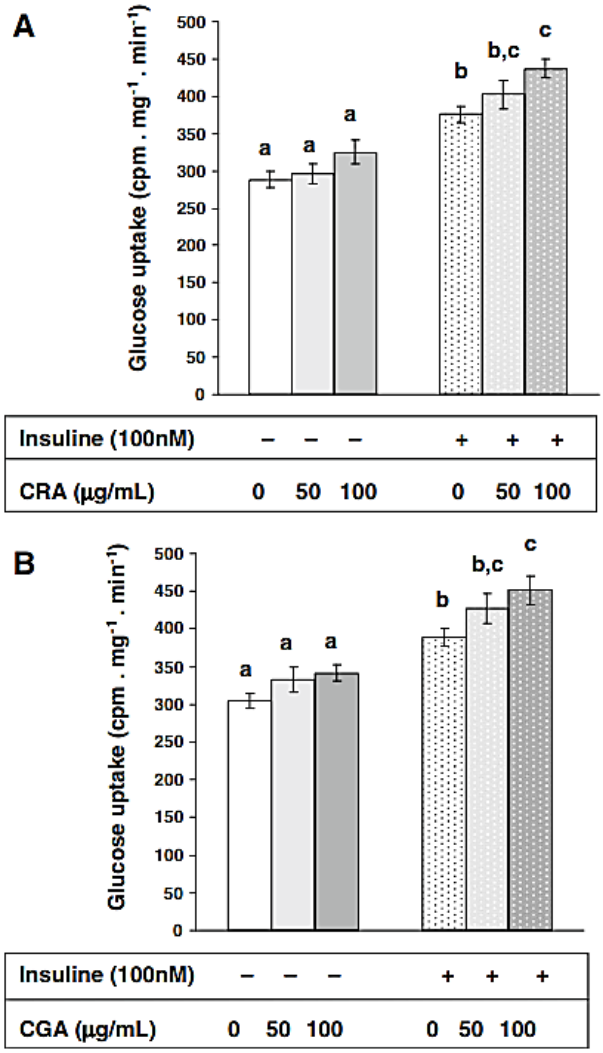
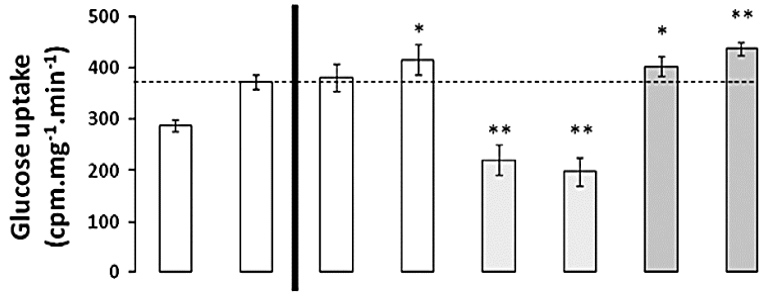


Figure 7. Effect of CRA and CGA on glucose uptake in L6 cells [5].

The results also show that glucose uptake increased when insulin stimulated L6 muscle cells [12]. When insulin and NCRAE stimulate L6 muscle cells at the same time, glucose intake increases significantly (Figure 8). This suggests that in the presence of insulin, NCRAE can enhance muscle glucose uptake to lower blood sugar [12].



Insulin (100 nM)	-	+	+					
Caffeic acid (µg.mL-1)	-	-	50	100	-	-	-	
Ferulic acid (µg.mL-1)	-	-	-	-	50	100	-	
NCRAE (µg.mL-1)	-	-	-	-	-	-	50	100

Figure 8. Effect of caffeic acid, ferulic acid and NCRAE on glucose uptake in L6 muscle cells [12].

4. Conclusion

This article analyzes the hypoglycemic properties of natural active substances in chicory in the treatment of diabetes and analyzes their mechanism of action. For the therapeutic effect, chicory natural active substances are of great help for the treatment of diabetes to a certain extent. Through the analysis of the mechanism of action, there are three primary hypoglycemic mechanisms attributed to chicory's natural active ingredients.

Both CRA and CGA could enhance insulin secretion to reduce blood glucose concentration to a certain extent. CRA can also increase insulin secretion by regulating pancreatic cell apoptosis and the expression of pancreatic endocrine-related genes.

Chicory's natural active substances improve insulin sensitivity and glucose metabolism by regulating key insulin signaling pathway proteins.

CRA can inhibit SOCS3 transcription to prevent insulin resistance, thus playing a hypoglycemic role. In the presence of insulin, CRA and CGA can increase glucose uptake by L6 muscle cells to lower blood sugar.

In summary, while chicory emerges as a promising therapeutic option for metabolic diseases, there is a clear need for extensive, long-term, high-quality, multi-center clinical trials to assess its efficacy and safety in the treatment of diabetes, which would facilitate its development and clinical application.

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