

## Mechanism and Clinical Aspects of the Effects of Chicory on Diabetes

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### Authors' contributions

This work was carried out in collaboration between all authors. Author PSN designed the study, wrote the protocol, and wrote the first draft of the manuscript. Authors MM, LR and SB performed the analyses of the study, managed the literature searches, and corrected the manuscript. All authors read and approved the final manuscript.

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### ABSTRACT

At present, there is no cure for diabetes. However, due to the side effects of synthetic drugs, medicinal plants, have been variously used to treat it. One such anti-diabetic plant is chicory. The aim of this study is to review and summarize the clinical aspects and mechanisms of the effects of chicory and its products on the key factors involved in diabetes in different environments. Accordingly, it seems chicory is effective in almost all tissues and organs involved in blood sugar control. For instance, chicory has been shown to (i) inhibit the breakdown of disaccharides in the gastrointestinal tract and glucose absorption in the intestine, (ii) prevent the release of glucose from the liver, (iii) increase glucose uptake by the peripheral tissues, especially in muscles and the liver, (iv) stimulate insulin secretion from the pancreas, (v) enhance the insulin signaling pathways

downstream and thereby reduce the diabetic complications. Consequently, blood glucose reduction after the administration of chicory is notable. The administration of chicory products appeared to have short-term and/or long-term effects on diabetes. This claim is approved by the results from the glucose tolerance test and HbA1c measurement. In addition, chicory fights against some primary agents responsible for diabetes and obesity. Since chicory reduces blood glucose and it has anti-diabetic effects, it is recommended that the involved mechanisms be investigated.

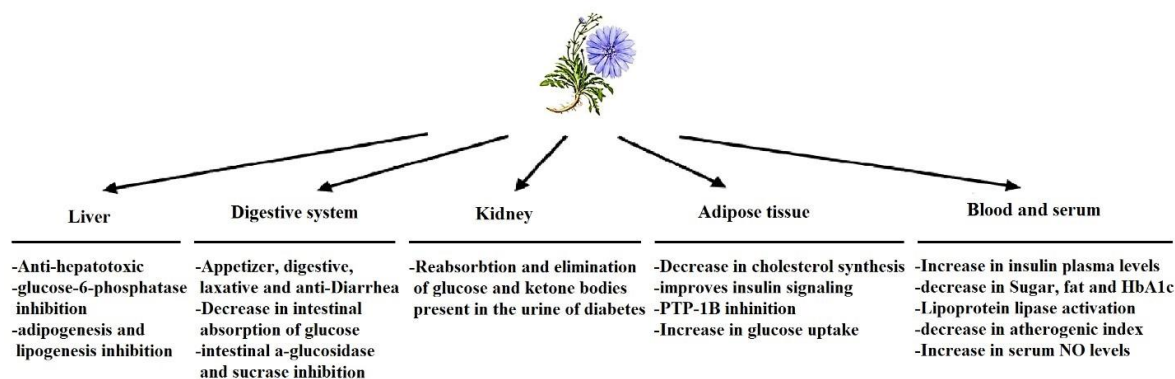
**Keywords:** Diabetes; chicory; blood sugar; insulin.

## 1. INTRODUCTION

A major concern of clinicians is that patients with type 2 diabetes have increased substantially in recent years. Currently, about 180 million people worldwide suffer from the disease. The number of people with type 2 diabetes is increasing with a rate of three new cases every 10 seconds and the figure is expected to reach 325 million by 2025 [1,2]. Although there are many medications to control blood sugar, these drugs often cause side effects such as edema, weight gain, and heart failure [3]; patients often seek additional suitable remedies from among anti-diabetic herbal extracts. *Cichorium intybus* L. (Asteraceae) is one of the most important medicinal plants and there has been a lot of interest in this regard [4]. *Cichorium intybus* L. (chicory) has been used in traditional medicine to treat a variety of conditions such as high blood sugar [5]. Currently, chicory and its products are used to treat a range of diseases. All parts of the plant (roots, leaves and seeds) are anti-allergic, anti-bacterial, anti-ulcerative, anti-inflammatory, appetizer, digestive, tonic and diuretic [4,6,7]. However, most important of all, chicory is known for its having hypoglycemic and hypolipidemic properties [8].

The possible mechanism of the hypoglycemic effect of chicory can be through enhancing insulin secretion from beta cell islands or due to increased glucose transport into cells in peripheral tissues or inhibiting glucose absorption in the intestine or by other mechanisms such as inhibiting endogenous glucose production through the gluconeogenesis and glycogenesis pathways [9]. In the figure below, there is a schematic summary of the mechanisms of anti-diabetic effects of chicory on different organs and tissues in the body (see Fig. 1).

Some reports suggest that ethanolic extract can decrease serum glucose by reducing the activity of hepatic glucose-6-phosphatase [10]. Chicoric Acid, an active gradient of chicory leaves, increases the release of insulin from pancreatic beta cells and glucose uptake by cultured muscle cells [11]. These are some examples of the mechanisms and beneficial effects of chicory on diabetes discovered until now. However, it seems that no comprehensive study and review in connection with the anti-diabetic effects of chicory have been conducted yet.



**Fig. 1. A summary of the potential effects of chicory and products on different body organs or tissues of a person with diabetes**

## **2. CHICORY EFFECTS ON THE GASTROINTESTINAL TRACT**

Chicory has a long history of herbal use and, in particular, has great value for tonic effects on the liver and digestive tract. The roots and leaves are appetizer, digestive, laxative, hepatoprotective and tonic [6,12]. It seems the tonic properties of chicory may be useful for the treatment of diarrhea [6]. The chicory alcoholic extract is used for the treatment of pyuria (the presence of pus in the urine) [13].

Aqueous extract of chicory seed contains significant amounts of sucrose and an oligosaccharide include fructose and glucose [14,15]. However, these findings are in contrast with a lot of sugar found in the extract [14]; in streptozotocin-induced diabetic rats have shown that oral administration of chicory extract just 30 minutes before the test improves glucose tolerance test. According to the studies, it seems that the effect of chicory on the percentage of serum glucose reduction is much stronger than metformin [10]. Studies have shown that normal rats after the injection of the aqueous extract of chicory in jejunum reduced the glucose absorption [16]. Therefore, it seems that chicory may have the potential effect in reducing hyperglycemia after a meal [10].

Inulin is a polymer of the fructose present in the chicory [10]; in fact, the main composition of chicory roots [17]. Since this compound is water-soluble and is not digested by the human digestive enzymes, it possesses the hypolipidemic effect like soluble fibers [18,19]. Soluble fibers are non-digestible which fermented by anaerobic bacteria and the mechanism by which soluble fibers apply their hypolipidemic effects is still not clear, as many theories have been proposed in this field [20,21]. However, the observed changes in blood sugar caused by chicory or inulin were reversible after switching to a fiber-free perfusate [17]. In addition, a significant reduction in serum triglycerides and cholesterol levels in rats treated with insulin [21], chicory extract [16] or soluble fibers [22] has been reported. All of these studies suggest that the effects may be due to the presence of inulin [10]. However, in some studies the effects of chicory containing smaller amounts of inulin in improving bowel movements have been proven [23].

In another study conducted by Jurgoński et al. [15], some complications of metabolic syndrome,

such as hyperglycemia, triglyceridemia and increased blood serum atherogenicity were induced experimentally in rats. This diet also causes increase in intestinal sucrase activity and some impaired process such as production of short-chain fatty acids. However, the extract reduced the intestinal sucrase activity in these animals [15]. In this study, the extract of chicory seed decreased the serum concentration of glucose to observed levels in normal control group. The glycemia-lowering mechanism of the extract seems to be, at least in part, the consequence of local effects of chicory in the gastrointestinal tract. It was also reported that chlorogenic acid as one of the organic compounds contained in chicory might have an antagonistic effect on the intestinal glucose transporter [24]. Moreover, inhibition of  $\alpha$ -glucosidase activity caused by the extract of chicory seed is attributed to some triterpenoids [25].

## **3. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS**

In 2010, the effects of chicory on blood parameters in diabetic rats were studied by Ghamarian A et al. [14]. Late stage (severe) and early (mild) stage of Type 2 diabetes were induced in rats by injection of streptozotocin and a combination of STZ and niacinamide, respectively. Body weight, fasting blood sugar (FBS), glycosylated hemoglobin A1c(HbA1c), serum enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), nitric oxide (NO), triglycerides, total cholesterol, total protein and insulin levels on days 10 and 18 days after treatment were measured [14].

## **4. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS: BLOOD SUGAR**

According to the results of Ghamarian A et al. study, during the three weeks of treatment, induction of severe and mild diabetes in rats increased FBS about 3.5 and 1.8-fold, respectively. While the chicory treated diabetic rats were able to resist excessive increases in FBS. An overall comparison of the groups suggested that chicory helped prevent the increase of blood glucose in both mild and severe diabetic rats [14].

While HbA1c had almost doubled in severe diabetic rats, chicory administration reduced HbA1c and FBS during this period; however,

these two parameters were still higher than normal. A slight reduction of HbA1c in diabetic rats treated with chicory indicated that the blood sugar levels remained relatively low following the administration of chicory. Because of the lack of insulin in severe diabetes, the assessment on blood parameters indicates that chicory may also work through insulin-independent mechanisms. Based on the results achieved from glucose tolerance test (GTT) and HbA1c, in general, it seems that chicory has short-term and long-term effects on diabetes. From these results, it seems that chicory may be a useful natural food supplement to improve the diabetes condition or delay the development of diabetes and its complications [14].

It has been recently shown that acute administration of chicory extract (500 mg/kg) significantly reduced blood glucose levels and this effect remained active for up to 6 hours. The decrease in the chronic daily treatment with chicory was substantially higher than the acute treatment [26]. Some studies indicate that the chronic administration of chicory extract causes the elimination of glucose and ketone bodies traces that were present in the urine of experimental induced diabetic rats before treatment [9]. According to Pourfarjam et al. (2015), however, it seems that chicory has no significant effect on the expression sodium-glucose transporters in the kidney (SGLT-1 and SGLT-2) [27]. Based on the obtained results, it is clear that the elimination of glucose and ketone bodies traces could be due to a decrease in blood glucose caused by various reasons.

As mentioned above, several mechanisms may be involved in anti-hyperglycemic effects of chicory. However, among these mechanisms, the ability to inhibit the activity of the enzyme glucose-6-phosphatase in the liver can not be ignored. Glucose-6-phosphatase as a key determinant of the glucose production catalyzes the terminal step in the release of glucose from the liver and it plays a key role in blood glucose homeostasis. It is demonstrated that the activity of this enzyme is increased in diabetic patients [28,29].

Pushparaj et al. results showed that the activity of glucose-6-phosphatase in the liver of diabetic rats were significantly higher than normal rats but its activity significantly decreased by chicory-rich diet [10]. The lowered activity of this enzyme is associated with decreased serum glucose; that's

because less glucose was being produced and released into the blood stream [10].

## 5. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS: INSULIN

In the study of Ghamarian et al. [14], chicory effects on blood insulin levels in mild diabetic rats were more obvious than the severe group, after the induction of experimental diabetes, since the number of pancreatic beta cells in mild diabetic rats had been still remained for the production and secretion of insulin, whereas plasma insulin concentrations in the severe diabetic rats before and after treatment with chicory was about zero. However, this effect was not observed in some other studies, which can be the same with the severe diabetic group in the study of Ghamarian et al., due to highly destruction of pancreatic beta cells [30]. In fact, the destruction of beta cells by streptozotocin administration in the pancreatic islets of rats induces insulin-dependent diabetes mellitus [31]. Thus, the ability of the extracts to reduce blood glucose levels in severe diabetic rats (almost have no insulin), further substantiates an insulin-independent and extra pancreatic mode of action of the chicory [26]. In support of the above observations, in the study of Pushparaj et al. [10], despite a significant decrease in blood glucose levels, no significant changes were observed in the serum insulin of all groups. In fact, in this case, anti-hyperglycemic activity of chicory is not through the insulin secretion [26].

A number of in-vitro studies have attempted to investigate the effects of chicory upon insulin secretion. The in-vitro studies give us more confidence in the ability of some compounds present in chicory to stimulate insulin secretion. In such studies, the results of in-vitro study of the effects of chicoric acid (CRA) and chlorogenic acid (CGA) isolated from chicory on insulin secretion in glucose-responsive and insulin secreting pancreatic  $\beta$ -cell line INS-1 and also the pancreatic islets isolated from rats as expected suggest that CRA and CGA only in the presence of high concentrations of glucose (8.3 mM), increase significantly insulin secretion [32].

Studies have shown that the mechanism by which the compounds stimulate insulin secretion is different from that of sulfonylurea drugs [32]; moreover, the sulfonylurea drugs can also increase insulin secretion even in the absence of hyperglycemia, which potentially leads to hypoglycemia and can also cause some side

effects [33,34]. The present data show that, in contrast to sulfonylureas, CRA and CGA are ineffective on insulin secretion from isolated islets under low glucose concentration (2.8 mM) and their insulinotropic effects occur at intermediate glucose concentration. In addition, the insulinotropic ability of these compounds will be enhanced by increasing the glucose concentration [32].

Experimental studies on the effects of chicory on insulin are not restricted to its ability to stimulate insulin secretion; in most cases, chicory ability to reduce insulin resistance and improve its effects on peripheral tissues have been proven. In the study of Ghamarian et al., the comparison of GTT plots for mild diabetic rats may suggest a relative improvement of insulin sensitivity and in the chicory-treated group. According to the papers, the alleviation of hyperinsulinemia together with the decrease of ALT activity in the chicory-treated mild diabetic rats suggest an amelioration of insulin resistance [14,35].

In the study, the change in the peak insulin time point in chicory-treated mild diabetic group compared to its control (60 minutes versus 90 minutes) indicates that pancreatic beta cells respond quicker to postprandial hyperglycemia and further support insulinotropic ability of chicory. However, the same effect was not observed in mild diabetic rats; that is probably due to the lack of insulin in the severe diabetics. It can be inferred that chicory plays a key role as insulin-sensitizer and in the case of severe diabetic rats which receive exogenous insulin should also be able to act [14]. To investigate this hypothesis, Nowrouzi et al who had previously demonstrated the effects of chicory on mild diabetic mice (in a joint study by Ghamarian and Nowrouzi), examined these effects in another small study [27]. In the study, the effect of chicory extract on glucose tolerance test in the presence and absence of exogenous insulin in the severe diabetic rats (with highly destructed pancreatic beta-cells) was examined [36]. The results showed that the administration of exogenous insulin lowered blood glucose, but the chicory extract exhibited synergistic effects in lowering blood glucose. These results indicate that the glucose-lowering effect of chicory mainly relies on the presence of insulin; in type 2 diabetes, chicory acts as an insulin sensitizer that leads to the alleviation of insulin resistance in target organs [36].

## 6. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS: LIPIDS

Diabetic conditions are often associated with increased levels of blood sugar and lipids along with the lipoprotein disorders [37]. It is well known that insulin activates the enzyme lipoprotein lipase, and thereby hydrolyzes blood triacylglycerols [38]. Destruction of pancreatic beta cells leads to depletion of plasma insulin, which causes hyperlipidemia. Furthermore, diabetes mellitus due to increase in triacylglycerols, LDL and decrease in HDL and in fact increase in cholesterol is associated with the risk of atherosclerosis [39]. Similarly, the results of studies indicate that the experimental induction of diabetes in rats, increases serum levels of lipids such as triglycerides and cholesterol [26]. It was recently shown that the administration of chicory extract to diabetic rats alleviates serum cholesterol and triglyceride levels [9]. This effect may be due to a decrease in the activity of cholesterol biosynthesis enzymes or decreasing the rate of lipolysis which are under the control of insulin [40].

In the study of Ghamarian et al., in the mild diabetic rats, the main variations included slight increases in TG. After chronic daily treatment with chicory, the TG levels decreased to the normal range [14]. Significant and remarkable control of plasma lipid concentrations caused by chicory extract may be due to amelioration of insulin secretion [9]. However, the severe lack of insulin did not stop long-term positive effects of chicory on blood parameters in experimental induced severe diabetic rats [14]. Moreover, decrease in plasma triglycerides and cholesterol in this group may be a secondary response to amelioration of lipid metabolism [14,35], and inhibition of adipogenesis [41]. Of course, similar to blood sugar, the administration of chicory did not produce any significant changes in lipid levels in the serum of normal rats [10,14].

It can be concluded that Chicory effects on lipid parameters in diabetic rats are similar to those caused by the injection of insulin. As in the study of Kaskoos RA et al. (2012), similar to chicory treatment, insulin restored the altered lipid parameters such as total cholesterol, LDL, HDL, VLDL and triglycerides in STZ-induced diabetic rats significantly closer to normal ranges. And also chicory has been shown to decrease the atherogenic index significantly [26]. The

atherogenic index represents the ratio of LDL and VLDL to HDL [42].

## **7. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS: PLASMA NO**

Insulin resistance is usually associated with impaired nitric oxide (NO), so that endothelial NO (eNO) synthesis is reduced in subjects with type 2 diabetes [43,44]. Because NO inhibits protein tyrosine phosphatase-1 B (PTP-1B) after entering the muscle and fat cells, and thereby enhances the effects of insulin (see Fig. 2) [45,46]. In addition, it directly increases glucose uptake by enhancing the translocation of vesicles containing glucose transporter-4 (GLUT-4) [46-48]. In the study of Ghamarian et al., STZ-induced experimental diabetes was associated with a significant reduction in serum NO; while, treatment with chicory extract prevented the reduction of NO [14]. In addition to the beneficial effects on improving insulin resistance (since NO is also an important player in the nervous system), chicory may provide a beneficial role in the prevention of neurological complication of diabetes [49].

## **8. EFFECTS OF CHICORY ON SERUM BIOCHEMICAL MARKERS: NON-FUNCTIONAL PLASMA ENZYMES**

Usually an increase in the activity of enzymes ALT and AST in serum is considered a sensitive indicator of the liver disease; but several studies have shown that high levels of serum ALT activity and the increase of ALT/AST ratios are associated with insulin resistance and metabolic syndrome [35,50,51]. In this study, Ghamarian et al., experimental diabetes induced by streptozotocin was associated with significant increase in serum ALT activities which were lowered significantly by chronic daily oral administration of chicory; this confirmed the properties of chicory to protect the liver, improve metabolic syndrome and insulin resistance. The results confirm the benefit of chicory in the treatment and prevention of metabolic syndrome and insulin resistance [14].

## **9. EFFECTS OF CHICORY ON INSULIN SIGNALING PATHWAY**

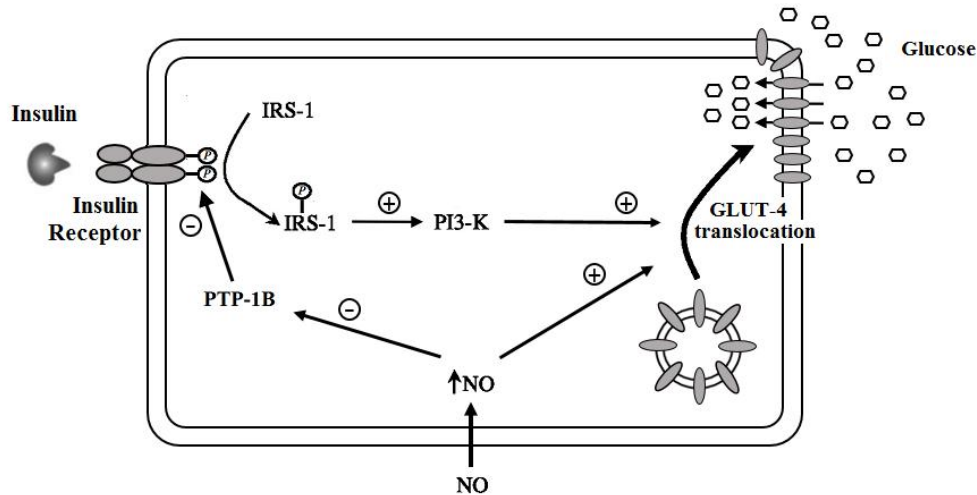
Under normal conditions, the rate-limiting step of glucose metabolism is the transport of glucose into muscle and adipose cells, that is regulated physiologically by insulin dependent and

independent signaling pathways which rely on GLUT4 vesicles translocation to the plasma membrane [52]. The major pathological changes in patients with type 2 diabetes include a relative deficiency in insulin secretion and progressive development of insulin resistance leading to hyperglycemia [53]. The general consensus is that insulin resistance is due to a defect in one or more of the cascades of insulin signaling in insulin-responsive tissues such as skeletal muscle, fat and liver which quantitatively constitute the major consumers of glucose in the body [54].

Under normal circumstances, insulin binds to its trans-membrane receptor tyrosine kinase on the cell surface which results in receptor auto-phosphorylation and the tyrosine phosphorylation of insulin receptor substrate family of proteins [55]. Within the insulin signaling cascade, it is clear that the activation of phosphatidylinositol 3-kinase (PI3K) by insulin receptor substrate (IRS) is essential, for insulin is necessary in order to induce Glut4 translocation and glucose uptake through the channels [56-58].

On the other hand, insulin-dependent glucose uptake is downregulated by protein tyrosine phosphatases (PTPs). It is clear that under normal and diabetic conditions, protein tyrosine phosphatases play a key role in cellular signaling pathways. Among the several protein tyrosine phosphatases, PTP-1B appears to be a key modulator of insulin signaling transduction which affects components, such as IRS1 and PI3K (see Fig. 2) [59].

PTP-1B as an intracellular phosphatase in the insulin signaling cascade is capable to dephosphorylate and thus inactivate insulin receptor (IR) and also IRS [60,61]. The phosphatase, due to its central role and significance in governing the adipogenesis and insulin signaling has emerged as a potential target for diabetes and obesity [62]; so that overexpression of PTP-1B in obesity-related insulin resistance has been reported [63]. A fine balance between kinases involved in the insulin downstream signaling (such as IRTK) and the phosphatases (such as PTP-1B) is necessary to a normal physiological condition. Moreover, for the improvement of insulin resistance, it is required to shut down the signals that are caused by PTP-1B [59]. However, it has been proved that the discovery of effective PTP-1B inhibitors with selective properties is difficult [64].



**Fig. 2. Insulin signal transduction pathways initiated by insulin binding to its cell surface receptor; resulting in activation of receptor tyrosine kinases. Insulin receptor autophosphorylation and receptor-mediated IRS-1 phosphorylation followed by activation of enzyme PI3K. Activating the last enzyme through a series of enzyme-mediated steps resulting in GLUT4 translocation and glucose uptake increase in peripheral tissue cells such as muscle and fat. In addition, the entry of NO into the cells under normal conditions appears in different ways can reinforce insulin signaling cascade. Dysfunction of each of the proteins may be associated with insulin resistance and type 2 diabetes. Chicory extract may potentially enhance cell surface GLUT4 by mimic or reinforce the effects of each step, and thereby improve the diabetic condition**

Muthusamy V et al. (2010) indicated that the incubation of 3T3L-1 cells with the chicory extract and chlorogenic acid (as one of the active compounds present in the chicory extract) resulted in significant increase in 2-deoxy glucose uptake. Extending to an in-vivo model, the effect of chicory extract was also investigated on insulin sensitivity in experimentally induced type 2 diabetic rats, and it was found that feeding the rats with chicory extract for 2 weeks might be sufficient to fully reinstate insulin sensitivity. In this study, as the effect of this treatment, downstream effectors of insulin signaling pathway such as IR, PI3K, protein kinase B (PKB) and GLUT-4 were also significantly reinstated. In fact, the chicory extract may improve the insulin signal transduction pathway by increasing the expression of each of the markers [65]. However, the ability of chicory to influence PI3K-independent pathways have been proved previously [41].

## 10. CONCLUSION

The administration of chicory products appeared to have short-term and long-term effects on

diabetes. This claim is approved by the results from the glucose tolerance test and HbA1c measurement. Possible mechanism of the hypoglycemic effect of chicory can be through enhancing insulin secretion from beta cell islands or due to increased glucose transport into cells in peripheral tissues or inhibiting glucose absorption in the intestine or by other mechanisms such as inhibiting endogenous glucose production through the gluconeogenesis and glycogenesis pathways. Thus, it is suggested comprehensive studies be conducted in connection with the anti-diabetic mechanisms of chicory. Also, it seems that the effect of chicory on the percentage of serum glucose reduction is much stronger than some of anti-diabetic drugs that are recommended to be investigated through comparative assessments.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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