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Effects of a dietary compound tablet on glucose metabolism in a hyperglycemic mouse model

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ABSTRACT

Objective: This study evaluates the hypoglycemic effects and glucose tolerance improvement of a dietary compound tablet containing cinnamon extract, chromium-rich yeast, mulberry leaf extract, zinc citrate, and selenium-rich yeast in alloxan-induced hyperglycemic mice.

Methods: Hyperglycemia was induced in SPF-grade Kunming mice through intravenous administration of alloxan at a dose of 45 mg/kg. Subsequently, the mice were randomly divided into a control group and treatment groups receiving low (66.67 mg/kg), medium (133.34 mg/kg), or high (400 mg/kg) doses of the compound tablet. Following 30 days of continuous oral gavage, fasting blood glucose levels, glucose tolerance, and the area under the glucose curve (AUC) were assessed. Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA).

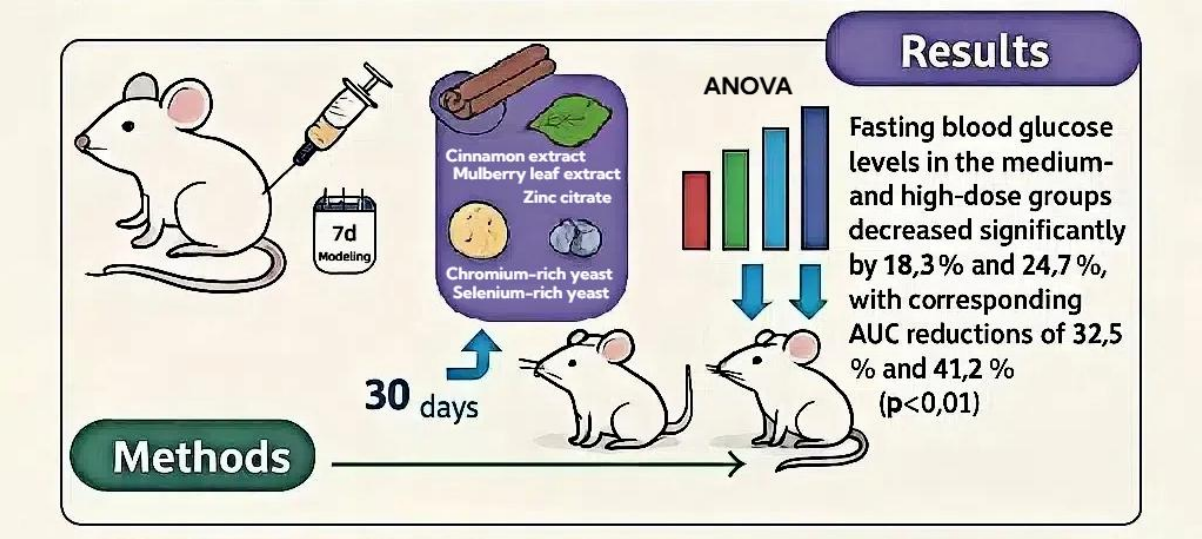
Results: Fasting blood glucose levels in the medium- and high-dose groups decreased significantly by 18.3% and 24.7%, with corresponding AUC reductions of 32.5% and 41.2% ($p<0.01$) compared with the control. No significant changes were observed in the low-dose group ($p>0.05$). Body weight remained unchanged across all groups ($p>0.05$).

Novelty: This study uniquely evaluates a novel dietary compound tablet containing cinnamon, chromium, mulberry leaf, zinc, and selenium for hyperglycemia management. Unlike previous research focusing on individual components, this work demonstrates the significant, dose-dependent glucose-lowering effects and improved glucose tolerance of this specific combination in alloxan-induced hyperglycemic mice. This finding highlights the enhanced potential of this multi-ingredient formulation as an adjuvant treatment for diabetes, warranting further clinical investigation.

Conclusion: In hyperglycemic mice, administration of the dietary compound tablet resulted in significant, dose-dependent reductions in blood glucose levels and enhanced glucose tolerance. These results highlight its potential utility as an adjunctive therapy for diabetes. However, further clinical investigations are necessary to validate its efficacy and safety.

Keywords: Dietary compound tablet, alloxan, hyperglycemic model, glucose tolerance, bioactive compounds.

Graphical Abstract: Effects of a Dietary Compound Tablet on Glucose Metabolism in a Hyperglycemic Mouse Model



INTRODUCTION

Diabetes mellitus is a common metabolic condition marked by increased blood sugar levels due to inadequate insulin production, resistance to insulin, or both. Oftentimes, it is linked to complications such as nerve damage and various cardiovascular disorders [1]. Although conventional hypoglycemic agents like metformin and insulin are widely prescribed, many patients still suffer from adverse effects and suboptimal therapeutic outcomes [2]. In recent years, herbal and natural remedies received increasing attention due to their potential to offer effective glycemic control with fewer side effects and reduced costs compared to synthetic medications. Numerous medicinal plants demonstrate the ability to improve pancreatic β-cell function and stimulate insulin release, largely attributed to their potent antioxidant activities [3]. Notably, these natural substances are often regarded as functional foods due to the presence of bioactive constituents that contribute to their health-promoting properties. These compounds are considered the principal agents underlying the physiological activity of functional food products. Examples include prebiotics, probiotics, synbiotics, polyunsaturated and essential fatty acids, various vitamins, dietary minerals, phytochemicals, antioxidants, and phytosterols [4]. With the advancement of society, functional foods are increasingly recognized for their important role in partially substituting conventional pharmaceuticals. Their growing acceptance highlights their potential as

complementary or alternative options in health management.

Natural products have garnered increased interest as adjunctive therapies for diabetes, owing to their multi-component synergistic actions and favorable safety profiles. Research demonstrates that plant-derived extracts—such as those obtained from mulberry leaves and cinnamon—as well as essential trace elements like chromium, zinc, and selenium, can modulate glucose metabolism through diverse biological pathways. The hypoglycemic potential of mulberry leaves is largely associated with bioactive components such as 1-deoxynojirimycin, flavonoids, phenolic compounds, and polysaccharides [5]. These compounds have been shown to inhibit α-glucosidase activity, which may contribute to moderating postprandial blood glucose levels by slowing carbohydrate digestion and absorption [6-8]. Cinnamon-derived polyphenols contribute to insulin signaling by activating insulin receptor kinase, thereby promoting glucose uptake in peripheral tissues [9–10]. Chromium has been reported to enhance the expression of insulin receptors, potentially improving cellular responsiveness to insulin [11]. Zinc plays a critical role in insulin biosynthesis and release within pancreatic β-cells, with ZnT8 acting as a key transporter for maintaining intracellular zinc levels. Insufficient zinc impairs insulin secretion and perturbs glucose regulation, underscoring its importance in glycemic balance [12–13]. Selenium contributes to β-cell protection primarily through its antioxidant capacity [14–15]. Based on these complementary mechanisms, the dietary compound tablet—comprising multiple bioactive ingredients—is formulated to modulate blood glucose via multiple targets, aiming to achieve synergistic therapeutic effects.

This study aimed to investigate the effects of a dietary compound tablet on glycemic control and glucose tolerance in a mouse model of alloxan-induced hyperglycemia, with the goal of generating preclinical evidence to support its potential application in human clinical settings.

Materials

***Experimental Sample*:** The dietary compound tablet (provided by Sirio Healthcare (Anhui) Co., Ltd. with a specification of 0.4 g per tablet, and the recommended daily oral dose for humans is 0.8 g, i.e., 2 tablets per day). The main ingredients and their contents per tablet are as follows: cinnamon extract 62.5 mg, chromium-rich yeast 39.4 mg, mulberry leaf extract 30 mg, zinc citrate 16.8 mg, and selenium-rich yeast 13.1 mg. Cinnamon extract, rich in cinnamon polyphenols, was obtained by water extraction (8×, 6×, 6×), followed by concentration and spray drying. Mulberry leaf extract, with flavonoids as the main bioactive constituents, was prepared by refluxing the leaves twice with 50% ethanol (10×), then concentrated, purified via macroporous resin column chromatography, and spray-dried.

Experimental Animals: SPF-grade Kunming male mice (weight 24–28 g) were obtained from Hunan Slake Jingda Experimental Animal Co., Ltd., with license number SCXK (Xiang) 2019-0004.

Instruments and Reagents: JA3003 electronic analytical balance, TP-3KE electronic balance, Aike Lean blood glucose meter, and blood glucose test strips (production batch number: 202009133) were purchased from Acon Biotechnology (Hangzhou) Co., Ltd. Alloxan was obtained from Sigma (USA), batch number BCBX0671.

METHODS

Fasting blood glucose test: Modeling: Mice were fasted for 24 hours and then injected intravenously with alloxan (45 mg/kg) via the tail vein. After 7 days, individuals with fasting blood glucose levels between 10–25 mmol/L were selected as successful models.

Grouping: A total of 60 model mice were randomly divided into four groups: model control group (administered pure water), low-dose group (66.67 mg/kg), medium-dose group (133.34 mg/kg), and high-dose group (400 mg/kg), with 15 mice in each group. The

test substances were administered via gavage at regular intervals daily for 30 consecutive days, and body weight was measured once weekly.

Observation indicators: After continuous oral administration of the test substance for 30 days, the animals in each group fasted for 5 hours (free drinking water), and the tail blood was taken to measure the blood glucose level. The blood glucose level, blood glucose reduction value and blood glucose reduction percentage (RBG%) of each group of animals were calculated, and the blood glucose reduction percentage (RBG%) was calculated according to the following formula:

$$\mathbf{RBG\%} = \frac{\mathbf{G_{before} - G_{after}}}{\mathbf{G_{before}}} \times \mathbf{100\%}$$

G_{before}: blood glucose value before the experiment (mmol/L).

G_{after}: blood glucose value after the experiment (mmol/L).

Glucose tolerance test in hyperglycemia model animals: Animal modeling, animal screening, dose grouping and test samples were performed as "fasting blood glucose test".

Observation indicators: After continuous oral administration of the test substance for 30 days, the diabetic model animals in each group fasted for 5 hours (free drinking water), and the blood glucose level before glucose administration (i.e., 0 hours) was measured. Then the animals in each dose group were given test samples of different concentrations, and the model control group was given an equal volume of pure water. After 20 minutes, each group of mice was orally given 2 g/kg body weight of glucose, and the blood glucose levels at 0.5 h and 2 h after glucose administration were measured. The blood glucose reduction value, blood glucose reduction percentage (RBG%) and changes in the area under the blood glucose curve at each time point after glucose administration were calculated for each group of animals.

The area under the blood glucose curve (AUC) was calculated according to the following formula:

$$\mathbf{AUC} = \frac{(\mathbf{G_0 + G_{0.5}}) \times \mathbf{0.5}}{\mathbf{2}} + \frac{(\mathbf{G_{0.5} + G_2}) \times \mathbf{1.5}}{\mathbf{2}}$$

G_0: 0 hour blood glucose (mmol/L).

$G_{0.5}$: 0.5 hour blood glucose (mmol/L).

G_2: 2 hour blood glucose (mmol/L)

Data statistics: SPSS statistical software (V13.0) was used to perform one-way analysis of variance (ANOVA) on the data, with a significance level of α=0.05.

RESULTS

Effects on body weight: There was no statistically significant difference in the body weight of mice in each dose group at each time point compared with the model control group ($p > 0.05$). (e.g. Figure 1)

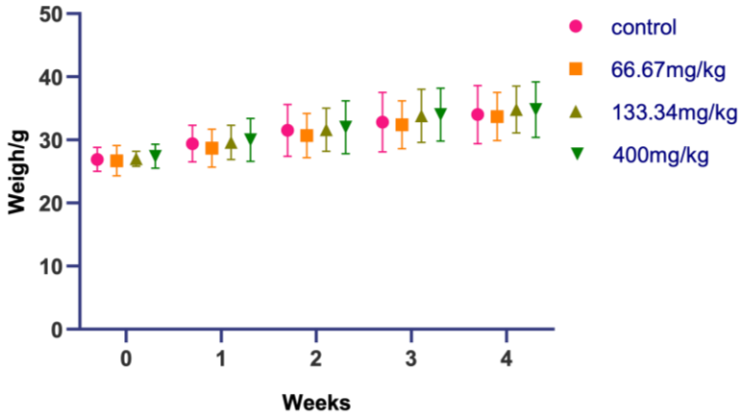


Figure 1. Body weights of mice in each dosing group were recorded at each time point. Data are expressed as means ± standard deviation (SD) with a sample size of n = 15.

Effects on fasting blood glucose: At baseline, there were no statistically significant differences in fasting blood glucose (FBG) levels among the different dosage groups and the model control group (P > 0.05), as shown in Figure 2.

Following 30 days of oral administration of the test compound, mice in the medium- and high-dose groups exhibited notably lower FBG levels compared to the model control group. These reductions were statistically significant ($p < 0.05$ or $p < 0.01$) (see Figure 2). Both the absolute and percentage decreases in blood glucose were significantly greater in the medium- and high-dose groups relative to the model control ($p < 0.01$).

In contrast, the low-dose group showed no meaningful difference in FBG, reduction amount, or reduction rate when compared with the model control group (P > 0.05) (refer to Figure 2).

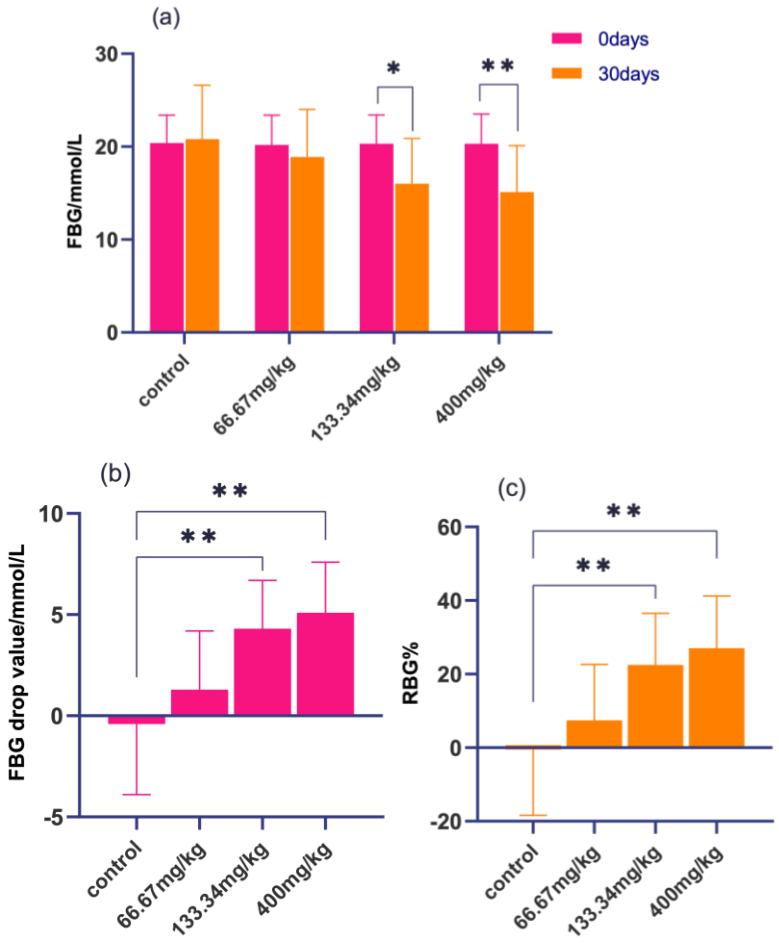


Figure 2. Results of fasting blood glucose (FBG) in hyperglycemia model mice before and after administration at different doses. (a) FBG levels before and after the experiment. (b) Degree of decrease in FBG after 30 days of administration. (c) The blood glucose reduction percentage (RBG%). The data are presented as the means ± SD (n=15), *P < 0.05, ** p < 0.01 vs the Model Control group.

Effects on glucose tolerance: The blood glucose levels of animals in the medium and high dose groups before (i.e. 0 h), 0.5 h and 2 h after glucose administration were lower than those in the model control group, and the difference was statistically significant (P<0.01 or P<0.05). There was no statistically significant difference in the blood glucose levels of animals in the low dose group before (i.e. 0 h), 0.5 h and 2 h after glucose administration compared with the model control group (P>0.05).

There was no statistically significant difference in the blood glucose drop value and blood glucose

reduction percentage of animals in each dose group after 0.5 h and 2 h after glucose administration compared with the model control group (P>0.05).

The area under the blood glucose curve (AUC) of animals in the medium- and high-dose groups decreased after glucose administration at 0 h, 0.5 h, and 2 h, and the difference was statistically significant compared with the model control group (p<0.01). There was no statistically significant difference in the area under the blood glucose curve of animals in the low dose group at 0 h, 0.5 h and 2 h after glucose administration compared with the model control group (p>0.05).

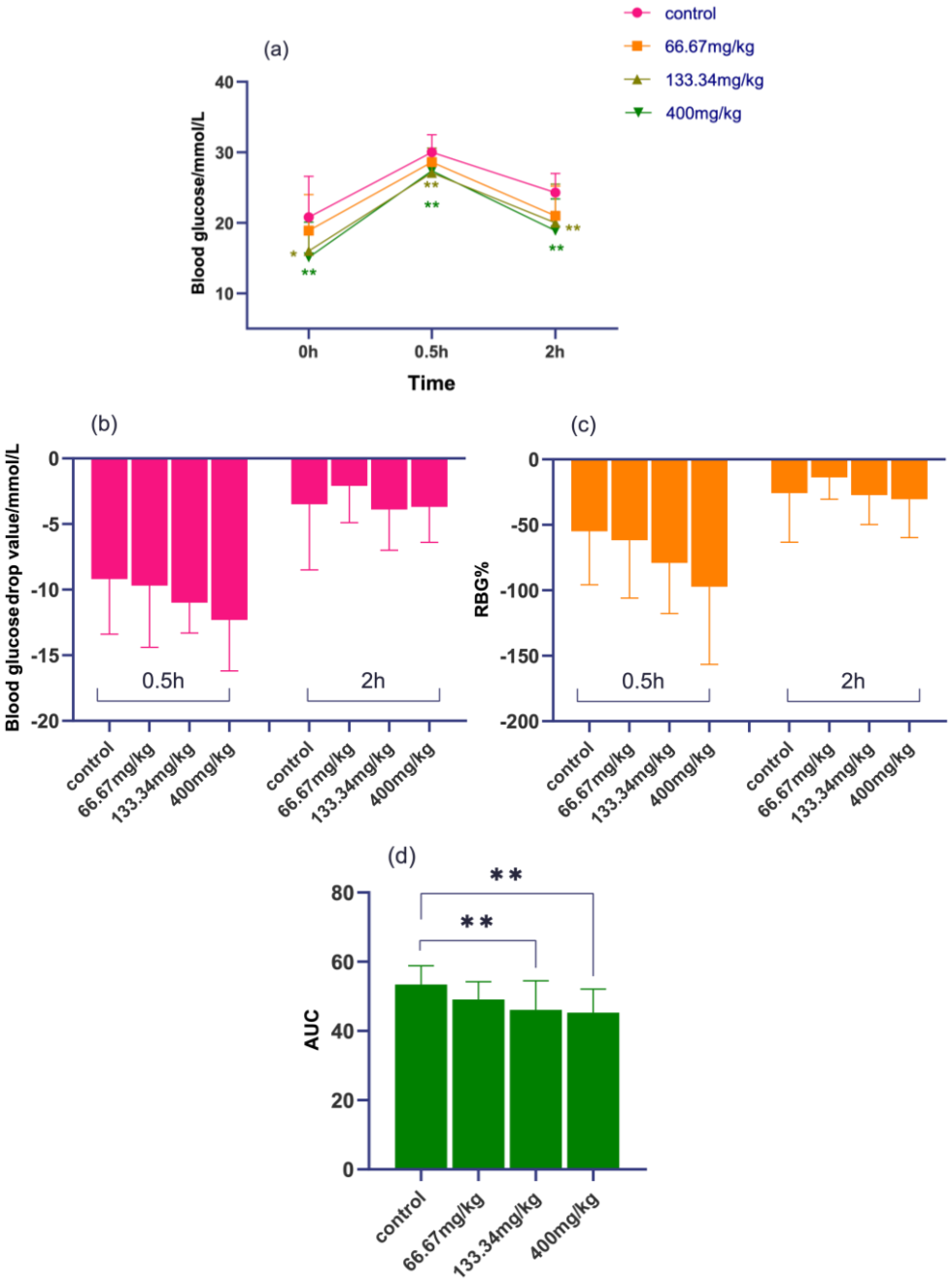


Figure 3. (a) Blood glucose levels of mice at 0.5 h and 2 h after intragastric administration of glucose. (b) Blood glucose rises after intragastric administration of glucose, and the value calculated by the formula is negative. Each group had different degrees of reduction in the peak blood glucose level after intragastric glucose administration. The higher the dose, the more pronounced the effect, but still no significant difference was seen. (c) The blood glucose reduction percentage (RBG%). (d) The area under the blood glucose curve (AUC). As the dose increases, the effect of improving glucose tolerance increases. The data are presented as the means ± SD (n=15), *P < 0.05, ** p < 0.01 vs the Model Control group.

DISCUSSION

In an alloxan-induced hyperglycemic mouse model, administration of the dietary compound tablet effectively modulated blood glucose levels and enhanced glucose tolerance. Medium and high doses resulted in a significant reduction in fasting blood glucose, accompanied by a pronounced decrease in the area under the blood glucose curve (AUC). These outcomes suggest that the tablet exerts meaningful hypoglycemic effects, potentially through multiple underlying pathways.

Mechanisms of Glucose-Lowering Action: This study revealed that a multi-ingredient tablet—comprising cinnamon extract, chromium-rich yeast, mulberry leaf extract, zinc citrate, and selenium-rich yeast—significantly reduced both fasting blood glucose and the area under the glucose curve (AUC) in mice with alloxan-induced hyperglycemia. The glycemic improvements observed in a dose-dependent manner underscore the formulation's potential as a therapeutic agent. These benefits are likely driven by the synergistic actions of bioactive constituents from each component, collectively contributing to glucose metabolic regulation through distinct but complementary pathways.

Cinnamon extract contains abundant cinnamaldehyde and various polyphenols that have been reported to enhance insulin receptor autophosphorylation and stimulate GLUT4 translocation, thereby promoting glucose uptake in peripheral tissues [16]. In addition, these polyphenols exhibit anti-inflammatory properties and regulate hepatic gluconeogenesis, which collectively contribute to the enhancement of insulin sensitivity.

Chromium-rich yeast supplies trivalent chromium (Cr^{3+}), an essential cofactor involved in insulin signaling pathways. By interacting with low-molecular-weight chromium-binding substances, chromium facilitates the activation of insulin receptor kinase, thereby enhancing glucose uptake and increasing cellular insulin sensitivity [17]. Recent evidence further supports that chromium supplementation ameliorates glucose tolerance and lipid profiles in diabetic models, reinforcing its significance in metabolic homeostasis.

Mulberry leaves are rich in bioactive compounds with hypoglycemic activity, notably 1-deoxynojirimycin (DNJ), flavonoids, and polysaccharides. Flavonoids, in particular, mediate glucose reduction via several pathways. They inhibit α-glucosidase, which slows carbohydrate breakdown and diminishes postprandial glucose spikes [18]. Additionally, flavonoids improve insulin sensitivity by activating the PI3K/Akt signaling cascade and facilitating GLUT4 translocation to the plasma membrane, thereby enhancing peripheral glucose uptake [19]. These compounds may also suppress intestinal glucose transporters such as SGLT1 and GLUT2, further limiting glucose absorption [20]. Together, these complementary actions contribute to better glycemic control and suggest mulberry flavonoids as promising agents for adjunct diabetes management.

Zinc citrate provides bioavailable zinc ions that are crucial for the synthesis, storage, and secretion of insulin. Beyond its role in insulin production, zinc exhibits antioxidant properties by neutralizing reactive oxygen species and regulating inflammatory signaling pathways, which helps preserve pancreatic β-cell integrity [21]. Furthermore, zinc contributes to insulin signaling, promoting enhanced glucose uptake at the cellular level.

Selenium-rich yeast supplies selenomethionine, a bioavailable organic form of selenium that contributes to antioxidant defense systems through selenoproteins such as glutathione peroxidase (GPx). Selenium plays a critical role in alleviating oxidative stress, which is closely associated with insulin resistance, pancreatic β-cell impairment, and disrupted insulin secretion—central features in type 2 diabetes mellitus (T2DM) pathogenesis [22]. Studies indicate that selenium deficiency reduces GPx activity, increasing oxidative damage and thereby

accelerating T2DM progression. By attenuating oxidative stress and safeguarding β-cell functionality, selenium may help maintain glucose balance [23].

Together, these bioactive compounds exert synergistic effects that target multiple aspects of glycemic regulation. Cinnamon extract and chromium-rich yeast primarily improve insulin signaling and facilitate glucose uptake in peripheral tissues, whereas mulberry leaf extract influences carbohydrate metabolism to limit glucose absorption. Zinc and selenium support pancreatic β-cell health and mitigate oxidative stress, thereby sustaining endogenous insulin synthesis and function. By concurrently addressing several key pathological mechanisms underlying hyperglycemia, this multi-component formulation may offer superior therapeutic benefits compared to single-agent treatments. This also suggests that these multi-bioactive compound formulations have the potential to be developed into various dosage forms in future applications. Such diversification could lead to the creation of a range of functional food products with enhanced versatility and targeted health benefits.

Dose dependence and implications for therapeutic use in diabetes: A key finding of this study is the dose-dependent glucose-lowering effect of the dietary compound tablet, with significant efficacy observed at medium and high doses, whereas the low-dose group showed no statistically meaningful difference from the control. This dose-response relationship highlights the importance of determining an optimal therapeutic dose that maximizes efficacy while ensuring safety. These results provide a foundation for future clinical investigations in humans to confirm the tablet's potential as an adjunctive therapy for diabetes management.

Improvement of glucose tolerance and implications for prediabetes: Impaired glucose tolerance is a defining feature of prediabetes and serves as a strong predictor for the development of diabetes. Consequently, enhancing glucose tolerance is a critical component of diabetes prevention strategies. In the present study, administration of the compound tablet significantly decreased the area under the glucose curve (AUC) in hyperglycemic mice, reflecting improved glucose tolerance. These findings imply that the formulation could be effective not only in managing established diabetes but also in postponing disease onset among individuals with compromised glucose metabolism.

This possibility aligns with previous research outcomes. For example, multiple clinical studies have demonstrated that cinnamon supplementation can significantly lower fasting blood glucose and enhance glucose tolerance in individuals with prediabetes [24–26]. Moreover, a randomized controlled trial showed that daily administration of 30 mg zinc sulfate for six months notably improved fasting glucose levels, insulin sensitivity, and β-cell function in prediabetic patients [27]. These results suggest that a multi-component tablet similar to the one investigated here could serve as a promising strategy for diabetes prevention in at-risk populations. However, further clinical investigations are necessary to validate its effectiveness in this group.

Study Limitations and Future Directions: Although this study yielded encouraging results in an animal model, several limitations should be acknowledged. Firstly, the data derive from a mouse model, which may limit the direct applicability of the findings to human physiology, particularly in populations with prediabetes or diabetes. Secondly, as an initial proof-of-concept investigation, the detailed molecular mechanisms by which the compound tablet exerts its effects were not thoroughly examined. Recent studies suggest that bioactive components of mulberry leaf extract—such as alkaloids, flavonoids, and polysaccharides—play roles in regulating glucose, amino acid, and lipid metabolism. Notably, compounds like 1-deoxynojirimycin (DNJ) and isoquercitrin (QG) have been shown to enhance glucose uptake, stimulate

differentiation in HepG2 cells, and upregulate critical metabolic regulators including PPARγ, C/EBPα, and SREBP-1 in 3T3-L1 adipocytes. Furthermore, these constituents may offer protection against advanced glycation end-products (AGEs)-induced damage and apoptosis in GLUTag cells via modulation of the AGEs/RAGE axis and p38 MAPK/NF-κB signaling pathways [28].

To gain a thorough understanding of the underlying mechanisms, future research should employ molecular and cellular techniques to elucidate the specific biological targets of each constituent and evaluate their potential synergistic effects. These mechanistic insights are crucial for refining the formulation and facilitating its advancement toward clinical use.

CONCLUSIONS: In conclusion, this study presents preliminary evidence that the dietary compound tablet effectively lowers blood glucose levels and enhances glucose tolerance in a hyperglycemic mouse model. The results provide an initial basis for dosing considerations in its potential application as an adjunctive therapy for diabetes. Nevertheless, further investigations are necessary to confirm clinical efficacy and safety, as well as to clarify the molecular mechanisms involved.

Abbreviations: FBG: fasting blood glucose, RBG: blood glucose reduction percentage, AUC: The area under the blood glucose curve, G_{before}: blood glucose value before the experiment, G_{after}: blood glucose value after the experiment, G_0: 0 hour blood glucose, $G_{0.5}$: 0.5 hour blood glucose, G_2: 2 hour blood glucose

Author contributions: B.X.: Conceptualization, methodology, formal analysis, data curation, supervision, writing – original draft. P.C.: Conceptualization, methodology, writing – review & editing. C.X.: and Y.H.: Conceptualization, investigation, resources. W.Z.: Writing – review & editing, supervision.

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Conflict of interest: Authors B.X., P.C., C.X., Y.H. were employed by the company SIRIO Pharma Co., Ltd. W.Z. serves as a senior expert, providing nutrition consultancy to Sirio Pharma. The funding source was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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