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Comparative Evaluation of the Antidiabetic Effect of Flavonoids Dihydroquercetin and Thamiflaside

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Abstract

Diabetes mellitus (DM) is a major global health burden, ranking among the top three diseases leading to disability and mortality. Although some flavonoids exhibit antidiabetic properties, the effects of many remain insufficiently explored. This study investigates the potential of 2 flavonoids—dihydroquercetin (DHQ) and thamiflaside (TF)—to mitigate alloxan-induced diabetes in rats, thereby addressing an important gap in current knowledge. Male rats were divided into 4 groups: Negative control, diabetic (positive control), and two treatment groups receiving either DHQ or TF (30 mg/kg/day, per os) following alloxan induction (50 mg/kg/day, intraperitoneally for 3 days). Alloxan administration resulted in significant hyperglycemia, polydipsia, polyuria, and elevated levels of serum glucose, triglycerides, cholesterol, α-amylase, ALT, and AST, as well as increased maltase and sucrase activity in the small intestinal mucosa. Conversely, levels of insulin, total protein, alkaline phosphatase, and glutathione peroxidase were significantly reduced. DHQ treatment led to marked improvements in fluid balance, glycemic control, lipid profile, enzyme activity in serum, and disaccharidase activity in the intestinal mucosa. Notably, DHQ showed a stronger corrective effect than TF across most parameters. These findings highlight DHQ as a promising candidate for the treatment of diabetes and its associated metabolic disturbances, while also supporting TF as a potential alternative.

Keywords: Alloxan diabetes, Dihydroquercetin, Thamiflaside, Blood biochemical parameters, Intestinal alpha glucosidases activity

Introduction

Diabetes mellitus is one of the most serious metabolic disorders, characterized by impaired metabolism of carbohydrates, proteins, and fats [1]. It is projected that the global number of diabetic patients will reach 366 million by 2030 [2]. The disease arises either from insufficient insulin secretion or reduced sensitivity of insulin receptors [3,4]. Hyperglycemia-induced oxidative stress is considered a major mechanism of pancreatic β-cell damage, leading to elevated blood glucose levels and the progression of diabetes mellitus [5,6]. Additionally, enhanced glucose absorption in the small intestinal epithelium, particularly in type 2 diabetes, further exacerbates hyperglycemia [7,8]. Since α-glucosidases located in the small intestinal epithelium mediate the final step of carbohydrate digestion, their inhibition is a rational therapeutic target in diabetes management [9-13].

Despite the widespread use of antidiabetic drugs, many are associated with significant side effects, such

as hypoglycemia, cytotoxicity, and increased risk of bone fractures and other complications [14-22]. This has prompted a growing interest in alternative therapies, especially those with antioxidant and anti-inflammatory properties. Flavonoids—polyphenolic compounds found in various plants—have attracted considerable attention due to their potential roles in modulating insulin signaling, secretion, carbohydrate metabolism, and lipid homeostasis [23,24]. However, the antidiabetic potential of many naturally occurring flavonoids remains underexplored.

Among these, dihydroquercetin (DHQ), a flavonoid with well-established antioxidant activity [25-27], has also been reported to exert anti-inflammatory, anticancer, reparative, and nephroprotective effects [28-30]. Thamiflaside (TF), another bioactive compound, together with DHQ, has demonstrated protective effects on pancreatic enzyme secretion in L-arginine-induced pancreatitis models [31]. Considering the known interplay between exocrine and endocrine pancreatic dysfunctions in diabetes, it is crucial to evaluate whether these compounds can also correct endocrine pancreatic disturbances.

The aim of this study is to compare the corrective effects of DHQ and TF on selected biochemical and functional parameters in rats with alloxan-induced diabetes.

Materials and methods

Chemicals

In this study, 2 flavonoid-based compounds were utilized: The natural antioxidant dihydroquercetin (DHQ) and the semi-synthetic derivative thamiflaside. DHQ is well known for its cardioprotective, antioxidant, and glucose-regulating properties. Thamiflaside, designed based on a flavonoid backbone, was evaluated in parallel to assess its pharmacokinetic and therapeutic potential [32]. Both compounds were investigated using an alloxan-induced diabetes model in rats to compare their antidiabetic efficacy (**Figure 1**).

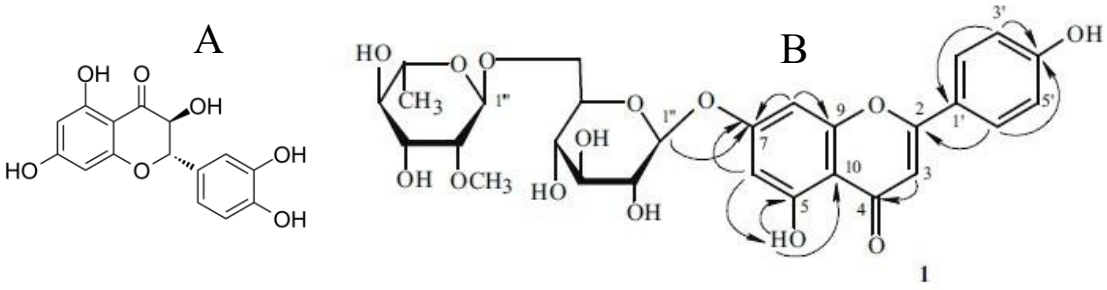

Figure 1 Chemical structures of the investigated flavonoid compounds: (A) Dihydroquercetin (DHQ) – a naturally occurring flavanonol with known antioxidant and cardioprotective properties; and (B) Thamiflaside – a synthetic flavonoid derivative structurally modified to enhance solubility and potential therapeutic activity.

Animal ethics

The experiments were performed on white inbreed male rats weighing 10 - 200 g, grown in the vivarium of the National University of Uzbekistan. The animals were kept in plastic cages measuring 36×20×15 cm^3, 4 in each, on a vivarium diet, at room temperature and natural light-dark conditions with unlimited access to water and food. The experiments were conducted according to the Helsinki Declaration of the World Medical Association 2010. Permission to conduct experiments was also obtained from the Committee of the Institute of Biochemistry and Physiology at the University of Uzbekistan on the Humane Treatment of Laboratory Animals and Bioethics (No. BEC/IBB-NUU2024/13-1).

Alloxan diabetes model

Diabetes in rats was induced by intraperitoneally injection of alloxan monohydrate (Chemlaborreaktiv LLC, Ukraine) at a dose of 50 mg/kg/24 h for 3 days. If the blood glucose level exceeded 15 mmol/l, the rats were considered diabetic and were used for further observations. Rats with alloxan diabetes (AD) were divided into 3 equal groups (n = 6). The first group of rats with AD was treated intragastrically with 0.3% dimethyl sulfoxide (DMSO) solution, i.e. it served as a negative control. Other 2 groups of diabetic rats, were

treated intragastrically with a well-known flavonoid DHQ (Elavar, Russia), and a little-studied one TF separated from *Thalictrum minus* in the laboratory of flavonoids and coumarins in the Institute of the Chemistry of Plant Substances of Uzbekistan [33]. Solutions of DHQ and TF in 0.3% DMSO solution were received by rats intragastrically for 28 days daily at a dose of 30 mg/kg/24 h in the morning between 9.00 and 10.00. The positive control group of rats instead of flavonoids was intragastrically received 0.3% DMSO solution at the same time and in an equivalent volume as in the experimental groups.

Urine analysis

Determination of the volume of drunken water and excreted urine was carried out using special metabolic cages DXL-D (China) for rodents. The cage has a special design that ensures the measure of the water volume from a graduated drinking bottle and collects urine in a graduated cylinder. The design of the cage allows to reduce the stress level to a minimum. Funnel for collecting urine is easily removed when turning around the axis of the cage, without causing discomfort to the animal.

Blood analysis

Blood for biochemical analyses was obtained during decapitation of overnight-fasted rats. The decapitation was made at the end of the second and forth weeks of observation, respectively. Blood samples were settled and then centrifuged in a DLAB D2012 centrifuge (China) at 3,000 rpm for 10 min. Serum was carefully is carefully removed using a Pasteur pipette and used for biochemical analyses. The insulin level and glutathione peroxidase (GPO) activity were determined using the ELISA Kits (Dublin, Ireland) reagent kit on the immunoassay analyzer RT-2100C Microplate Reader Rayto (China).

The content of glucose, triglycerides, cholesterol, as well as the activity of α-amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and the total protein content in the blood serum and supernatant of the small intestinal mucosa were determined on a biochemical analyzer RT-1904C (China) using the kits “Human”, (Germany).

To determine the activity of intestinal disaccharidases after decapitation, the abdominal cavity of rats was opened, the small intestine was removed, cleaned of fatty tissue and weighed. Then the small intestine was washed with 10 mL of cooled Ringer’s solution and cut lengthwise. The mucosal layer was carefully separated with a plastic spatula. The mucosa was diluted in a ratio of 1/9 with cooled Ringer’s solution (pH –7.4) and was ground using a Teflon homogenizer at 300 rpm for 1 min, then centrifuged at 1,500 rpm for 15 min. In the obtained supernatant, the activities of maltase (EC 3.2.1.20) and sucrase (EC 3.2.1.48) were determined.

Sucrase and maltase activities

To determine sucrase and maltase activities, 0.1 mL of 2% sucrose (Sigma-Aldrich, USA) or maltose (Sigma-Aldrich, USA) solution was added to 0.1 mL of small intestine supernatant. The resulting mixture was incubated for 30 min at 37 - 38 °C. The glucose concentration in the incubate increased due to the monomer formed during maltose and sucrose hydrolysis under the influence of small intestinal α-glucosidases. The glucose content in incubate was determined using an RT-1904C biochemical analyzer (China). The enzyme activity was expressed as μmol of reducing glucose per min of incubation per 1 g of protein of intestinal mucosa.

Statistics

Calculation of the mean and standard error was carried out by pairwise comparison using Student’s t-test. The arithmetic mean (M), the standard error of the mean (m), and the significant coefficient (P) were defined. If the p value was less than 0.05, the difference between the control and experimental rat groups was considered statistically significant.

Results and discussion

The body weight

The body weight of rats with AD decreased by 8.6% compared to the control value. In diabetic rats that were given DHQ intragastrically, the body weight was at the same level as in the control group, but In rats with induced pathology, which were administered TF daily, body weight was at the same level as in rats with AD (**Figure 2**).

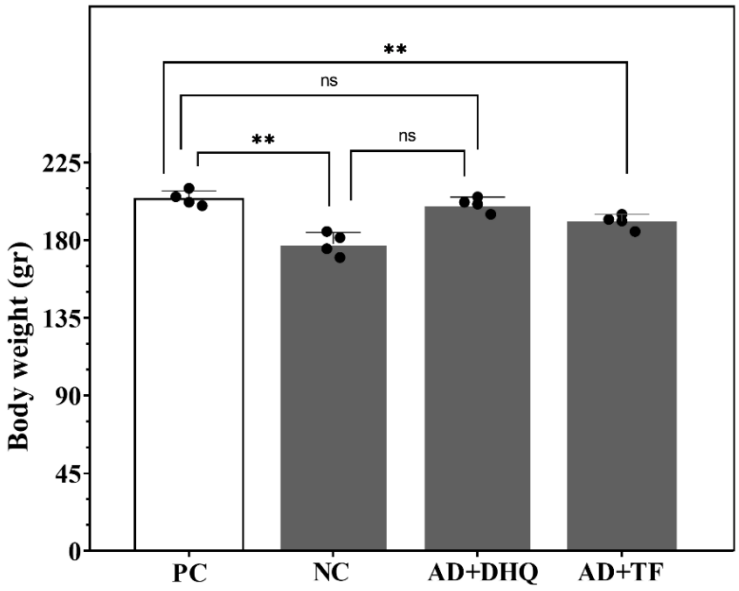

Figure 2 Effect of intragastric administration of DHQ and TF on the body weight (g) of rats with AD (M ± m, n = 6).
Note: PC, NC, AD+DHQ and AD+TF – positive control, negative control as well as groups of rat with AD that were daily administered DHQ and TF, respectively: * - $p < 0.05$; ** - $p < 0.01$ regarding to the positive control; & - $p < 0.05$ – regarding to the negative control.

Consumed water and excreted urine.

As expected, AD led to a significant increase in the volume of drunk water. Thus, on the end of the 2th week of observations in rats with AD, the volume of drunk water was 2.4 times more than in the positive control group rats. In diabetic rats that were administered DHQ and TF, the increasing of volume of drunk water was, respectively 2.2 and 2.3 times greater, compared to parameters of negative control animals i.e. it remained quite high. By the end of the 4th week of observation, the volume of water drunk by rats that had received alloxan intragastrically had increased even more, by 2.7 times, compared to rats treated with solvent. However, in diabetic animals that had been administered DHQ, although water consumption had decreased compared to the 2nd week, it remained 1.7 times greater than the positive control values. An increase in the duration of TF administration to rats with AD had no effect on the volume of their water drunk (**Table 1**).

An increase in the volume of drunk water in diabetic rats also affected the excreted urine volume. In the second week of observations the rats of negative control group and diabetic rats treated with DHQ and TF produced 2.7, 1.8 and 2.4 times more daily urine than positive control animals respectively on the 2th week of experiments. By the end of the observation, in rats with AD increasing of the urine volume had got 3 times, in diabetic rats administered DHQ the execrated urine volume was decreased but it was higher than in control rats. The duration of TF treatment did not affect on the intensity of urination in rats (**Table 1**).

Table 1 Effect of intragastric administration of DHQ and TF on the volume of consumed water (mL) and excreted urine (mL) in rats with AD (M ± m, n = 6).

Animal groups	Experiment days	
	14	28
	Water	
PC	16.1 ± 1.2	12.6 ± 0.9
NC	38.4 ± 2.1***	37.3 ± 1.8***

Animal groups	Experiment days	
	14	**28**
AD+DHQ	34.9 ± 2.2***&&&	24.1 ± 1.2***&&&
AD+TF	36.9 ± 2.3***	29.4 ± 2.3***&&
	Urine	
PC	12 ± 0.6	12.6 ± 0.9
NC	32.3 ± 1.1***	37.3 ± 1.8***
AD+DHQ	22.1 ± 1.6***&&&	24.1 ± 1.2***&&&
AD+TF	29.6 ± 0.0	29.4 ± 1.3***&&&

Note: bPC, NC, AD+DHQ and AD+TF – positive control, negative control and groups of rats with AD that were daily administered DHQ and TF, respectively: * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$ regarding to the positive control; &&& - regarding to negative control.

Insulin level. On the 14th day of observation in rats with AD, the serum insulin level decreased by 35.9% compared to the parameters of healthy animals. However, in diabetic rats administered with DHQ the insulin level increased by 20% compare level in rats with AD, but it remained below the positive control values by 23.1%. The corrective effect of TF on the restoration of insulin was not registrated on the 14th day of experiment.

By the end 4th week of observation, the insulin level in diabetic rats compared to healthy animals decreased even more by 42.1% compared to the second week. But in diabetic rats treated with DHQ, the serum insulin level was by 63.6 % higher than in rats with AD and manifested itself at the control level. The corrective effect of TF on insulin restoration has already been demonstrated; the hormone level in diabetic rats receiving TF was 27.3% higher than in negative control rats, but lower by 21.4% than in animals in the positive control animals (**Figure 3**).

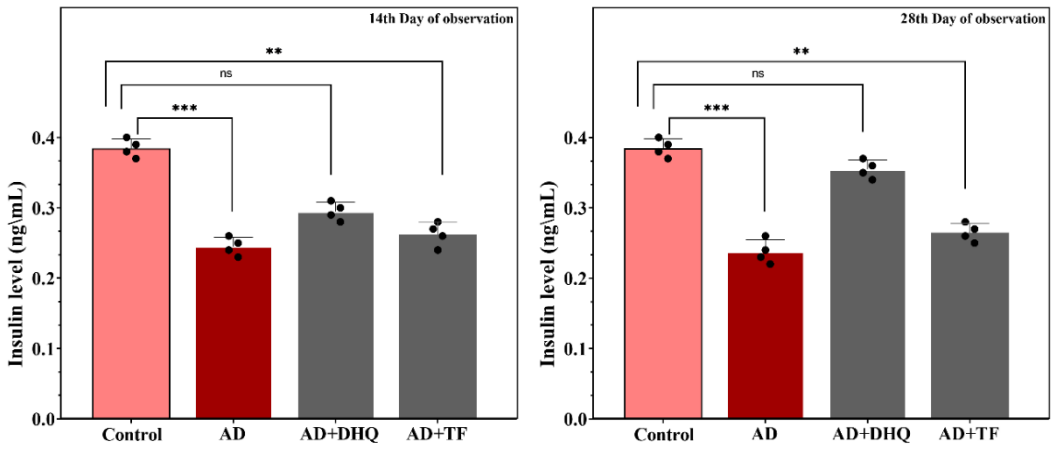

Figure 3 Effect of intragastric administration of DHQ and TF on the serum insulin level (ng/mL) of rats with AD (M±m, n = 6). PC, NC, AD+DHQ and AD+TF – positive control, negative control and groups of rats with AD that were daily administered DHQ and TF, respectively: * - $p < 0.05$; ** - $p < 0.01$ regarding to the positive control. ** - $p < 0.05$; *** - $p < 0.01$ regarding to positive control; &- $p < 0.05$; &&$ - $p < 0.001$ regarding to negative control.

Glucose level

On the 14th day of observation in negative control group rats the serum glucose level increased by 241.2%, while in diabetic rats treated with DHQ and TF such an increase compared to the positive control animals was 102.0% and 211.8%, i.e. a slightly normalizing effect on

the glucose level in the blood serum was manifested only for DHQ. By the end of the experiments, i.e. on the 28th day of observation, the glucose level in diabetic rats was increased by 269.4%; and in diabetic rats treated with DHQ and TF by 71.4% and 162.2%, respectively, compared to the positive control. In that case although glucose did not reach the control level the normalizing effect of DHQ on the glucose level in the blood was more pronounced compared to TF (**Figure 4**).

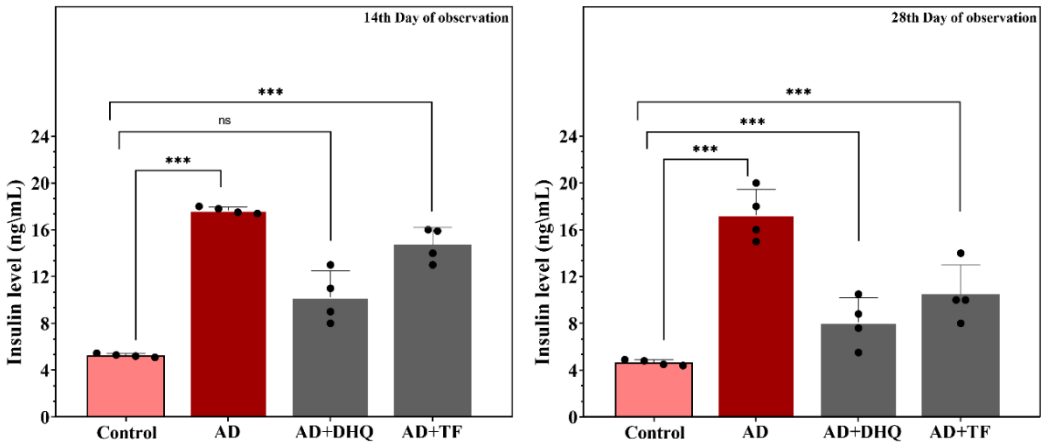

Figure 4 Effect of intragastric administration of DHQ and TF on the glucose (mmol/l) of rats with AD (M±m, n = 6). Note: PC, NC, AD+DHQ and AD+TF – positive control, negative control and groups of rats with AD that were daily administered DHQ and TF, respectively: *- $p < 0.05$; ** - $p < 0.01$ regarding to the positive control. $^{\&\&}$- $p < 0.01$; $^{\&\&\&}$ - $p < 0.001$ regarding to negative control.

Triglycerides, cholesterol and total protein level

The serum triglycerides, cholesterol level in rats with AD increased by 37.5% and 31.2% compared to the control animals. After 28 administration of DHQ to rats with AD, the triglyceride and cholesterol content reached the level of positive control animals. The total protein content in rats with AD did not increase, but on the contrary, decrease by 17.9%. The introduction of both DHQ and TF to rats with AD led to an increase in the total protein level to the positive control level (**Table 2**).

Table 2 Effect of intragastric administration of DHQ and TF on the level of triglycerides, total protein and cholesterol in the serum of rats with AD (M ± m, n = 6).

Animal groups	Triglycerides (mg/dl)	Cholesterol (µ/L)	Total protein (g/L)
PC	151.3 ± 8.5	8.4 ± 0.9	74.5 ± 4.4
NC	208.1 ± 8.9***	11.1 ± 0.9**	61.2 ± 1.5**
AD+DHQ	159.2 ± 8.9	9.6 ± 1.2	72.4 ± 3.8$^{\&\&}$
AD+TF	199.2 ± 10.6**$^{\&}$	10.2 ± 0.9	74.4 ± 4.4$^{\&\&\&}$

Note: PC, NC, AD+DHQ and AD+TF – positive control, negative control and groups of rats with AD that were daily administered DHQ and TF, respectively: **- $p < 0.05$; *** - $p < 0.01$ regarding to the positive control; &- $p < 0.05$; && - $p < 0.01$; &&& - regarding to the negative control.

Serum enzyme

The activity of blood enzymes was determined after 28-daily administration of flavonoids to rats. In rats with AD, the activities of α-amylase, ALT and ACT were increased by 24.1%, 159.6% and 91.4%, respectively compare to positive control value. Activities of ALP and GPO, on the contrary, were decreased by 24.2% and 33.3%, accordingly. The treatment with DHQ resulted in complete restoration of the activities of α-amylase and ALT. Under the

influence of DHQ, the activities of ACT in diabetic rats remained 45.5% higher than the positive control values, although it was lower than in rats with diabetes. DHQ led to some normalization of ALP and GPO activity, but enzymes activity still remained lower by 21.0% and 12.5%, respectively.

Table 3 Effect of intragastric administration of DHQ and TF on the serum enzyme activity in rats with AD (M ± m, n = 6).

Animal groups	Enzymes				
	α- Amylase	ALT	ACT	ALP	GPO
Control	402.2 ± 32.5	66.4 ± 7.6	58.2 ± 4.	49.5 ± 1.9-	2.4 ± 0.2
NC	499.2 ± 12.1**	172.4 ± 22.1***	111.4 ± 8.8***	37.5 ± 3.0*	1.6 ± 0.1**
AD+DHQ	391.9 ± 24.3$^{\&\&\&}$	82.0 ± 4.1$^{\&\&}$	84.7 ± 4.4**$^{\&}$	39.09 ± 3.1*	2.1 ± 0.3$^{\&}$
AD+TF	489.9 ± 22.1***	123.2 ± 10.1***	101.3 ± 6.1***	39.4 ± 2.7**	1.9 ± 0.1***$^{\&\&}$

Note: *-$p < 0.05$; ** - $p < 0.01$; ***- $p < 0.001$ regarding to positive control; &- $p < 0.05$; &&& - $p < 0.001$ regarding to negative control.

After intragastric administration of TF to rats, the restoration of the enzyme activity took place only for α-amylase. The activity of other enzymes was somewhat close to the positive control values. It should be noted that the corrective effect for TF was less pronounced than for DHQ

Activity of digestive disaccharidases

The small intestine maltase and sucrase activity in rats with AD, as well as the activities of blood enzymes, were also determined at the end of the experiment.

AD led to increase of the activity of disaccharidases in the small intestinal mucosa. In diabetic rats, maltase and sucrase activity was increased by 43.8% and 48.8% respectively. Intragastric administration of DHQ normalized both enzyme activity in rats with AD. Treatment diabetic rats with TF reduced maltase activity by 25.7%, but it was 12.7% higher than in the control. Whereas after the introduction of TF to rats with AD the sucrase activity of the small intestinal mucosa remained at the level of the negative control (**Figure 5**).

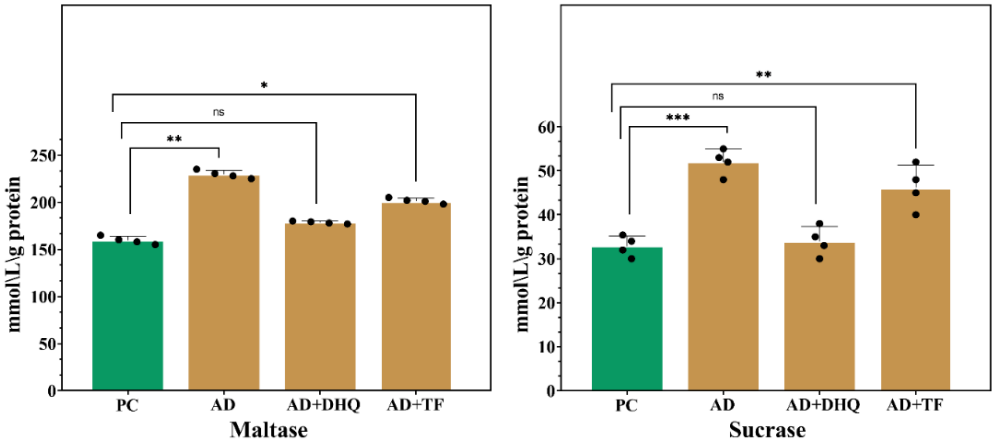

Figure 5 Effect of intragastric administration of DHQ and TF on disaccharidases activity (μ/min/g protein) of the small intestine in rats with AD (M±m, n = 6) Note: *- $p < 0.05$; ** - $p < 0.01$; ***- $p < 0.001$ regarding to positive control; $^{\&}$ - $p < 0.05$; $^{\&\&\&}$ - $p < 0.001$ regarding to negative control.

Triketone alloxan contains a 5-keto group in its structure, which selectively penetrates into pancreatic islet β-cells through a specific glucose transporter GLUT2 and destroys them. In this case, alloxan, binding with glutathione (GSH), generates cytotoxic ROS and, thus, insulin deficiency develops [34]. A decrease in the

level of serum insulin leads to an increase in the glucose level, since insulin is the only hormone that reduces the level of serum glucose by promoting the conversion of blood glucose into glycogen, which is deposited in the liver and muscles [35]. The obtained data indicate that the introduction of alloxan to rats causes disturbances not only in insulin and glucose level, but also in other physiological and biochemical processes, which is manifested in polydipsia, polyuria, hyperlipidemia, hypoproteinemia, changes in the activity of enzymes in the serum and small intestine mucous. It is proven that hyperglycemia and hyperlipidemia promote the accumulation of reactive oxygen species, leading primarily to damage to cell membranes [36]. In chronic hyperglycemia, the biological antioxidants also get depleted along with a reduction in glutathione (GSH), an increase in the oxidized glutathione (GSSG)/GSH ratio, and a depletion of non-enzymatic antioxidants [37].

Currently, plant compounds are increasingly used to correct diabetes, as they have fewer side effects than other anti-diabetic drugs used. Among them, flavonoids are of particular interest, because their antioxidant activity prevents the development of oxidative stress and they can affect the signaling and regulatory cellular systems [6]. The hypoglycemic and hypolipidemic effects of rutin, kaempferol, naringenin and other plant flavonoids have been widely studied *in vitro* and *in vivo*, as well as in clinical practice [38]. The antidiabetic properties of the DHQ analogue quercetin have been also well researched [23,39]. However, the antidiabetic properties of many other flavonoids including DHQ and TF, have not yet been analyzed.

The results have shown that the applied flavonoids have different effects on the normalization of water intake and urine output in rats with AD, as well as blood parameters and carbohydrate hydrolysis in the small intestine. Serum glucose, triglyceride, cholesterol and total protein levels in DHQ-treated diabetic rats were closer to those of the positive control compared to those in TF-treated diabetic rats. Similarly, the decreased serum insulin levels in diabetic rats were markedly restored by intragastrically administration of DHQ and somewhat approached those of healthy animals by the same treatment of TF.

The results showed that the levels of amylase, ALT and AST activity in diabetic rats treated with DHQ or TA were close to normal, whereas in rats treated with alloxan the levels were significantly increased (ALT, AST) or, on the contrary, decreased (ALP) compared to the positive control. These shifts were largely prevented by DHQ and partially by TA. Diabetes-induced oxidative stress was largely prevented by DHQ and partially by TA. This is evidenced by the fact that in diabetic animals treated with DHQ the level of GPO reached the norm, and in rats treated with TF the level of this antioxidant enzyme, although approaching the norm, was statistically significantly lower than the positive control. Based on these data, it can be assumed that the change in the activity of α-amylase, ALT, AST in diabetic rats is most likely due to diabetes-dependent glycolytic oxidative stress. The hypoglycemic effects of DHQ and TF in diabetic rats may be associated with the restoration of the activity of pancreatic (α-amylase) or liver (ALT, AST) enzymes directly or indirectly involved in the regulation of serum glucose levels.

In addition to the obvious antioxidant properties of DHQ, which, unlike TF, completely restores GPO activity in diabetic rats, DHQ suppresses AD-induced intestinal maltase activity to a greater extent than TF. Maltase, in turn, is an enzyme that leads to the formation of glucose from maltose, which is involved in increasing blood glucose levels. Consequently, the possibility of glucose entering the bloodstream from the small intestinal cavity during the correction of diabetes with DHA is less than during the correction of diabetes with TF.

Thus, alloxan diabetes causes the development of metabolic changes in rats, which are partially normalized in blood parameters and completely in the small intestinal mucosa after chronic intragastric administration of DHQ. The antidiabetic effect of TF on these parameters. is expressed somewhat weaker. The obtained data indicate that the spectrum of positive therapeutic properties of DHQ can be expanded by adding to them its antidiabetic properties, which were discovered in this experimental study.

In silico ADMET and druglikeness profile of dihydroquercetin and thamiflaside

The pharmacokinetic profiles, drug-likeness properties, and medicinal chemistry alerts of dihydroquercetin (DHQ) and thamiflaside were comparatively analyzed using computational prediction

tools (Table X). In terms of water solubility, both compounds were moderately soluble, with DHQ showing a slightly lower Log S (Ali: –3.21) than thamiflaside (–2.22), indicating reduced aqueous solubility. Nevertheless, DHQ exhibited high gastrointestinal (GI) absorption, whereas thamiflaside showed low absorption, suggesting limited oral bioavailability. Neither compound was predicted to be blood-brain barrier (BBB) permeant, which could be beneficial in limiting central nervous system side effects [11,12]. DHQ demonstrated more favorable skin permeability (Log K_p: –7.48 cm/s) compared to thamiflaside (–11.83 cm/s), suggesting better dermal diffusion potential. Caco-2 permeability, a marker for intestinal absorption, was slightly more favorable for DHQ (–6.311) than for thamiflaside (–6.399), albeit both values fall within the range of poor permeability. In terms of druglikeness, DHQ satisfied all three major filters (Lipinski, Ghose, and Muegge), whereas thamiflaside failed to comply with any, suggesting a less favorable pharmacophore profile. Additionally, the bioavailability score of DHQ (0.55) was significantly higher than that of thamiflaside (0.17), reinforcing the superior drug-like nature of DHQ [39,40]. From a medicinal chemistry perspective, DHQ showed one structural alert for PAINS (Pan Assay Interference Compounds), and was flagged as lead-like. Conversely, thamiflaside exhibited no PAINS liability but was not considered lead-like. Taken together, these *in silico* findings indicate that dihydroquercetin possesses a more favorable ADMET and druglikeness profile compared to thamiflaside, supporting its potential as a promising candidate for further preclinical evaluation (**Table 4**).

Table 4 Comparison of pharmacokinetic properties, water solubility, druglikeness, and medicinal chemistry alerts of dihydroquercetin and thamiflaside.

Compounds	Water solubility		Pharmacokinetics				Druglikeness			Medicinal chemistry		
	Log S (ESOL)	Log S (Ali)	G_i absorption	BBB permeant	Log K_p	Caco-2 Permeability	Lipinski	Ghose	Muegge	Bioavailability Score	PAINS	Leadlikeness
Dihydroquercetin	−2.66	−3.21	High	No	−7.48 cm/s	−6.311	Yes	Yes	Yes	0.55	1	Yes
Thamiflaside	−1.75	−2.22	Low	No	−11.83 cm/s	−6.399	No	No	No	0.17	0	No

The table summarizes key ADMET parameters including predicted water solubility (LogS), gastrointestinal absorption, blood-brain barrier (BBB) permeability, lipophilicity (Log K < sub > p < /sub >), Caco-2 permeability, compliance with drug-likeness filters (Lipinski, Ghose, Muegge), bioavailability score, and medicinal chemistry alerts (PAINS and lead-likeness).

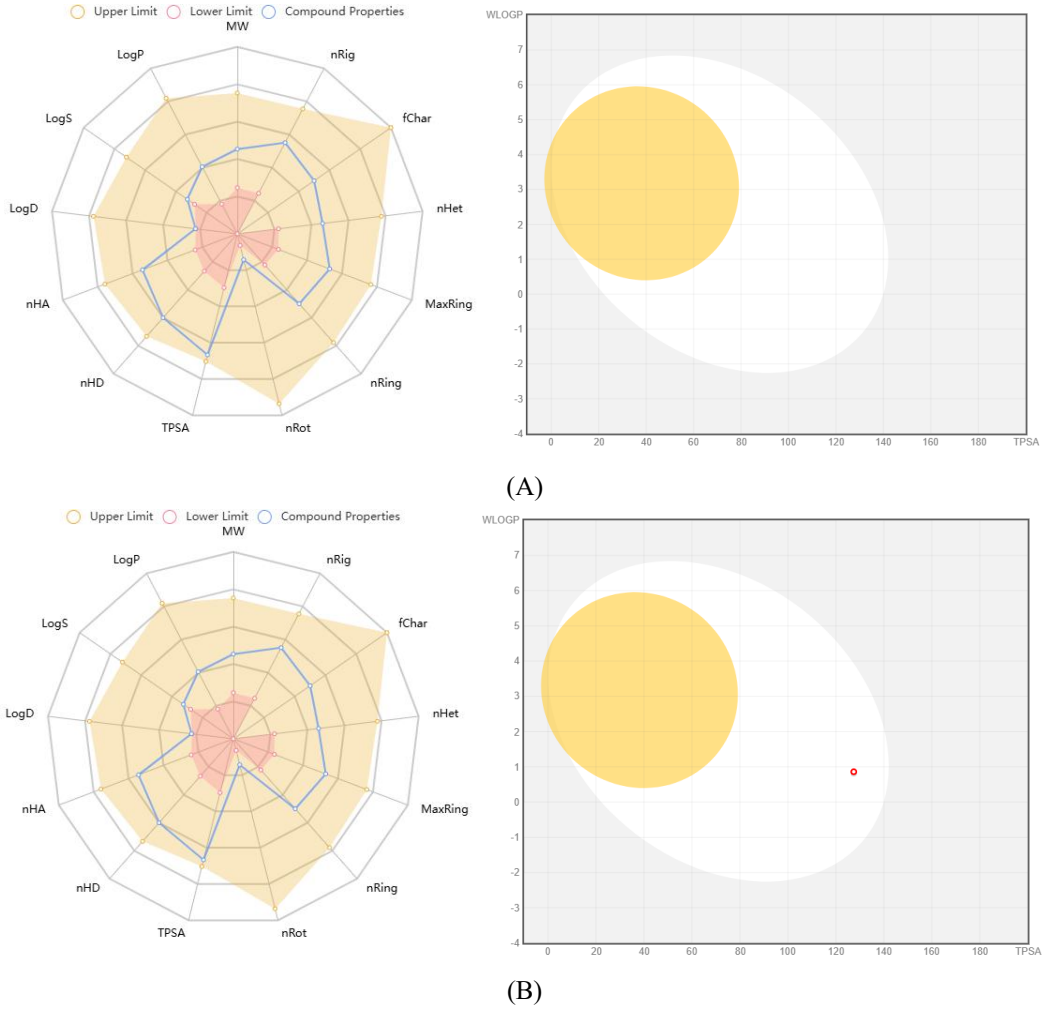

Figure 6 Pharmacokinetic analysis of (A) Thamiflaside and (B) Dihydroquercetin using ADMETlab and SwissADME platforms. Radar plots represent key physicochemical and drug-likeness parameters (e.g., MW, LogP, TPSA, rotatable bonds, H-bond donors/acceptors) in relation to optimal ranges for oral bioavailability. The adjacent ellipsoid diagrams indicate the bioavailability radar, where yellow regions reflect favorable pharmacokinetic space. The position of each compound illustrates its compliance with drug-likeness and oral bioavailability criteria.

Discussion

The present study evaluated the antidiabetic efficacy of 2 flavonoid compounds—Dihydroquercetin (DHQ) and Thamiflaside (TF)—in a rat model of alloxan-induced diabetes (AD). The investigation encompassed physiological, biochemical, enzymatic, and pharmacokinetic parameters, with the results demonstrating that DHQ exerted more pronounced protective effects than TF across most endpoints.

Pharmacokinetic profiling indicated that DHQ possessed more favorable drug-likeness and bioavailability characteristics compared to TF. *In silico* predictions (SwissADME and ADMETlab) showed that DHQ met several key drug-likeness criteria, including Lipinski, Ghose, and Muegge rules. It exhibited higher gastrointestinal absorption, moderate water solubility, and a favorable bioavailability score (0.55), supporting its suitability for oral administration. Conversely, TF demonstrated lower predicted GI absorption, failed multiple drug-likeness filters, and showed a considerably lower bioavailability score (0.17). These factors likely contributed to the superior *in vivo* performance of DHQ in ameliorating diabetic symptoms due to better systemic absorption and distribution.

In terms of body weight regulation, DHQ-treated rats-maintained a near-normal growth trajectory, while those treated with TF exhibited no significant improvement compared to untreated diabetic animals. Similarly, DHQ more effectively normalized water

intake and urine output—parameters typically elevated in diabetic conditions—by the fourth week of treatment.

Biochemical analysis revealed that DHQ significantly improved serum insulin levels and reduced hyperglycemia by day 28, restoring insulin concentrations close to those of healthy controls. In contrast, TF had a delayed and less pronounced effect on insulin secretion and glycemic control, likely due to its poor absorption and pharmacokinetic limitations.

DHQ also demonstrated superior efficacy in correcting lipid metabolism abnormalities, significantly lowering elevated triglyceride and cholesterol levels, and reversing hypoproteinemia. TF was less effective in modulating these metabolic disturbances. Antioxidant enzyme assays further supported these outcomes: DHQ normalized glutathione peroxidase (GPO) and α-amylase activities and partially restored liver transaminase levels (ALT, AST), while TF showed minimal impact.

Furthermore, DHQ significantly regulated disaccharidase activity, particularly maltase, thereby reducing glucose absorption in the gut—a key mechanism contributing to its hypoglycemic action. TF did not significantly affect this parameter, further highlighting its inferior pharmacodynamic performance.

In conclusion, DHQ demonstrated a more favorable pharmacological and pharmacokinetic profile than TF in the treatment of experimental diabetes. Its multifactorial mechanism—encompassing enhanced insulin secretion, improved glucose and lipid metabolism, antioxidant activity, and high oral bioavailability—positions DHQ as a promising candidate for further preclinical and clinical research in diabetes therapy.

Conclusions

The present study demonstrates that both DHQ and TF flavonoids exhibit promising hypoglycemic and metabolic regulatory effects in a rat model of alloxan-induced diabetes. Notably, DHQ showed superior efficacy in normalizing not only blood glucose and insulin levels but also intestinal disaccharidase activity (maltase and sucrase), indicating its broader corrective potential in diabetes-related metabolic dysfunctions.

While TF also improved several biochemical markers, its overall performance was less pronounced, particularly in enzyme modulation. However, this does not preclude its therapeutic potential. Future research may explore formulation strategies such as nanoparticle encapsulation, glycoside conjugation, or combination therapy to enhance its bioavailability and target-specific activity.

From a translational perspective, DHQ emerges as a more promising candidate for further development as an antidiabetic agent. Long-term preclinical studies evaluating chronic toxicity, pharmacokinetics, and tissue-specific effects are warranted. In addition, pilot clinical trials would be necessary to validate its efficacy and safety in human subjects.

Together, these findings contribute to the growing evidence that naturally derived flavonoids, particularly DHQ, may serve as effective cytoprotective agents in the management of diabetes and other oxidative stress–related disorders.

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Declaration of Generative AI in Scientific Writing

Only minimal assistance was used from QuillBot for paraphrasing selected sentences. All scientific content, interpretation, and conclusions were developed independently by the authors.

CRediT Author Statement

L Kuchkarova: supervised the study and revised the manuscript. **K Kayumov:** designed the methodology and wrote the draft. **K Eshbakova** and **M Agzamova:** conducted experiments and analyzed data. **N Ergashev** and **I Karimova:** contributed to biochemical assays and interpretation. **S Berdiyarova** and **J Abdurakhmonov:** assisted with animal handling and data collection. **I Abdullaev** and **R Achilov:** contributed to writing and editing. All authors read and approved the final manuscript.

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