

Effect of *Ferula foetida* Extract on the Activity of Disaccharidases in the Small Intestine

Kuchkarova Lubov Salijanovna¹, Qiyomova Nozigul Farxod qizi², Qurbanov Shaniyaz Qurbanovich²,
Eshbakova Kamila Alibekovna³, Kayumov Khasan Yusuf Ogli¹

¹National University of Uzbekistan, Tashkent, Uzbekistan

²Karshi State University, Karshi, Uzbekistan

³Institute of the Chemistry of Plant Substances, Tashkent, Uzbekistan

Abstract Currently, much attention is paid to therapy using herbal medicines, as they have a smaller spectrum of side effects compared to artificial drugs. However, despite the wide range of pharmaceutical properties of widely used in folk and traditional medicine *Ferula foetida*, its effect on the ability to digest carbohydrates in the small intestine has not been studied. Meanwhile, when *F. foetida* or its derivatives enters the small intestine with food and spices, they directly encounter enzymes and can affect the activity of brush border disaccharidases. In this study, the effect of *F. foetida* stem extract on the activity of intestinal disaccharidases, which play a decisive role in regulating the glycemic status of the body, was studied. The results show that daily intragastric administration of *F. foetida* extract for 28 days leads to inhibition of disaccharide digestion in the small intestine of rats. This is manifested in the repression of maltase and sucrase activity against the background of unchanged lactase activity in rats treated with the extract. The inhibitory effect was significantly expressed in the proximal and medial parts of the small intestine, where the disaccharidase activity was highest. These results suggest that *F. foetida*-based spices may be used as an ingredient in products that help prevent hyperglycemia.

Keywords *Ferula foetida*, Small intestine, Maltase, Sucrase, Lactase

1. Introduction

It is known that herbal therapy has a smaller range of side effects compared to artificial drugs due to their natural origin and the presence of many useful components. A synergistic or buffering effect is often observed due to the presence of several compounds that potentially reduce the risk of side effects [1]. For example, *Ferula foetida*, widely used in Ayurveda and traditional medicine, as well as in Asian cuisine, has antioxidant, anti-inflammatory, antispasmodic, neuroprotective, anticancer, anthelmintic and other pharmacological properties [2,3]. However, not all pharmacological effects of this plant have been studied. Indeed, despite the fact that spices and pharmacological agents based on *F. foetida* enter the small intestine with food, their effect on the digestive capacity of the small intestine has been practically unstudied. Meanwhile, the substances of *F. foetida*, having direct contact with brush border digestive enzymes, including disaccharidases, can change their structure and activity.

Mammalian intestinal disaccharidases catalyze the final step in the digestion of carbohydrates, which are abundant in the human diet. Small intestinal brush border

disaccharidases cleave glycosidic bonds in oligosaccharides and glycoconjugates and play an essential role in carbohydrate digestion [4]. Possible changes in disaccharidase activity under the influence of *F. foetida* extract may play a significant role in the regulation of glucose homeostasis in the body, the disruption of which leads to serious diseases. Therefore, the purpose of the work was to study the effect of *F. foetida* extract on the activity of intestinal disaccharidases.

2. Materials and Methods

2.1. Animals

The experiments were conducted on the outbred white male rats weighing 180–200 g, raised in the vivarium of the National University of Uzbekistan. Rats were kept in plastic cages of 50x30x28 cm in size 4 animals each under natural light and humidity and room temperature with unlimited access to water and standard vivarium feed.

2.2. *F. foetida* Extract Preparation and Dosage

F. foetida was collected in the mountainous areas of the Dekhkonobad district of the Kashkadarya region, Uzbekistan. An alcoholic-aqueous extract of the plant stem was prepared as described by Tabassam et al. [5].

Rats were divided into two experimental and one control groups. The rats of the first and second experimental group were administered *F. foetida* extract intragastrically daily for 28 days at a dose of 1 mg/kg and 2 mg/kg respectively. The animals of the control group were similarly administered saline. It has been shown that chronic extract administration at doses of 3–22 mg/kg body weight reduced the mean arterial blood pressure [6] and high-dose administration of this preparation causes liver damage [7]. To prevent side effects of the extract, two relatively low doses that cause effect were used to treat animals.

2.3. Preparation of an Enzymatically Active Preparation and Determination of Disaccharidase Activity

After decapitation of the rats, the small intestine was removed from the abdominal cavity, cleared of fatty tissue, divided into 3 sections (proximal, medial and distal) and each section was washed with Ringer's solution (pH 7.2) at a rate of 1 ml per 1 cm of intestinal length. The mucosa of each section was separated with a plastic spatula, weighed and diluted with Ringer's solution in a ratio of 1:9. The separated mucosa was homogenized, centrifuged, and the supernatant was analysed for disaccharidases activity. All operations were carried out in cold conditions. The activities of maltase (EC 3.2.1.20), sucrase (EC 3.2.1.48), and lactase (EC 3.2.1.23) were determined by the Dahlquist method [8]. Enzyme activity were expressed in μmol of glucose per minute per gram of wet weight of tissue.

2.4. Statistics

Statistical analysis was performed using Student t-test, to compare the means of two groups. When P was less than 0.05, the differences between the values were considered statistically significant.

3. Results

The activity of intestinal α -glucosidases (maltase, sucrase) and β -galactosidases (lactase) was studied in the proximal, medial and distal regions of the small intestine.

3.1. Maltase Activity

Data reflecting the effect of *F. foetida* extract on the intestinal maltase activity are presented in Table 1.

First of all, it should be noted that intragastric administration of *F. foetida* extract in both doses resulted in a decrease in maltase activity throughout the small intestine. No statistically significant difference in the effect of the drug doses on the average maltase activity along the small intestine was found.

However, the decrease in enzyme activity was not uniform in all segments of the small intestine. Administration of the extract at a dose of 1 mg per kg resulted in a decrease in enzyme activity by 14.77% in the proximal segment, by 21.92% in the medial segment and did not change it in the distal segment of the small intestine. Administration of the

extract at a dose of 2 mg/kg decreased enzyme activity by 12.75%, 30.14% and 16.96% in the proximal, medial and distal parts of the small intestine, respectively.

Table 1. Effect of *F. foetida* extract on the intestinal maltase activity ($\mu\text{mol}/\text{min}/\text{g}$ wet tissue) in rats ($M \pm m$; $n=6$)

Intestinal Segment	Groups of animals		
	Control	<i>F.foetida</i> (1 mg/kg)	<i>F.foetida</i> (2 mg/kg)
Whole Intestine	7.18 \pm 0.28	6.23 \pm 0.13	5.74 \pm 0.32
	-	<0.01	<0.001
	100.00	86.73	79.85
Proximal P %	7.89 \pm 0.34	6.72 \pm 0.12	6.88 \pm 0.59
	-	<0.01	>0.2
	100	85.23	87.25
Medial	7.73 \pm 0.42	6.04 \pm 0.12	5.0 \pm 0.25
	-	<0.001	<0.001
	100.00	78.08	69.86
Distal	5.93 \pm 0.07	5.93 \pm 0.16	4.92 \pm 0.14
	-	>0.5	<0.001
	100.00	100.00	83.04

Note: the statistical significance was determined in comparison with control values.

It should be noted that in animals of the control group, maltase activity was expressed unevenly along the entire length of the small intestine. In the proximal segment of the small intestine it was 1.3 times greater ($P<0,001$) than in the distal one. After the introduction of the *F. foetida* extract, the gradient of enzyme activity distribution along the length of the small intestine was expressed less strongly, since intragastric administration of the extract led to a decrease in enzyme activity in the initial and middle intestine sections.

3.2. Sucrase Activity

The effect of *F. foetida* extract on sucrase activity in different segments of the small intestine is presented in Table 2.

Table 2. Effect of *F. foetida* extract on the intestinal sucrase activity ($\mu\text{mol}/\text{min}/\text{g}$ wet tissue) in rats ($M \pm m$; $n=6$)

Intestinal Segment	Groups of animals		
	Control	<i>F.foetida</i> (1 mg/kg)	<i>F.foetida</i> (2 mg/kg)
Whole Intestine	2.28 \pm 0.12	2.04 \pm 0.17	1.91 \pm 0.05
	-	>0.3	<0.01
	100	89.46	83.29
Proximal P %	2.68 \pm 0.09	2.21 \pm 0.22	2.12 \pm 0.06
	-	>0.051	<0.001
	100	82.24	78.95
Medial	2.47 \pm 0.09	2.07 \pm 0.12	1.94 \pm 0.05
	-	<0.01	<0.01
	100	83.57	78.57
Distal	1.71 \pm 0.18	1.87 \pm 0.18	1.66 \pm 0.05
	-	109.28	96.91
	100	>0.5	>0.5

Note: the statistical significance was determined in comparison with control values.

The activity of sucrase was expressed weaker compared to the activity of maltase in rats. The average sucrase activity of the entire small intestine in animals of the control group was 3.1 times lower than the maltase activity. The same tendency of expression of sucrase activity was noted in animals of the experimental groups. This indicates a lesser role of intestinal sucrase in glucose absorption compared to maltase.

The average sucrase activity along the entire length of the small intestine after intragastric administration of *F. foetida* extract was statistically insignificantly reduced when animals were administered the extract at a dose of 1 mg/kg and was statistically significantly reduced when animals were administered the extract at a dose of 2 mg/kg.

Intragastric administration of the extract at a dose of 1 mg/kg resulted in a decrease in sucrase activity by 17.6% in the proximal and by 16.4% in the medial segments of the small intestine. Chronic treatment of animals with the extract at a dose of 2 mg/kg caused approximately the same decrease in sucrase activity by 21.1% and 21.4% in the proximal and medial segments of the small intestine respectively. In the distal segment of the small intestine, the effect of the extract at both doses was statistically insignificant.

Distribution of the proximal-distal gradient of sucrase activity along the length of the small intestine showed that in animals of the control group, the enzyme activity in the proximal section was 1.5 times higher than in the distal section ($P < 0.001$). When the extract was administered at both doses, the enzyme activity in the initial section of the small intestine was greater than in the distal section, but this difference was statistically insignificant.

3.3. Lactase Activity

Data on the changes in the activity of intestinal β -galactosidase – lactase under the influence of *F. foetida* extract are presented in Table 3.

Table 3. Effect of *F. foetida* extract on the intestinal lactase activity ($\mu\text{mol}/\text{min}/\text{g}$ wet tissue) in rats ($M \pm m$; $n=6$)

Intestinal Segment	Groups of animals		
	Control	<i>F. foetida</i> (1 mg/kg)	<i>F. foetida</i> (2 mg/kg)
Whole Intestine	1.27 \pm 0.08	1.14 \pm 0.06	1.12 \pm 0.09
	-	>0.2	>0.2
	100.00	89.81	87.96
Proximal P %	1.34 \pm 0.09	1.24 \pm 0.07	1.20 \pm 0.05
	-	>0.5	>0.2
	100	92.11	89.47
Medial	1.25 \pm 0.07	1.18 \pm 0.05	1.24 \pm 0.05
	-	>0.5	>0.5
	100.00	94.37	98.59
Distal	1.22 \pm 0.07	1.01 \pm 0.18	0.92 \pm 0.05
	-	<0.01	<0.01
	100.00	82.61	75.36

Note: the statistical significance was determined in comparison with control values.

First of all, it should be noted that the lactase activity of

the small intestine was expressed less than maltase and sucrase one. In healthy animals, the average lactase activity of the entire mucosa of the small intestine compared to maltase and sucrase was 5.6 and 1.8 times lower, respectively. The low activity of lactase compared to maltase and sucrase activity indicates its lesser importance in delivering glucose into the blood circulation.

The lactase activity of the small intestinal mucosa unlike α -glucosidases was distributed evenly along the intestine in both control and experimental groups.

Although administration of the extract at both doses resulted in a decrease in enzyme activity in the distal small intestine, the average lactase activity along the entire length of the small intestine did not change. No dose dependence of the extract on the lactase activity response was observed.

4. Discussion

The results have shown that the activity of maltase and sucrase in the small intestine of rats is more pronounced than the activity of lactase, which indicates a greater participation of α -glucosidases in glucose absorption compared to β -galactosidases. Maybe that's why inhibition of the activity of digestive α -glucosidases by herbal preparations is considered one of the advanced methods for the treatment of postprandial hyperglycemia and one of the accepted strategies for combating diabetes [9]. In the experiment, an inhibitory effect of *F. foetida* extract on the activity of digestive α -glucosidases, but not lactase, was found. This effect is confirmed by the fact that intragastric administration of *F. foetida* extract to rats reduces the hydrolytic capacity of the entire intestine for maltose and sucrose, but not for lactose. The same specificity of the effect on the activity of α -glucosidases and β -galactosidases was revealed for acarbose, a standard artificial inhibitor of the activity of digestive α -glucosidases [10]. Experiments have shown that the activity of α -glucosidases is concentrated in the proximal and medial sections of the rat intestine, but after treating rats with *F. foetida* extract, their specific activity lost its distribution gradient due to a decrease in the sections where it was highest.

F. foetida is a traditional plant that has long been used in food and medicine. Millions of people use the plant daily as a spice, and its safety has been proven [11]. The plant contains many compounds (sulfur-containing compounds, terpenes, flavonoids, coumarins, phenolic acids, monosaccharides and other substances) with various pharmacological properties. [11-17]. Therefore, most likely, the inhibitory effect of *F. foetida* extract on the activity of intestinal α -glucosidases – maltase and sucrase, is the result of the synergistic action of many substances.

The standard drug acarbose due to its high affinity for α -glucosidase, inhibits the activity of intestinal α -glucosidases in a competitive manner [10]. The competitive mechanism of inhibition of α -glucosidase activity is also evident for the flavonoids naringenin, taxifolin, and some sulfur-containing compounds present in the composition of *F. foetida* extract

[17-19]. These substances bind to the same active site of the enzyme as the substrate, preventing its binding and cleavage. Taxifolin has been shown to have a dose-dependent inhibitory effect on α -glucosidase activity [19].

Other substances found in *F. foetida*, such as L-arabinose and ferulic acid [13,20-22], inhibit the activity of intestinal α -glucosidases through an uncompetitive inhibition mechanism. L-arabinose binds to the sucrase-sucrose complex, and leads to a reduction in the rate of sucrose digestion [20]. This monosaccharide is not digested but accumulates in the intestine, which prolongs its inhibitory effect [21]. Ferulic acid alters the secondary structure of α -glucosidase and changes the microenvironment of certain amino acid residues. The interaction involves non-covalent bonds, including hydrogen bonds, and results in a moderate binding affinity [22].

The third group of substances (coumarins, phenolic acids, terpenes and rutin) present in *F. foetida* can inhibit the activity of α -glucosidases by a mixed mechanism of action: competitive binding to the active center of the enzyme and non-competitive, causing protein aggregation [23-27].

The absence (maltase, lactase) or weak (sucrase) dose-dependence of the effect of the extract on the activity of brush border disaccharidases may be due to the fact that plant extracts, unlike pure compounds, contain multiple biologically active substances that can interact with each other in complex ways [28].

Therefore, it can be concluded that intestinal α -glucosidases are the target of many substances contained in the *F. foetida* extract. Inhibition of their activity can occur through various pathways, including competitive mechanism, non-competitive inhibition, as well as both mechanisms simultaneously.

Natural product-based α -glucosidase inhibitors are particularly attractive because their side effects are minimal, they also typically have other therapeutic properties, and therapy is well tolerated compared with other oral hypoglycemic agents currently available [1-3,28-32]. Many α -glucosidase inhibitors not only help prevent and/or correct hyperglycemia, but also have a beneficial effect on a number of cardiovascular diseases, preventing obesity, hypertension and high glycemic variability [28-30]. So, the obtained data indicate the possibility of expanding the use of food products, spices and preparations based on *F. foetida*, considering them as suitable candidates for the prevention and/or correction of hyperglycemia and associated diseases.

5. Conclusions

In general, chronic consumption of *F. foetida* extract reduces the ability of the small intestine to absorb carbohydrates, which is manifested in a decrease in the activity of brush border maltase and sucrase. This phenomena helps prevent excessive glucose from entering the bloodstream after eating carbohydrate-rich foods, i.e. preventing hyperglycemia. The use of food additives based on *F. foetida* extracts, through inhibition of the small intestinal enzymes involved in carbohydrate digestion, will help prevent not only

hyperglycaemia, but also diabetes, hypertension, some types of nephropathy and other associated diseases.

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