Araştırma Makalesi – Original Article

Total Fenolic Contents of *Ferula elaeochytris* Root Extract and Its Effect on Glucose Levels*

Ferula elaeochytris Kök Ekstresinin Toplam Fenolik Bileşikler ve Glukoz Seviyesi Üzerine Etkisi

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ABSTRACT

Nowadays, diabetes is a metabolic disease characterized by hyperglycemia by a problem in insulin secretion, insulin action, or both. It is known that oxidative damage plays an important role in the development of vascular and neurogenic complications of diabetes and antioxidants are effective on these pathologies. The aim of this study was to investigate the possible antidiabetic and antioxidant effects of *Ferula elaeochytris* root extract, commonly known as "ÇAKŞIR" in South and Southeastern Anatolia. *Ferula elaeochytris* was collected from the Engizek plateau of Kahramanmaraş. The plant root was prepared on a clean and dry surface and ground for grinding. The inhibitory effect of *Ferula eleaochytris* on glucose was determined electrochemically with the biosensor device, and total phenolic content was determined by Folin-Ciocalteu method as an indicator of antioxidant activity. In this study, according to electrochemical analysis with biosensor device, a linear decrease in glucose levels was observed depends on the decrease of enzyme-substrate interaction as a result of the addition of 100 µl cumulatively 1 minute (min) intervals of *Ferula elaeochytris* root extract (N=120). In addition, the total phenolic content of this plant was detected (41.45±2.38 mg GAE/g, n:3) by Folin-Ciocalteu method. It can be concluded that *Ferula elaeochytris* may have a hypoglycemic effect owing to its inhibitory effect on glucose levels and *Ferula elaeochytris* may also have a possible antioxidant source by means of the plant has a high capacity of total phenolic content. With the advanced studies to be done, it will be able to provide a more conscious utilization in accordance with the purpose of this unconsciously used plant by many people.

Anahtar Kelimler: *Ferula elaeochytris*, biosensor, total phenolic contents, glucose

ÖZ

Günümüzde önemli bir sorun haline gelen diyabet, insülin sekresyonu, insülin etkisi veya her ikisindeki sorunlardan kaynaklanan hiperglisemi ile karakterize bir metabolik hastalıktır. Diyabet hastalığının vasküler ve nörojenik komplikasyonlarının gelişiminde oksidatif hasarın önemli rol oynadığını ve bu patolojiler üzerinde antioksidanların etkili olduğu bilinmektedir. Güney ve Güneydoğu Anadolu bölgesinde sıkça kullanılan "ÇAKŞIR" diye bilinen *Ferula elaeochytris* kök ekstresinin toplam fenolik içeriği ve glukozu inhibe edici etkisinin araştırılması amaçlanmıştır. Kahramanmaraş Engizek yaylasından toplatılan *Ferula elaeochytris* bitkisinin kök kısmı temiz ve kuru bir zeminde kurutulduktan sonra öğütülerek, işleme alınmak üzere hazırlanmıştır. *Ferula eleaochytris*'in glukoz üzerine etkisi biyosensör cihazı ile elektrokimyasal olarak; antioksidan etkinliğinin bir göstergesi olarak da Folin-Ciocalteu yöntemi ile toplam fenolik içeriği tayin edilmiştir. Bu çalışmada, biyosensör cihazı ile elektrokimyasal incelemesinde, *Ferula elaeochytris* kök ekstresinin 100'er µl kümülatif olarak 1 dakika (dk) aralıkla eklenmesi sonucu enzim-substrat etkileşiminin azalmasına bağlı olarak glukoz seviyeleri üzerinde doğrusal bir düşüş olduğu gözlemlenmiştir (N=120). Ayrıca, bu bitkinin Folin-Ciocalteu yöntemi ile toplam fenolik içeriği 41.45±2.38 mg GAE/g (n:3) olarak tespit edilmiştir. *Ferula elaeochytris*'in glukoz seviyesini inhibe edici etkisinden dolayı hipoglisemik ve toplam fenolik içeriğinin yüksek kapasiteye sahip olması yönüyle ise antioksidan kaynağına sahip olduğu söylenebilir. Yapılacak olan ileri çalışmalarla, insanlar tarafından bilinçsizce kullanılan bu bitkinin yerinde ve amacına uygun daha bilinçli bir kullanımı sağlanabilir.

Keyword: *Ferula elaeochytris*, biyosensör, toplam fenolik içerik, glukoz

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INTRODUCTION

With its increasing prevalence day after day, *diabetes mellitus* is a serious health problem mostly coursing with metabolic derangement associated with functional and structural complications. Insulin-dependent *diabetes mellitus* results from chronic autoimmune destruction of the insulin-producing pancreatic β cells whereof insulin deficiency leads to death arising from hyperglycemia and ketoacidosis.[1] Oxidative stress, defined as an imbalance between the production of reactive oxygen species and antioxidant defenses of the body, is known as the underlying mechanism of diabetic complications such as diabetes and many other diseases.[2] Many experimental and clinical studies have shown that there is an increase in reactive oxygen species (ROS) during diabetes.[3] Studies on diabetes have revealed that oxidative damage plays an important role in the progress of vascular and neurogenic complications of diabetes and that antioxidants have an effect on these pathologies.[2,3,4] In experimental animal models, it has been reported that oxidative stress occurs in the first month after the onset of the diabetes.[5] In a previous study, neurogenic and vascular dysfunction in the penis tissue of diabetic mouse was reversed with vitamin E and selenium.[6] It has been reported in some experimental diabetic animal models that various antioxidants prevent the development of diabetic impotence.[3,7,8]

Ferula L. (Apiaceae) is a perennial plant of about 185 species of flowering plants in the carrot family, distributing in eastern regions of Mediterranean and central Asia and mostly growing in arid climates. There are 23 species of *Ferula communis* (regionally named as "ÇAKŞIR/ÇAĞŞIR") in Anatolia. These plants are known to be a rich source of tannins, saponins, terpenoids, starch, resins, volatile oil and alkaloids[9]. In several scientific studies done with some species of Ferula genus, various medicinal properties such as antioxidant[10], antimicrobial[11], antihelmentic[12], cytotoxic[13], antidiabetic[14], antispasmodic[15], antifungal[16], anti-ulcerative[17], hepatoprotective[18], anti-inflammatory[19] activities have been reported. In addition, it has been suggested that it is useful for corpus cavernosum dysfunction.[20]

In recent years, the attention of people towards alternative treatment methods, phytotherapy, in particular, has strikingly increased not only in the developing countries but also in developed countries. Phytotherapy is a science-based medical practice where the plant-derived medications are used in the treatment and prevention of disease.[21] In general, the original components of plants and/or different components of plants are used for different medical purposes. This study aims to show that *F. elaeochytris* plant which unconsciously consumed by the public, whether has the possible antidiabetic and antioxidant capacity, as well as to lead the way for further studies with this plant extract.

MATERIALS AND METHODS

Preparation of *F. elaeochytris* Root

F. elaeochytris was collected from Engizek Plateu, Kahramanmaraş province (37° 33'39 "N, 41° 45'53" E) in the first week of June 2017. It was identified and authenticated by Dr. Mustafa Aslan (a taxonomist). A voucher specimen (Voucher number HURUB 4588-4589) of *F. elaeochytris* has been deposited at the Herbarium of the Department of Biology, Faculty of Education, Harran University, Sanlıurfa, Turkey. After the soil and foreign matters on the outer surface of the material was removed and general cleaning was made, it was sundried on a clean and dry ground by avoiding the decay of roots and finally it was pulverized by sifting through a 1 mm-screen. Thereafter, the material was dried at room temperature and used in the study.

Electrochemical Analysis of *F. elaeochytris* Root Extract

For electrochemical determination, the gold working electrodes bioactive layer of biosensor include both glucose oxidase and hydrogen peroxidase enzymes. Firstly, the glucose oxidase enzyme converts the glucose to glucuronic acid and hydrogen peroxide, then hydrogen peroxidase enzyme turns the hydrogen peroxide to H_2O and O_2. Finally, biosensor detects the potential changing of the bienzymatic reaction. The inhibitory effect of *F. elaeochytris* on glucose levels was examined electrochemically using a biosensor device (Palm Sens Biosensor, The Netherlands).[22] Following the cross-linking of glucose oxidase enzyme and peroxidase enzyme with bovine serum albumin/gelatin and glutaraldehyde, it was fixed on the gold electrode (CHI, USA) surface and glucose measurements were made by an amperometric method in the range of 0.7-0.9 V.[22] To create a physiological environment, phosphate buffer (pH 7.5) was used. Firstly, the standard curve was formulated by adding 100 µl from the standard solution with a glucose concentration of 100 mg/dL, afterward, 100 µl of 0.01 g/ml *F. eleaochytris* were cumulatively added to the environment at every 1 minute, then, consecutive measurements were taken and the results were saved. 120 samples were measured in order to provide the standardization. The same samples were evaluated spectrophotometrically, and the results were compared with the biosensor device (Table 2).

Determination of Total Phenolic Content of *F. elaeochytris* Root Extract

Phenolic compounds were measured by using Folin-Ciocalteu's phenol reagent[23] with making minor modifications. 200 µL extract was mixed with 1 ml Folin-Ciocalteu's phenol reagent (1 N) and 0.8 ml 7.5% Na_2C0_3. The mixture was allowed to incubate in the dark for 120 minutes at room temperature (24 ± 2 ° C). Absorbance values were measured at 760 nm using a spectrophotometer (Perkin Elmer, USA). Samples were made in triplicates (n:3). The results were expressed in mg Gallic Acid Equivalent (GAE) / 1g extract (dry weight).

Statistical Analysis

The literature indicates that it is not appropriate to evaluate the method comparison studies with correlation coefficient and regression analysis, therefore, it is emphasized that the method developed by Bland and Altman should be used instead. When literature is examined, it was seen that correlation evaluation was also performed together with Bland Altman analysis. Therefore, Pearson correlation analysis was performed to evaluate the correlation between the two measurement methods (***Table 1***).

Table 1. Descriptive statistics

Descriptive statistics	N	Mean difference	Std. Deviation
Differences	6	1,6667	1,07309
Valid N (listwise)	6		

RESULTS

Electrochemical Results of *F. elaeochytris* Root Extract

As a result of electrochemical analysis of the effect of *F. elaeochytris* on glucose levels by a biosensor device, after adding of *F. elaeochytris* to the environment, glucose concentration on the electrode surface was determined by enzymatic reaction with glucose oxidase. With catalyzing of hydrogen peroxide and peroxidase elicited in reaction, quinone imine, water, and molecular oxygen form. The amount of oxygen formed is directly proportional to glucose concentration. As a result of adding 100 µl cumulatively at each 1 minute, it was observed that there was a linear decrease in glucose levels due to decreased enzyme-substrate interaction (***Figure 1***).

The spectrophotometric and biosensor results of *F. elaeochytris* root extract were compared with correlation analysis (***Table 2***). When the results of the correlation analysis are examined, since r value is 0.999 and p value is <0.01, it was seen that there was a strong and significant correlation between both methods (***Table 3***).

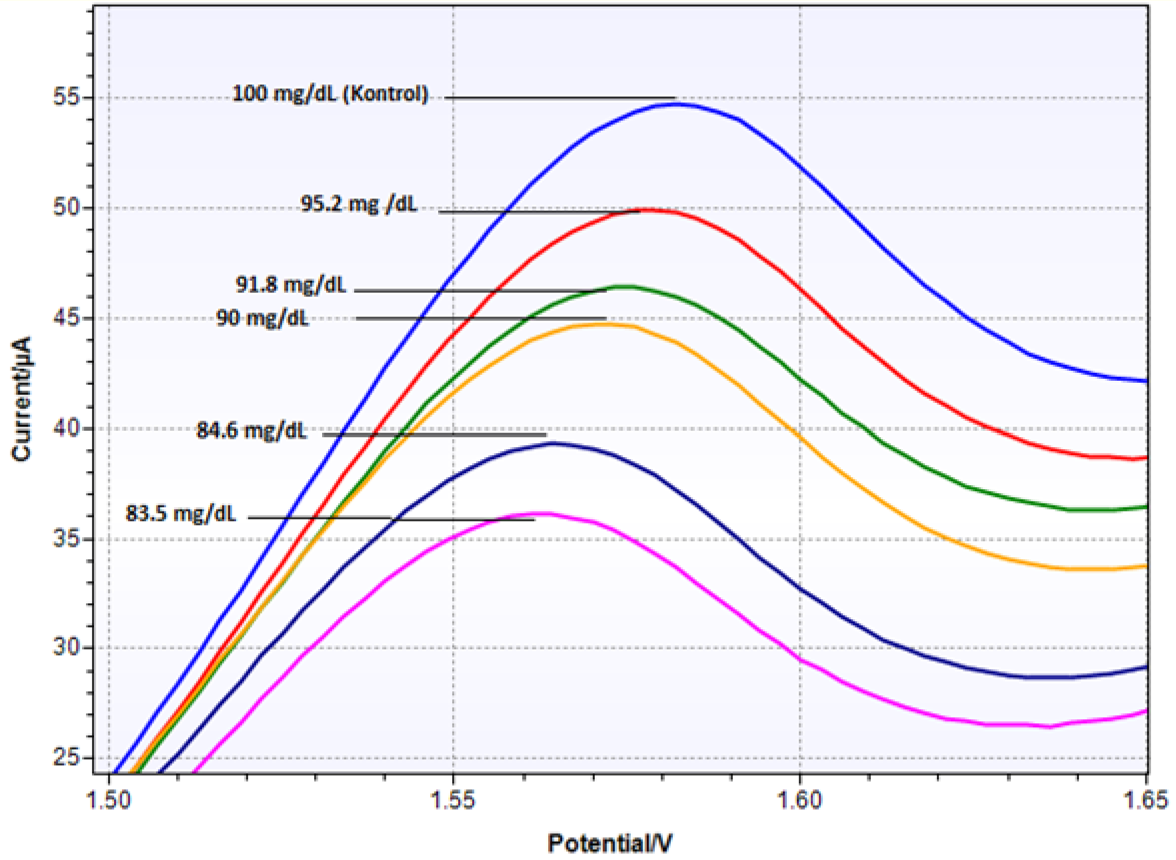

Figure 1. Linear Sweaps of the biosensor responses obtained with electrochemical examination of Ferula elaeochytris root extract (N=120). (Blue line: 100 mg/dl concentration, Orange line: 95.2 mg/dl concentration, Green line: 91.8 mg/dl concentration, Yellow line: 90.0 mg/dl concentration, Dark Blue line: 84.6 mg/dl concentration, Pink line: 83.5 mg/dl concentration)

Table 2. Spectrophotometric and biosensor results of *Ferula elaeochytris* root extract

Spectrophotometric Results (mg/dL)	Biosensor Results (mg/dL)
100	100.5
95.2	95
91.8	92
90	90
84.6	85
83.5	84.3

Table 3. Correlation Analyses

Correlation		Spectrophotometry	Biosensor
Spektro.	Pearson Correlation	1	,999**
	Sig. (2-tailed)		,000
	N	12	12
Bios.	Pearson Correlation	,999**	1
	Sig. (2-tailed)	,000	
	N	12	12

Total Phenolic Content Results of *F. elaeochytris* Root Extract

In this study, Folin-Ciocalteu's phenol reagent of *F. elaeochytris* plant was used and absorbance values were measured by spectrophotometer, total phenolic content was found to be 41.45±2.38 mg GAE/g.

DISCUSSION

Nowadays, folk medicine has started to be a significant part of human health for the treatment of some diseases such as diabetes, algesia, inflammation.[24,25,26] Biosensor technology that provides a powerful analytical tool with important applications in medicine is developing rapidly. Particularly glucose biosensors have developed more reliably, quickly and accurately, in addition, these sensors are more compact and easier to use.[22] In this study, in order to reveal the possible anti-diabetic effect of *F. elaeochytris* root extract, the effect of this plant on glucose was investigated electrochemically with a biosensor device. Used for the determination of phenolic compounds has been shown to be advantageous in many respects, such as the need for extracts at low volumes with numerous samples.[23] Singleton and Rossi (1965) have also identified total phenolic compounds by using Folin-Ciocalteu's phenol reagent.[27] In parallel to these, in our study, the total phenolic content of *F. elaeochytris* root extract was investigated using the Folin-Ciocalteu method and it was revealed to its possible antioxidant activity.

At the end of the present study, it was determined that *F. elaeochytris* root extract contains quite high total phenolic compounds. This study shows that F. elaeochytris root extract, which has the potential to be used as a natural alternative antioxidant source, is a rich source due to the high phenolic substances it contains. When Yeşilsu (2018) examined the total contents of phenolic substances, it was reported that rosemary extract (31.73 mg GAE/g) had the highest total phenolic content, followed by oregano extract with 28.66 mg GAE/g.[28] Besides, Yeşilsu (2018) reported the lowest total phenolic content was observed in laurel extract as 25.71 mg GAE/g.[28] Abeysinghe et al., (2007) reported that the total phenolic content of *Citrus unshiu* (Satsuma mandarin), *Citrus reticulata* (mandarin) and *Citrus sinensis* (orange) ranged from 18.5 to 38.5% and that the main phenolic component was hesperid.[29] The fact that the content of our extract may have a stronger antioxidant property, suggests that higher amounts of TPC have been released from the aromatic plants studied by the above researchers, who have reported antioxidant activities. In previous studies, the content of this extract was determined as follows. Deveci et al., (2018) reported that the total phenolic concentration of phenolic compounds in the extracts ranged from 1.77 ± 0.18 to 141.05 ± 0.11 μg PEs/mg.[30] The acetone extract (21.62 ± 0.73 μg PEs/mg) of *F. elaeochytris* exhibited the highest concentration of phenolic compounds, followed by the water extract (19.23 ± 0.21 μg PEs/mg). Our current results appear to contain very high amounts of TPC when compared to some other aromatic plant species.

One of the striking results of our study was to find this plant high in terms of total phenolic acids and flavonoid (41.45±2.38 mg GAE/g). Phenolic compounds exist in different amounts in each plant and are an important indicator of the antioxidant capacity of a plant.[31] Phenolic compounds show that this plant extract, have free-radical scavenger activities and potential natural alternative antioxidant source.[32] The TPC content we found in our current study may also be due to similar compounds. In a study carried out with streptozotocin-induced diabetic rats; the leaf of *Vitis vinifera L.* has been shown to have anti-diabetic and antioxidant activity. Besides, tannins and flavonoids are thought to be responsible for this activity.[33] Indeed, the antidiabetic activity of these compounds has been previously shown. Therefore, in present study, we evaluated the effectiveness of inhibiting this extract on glucose.

In the present study, as a result of electrochemical investigations, *F. elaeochytris* root extract is thought to be causing a conformational change in amino acids in the active center of glucose oxidase enzyme. In parallel with some studies, the fact that *F. elaeochytris* metabolically reduces the glucose levels suggests that *F. elaeochytris* may have a possible antidiabetic effect.[16,34,35] In our previous study on diabetic rats, it has been shown that *F. elaeochytris* root extract (oral, 8 weeks) reduced the blood glucose levels and increased the intracavernosal pressure (ICP) in furtherance the possible antidiabetic effect of *F. elaeochytris.*[36,37] In some studies, saponins, and flavonoids, found in many plant species such as *F. elaeochytris*, have been shown to have a potential antidiabetic effect[38,39]; in another study conducted with a different species of *Ferula*, its antidiabetic and hypoglycemic effect has been also shown.[36] Due to containing lower levels of antioxidant enzymes such as catalase, glutathione peroxidase, superoxide dismutase, beta cells are more sensitive to reactive oxygen species.[40] Therefore, oxidative stress causes damage to mitochondria and significantly reduces insulin secretion.[41] Flavonoids have been reported to have antidiabetic activity by preventing the formation of diabetes-induced reactive oxygen species (ROS) and preserving pancreatic β-cell function.[42] In a study, some flavonoids have been shown to increase insulin release from isolated rat islets of Langerhans.[43] In their study, Chica and Bello (2010) reported that some components such as terpenes and saponins contained in plants are responsible for hypoglycemic effect due to their ability to regenerate pancreatic cell.[44]

The possible mechanism of the hypoglycemic effect of *F. elaeochytris* may be due to the presence of components such as flavonoids and terpenes. In previous studies[42,43,44], based on the fact that components such as flavonoids and terpenes depend on the ability to regenerate pancreatic β-cells; the factors such as reducing the blood glucose level to normal values[36] and having these components[45] suggest that *F. elaeochytris* may have the ability to regenerate pancreatic β-cells.

CONCLUSION

It can be said that F. elaeochytris may has hypoglycemic activity due to its antioxidant contents. Thus, it is important to show that it can have an impact on diabetes which is one of the major health problems. It can be used in the treatment of diabetes by shedding light on the effects and mechanisms of preclinical and even clinical studies. It is believed that the mechanism of action of *F. elaeochytris* plant root extract on diabetes can be decisively revealed with further studies. Our study applies pioneering results in this respect.

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