RESEARCH ARTICLE
Eurasian J Bio Chem Sci, 6(2):104-108, 2023
https://doi.org/10.46239/ejbcs.1228402

EJBCS

Eurasian Journal of Biological and Chemical Sciences

Journal homepage: www.dergipark.org.tr/ejbcs

Investigation of *in vitro* antidiabetic and antioxidant activity of hawthorn vinegar obtained from Endemic *Crataegus tanacetifolia* (Poir.) Pers.

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Received : 03/10/2023
Accepted : 16/11/2023

Abstract: In this study, the *in vitro* antidiabetic, antioxidant activity and total flavonoid content (TFC) and total phenolic content (TPC) of vinegar obtained from endemic *Crataegus tanacetifolia* (Lam.) Pers. (Rosaceae), (hawthorn) were examined. The hawthorn vinegar obtained from Malatya province (MS) and the vinegar (TS) obtained from Konya were used as study material. Their antidiabetic activity was determined by α-amylase and α-glucosidase inhibitory methods. Antioxidant activities were determined using 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and ferrous iron chelating (FCA) assays. The absorbance were read in the Elisa reader and evaluated with Excel and GraphPad programs. The MS has been found to have higher α- amylase (95.12± 3.71%) and α-glucosidase inhibitory (81.62 ± 0.33%) effects. The TS demonstrated (94.13 ± 3.85%) α-amylase and (75.35 ± 2.19%) α-glucosidase inhibitory activity, respectively. The TPC was found to be in TS (467.59 ± 6.73) mg GAE/mL MS (328.46 ± 5.50) mg GAE/mL. The TFC was found as (1.94 ± 10.36) mg CE/mL and (1.32 ± 10.96) mg CE/mL in TS and MS vinegar, respectively. The FCA was found to be in TS (33.37 ± 0.53%) MS (31.08 ± 10.87%). The DPPH radical scavenging activity was found as (73.82 ± 2.12%) in TS and (80.12 ± 4.45%) in MS. ABTS radical scavenging activity was found to be the highest in TS with (82.51± 0.78%) and in MS found as (78.65 ± 0.55%). The antidiabetic, antioxidant activity, TPC and TFC determinations of these vinegars were performed for the first time with these methods.

Keywords: Bioactivity, *Crataegus tanacetifolia*, phytochemical, vinegar

1. Introduction

Diabetes is the most common metabolic disease worldwide. Diabetes is a disease in which the glucose level in the blood cannot be controlled due to the insulin hormone. The number of people suffering from diabetes is increasing due to nutritional disorders, hormonal and immune problems in Turkey and in the world (Asgari et al. 2022). Traditional treatment methods and herbal treatment options have become increasingly important in the treatment of many metabolic diseases such as diabetes.

During the onset and development of type 2 diabetes, the cellular balance of carbohydrate and lipid metabolism is affected by inappropriate glucose metabolism, resulting in elevated postprandial blood glucose levels. Prolonged hyperglycemia with diabetes leads to the formation of Advanced Glycation End Products (AGEs), which are involved in the generation of reactive oxygen species (ROS) and cause oxidative damage (Haidara et al. 2009). In the natural aging process, the accumulation of AGEs in the organism and their interaction with their receptors are accepted as one of the most important factors that damage cells and tissues, as in diabetes (Yılmaz and Karabudak 2018). Numerous studies have shown that cancer, aging or neurodegenerative diseases are mostly associated with excessive production of free radicals (Forman and Zhang 2021). Increased free radical production and oxidative stress caused by hyperglycemia are the main causes of cognitive dysfunction in diabetic patients (Kucukatay et al. 2007). It has been reported that diabetes accelerates the mild cognitive deterioration of dementia in the elderly (Xu et al. 2010). Moreover, diabetes independently increases the risk of atherosclerosis as an inflammatory response (Folli et al. 2011; Forbes and Cooper 2013). In this case, high homocysteine concentration has an important role in causing vascular complications of diabetes (Hoogeveen et al. 1998). One therapeutic approach for the treatment of diabetes is to reduce postprandial hyperglycemia by delaying glucose absorption through inhibition of enzymes that hydrolyze carbohydrates such as α-glucosidase and α-amylase in the digestive tract (Cheplick et al. 2010). Antioxidant is any substance that can act directly or indirectly on free radicals to delay, prevent or eliminate oxidative damage in target molecules (Halliwell 2020)

Bioactive components with antioxidant effects reported in recent years are mainly phenolics, polysaccharides and alkaloids (Kołodziej et al. 2019)

Vinegar has been used in the world for thousands of years and has many activities such as antioxidant, anti-hyperglycemic activity thanks to its bioactive components. Bioactive compounds are found in small amounts in foodstuffs and their effects on human health are constantly being researched (Butnariu 2014; Rashed and Butnarių 2014). Since vinegar is produced from many fruits and vegetables rich in amino acids, organic acids, phenolics, vitamins and minerals, and shows antioxidant, anti-obesity, antidiabetic and antimicrobial activities (Budak et al. 2011). Bakir et al. (2017). It also has regulatory effects on blood pressure and lipid metabolism. It is one of the most famous folk remedies used to fight infections (Samad et al. 2016). The consumption of vinegar as a home remedy for managing high blood sugar levels was noted before on the advent of today's antidiabetic drugs (OKeefe et al. 2008)

Crataegus L.(hawthorn) genus, belonging to the Rosaceae family, is widely found in Asia, Europe and America and consists of more than 1000 species (Alirezalu et al. 2020). 21 *Crataegus* species grow naturally in our country (Dönmez 2004). Hawthorn contains numerous bioactive compounds with multiple pharmacological activities and functions. These components have been used to treat inflammatory diseases and enhance human immunity (Li et al. 2022). Hawthorn's use dates back to ancient times, has gained an important place in phytotherapy and has become a popular herbal medicine due to its beneficial effects on the cardiovascular system, antioxidant and antimicrobial activity (Alirezalu et al. 2020). It has become a natural treatment option as an alternative to synthetic drugs with many side effects, and many studies have been conducted on some species such as *C. oxyacantha C. monogyna, C. pinnatifida* (Mecheri et al. 2021; Deveci et al. 2020; Chowdhury et al. 2014). Hawthorn contains aromatic amines, essential oils, phenolic acids, flavonoids (hyperine, quercetin, spirein, rutin, and apigenin), picantosivanidins as bioactive compounds (Bruneton 1999). Hawthorn polyphenols mainly contain quercetin (74.58%) and hyperoside (9.58%), which are important sources of biological activity to inhibit α-glucosidase (Li et al. 2022) Hawthorn berries contain a number of biologically active substances expected to have anti-proliferative effects on human cancer cells (Berghe 2012; Li et al. 2013). From the anti-cancer function of triterpenoids in hawthorn. (Qiao et al. 2015). Considering the rich content of flavonoids and polyphenols with strong antioxidant activity in hawthorn, it is expected to be applied in the development of functional foods by improving memory-related dysfunctions (Miguez et al. 2016, Sammari et al. 2021).

In the study, two different commercial products of vinegar were used as study material.. The DPPH and ABTS free radical scavenging test and Fe^{+2} chelating assay were performed to evaluate *in vitro* antioxidant potential of vinegar samples. Total flavonoid quantification (TFC) and total phenol quantification (TPC) were also conducted. In addition, the samples were also investigated against the digestive enzymes of α-amylase and α-glucosidase using 96-well microplate technique.

2. Materials and Method

Two different commercial products of vinegar were used as study material: one is hawthorn vinegar supplied from Malatya province (MS), another one is vinegar from Konya (TS).

2.1. Total Phenol Content (TPC)

The total phenolic content of the vinegars was measured according to the method described previously with some modifications (Ozdemir et al. 2022). 30 µL of TS and MS samples was taken and placed in a 96-well microplate. 150 µL of tenfold diluted F-C reagent was added to it and left for 5 minutes. After adding of 120 µL 7.5% $NaCO_3$ to stop the reaction, it was kept in the dark for 1 hour. Absorbances were read on an Elisa reader at 760 nm. Calibration curve was created by serial dilution of gallic acid. The TPC was calculated according to the equation and expressed as mg equivalent to gallic acid per mL. The equation obtained by the absorbance versus concentration of the serial dilution solution of gallic acid is $y = 0.0071x+0.1927$, $r^2 = 0.9937$.

2.2. Total Flavonoid Content (TFC)

The total flavonoid content of vinegar was determined by method previously reported with minor modifications (Özdemir et al. 2022). Catechin was used for creating calibration curve. 100 µL of TS and MS samples/catechin serial solutions were placed in a 96-well microplate. 30 µL of $NaNO_2$ was added on to it. After waiting for 5 minutes, 50 µL of $AlCl_3$ was added and the mixture was left in the dark for another 6 minutes. Then, 50 µL of NaOH was added and left for 10 min. Their absorbance was read at 510 nm on an Elisa reader. TFC was calculated according to the equation obtained from catechin serial dilutions and expressed as mg equivalent to catechin per mL. The equation obtained by the absorbance versus concentration of the serial dilution solution of catechin is: $y = 0.0003x – 0.0169$, $r^2 = 0.9918$.

2.3. In Vitro Antioxidant Activity

2.3.1. DPPH Radical Scavenging Activity

The DPPH radical scavenging activity of hawthorn vinegar was examined as described in previously published work (Özdemir et al. 2022). 12.5 µl of TS and MS samples were taken with micropipettes and placed in a 96-well microplate. Then 250 µl of 0.1 mM DPPH prepared in methanol was added on it. The BHA was used as positive control. After incubated for 1 hour in the dark at room temperature, the absorbances were read on an Elisa reader at 517 nm. The % radical scavenging activity value was calculated according to the formula:

$$\% \text{ Inhibition} = \frac{\text{Ablank} - \text{Asample}}{\text{Ablank}} \times 100$$

In the formula, A= Absorbance; A_{blank}: Absorbance of the solution without sample; A_{sample}: Absorbance of TS and MS Samples.

2.3.2. Fe^{+2} Chelating Activity (FCA)

The iron chelating activity of hawthorn vinegar was examined as described in previously published work (Özdemir et al. 2022). 50 µl of TS and MS samples were taken with micropipettes and placed in a 96-well microplate. Then, 160 µl of distilled water, 5 µl of 2mM $FeSO_4$ were added to it. After 1 min of incubation at room temperature, 10 µl of 5mM ferrozine was added. The mixture was kept at room temperature for 30 min. The EDTA used as a positive control. Absorbance was read at 562 nm.

2.3.3. ABTS Radical Scavenging Activity

The ABTS radical scavenging activity of hawthorn vinegar was examined as described in previously published work (Özdemir et al. 2022). Briefly, 50 µL of samples of TS and MS diluted with the dilution technique were taken with micropipettes and placed in a 96-well microplate. Trolox used as a positive control. The final volume was made up to 50 µL with distilled water. 100 µL of $ABTS^{\bullet+}$ working solution was added to the wells and kept in the dark at room temperature for 10 min. Absorbances were read on an Elisa reader at 734 nm. The % ABTS radical scavenging activity value was calculated according to the formula given in DPPH method.

2.4. In Vitro Antidiabetic Activity

2.4.1. α-Amylase Inhibition Activity

The α-amylase inhibition activity of hawthorn vinegar was determined with the Caraway Samogyi Iodine/Potassium Iodine (1_2/KI) method with minor modification (Özek 2018). Briefly, 25 µl of TS and MS samples were taken with micropipettes and placed in a 96-well microplate. 50 µl α-amylase (0.8 U/mL enzyme solution prepared with Phosphate buffer) was placed on it. After incubation at 37°C for 10 minutes, 50 µl of starch solution was added. After another 10 min of incubation, 25 µl of 1M HCl solution and 100 µl of 1_2/KI solution were added to stop the reaction. Acarbose was used as a positive control. Absorbances were read on an Elisa reader at 630 nm. The results were evaluated with the formula given in the DPPH assay.

2.4.2. α-Glucosidase Inhibition Activity

The α-glucosidase inhibition effect of hawthorn vinegar was determined with 96-well plate method as described previously (Palanisamy et al. 2011). In this assay, samples were run in 4 parallel. 50 µL of TS and MS samples, 10 µl of 0.4 U/mL α-glucosidase solution were taken and placed in a 96-well microplate, then incubated at 37°C for 20 min. 125 µl of 0.1M phosphate buffer solution (PBS, pH=6.8) was added and incubated for another 20 min at 37°C. After adding 20 µl of 5mM PNPG on the mixture, it was incubated at 37°C for 30 minutes. 50 µl of 0.1N Na_2CO_3 was added to stop the reaction. Acarbose was used as a positive control. The absorbance was measured at 405 nm on an Elisa reader. The results were evaluated with the formula given in the DPPH assay.

3. Results and Discussion

In our study, the vinegar sample obtained from TS from Konya and MS from Malatya were investigated and compared in terms of total phenolic and flavonoid content, antioxidant and inhibitory activity against digestive enzyme of α-amylase and α-glucosidase. Statistical evaluation and drawing graphs were done with Excel Program and GraphPad prism software (8.0).

3.1. Total Phenol and Flavonoid Content (TPC & TFC)

The total phenol and flavonoid amount of vinegar samples are given in Table 1. As seen in the results, the highest TPC was found to be 467.59 ± 6.73 mg GAE/mL in TS vinegar, it was followed by MS vinegar with TPC content of 328.46 ± 5.50 mg GAE/mL. The TFC was found as 1.94 ± 10.36 mg CE/mL and 1.32 ± 10.96 mg CE/mL in TS and MS vinegar, respectively. In a study on *C. tanacetifolia* (Ozdemir, et al. 2021), the total amount of phenol was found to be 0.51 mg/ml. In our study, this value was found to be higher in both vinegars.

3.2. In vitro Antioxidant Activity

The values of the DPPH, ABTS radical scavenging and ferrous chelating activity results are given in Table 1. According to the results, the highest DPPH radical scavenging activity was showed by MS with 80.12 ± 4.45% inhibition, while TS sample was found as 73.82 ± 2.12%. The ABTS radical scavenging activity was found to be highest in TS with 82.51± 0.78% and in MS found as 78.65 ± 0.55%. The FCA was found to be higher in TS (33.37 ± 0.53%) than in MS (31.08 ± 10.87%).

In a study by Murathan et al. (2016), DPPH radical scavenging activity were found to be 67.76% in *C. monogyna* and 74.76% in *C. sinaica*. The *C. tanacetifolia* and *C. sinaica* exhibited ABTS radical scavenging activity 51.62% and 68.61%, respectively. The TS and MS samples in the current study we used showed higher activity in both radical scavenging assay.

Table 1. The total phenolic and flavonoid content and antioxidant activity of *C. tanacetifolia* vinegar

Type of extract	Total Phenol content (TPC) GAE mg/mL sample	Total flavonoid content (TFC) CE mg/mL$_{sample}$	DPPH radical scavenging activity (%)	Fe^{+2} chelating activity (%)	ABTS radical scavenging activity (%)
TS	467.59 ± 6.73	1.94 ± 10.36	73.82 ± 2.12	33.37 ± 0.53	82.51 ± 0.78
MS	328.46 ± 5.50	1.32 ± 10.96	80.12 ± 4.45	31.08 ± 10.8	78.65 ± 0.55
BHA			90.33 ± 0.25	-	-
EDTA			-	23.86 ± 7.83	-
Trolox			-	-	49.15 ± 4.11

The datas were expressed as Mean ± Standard deviation (Mean ± SS) of three parallel mesarements.

3.3. In vitro enzyme inhibition activity

Enzyme inhibition results of vinegar samples and reference substance acarbose are given in Table 2. As can be seen from the table below, the MS has been found to have higher α- amylase (95.12± 3.71%) and α-glucosidase inhibitory (81.62 ± 0.33%) effects. The TS demonstrated 94.13 ± 3.85% α-amylase and 75.35 ± 2.19% α-glucosidase inhibitory activity, respectively. In a study on α- glucosidase inhibition of hawthorn, the percent inhibition activity value of hawthorn sample was found to be 3.37 ± 0.04 mg hawthorn mL^{-1} (Xiao et al., 2016). In our study, this value was higher in TS and MS vinegars.

Table 2. α-amylase and α-glucosidase inhibitory activity of vinegar samples and acarbose

Type of sample	α-amylase	α-glucosidase
TS	94.13 ± 3.85	75.35 ± 2.19
MS	95.13 ± 3.71	81.35 ± 0.33
Acarbose	71.71 ± 2.94	78.68 ± 0.88

Note: TS: The vinegar sample from Konya, MS: The vinegar from Malatya; Acarbose (1mg/ml);
% Inhibition= mean of three measurements ± standard deviation

4. Conclusion

Türkiye is home to many wild fruits. Hawthorn, which is among them, has an important place in terms of its beneficial effect on the cardiovascular system. In addition, although it is known that hawthorn vinegar, which is prepared from its fruit, has a sugar and cholesterol-lowering effect among the public, scientific studies on this are not enough. Therefore, in this study, the total phenol and total flavonoid content were investigated in the vinegar produced from the fruit of *C. tanacetifolia* obtained from Konya and commercial product hawthorn vinegar. In addition to this, in vitro antioxidant activity and inhibition against digestive enzymes of α-amylase and glucosidase were also Turkiye is home to many wild fruits. Hawthorn, which is among them, has an important place in terms of its beneficial effect on the cardiovascular system. In addition, although it is known that hawthorn vinegar, which is prepared from its fruit, has a sugar and cholesterol-lowering effect among the public, scientific studies on this are not enough. Therefore, in this study, the total phenol and total flavonoid content were investigated in the vinegar produced from the fruit of *C. tanacetifolia* obtained from commercial product hawthorn vinegar. In addition to this, *in vitro* antioxidant activity and inhibition against digestive enzymes of α-amylase and glucosidase were also investigated. When the results obtained were evaluated, it was observed that hawthorn vinegar had a significant antioxidant and enzyme inhibitory effect associated with antidiabetic activity. All these values show that hawthorn vinegar can be used to support health. It is recommended by us to support the production of hawthorn plant, which is produced only in certain regions in our country, in other provinces and to carry out studies to increase its consumption among the people.

Acknowledgements

We would like to thank the TUBITAK 2209/A Undergraduate Student Project for the financial support (NO: 1919B012102103).

Authors' contributions:

Study design (NE, YGA), Methodology (FA, NST, NE), Analysis and interpretation of the data (FA, NST, NE), Drafting of the paper (FA), Final approval of the version to be published (FA, NST, NE)

Conflict of interest disclosure:

There is no conflict of interest.

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