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ORIGINAL ARTICLE

The antioxidant, anti-inflammatory, and antiplatelet effects of *Ribes rubrum* L. fruit extract in the diabetic rats

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Abstract

The prothrombotic and inflammatory state plays a significant role in the occurrence of cardiovascular complications in type 2 diabetes mellitus. In this study, the antidiabetic, anti-inflammatory, and antiplatelet potentials of the extracts obtained from *Ribes rubrum* were investigated. The antidiabetic, anti-inflammatory, and antioxidant activities of the ethanol and water extracts of *R. rubrum* were evaluated by in vitro methods. The total phenolic and flavonoid contents were also determined. The experimental diabetes model in rats was induced with streptozotocin (STZ). After hyperglycemia occurred, the ethanol extracts of *R. rubrum* (RRE, at 100 mg/kg and 500 mg/kg doses) were administered to the treatment groups for 14 days. Blood glucose, lipid profile, plasma, and pancreas tumor necrosis factor-α (TNF-α) levels were determined and compared at the end of the experiments. P-selectin levels and mitochondrial membrane polarization (MMP) of platelets were also measured. In vitro study, the RRE showed potent anti-inflammatory activity. Administration of RRE (at 100 mg/kg doses) to diabetic rats lowered blood glucose level insignificantly. The results showed that there was an increment in levels of TNF-α in plasma and pancreas tissue of the diabetic group compared to the control group. *R. rubrum* extract regulated and normalized their levels in plasma and pancreatic tissue. RRE at both doses significantly decreased platelet P-selectin levels and prevented STZ-induced loss of MMP in platelets. The results of current research indicate that RRE extract has potent anti-platelet and anti-inflammatory effects and may be beneficial in preventing diabetic complications.

Practical applications

Hyperglycemia causes dyslipidemia, advanced oxidative stress, platelet activation, and inflammation in diabetes mellitus. Plants with various medicinal properties are of worldwide interest for the treatment of diseases due to their biological activities. In this study, the antidiabetic, anti-inflammatory, and antioxidant effects of extracts of *Ribes rubrum* (%100 ethanol, 50% ethanol, water) were evaluated by in vitro and in vivo methods. The diabetes model was induced with streptozotocin (STZ). The rats were divided into control, diabetic control, *R. rubrum*-100 mg/kg, and *R. rubrum*-500 mg/kg doses groups. Blood glucose levels, tumor necrosis factor-α (TNF-α), platelet P-selectin levels, mitochondrial membrane polarization of platelets were examined. The present study has shown that *R. rubrum* has anti-inflammatory and antiplatelet

activity. *R. rubrum* may be beneficial in the prevention and treatment of DM complications due to its anti-inflammatory and antithrombotic effects.

1 | INTRODUCTION

In the treatment of diabetes mellitus (DM), the incidence of which is increasing worldwide, it is important to ensure and maintain normoglycemia, as well as to prevent diabetes mellitus complications that may cause morbidity and mortality. Cardiovascular disease (CVD) is the most common cause of diabetes-related disability and death. It accounts for an important part of the macrovascular complications of DM (Lordan et al., 2019; The WHO CVD Risk Chart Working Group, 2019). Disinsulinemia and hyperglycemia cause dyslipidemia, advanced oxidative stress, platelet activation, and inflammation in DM, leading to atherosclerosis, the main pathological mechanism of CVD, and accelerating this process (Pereira et al., 2018).

In general, inflammatory processes contribute to diabetes, and increased blood levels of proinflammatory cytokines such as interleukin (IL)-1, IL-16, IL-18, and tumor necrosis factor (TNF)-α are observed in diabetic individuals. Among these proinflammatory cytokines, TNF-α, in particular, can induce insulin resistance leading to the development of Type 2 DM (T2DM) in adipocytes and peripheral tissues, and can induce cell death by apoptosis caused NFκB and caspase-3 activation (Akash et al., 2018; Çevik et al., 2017). Anti-TNF-α treatments can decrease the insulin resistance incidence and the development of T2DM and may also contribute to the improvement of diabetic complications.

Platelets are non-nucleated blood cells that result from the fragmentation of megakaryocytes which are large and nucleated. They are the building blocks of hemostasis and have a major role in the process such as inflammation and atherosclerosis (Holinstat, 2017). Increased polyol, protein kinase C pathways, hexosamine, and advanced glycosylation end products in hyperglycemia; contribute to oxidative stress, decreased release of nitric oxide (NO), deterioration of endothelial function, and inflammation (Brownlee, 2005; Chuah et al., 2013; Ott et al., 2014). Therefore, hyperglycemia can lead to an increase in platelet reactivity and alterations in mitochondrial function. The hyperglycemia-induced increase in platelet reactivity plays a major role in the development of cardiovascular complications of DM, by contributing to the atherosclerotic process (Ferreiro & Angiolillo, 2011).

In the 21st century, a lot of information has been obtained and is still being worked on regarding the pathogenesis and treatment of DM. In this context, plants with various medicinal properties are of worldwide interest for the treatment of diseases due to their biological activities. It is known that currants with red, black, and yellow colors have high antioxidant properties due to the phenols and flavonoids they contain. Due to these functional components, having a protective role against many diseases has increased the importance of black currant, especially in the food industry (Feng et al., 2016; Xıanlı, 2004). Moreover, they have been used as food for years, which indicates that they are safe for human consumption. *Ribes rubrum* L. is a common name for the red currant, which belongs to the genus *Ribes* in the family Grossulariaceae (Tim, 2012). Phytochemical analysis of *R. rubrum* revealed the presence of flavonoids, phenolic acids, and anthocyanidins. Phenolic compounds such as gallic acid, rutin, catechin, syringic acid, and chlorogenic acid were detected. Phenolic compounds are used therapeutically due to their antioxidant, anti-inflammatory, antifungal, and wound-healing properties. In addition, in vivo, and in vitro studies have indicated that anthocyanidins have anti-inflammatory properties (Garbacki et al., 2005). Traditionally, *R. rubrum* has been used in folk medicine for its antipyretic, menstrual, lactative, appetite stimulant, diuretic, antiscorbutic, and wound healing properties. The mixture of leaves is used to relieve rheumatic complaints. In addition, the fruits of *R. rubrum* are also used in cosmetic industry (Tim, 2012). Ribes species reportedly possess anti-diabetic activity (Pinto et al., 2010; Sivalingam & Sriram, 2013).

As a result, the present study investigated the antidiabetic, anti-inflammatory, and antiplatelet potential of the fruit extracts of *R. rubrum* L.

2 | MATERIALS AND METHODS

2.1 | Preparation of fruit extracts

The fruits of the *R. rubrum* plant were purchased from the local market. The taxonomic identity was confirmed by the botanist Dr. İsmail Şenkardeş. The fruit samples were stored in the Herbarium of the Faculty of Pharmacy, Marmara University (Mare No: 22298). For the in vitro studies, the fruits were extracted using the maceration method with ethanol, water, and 50% ethanol three times for 24 hr each. After extraction was completed, the sample was filtered using filter paper and the solvent was evaporated using a rotary evaporator at a temperature not exceeding 40°C. The crude extracts of ethanol, water, and 50% ethanol were coded as RRE, RRS, and RRE50, respectively, and stored sterile at about 4°C for further use. For analysis, stock solutions were prepared by dissolving each of the extracts in dimethyl sulfoxide (DMSO).

2.2 | Determination of in vitro antioxidant activity

The ABTS and DPPH radical scavenging activities of the extracts were determined following the study of Zou et al. (2011)).

2.3 | Determination of in vitro anti-inflammatory activity

Anti-inflammatory activities were evaluated with slight modifications according to the method described by Phosrithong and Nuchtavorn (2016) and Yıldırım et al. (2019)).

The method was concerted to the 96-well microplate format. Pure water (20 µl), ethanol (20 µl) and 0.1 M sodium borate buffer (25 µl, pH: 9), and the extracts (10 µl) at different concentrations were added to the wells. Then 25 µl of soybean lipoxygenase type V (20.000 U/ml) in sodium borate buffer was added. The mixture was incubated at 25°C for 5 min, and then 100 µl of a 0.6 mM linoleic acid solution was put in and mixed. The changing of absorbance at 234 nm was monitored for 6 min. Indomethacin was used as a standard. The inhibition percentage in terms of anti-inflammatory activity was calculated according to the following equation: % inhibition = $[(A_{control} - A_{sample})/A_{control}] \times 100$.

2.4 | Determination of in vitro antidiabetic activity

The in vitro antidiabetic effect of the extracts was evaluated through inhibition of alfa amylase and alfa glucosidase enzymes and with slight modifications according to the method described by Ramakrishna et al. (2017). The method was concerted to the 96-well microplate form. The inhibition percentage in terms of anti-inflammatory activity was calculated according to the following equation: % inhibition = $[(A_{control} - A_{sample})/A_{control}] \times 100$.

Alfa-amylase inhibitor activity: 25 µl of α-amylase enzyme (0.5 mg/ml-15 units) prepared within buffer and 10 µl of the extracts were mixed with 15 µl of 0.02 M sodium phosphate buffer (pH 6.9). The mixture was incubated for 10 min at 25°C, and 25 µl of starch solution (1%) prepared in buffer was added to the wells. One more time, the mixture was incubated for 10 min at 25°C. The reaction was ceased with dinitrosalicylic acid (50 µl) and incubated for 10 min within a boiling water bath. After incubation, the solutions were chilled to room temperature and diluted with 225 µl ultrapure water. The absorption was measured at 540 nm.

Alfa-glucosidase inhibitor activity: 100 µl of α-glucosidase prepared in buffer and 40 µl of 0.1 M sodium phosphate buffer (pH 6.9) were added to 10 µl of the extracts. The mixtures were incubated at 25°C for 10 min. Then 50 µl of 5 mM p-nitrophenyl-α-D-glucopyranoside prepared in buffer was added. The mixture was reincubated at 25°C for 5 min. The absorption at 405 nm was measured before and after incubation.

2.5 | Determination of total phenolic compounds (TPC)

The total phenolic content of the extracts was estimated by a colorimetric assay using solution Folin-Ciocalteau based on the procedure described by Gao, et al., (2000). The method was adapted to 96-well microplate format.

2.6 | Determination of total flavonoid compounds (TFC)

The level of total flavonoids in the extracts was measured in the 96-well microplate following the method described by Zhang et al. (2013). The extract (25 µl) and 125 µl of ultrapure water, 7.5 µl 5% NaNO2 were mixed and incubated at 25°C for 6 min. Then 15 µl 10% AlCl3.6H2O was added and incubated again at 25°C for 5 min. Fifty microliters 1 M NaOH was added to the solution and made up to 250 µl with ultrapure water. Then the absorption of the solutions was measured at 510 nm.

2.7 | Animals

Female adult Sprague–Dawley rats (200–250 g body mass) were used that were obtained from Marmara University Experimental Animal Implementation and Research Centre (DEHAMER). Rats were kept at constant temperature (22 ± 1°C) with 45%–50% humidity and 12/12-hr light/dark cycle. They were fed with standard rat chow and water ad libitum and were fasted for 12 hr before the experiment. All experimental protocols were approved by the Marmara University, Animal Experiments Local Ethics Committee (99.2018.mar).

2.8 | Experimental design

After the adaptation process, fasting blood glucose levels and body weight of rats were measured after a fasting night (t_{-3}). The mean blood glucose levels (t_{-3}) of the rats were 94 ± 7 mg/dL without forming groups. Then the rats were randomly divided into two groups as diabetic group ($n = 18$) and control group ($n = 6$). Diabetes was induced by a single dose injection of streptozotocin (STZ)/nicotinamide (NA) in intraperitoneal (i.p.). First, the diabetic rat groups were injected i.p. with a single dose of NA (Santa Cruz Biotechnology, Inc.) (100 mg/kg in normal saline) to minimize the pancreatic destruction. Fifteen minutes after the injection of NA, a single dose STZ (Santa Cruz Biotechnology, Inc.) (65 mg/kg in 0.1 M cold citrate buffer, pH 4.5) was injected. Rats received 10% dextrose solution for 24 hr after STZ injection. After 72 hr (t_0), blood glucose level was measured by glucometer (Accu-Check Performa Nano), and the rats with blood glucose level > 250 mg/dL were classified as diabetes. After the development of diabetes, the rats in the diabetic group were randomly divided into three subgroups as diabetic control ($n = 6$), RRE100 treatment ($n = 6$), and RRE500 treatment ($n = 6$). The groups were formed as follows: In the control group (C), the rats received the normal saline daily by gavage. In the diabetic control group (DC), the rats received the normal saline daily by gavage. In the *R. rubrum* group 1 (RRE100), the rats received RRE (100 mg/kg in normal saline) daily by gavage. In the *R. rubrum* group 2 (RRE500), the rats received RRE (500 mg/kg in normal saline) daily by gavage.

The selection of doses of RRE was based on previous reports (Sivalingam & Sriram, 2013).

Blood glucose levels were measured on day 5 (t_5), day 9 (t_9), and day 14 (t_{14}) after administration of the extract using a glucometer on blood

collected from the tail vein (Figure 1). On day 15, the rats were anesthetized with a maintenance dose of ether, and blood samples were collected from the orbital plexus into tubes containing 3.8% sodium citrate (at a ratio of 1: 9, v/v), by the capillary tube. Then the rats were decapitated and tissue samples of the pancreas were collected from all groups. The blood samples were incubated at room temperature for 15 min, and then centrifuged at 150 x g (Universal 32 Hettich) for 5 min at room temperature (22–25°C) to obtain platelet-rich plasma (PRP) (Sener et al., 2013). Platelet P-selectin level, mitochondrial membrane polarization were measured in the obtained PRP. The samples were centrifuged again, 1,300*g* (Universal 32 Hettich) at room temperature (22–25°C) for 10 min, and the obtained plasma samples were used for the determination of lipid profile and enzyme activities.

2.9 | Biochemical analyses

The levels of triglyceride (TG) (Biolabo), total cholesterol (TC) (Biolabo), urea (Biolabo, France), alanine aminotranferase (ALT; Biolabo), and aspartate amimotransferase (AST; Biolabo) were measured in the plasma samples. TNF-α levels of the plasma and pancreatic tissue were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Abcam); results were as follows pg/ml and ng/g tissue, respectively. Gamma-glutamyl tranfersae (GGT) level was determined by the spectrophotometric method using gamma-glutamyl-p-nitroanalide as substrate (Sener et al., 2012).

2.10 | Determination of platelet activation

Platelet activation was determined fluorometrically from the increase in P-selectin levels. We used the platelet surface using specific antibodies (CD62-P; Abcam) labeled with fluorescent isothiocyanate (FITC) for P selectin level. The flow cytometry method was adapted to fluorometric microplate reader. The 200 µl of PRP samples were incubated with 2.5 µl CD62P-FITC at room temperature for 10 min and centrifuged 1,300*g* for 5 min at room temperature (22–25°C). Platelets were resuspended with 200 µl normal saline and fluorescence density of samples was measured with a fluorescence microplate reader (excitation: 488 nm/emission: 515–545 nm). The results were reported as relative fluorescence units (RFU)/mg protein.

2.11 | Platelet mitochondrial membrane polarization (MMP)

Loss of platelet mitochondrial membrane poloarization is related to platelet activation and apoptosis (Hannah et al., 2019). MMP was measured using the cationic dye 5,5,6,6′-tetrachloro-1,1′,3,3′-tetr aethylbenzimidazoylcarbocyanine iodide (JC-1; Abcam) in a fluorometer. In living cells, JC-1 accumulates as clumps in mitochondrial membranes, consequencing in red fluorescence. The intensity of the red fluorescence is proportional to the membrane potential. In cells with impaired mitochondrial membrane potential, JC-1 is present in the green fluorescent monomeric form. 2.5 µl of JC-1 were added to 200 µl of PRP samples at room temperature for 10 min and then centrifuged at 1,300*g* at room temperature (22–25°C) for 5 min. The cells were suspended in 200 µl normal saline. The fluorescence intensity of the samples was measured using two filters (green excitation: 488 nm/emission: 500–550 nm, red excitation: 561 nm/emission: 560–610 nm). The results are expressed as the ratio of red RFU to green RFU.

2.12 | Histological examination

Pancreatic tissue samples were fixed in 10% neutral buffered formalin solution for light microscopic examination for routine histological

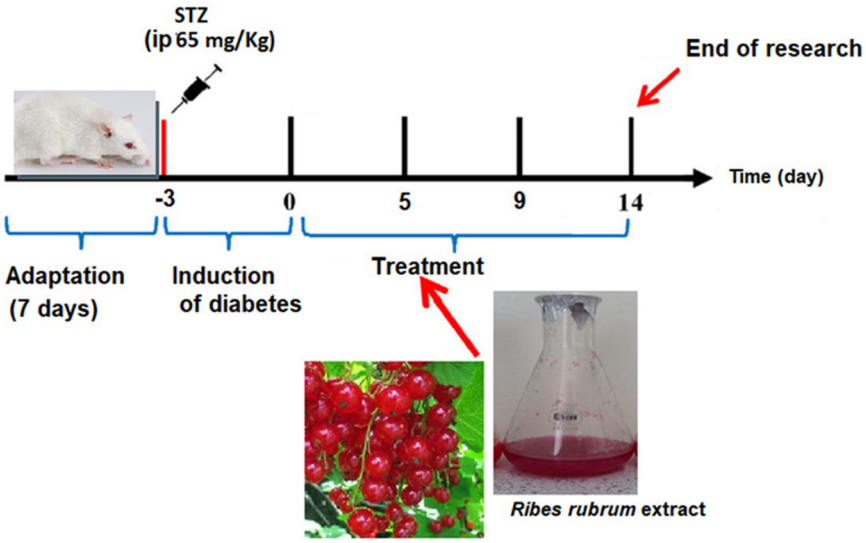

FIGURE 1 Schematic of the treatment schedule

tissue analysis. After fixation, tissue samples were dehydrated in graded ethanol series (%70, 90, 96, 100), and clarified in xylene (Leica TP1020). Paraffin-embedded samples (Leica EG1150H + C) were cut into 5 μm-thick sections using a microtome (Leica RM 2125RT). The sections were stained with hematoxylin and eosin (H&E) stain and evaluated for histopathological modifications and photographed under a light microscope (Olympos BX50).

2.13 | Total protein measurement

The total protein content of the homogenized pancreas tissue and platelets was estimated by Bradford method (Bradford, 1976).

2.14 | Statistical analysis

The program Graphpad Prism 5 (Graphpad Software) was used for statistical analysis. In vitro assay, IC_{50} values were calculated using the "nonlinear regression" plot.

In vivo assays were analyzed by one-way ANOVA and the Tukey post hoc test was used for the statistical significance declaration. The *t*-test was used to compare the paired groups. $P < .05$ level was considered significant.

3 | RESULTS

3.1 | Antioxidant, antidiabetic, and anti-inflammatory activities of the extracts

The IC_{50} values determined for the anti-inflammatory, antidiabetic effects, and antioxidant activity of RRE, RRE50, and RSS in vitro are shown in Table 1. The IC_{50} values of antioxidant activity of the extracts were found to be close to each other. While RRE and RRE50 showed the strongest anti-inflammatory activity, the antidiabetic effects of RRE and RRE50 were higher compared to RRS. However, the antidiabetic effect of ethanol extracts was also lower than the reference standard acarbose.

3.2 | Total phenolic and flavonoid contents of the extracts

TFM and TFLM values of *R. rubrum* extracts were expressed as gallic acid (GAE) and quercetin equivalents (QE), respectively (Table 2). The total phenolic and flavonoid values of the extracts were close to each other.

Considering these in vitro results, we decided to perform the in vivo study with RRE, which has the lowest anti-inflammatory and antidiabetic IC_{50} values.

3.3 | Body weight changes

The body weights of the groups at the beginning of the experiment (t_0), after STZ (after the development of diabetes) (t_0), 5th day (t_5), 9th day (t_9), and 14th day (t_{14}) are shown in Figure 2.

At t_0 and t_5, there was no remarkable difference in the weight of rats from different groups. It was observed that the body weights

TABLE 2 Total phenol and flavonoid contents of extracts

Extracts	TPC (mg GAE/g extract)	TFC (mg QE/g extract)
RRE	44.27 ± 0.01	4.58 ± 0.06
RRE50	41.76 ± 2.36	4.18 ± 0.25
RRS	40.09 ± 1.77	4.28 ± 0.13

Note: RRE, RRE50, and RRs show the ethanol, 50% ethanol, and water extracts, respectively, obtained from the fruits of *Ribes rubrum*. Results were expressed as gallic acid equivalent (GAE) for TPC, as quercetin equivalent (QE) for TFC. Each value was presented as mean ± standard deviation ($n = 3$).

TABLE 1 Comparison of the IC_{50} (μg/ml) values (antioxidant, antidiabetic, and anti-inflammatory) of the extracts of *Ribes rubrum* fruit

	Antioxidant activity		Anti-inflammatory effect	Antidiabetic effects	
Extracts*/ standards	DPPH• inhibition activity	$ABTS^{•+}$ inhibition activity	Lipoxygenase inhibition activity	Alpha-glucosidase inhibition	Alpha-amylase inhibition
RRE	434.8 ± 3.40	395.8 ± 3.61	20.67 ± 0.28	189.7 ± 8.80	130.2 ± 0.50
RRE50	273.6 ± 1.13	356.1 ± 4.17	17.87 ± 0.82	227.0 ± 9.19	170.4 ± 7.58
RRS	315.3 ± 2.40	352.2 ± 22.77	29.91 ± 1.87	353.8 ± 23.12	181.8 ± 5.18
Ascorbic acid	17.6 ± 0.37	14.5 ± 0.32			
Trolox C	14.54 ± 0.18	13.00 ± 0.21			
Indomethacine			22.39 ± 0.26		
Acarbose				95.41 ± 1.48	2.51 ± 0.12

Note: RRE, RRE50, and RRS show the ethanol, 50% ethanol, and water extracts, respectively, obtained from the fruits of *R. rubrum*. Each value was presented as mean ± standard deviation ($n = 3$).

decreased significantly in the DC ($P < .01$), RRE100 ($P < .05$), and RRE500 ($P < .05$) groups compared to the C group at t_9.

The DC group was found to have a 22% decrease in body weight at t_{14} compared to the C group ($P < .001$). The RRE100 and RRE500 treatments were able to avoid weight loss in diabetic rats and increased the body weight of the diabetic group by 10% and 9.5, respectively. However, these observed changes in the body weight were not found to be statistically significant.

3.4 | The effect of RRE on blood glucose levels

After the induction of diabetes, the diabetic rats were randomly distributed among the groups and as explained in the "Materials and method" section, the experimental studies were started. When blood glucose levels measured at time t_0 (after administration of STZ 72 hr) were evaluated, blood glucose levels were significantly increased in all diabetic groups compared to the C group ($P < .001$). It was observed that blood glucose levels of RRE100 group decreased by ~11%, 15%, and 23%, respectively, at t_5, t_9, and t_{14} when compared to the DC group, but this decrease was not statistically significant (Table 3). Conversely, the treatment with RRE500 was failed to decrease the mean plasma levels of glucose compared to the DC group. However, it did not make an additional contribution to increase in hyperglycemia.

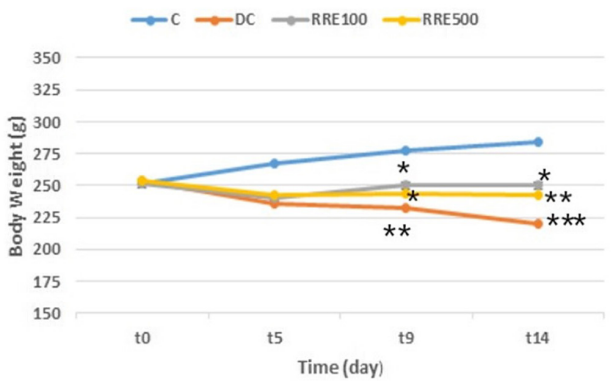

FIGURE 2 Change of body weight in all groups. (C: Control; DC: Diabetic control; RRE100: Ethanol extract of *Ribes rubrum* at the dose of 100 mg/kg; RRE500: Ethanol extract of *R. rubrum* at the dose of 500 mg/kg. t_0: 72nd hour after injection of STZ; t_5: 5th day of experiment; t_9: 9th day of experiment; t_{14}: 14th day of experiment. Each value was presented as mean ± standard deviation. $^*P < .05$, $^{**}P < .01$ and $^{***}P < .01$ compared to the C group)

3.5 | The effect of RRE on plasma lipid profile and enzyme activities

While the urea and TC values of the DC group were significantly higher than those of the C-group ($P < .01$), TG levels showed no statistically significant difference. The TC levels of the RRE100 and RRE500 groups were significantly lower than those of the DC group ($P < .01$ and $P < .001$, respectively), but the urea and TG levels of RRE100 and RRE500 groups were slightly reduced and this reduction was not statistically significant compared to the DC group (Table 4).GGT activity was significantly higher in the DC group than in the C group ($P < .01$). On the other hand, the levels of ALT and AST were not statistically significant increased. Although GGT levels were lower in RRE100 and RRE500 groups when compared to the DC group, these results were not statistically significant. ALT, AST levels of RRE100 and RRE500 groups showed no statistically significant difference when compared to DC and C groups.

3.6 | The levels of TNF-α in the plasma and pancreas tissue

TNF-α levels of the plasma and pancreas were significantly higher in group DC than in group C ($P < .05$ and $P < .01$), respectively. Plasma TNF-α levels were significantly lower in RRE100 and RRE500 groups than in DC group ($P < .05$). It was observed that the plasma TNF-α levels of the RRE100 and RRE500 groups were close to those of the C group. The pancreatic TNF-α levels of RRE100 and RRE500 groups were significantly lower than those of the DC group ($P < .001$) (Figure 3).

TABLE 3 Blood glucose (mg/dl) levels of the groups

Groups	t_0	t_5	t_9	t_{14}
C (vehicle)	119 ± 10	118 ± 08	105 ± 06	104 ± 04
DC (STZ)	429 ± 90***	439 ± 73***	440 ± 198***	450 ± 154***
RRE100		387 ± 123**	370 ± 70**	343 ± 60**
RRE500		414 ± 150***	432 ± 130***	444 ± 150***

Note: Each value was presented as mean ± standard deviation.

Abbreviations: C, Control; DC, Diabetic control; RRE100, ethanol extract of *Ribes rubrum* at the 100 mg/kg dose; RRE500, ethanol extract of *R. rubrum* at the 500 mg/kg dose. t_{-3}, before injection of STZ; t_0, 72nd hour after injection of STZ; t_{14}, 14th day of experiment.; t_5, 5th day of experiment; t_9, 9th day of experiment.

$^{**}P < .01$.; $^{***}P < .001$ compared to the C group.

3.7 | Histological examination of pancreas

Light microscopic evaluation of the pancreatic tissue samples revealed that parenchymal and acinar structures with regular morphology were observed in the C group (Figure 4). However, minimal degeneration and vascular congestion, fibrosis, and neutrophilic infiltration were observed in the parenchyma in the islets of Langerhans group DC. In the RRE100 group, mild vascular congestion, and edema were detected in the parenchyma. Although the general morphological appearance of the RRE500 group was similar to the control group very mild vascular congestion and fibrosis were observed and in addition, acinar structures were generally normal.

3.8 | The effect of RRE on platelet P-selectin levels

Platelet P-selectin levels were significantly higher in DC ($P < .001$). RRE100 ($P < .05$) and RRE500 ($P < .01$) groups also compared to the C group. Moreover, the results showed that it was significantly lower in RRE100 ($P < .05$) and RRE500 ($P < .01$) groups compared to the DC group. Among the all diabetic groups, P-selectin levels were lower in the R100 group (Figure 5).

3.9 | The effect of RRE on platelet MMP

Figure 5 shows the changes in MMP in all experimental groups. The group DC showed a significant decrease in loss of MMP when compared to the C group. A significant increase in MMP was observed in RRE100 ($P < .01$) and RRE500 ($P < .001$) groups as compared to DC group. Thus, administration of RRE normalizes MMP in platelets of diabetic rats.

4 | DISCUSSION

In our study, the antidiabetic, anti-inflammatory, and antiplatelet effects of *R. rubrum* extracts were investigated. In vivo and in vitro studies have demonstrated that plants and fruits high in flavonoids and phenolic compounds may have antidiabetic and anti-inflammatory effects (Garbacki et al., 2005; Mejia & Johnson, 2015; Pinto et al., 2010). It has been reported that syringic acid and (+)—catechin which has anti-inflammatory activity were found to be the major phenolic compounds in fruits of *R. rubrum* (Adina et al., 2017; Cheng et al., 2019; Ham et al., 2016). However, differences were observed in the phenolic content and antioxidant activity depending on the solvent used during extraction, solvent concentration differences,

TABLE 4 Comparison of plasma urea, lipid profile, and enzyme activities of the groups

Experimental groups	Urea (mg/dl)	TG (mg/dl)	TC (mg/dl)	GGT (U/l)	ALT (U/l)	AST (U/l)
C	33.33 ± 5.33	55.69 ± 9.90	115.65 ± 8.18	25.49 ± 2.47	22.11 ± 6.17	17.31 ± 4.03
DC	47.33 ± 7.61**	64.28 ± 30.54	144.00 ± 6.12**	39.05 ± 10.97**	29.53 ± 9.50	23.57 ± 13.56
R100	40.10 ± 2.46	43.33 ± 7.06	116.88 ± 9.92++	28.62 ± 4.36	29.25 ± 17.15	27.93 ± 9.33
R500	38.75 ± 3.72	57.01 ± 14.47	110.42 ± 15.18+++	29.62 ± 5.78	35.5 ± 11.50	24.15 ± 8.86

Note: Each value was expressed as mean ± standard deviation.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate amino transferase; C, Control; DC, Diabetic control; RRE100, ethanol extract of *Ribes rubrum* at the 100 mg/kg dose; RRE500, ethanol extract of *R. rubrum* at the 500 mg/kg dose. GGT, gammaglutamyltranfersae.

**$P < .01$ compared to C; ++$P < .01$; +++$P < .001$ compared to DC.

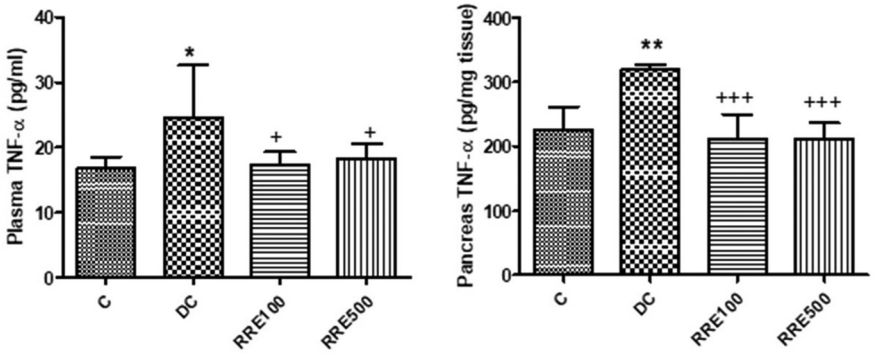

FIGURE 3 TNF-α levels in the plasma and pancreas. (C, control; DC, diabetic control; RRE100, Ethanol extract of *Ribes rubrum* at the dose of 100 mg/kg; RRE500, Ethanol extract of *R. rubrum* at the dose of 500 mg/kg. *$P < .05$, **$P < .01$ compared to the C group; +$P < .05$, +++$P < .001$ compared to the DC group)

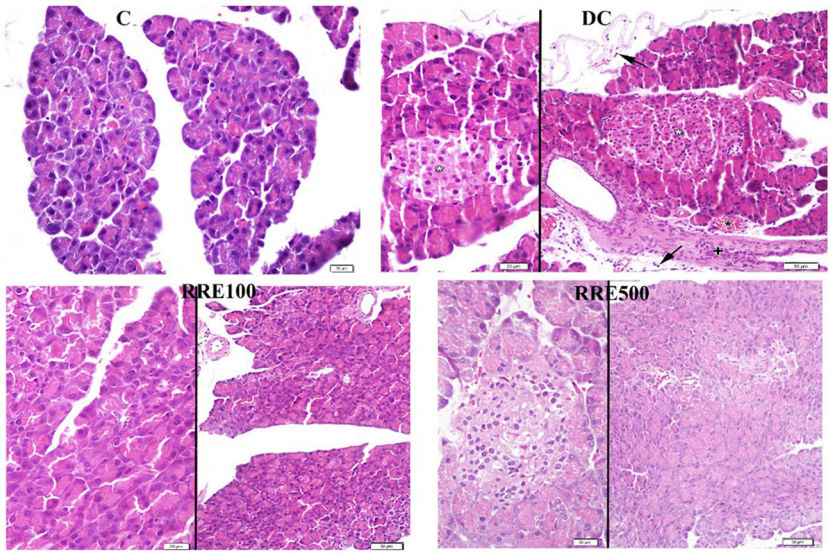

FIGURE 4 The results of histological analysis. For the DC: Arrow: Neutrophil infiltration; plus (+) Fibrosis; black asterisk (*) Vascular congestion; white asterisk (*) Langerhans islet. Hematoxylin–eosin dye

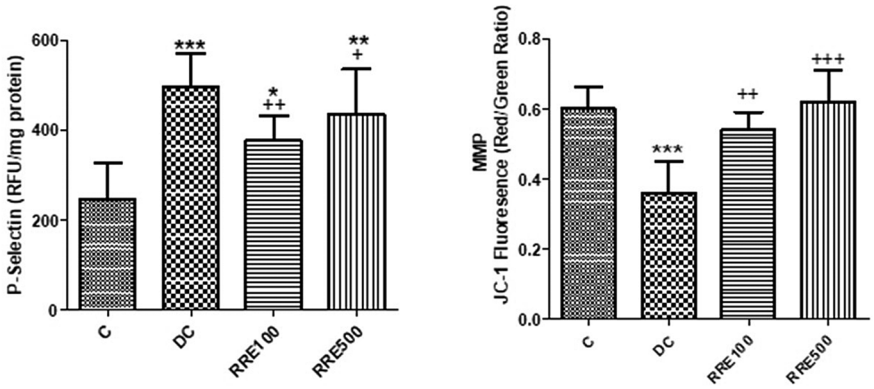

FIGURE 5 Platelet P-selectin levels and MMP changes. (C: Control; DC: Diabetic control; RRE100: Ethanol extract of *R. rubrum* at the dose of 100 mg/kg; RRE500: Ethanol extract of *R. rubrum* at the dose of 100 mg/kg. $^{*}P < .05$, $^{**}P < .01$,$^{***}P < .001$ compared to the C group; $^{+}P < .05$, $^{++}P < .01$, $^{+++}P < .01$ compared to the DC group)

and harvesting of the fruit in a different time (Feng et al., 2016; Pinto et al., 2010; Zöld et al., 2018).

Glycemic control remains the most important strategy in the treatment of T2DM. Inhibitors of α-glucosidase and α-amylase enzymes involved in the digestion of carbohydrate can reduce the post-prandial rise in blood glucose levels. Therefore, they may be an important strategy for managing blood glucose levels in type 2 diabetic and prediabetic patients. Natural α-amylase and α-glucosidase inhibitors found in fruits and vegetables may be helpful in controlling hyperglycemia. The previous report has shown that the fruits of *R. rubrum* have α-amylase and α-glucosidase inhibitory activity with in vitro study (Pinto et al., 2010). In our study, it was observed that ethanol extracts of *R. rubrum* performed stronger α-amylase and α-glucosidase inhibition than their water extract. However, their antidiabetic activity in in vitro was not as strong as that of the reference standard (acarbose).

In another acute in vivo study (for 5 hr), it was reported that the dose of 500 mg/kg fruit extract of *R. nigrum* showed significant antidiabetic effect. In this study, fruit extract of *R. nigrum* at the dose of 100 mg/kg caused an insignificant reduction in blood glucose level. The fruit extracts were not shown to cause hyperglycemia in this study. In the sub-acute study (for 7 days), fruit extract of *R. nigrum* at the doses of 500 mg/kg and 100 mg/kg showed significant activity at the seventh day (Sivalingam & Sriram, 2013). In our in vivo study, the doses used in the study of Sivalingam and Sriram were used. The effect of *R. rubrum* on blood glucose levels in rats receiving RRE at two different doses (100 mg/kg and 500 mg/kg) was compared with the diabetic control group. Our results show that blood

glucose levels decreased by 24% in the RRE100 group compared to the diabetic control group at t_{14}. However, this decrease was not statistically significant. At the dose of 500 mg/kg, it had no effect on blood glucose levels. Unexpectedly, we observed that the in vivo antidiabetic effect of RRE extract was not dose dependent. When comparing the body weight changes of the animals, a weight reduction of 22% was observed in the diabetic group at day 14 compared to the control group. This weight loss was lessened to approximately 12% and 11.5% with RRE100 and RRE500, respectively. Consistent with these findings, the increase of STZ-induced cholesterol level observed in the diabetic group was remarkably reduced with both doses of RRE extracts.

Dysregulation in carbohydrate and lipid metabolism observed in diabetes has been demonstrated to induce a pro-inflammatory process in macrophages that reside in or invade adipose tissue, pancreatic islets, vascular tissue, and other tissues (Donath & Shoelson, 2011). TNF-α plays a role in the inflammatory pathogenesis of many diseases including diabetes. It has also been shown to be a factor affecting the vascular complications of diabetes Therefore, treatment strategies for type 2 diabetes includes suppressing inflammation as well as diabetes improving glycemia (Alexandraki et al., 2008).

In the literature, it has been reported that *R. rubrum* is used in inflammatory diseases such as rheumatoid arthritis in traditional folk medicine (Duke et al., 2002; Tim, 2012). There are no clinical and experimental studies on the anti-inflammatory activity of *R. rubrum*. But, there are studies with other *Ribes* species. It has been reported that the leaf extract of *R. nigrum* has potent anti-inflammatory effect on leukocytes depending on its phenolic content (Tabart et al., 2012). Similar to this study, we observed that the *R. rubrum* fruit extracts (ethanol, 50% ethanol, and water) have potent anti-inflammatory activity in our in vitro study. In parallel with our in vitro study, the increase of STZ-induced plasma and pancreasTNF-α levels was suppressed by RRE100 and RRE500 administration. Both doses of *R. rubrum* extract suppressed TNF-α production in the pancreas. Our histological studies supported these findings. *R. rubrum* extracts ameliorated STZ-induced damage (such as degeneration, leukocyte infiltration, and fibrosis) in the pancreas.

Hyperglycemia promotes the glycation of platelet proteins and has an important role in platelet reactivity in diabetes (Schneider, 2009). Systemic inflammation triggered by diabetes may also contribute to increased platelet reactivity. Otherwise, activated platelets contribute to systemic inflammation in diabetes by secreting proinflammatory cytokines. Diabetics exhibit increased indication of both platelet activation and inflammation. One of the most important indicators of platelet activation is the level of P-selectin on the cell surface. P selectin is located in the α-granules of resting platelets and is translocated from the α-granules to the cell surface upon platelet activation (Wasiluk, 2004). It has been shown that ethylacetate and butanol extractions of *R. nigrum* fruits have potent inhibitory activity against platelet aggregation (Kim & Sohn, 2016). There is no study in the literature investigating the effect of *R. rubrum* on platelet activity. We have previously shown in a preliminary study conducted ex vivo that *R. rubrum* fruit juice significantly suppresses the human platelet aggregation and expression of P-selectin (unpubl data). Also in this study, we have shown that ethanol extract of *R. rubrum* can suppress diabetes-related increased platelet activity, on platelet P-selectin level in diabetic rats.

The loss in MMP is an indicator of mitochondrial dysfunction and apoptosis. Platelets are non-nucleated cells and platelet health is largely estimated by mitochondrial health (Elefantova et al., 2018; Perelman et al., 2012). To this end, we investigated the effect of *R. rubrum* on platelet MMPs along with P-selectin levels. As a result, we showed that the STZ-induced loss of platelet MMP was reduced by both concentrations of *R. rubrum* extract.

In our study, STZ-induced diabetes (14-day period) did not cause any change in plasma ALT and AST levels, which are liver function tests. At the same time, no significant changes were observed in ALT and AST levels in the groups that received RRE extracts. Serum GGT level is widely used as a marker of liver disease and damage of the bile ducts. Moreover, its increase within the reference range may be early and sensitive indicator of oxidative stress. Serum GGT activity has been found to be elevated in diabetic patients, which has been associated with increased oxidative stress (Lee et al., 2004). In parallel with the previous studies, it was observed in this study that GGT activity was significantly increased in the diabetic control group. Although not significant, the extract of *R. rubrum* caused a decrease in GGT levels, at both doses compared to the diabetic control group. The decrease in plasma GGT activity by the extract of *R. rubrum* could be a sign that the extract suppresses the oxidative stress caused by diabetes.

5 | CONCLUSION

Although there are in vitro studies in the literature on the antioxidant capacity, pharmacological properties, antidiabetic, and anti-inflammatory activity of *R. rubrum*, the in vivo studies are limited. The ethanol extract of RRE100 causes a moderate change in blood glucose level and this effect is not dose dependent. The present study has shown that *R. rubrum* has anti-inflammatory and antiplatelet activity. It was shown for the first time to prevent diabetes-induced platelet activation and mitochondrial potential depolarization. *R. rubrum* may be beneficial in the prevention and treatment of DM complications due to its anti-inflammatory and antithrombotic effects.

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CONFLICT OF INTEREST

The authors confirm that they have no conflicts of interest with respect to the work described in this manuscript.

AUTHOR CONTRIBUTIONS

Gizem Gülmez: Conceptualization; investigation; writing – original draft. **ali şen:** Project administration; supervision. **Azize Şener:** Project administration; supervision; writing – review and editing. **Turgut Şekerler:** Investigation. **Ozlem Tugce Cilingir-Kaya:** Formal analysis; investigation. **Fatma Kader Algül:** Investigation.

ETHICS STATEMENT

The ethical approval was obtained Marmara University Animal Care and Use Committee (Protocol number: 99.2018.mar).

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REFERENCES

Adina, F., Cecilia, G., Felicia, G., Carmen, D., & Ovidiu, T. (2017). Identification and quantification of phenolic compounds from red currant (*Ribes rubrum* L.) and raspberries (*Rubus idaeus* L.). *International Journal of Pharmacology Phytochemistry and Ethnomedicine*, *6*, 30–37. https://doi.org/10.18052/www.scipress.com/IJPPE.6.30

Akash, M. S. H., Rehman, K., & Liaqat, A. (2018). Tumor necrosis factor-alpha: Role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *Journal of Cellular Biochemistry*, *119*(1), 105–110. https://doi.org/10.1002/jcb.26174

Alexandraki, K. I., Piperi, C., Ziakas, P. D., Apostolopoulos, N. V., Makrilakis, K., Syriou, V., Diamanti-Kandarakis, E., Kaltsas, G., & Kalofoutis, A. (2008). Cytokine secretion in long-standing diabetes mellitus type 1 and 2: Associations with low-grade systemic inflammation. *Journal of Clinical Immunology*, *28*(4), 314–321. https://doi.org/10.1007/s10875-007-9164-1

Bradford, M. M. (1976). A rapid and sensitive method for quantitation of microgram quantities of protein utilizing the principle of protein dye binding. *Analytical Biochemistry*, *72*, 248–254. https://doi.org/10.1006/abio.1976.9999

Brownlee, M. (2005). The pathobiology of diabetic complications a unifying mechanism. *Diabetes*, *54*(6), 1615–1625. https://doi.org/10.2337/diabetes.54.6.1615

Cheng, A., Tan, X., Sun, J., Gu, C., Liu, C., & Guo, X. (2019). Catechin attenuates TNF-α induced inflammatory response via AMPK-SIRT1 pathway in 3T3-L1 adipocytes. *PLoS One*, *14*(5), e0217090. https://doi.org/10.1371/journal.pone.0217090

Chuah, Y., Basir, R., Talib, H., Tie, T., & Nordin, N. (2013). Receptor for advanced glycation end products and its ınvolvement in inflammatory diseases. *International Journal of Inflammation*, *45*, 1–15. https://doi.org/10.1155/2013/403460

Çevik, Ö., Adıgüzel, Z., Baykal, A. T., & Şener, A. (2017). Tumor necrosis factor-alpha induced caspase-3 activation-related iNOS gene expression in ADP-activated platelets. *Turkish Journal of Biology*, *41*, 31–40. https://doi.org/10.3906/biy-1509-64

Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. *Immunology*, *11*(2), 98–107. https://doi.org/10.1038/nri2925

Duke J, Bogenschutz-Godwin M, duCellier J and Duke P. (2002) *Red Currant (Ribes rubrum L.) (2nd ed.) Handbook of Medicinal Herbs*. pp. 615–615. CRC Press.

Elefantova, K., Lakatos, B., Kubickova, J., Sulova, Z., & Breier, A. (2018). Detection of the mitochondrial membrane potential by the cationic dye JC-1 in l1210 cells with massive overexpression of the plasma membrane ABCB1 drug transporter. *International Journal of Molecular Sciences*, *7*(7), 19. https://doi.org/10.3390/ijms19071985

Feng, C., Su, S., Wang, L., Wu, J., Tang, Z., Xu, Y., Shu, Q., & Wang, L. (2016). Antioxidant capacities and anthocyanin characteristics of the black–red wild berries obtained in Northeast China. *Food Chemistry*, *204*, 150–158. https://doi.org/10.1016/j.foodchem.2016.02.122

Ferreiro, J., & Angiolillo, D. (2011). Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation*, *123*, 798–813. https://doi.org/10.1161/CIRCULATIONAHA.109.913376

Gao, X., Ohlander, M., Jeppsson, N., Björk, L., & Trajkovski, V. (2000). Changes in antioxidant effects and their relationship to phytonutrients in fruits of sea buckthorn (*Hippophae rhamnoides* l.) during maturation. *Journal of Agricultural and Food Chemistry*, *48*, 1485–1490. https://doi.org/10.1021/jf991072g

Garbacki, N., Kinet, M., Nusgens, B., Desmecht, D., & Damas, J. (2005). Proanthocyanidins from *Ribes nigrum* leaves, reduce endothelial adhesion molecules ICAM-1 and VCAM-1. *Journal of Inflammation*, *2*, 1–12. https://doi.org/10.1186/1476-9255-2-9

Ham, J. R., Lee, H., Choi, R., SimM, S. K., & Lee, M. (2016). Anti-steatotic and anti-inflammatory roles of syringic acid in high-fat diet-induced obese mice. *Food & Function*, *7*(2), 689–697. https://doi.org/10.1039/c5fo01329a

Hannah, M., Kanika, J., Tarun, T., & John, H. (2019). Role of platelet mitochondria: Life in a nucleus-free zone. *Frontiers in Cardiovascular Medicine*, *6*, 153–157. https://doi.org/10.3389/fcvm.2019.00153

Holinstat, M. (2017). Normal platelet function. *Cancer and Metastasis Reviews*, *36*(2), 195–198. https://doi.org/10.1007/s10555-017-9677-x

Kim, M.-S., & Sohn, H.-Y. (2016). Anti-oxidant, anti-coagulation and anti-platelet aggregation activities of black currant (*Ribes nigrum* L.). *Journal of Life Science*, *26*(12), 1400–1408. https://doi.org/10.5352/JLS.2017.26.12.1400

Lee, D. H., Blomhoff, R., & Jr, J. (2004). Is serum gamma glutamyltransferase a marker of oxidative stress? *Free Radic Research*, *38*(6), 535–539. https://doi.org/10.1080/10715760410001694026

Lordan, R., O'Keeffe, E., Dowling, D., Mullally, M., Heffernan, H., Tsoupras, A., & Zabetakis, I. (2019). The in vitro antithrombotic properties of ale, lager and stout beers. *Food Bioscience*, *28*, 83–88. https://doi.org/10.1016/j.fbio.2019.01.012

Mejia E and Johnson M. (2015). Anthocyanıns from berrıes: Chemistry and roles in inflammation and diabetes, nutraceuticals and fundamental foods (pp. 226-241) United Kingdom, encyclopedia of life support systems.

Ott, C., Jacobs, K., Haucke, E., Santos, A., Grune, T., & Simm, A. (2014). Role of advanced glycation end products in cellular signaling. *Redox Biology*, *2*, 411–429. https://doi.org/10.1016/j.redox.2013.12.016

Pereira, A., Oliveira, L., Lopes, T., Baldissarelli, J., Palma, T., Soares, M., Spohr, L., Morsch, V., Andrade, C., Schetinger, M., & Spanevello, R. (2018). Effect of gallic acid on purinergic signaling in lymphocytes, platelets, and serum of diabetic rats. *Biomedicine & Pharmacotherapy*, *101*, 30–36. https://doi.org/10.1016/j.biopha.2018.02.029

Perelman, A., Wachtel, C., Cohen, M., Haupt, S., Shapiro, H., & Tzur, A. (2012). JC-1: Alternative excitation wavelengths facilitate mitochondrial membrane potential cytometry. *Cell Death & Disease*, *3*, 1–7. https://doi.org/10.1038/cddis.2012.171

Phosrithong, N., & Nuchtavorn, N. (2016). Antioxidant and anti-ınflammatory activites of clerodendrum leaf extracts collected in Thailand. *European Journal of Integrative Medicine*, *8*(3), 281–285. https://doi.org/10.1016/j.eujim.2015.10.002

Pinto, M., Kwon, Y., Apostolidis, E., Lajolo, F. M., Genovese, M. I., & Shetty, K. (2010). Evaluation of red currants (*Ribes rubrum* L.), black

currants (*Ribes nigrum* L.), red and green gooseberries (*Ribes uva-crıspa*) for potentıal management of type 2 diabetes and hypertension using *in vıtro* models. *Journal of Food Biochemistry*, *34*, 639–660. https://doi.org/10.1111/j.1745-4514.2009.00305.x

Ramakrishna, R., Sarkar, D., Schwarz, P., & Shetty, K. (2017). Improving phenolic bioactive-linked anti-hyperglycemic functions of dark germinated barley sprouts (*Hordeum vulgare* L.) using seed elicitation strategy. *Journal of Food Science Technology*, *107*, 509–517. https://doi.org/10.1007/s13197-017-2828-9

Schneider, D. J. (2009). Factors contributing to increased platelet reactivity in people with diabetes. *Diabetes Care*, *32*(4), 525–527. https://doi.org/10.2337/dc08-1865

Sener, A., Cevik, O., Yanikkaya-Demirel, G., Apikoglu-Rabus, S., & Ozsavci, D. (2012). Influence of platelet γ-glutamyltransferase on oxidative stress and apoptosis in the presence of holo-transferrin. *Folia Biologica (Praha)*, *58*(5), 193–202.

Sener, A., Egemen, G., Cevik, O., Yanikkaya-Demirel, G., Apikoglu-Rabus, S., & Ozsavci, D. (2013). In vitro effects of nitric oxide donors on apoptosis and oxidative/nitrative protein modifications in ADP-activated platelets. *Human & Experimental Toxicology*, *32*(3), 225–235. https://doi.org/10.1177/0960327112455673

Sivalingam, G., & Sriram, N. (2013). Anti-diabetic activity of *Ribes nigrum* fruit extract in alloxan induced diabetıc rats. *International Journal of Pharmaceutical Sciences and Research*, *4*(3), 1196–1201. https://doi.org/10.13040/IJPSR.0975-8232

Tabart, J., Franck, T., Kevers, C., Pincemail, J., Serteyn, D., Defraigne, J. O., & Dommes, J. (2012). Antioxidant and anti-inflammatory activities of *Ribes nigrum* extracts. *Food Chemistry*, *131*, 1116–1122. https://doi.org/10.1016/j.foodchem.2011.09.076

The WHO CVD Risk Chart Working Group. (2019). World Health Organization cardiovascular disease risk charts: Revised models to estimate risk in 21 global regions. *Lancet*, *7*, 1332–1345. https://doi.org/10.1016/S2214-109X(19)30318-3

Tim K. (2012). *Ribes rubrum*, Edible Medicinal and Non-Medicinal Plants. Fruits. (p: 43-50). Dordrecht,4, Springer.

Wasiluk, A. (2004). Markers of platelets activation, CD 62P and soluble P-selectin in healthy term neonates. *Journal of Perinatal Medicine*, *32*(6), 514–515. https://doi.org/10.1515/JPM.2004.123

Xıanlı, W. J. (2004). Characterization of anthocyanins and proanthocyanidins in some cultivars of *Ribes*, *Aronia* and *Sambucus* and their antioxidant capacity. *Journal of Agricultural and Food Chemistry*, *52*(26), 7846–7856. https://doi.org/10.1021/jf0486850

Yıldırım, A., Şen, A., Doğan, A., & Bitis, L. (2019). Antioxidant and anti-ınflammatory activity of capitula, leaf and stem extracts of *Tanacetum cilicicum* (Boiss.). *Grierson International Journal of Secondary Metabolite*, *6*(2), 211–222. https://doi.org/10.21448/ijsm.510316

Zhang, R., Zeng, Q., Deng, Y., Zhang, M., Wei, Z., Zhang, Y., & Tang, X. (2013). Phenolic profiles and antioxidant activity of litchipulp of different cultivars cultivated in southern China. *Food Chemistry*, *136*, 1169–1176. https://doi.org/10.1016/j.foodchem.2012.09.085

Zou, Y., Chang, C., Gu, Y., & Qian, Y. (2011). Antioxidant activity and phenolic compositions of lentil (*Lens culinaris* var. *Morton*) extract and its fractions. *Journal of Agricultural and Food Chemistry*, *59*, 2268–2276. https://doi.org/10.1021/jf104640k

Zöld, E., Komlósi, A., Ülker, T., Fogarası, E., Croıtoru, M., Fülöp, I., Domokos, E., Ştefănescu, R., & Varga, E. (2018). Extractability if polyphenols from black currant, red currant and gooseberry and their antıoxidant activity. *Acta Biologica Hungarica*, *69*(2), 156–169. https://doi.org/10.1556/018.69.2018.2.5

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