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ANTI-INFLAMMATORY ACTIVITY OF ANTHOCYANIN EXTRACT ON DIABETIC AND HYPERTENSIVE PATIENTS

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Anthocyanins pigments are a major class of plant phenolic components, flavonoids. The distinctive purple or red colours of many fruits and vegetables are attributed to the presence of these flavonoids. They are highly water-soluble pigments and have been well known to possess general health-promoting characteristics.

The aim: *This study aimed to evaluate the anti-inflammatory and antioxidant activity of anthocyanin extract. It also looked at how the extract consumption affected people with hypertension and diabetes in terms of lowering blood pressure and blood glucose levels and in preventing their complications, including oxidative stress and inflammatory status.*

Material and method: *The subjects included in the study were hypertensive and diabetic patients divided into control and test groups. Total reactive oxygen species concentrations and C-reactive protein levels were used to assess the oxidative stress and inflammatory status before and after consuming anthocyanin extract for thirty days using an enzyme-linked immunosorbent assay.*

Results: *The results revealed that consumption of anthocyanin extracts for 30 days did not significantly lower blood pressure or blood glucose levels in comparison to the control group and also when compared with day zero values. However, quantitative analysis of the C-reactive protein levels for the inflammatory status and the overall oxidative stress levels measurements demonstrated a significant decline compared to both the control group (placebo) and baseline values (day zero).*

Conclusion: *The findings highlighted the prophylactic, as anti-inflammatory, rather than the curative effects of anthocyanin extracts in preventing or delaying the complications associated with various chronic conditions, including hypertension and diabetes mellitus*

Keywords: *anthocyanin extract, diabetes mellitus, hypertension, inflammatory response, C-reactive protein, oxidative stress*

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1. Introduction

Recently, there has been interest in experimental research that evaluates the chemical and medicinal activities of functional groups and the properties of naturally occurring compounds from dietary sources [1]. Anthocyanins and their related molecules, which are found in large quantities in several plants and fruits, are one of these products. The majority of the plant kingdom's water-soluble pigments, also referred to as flavonoids, are anthocyanins. By the year 2020, more than 8000 flavonoids and 500 anthocyanin structures have been documented, and new ones are still being discovered [2].

Anthocyanins possess anti-oxidative activity, the ability to scavenge free radicals, and the capability to decrease the expression of inflammatory genes. As a result, they offer protection against oxidant-induced and inflammatory cell damage and cytotoxicity [3].

Although the lack of anthocyanin consumption has not been linked to any deficiency disorders, and anthocyanins are not necessary nutrients, their ability and other dietary bioactive substances to support long-term health maintenance may be what makes them valuable.

Consuming colourful fruits and vegetables on a regular basis is an imperative part of a healthy lifestyle and offers protection from chronic diseases. An estimated 1.7 million deaths worldwide are attributed to low intakes of fruits and vegetables, including but not limited to those brought on by stroke (9%), cardiovascular disorders (11%), and gastrointestinal cancer (14%) [4].

In this study, we investigated the potential effects of anthocyanin extract consumption in lowering blood glucose levels and blood pressure in currently diagnosed diabetic or hypertensive patients, respectively. The extent of change in the total antioxidant capacity after the extract treatment was also investigated in both disease groups. Furthermore, C-reactive protein levels were measured with and without extract consumption to illustrate the ability of the anthocyanin extract to lower inflammatory response.

2. Research planning (methodology)

The research stages are:

1. Selecting patients suffering from hypertension or diabetes mellitus, the most common chronic diseases

in Iraq, which are usually associated with various complications with time despite receiving adequate treatment.

2. Dividing patients into control and test groups receiving anthocyanin extract and placebo.

3. Anthocyanin was given as a capsule for 30 days for patients to examine the anti-inflammatory and ant-oxidant status.

Anthocyanin was selected in the study, as it is a natural and safe substance, which is widely abundant in various fruits and supplements, to investigate its effect on the participants.

3. Materials and method

3. 1. Subjects selection

Patients visiting private pharmacies to pick up their prescription drugs for diabetic mellitus (DM) or hypertension served as the study's source of participants. Participants who fit the World Health Organization's classification of type 2 diabetes patients [2] or hypertensive patients with a start of diagnosis of not more than two years were included in the inclusion criteria for identifying candidates. Participants had to be between the ages of 50 and 65 years [5]. Different-gender effects were not considered in this study. Diabetic participants exhibited impaired fasting glucose or impaired glucose tolerance (≥ 130 mg/dL), while hypertensive patients exhibited elevated blood pressure (more than 140 mmHg systolic or 90 and above mmHg diastolic) at their initial diagnosis prior to any medical treatment, according to the medical history reports. Subjects with other known disorders were disqualified, including those with liver issues, kidney issues, or cardiac conditions. Additionally, patients who smoked, drank alcohol, or were extremely obese were not included in the study.

The majority of the participants with diabetes were using oral antidiabetic medications, including glibenclamide (5–10 mg/day) and/or metformin (500–1500 mg/day), in addition to a restricted diet. Patients with hypertension were taking several antihypertensive drugs, including amlodipine (5–10 mg/day), captopril (25–50 mg/day) and candesartanyad/gm 61–8) . The diabetic and hypertensive patient groups were instructed to continue taking their prescribed medications at the same doses and according to the same schedules for the length of the trial. Additionally, the participants were instructed not to alter their regular routine and not to use any non-prescription drugs, vitamins, nutritional supplements, and herbal supplements throughout the study.

3. 2. Study design and data collection

The patients received 30 days stock of the capsules containing either anthocyanin extract or placebo capsules (containing starch only). Based on a random table designed by the study's designers, patients in both illness categories were assigned to either the extract (anthocyanin) or the placebo group. The study consisted of thirty days duration, randomised, blind, placebo-controlled intervention and data analysis for final results. Based on a random table designed by the study's designers, patients in both illness categories were assigned to

either the extract (anthocyanin) or the placebo group. Recruitment of candidates began in May 2022 and ended in July 2022, when the final participant was selected. Samples were collected from participants at the designated times at Alsadiq Center (for clinical research)/Karbala City. The researchers kept in contact with participants throughout the whole experiment period to monitor patients' compliance with the treatment received and follow up with them whether any unusual signs or symptoms emerged through telephone, messenger or WhatsApp. At day 0 of the experiment, blood glucose levels and blood pressure values were measured for corresponding patients and blood samples were collected from all patients to be used as a baseline in further analysis. All participants were required to revisit the researchers at the end of the experiment period for the last measurements of their blood glucose or blood pressure and blood sample collection. Of the 22 diabetic patients, two-thirds (14 patients) were supplied with the anthocyanin capsule and the rest were supplied with the placebo capsules (pure starch for medical uses obtained from Divine Foods/India, HSN code 11081200). While for the 28 hypertensive participants, 18 patients received the treatment, and 10 patients received the placebo.

3. 3. Anthocyanin extract capsules preparation

All participants consumed twice daily a 300 mg capsule of anthocyanin extract (total 600 mg/day) or a placebo for 30 days. The two types of capsules were identical in physical appearance. Both capsule types were prepared using coloured empty gelatin hard capsule size 00 utilising starch as diluent by using a manual Fetton filling machine. The weight variation test of capsules was performed to ensure that all prepared capsules were within the accepted weight range ($\pm 5\%$). The anthocyanin extract powder was obtained from Herbalife-India, 100 % natural blueberry powder of 25 % anthocyanin extract by HPLC, SKU 4801. The dose (600 mg of anthocyanin per day) was chosen based on other clinical studies that noted numerous health advantages with doses in a similar range [6]. The capsules were to be taken by the registered participants after breakfast and supper (at least 6 hours between the two doses).

3. 4. Measurements of blood glucose levels and blood pressure

The blood glucose levels of patients were measured using Accu-Chek® (blood glucose monitor and lancing device, Roche, Germany). The blood pressure was measured using a mercury sphygmomanometer. For more reliable results and to reduce variations, the same devices were used for all subjects.

3. 5. Total antioxidant capacity measurement

Blood samples at day 0 and at the end of the experiment (Day 30) were collected from all participants (both test and control group) using heparin tubes and centrifuge at 4 °C for 10 minutes. The plasma was obtained, and aliquot samples were stored in deep freeze at –20 °C for testing. The test was performed using Hu-

man reactive oxygen species (ROS) Elisa Kit, AFG Bioscience. Serum-coagulation was performed at room temperature for 10–20 minutes, followed by centrifugation at a speed of 2000–3000 rpm for 20 minutes and then the supernatant was removed to be assayed immediately. All reagents, samples, standards, and blank were prepared as instructed by the assay layout sheet supplied with the kit. A standard of 50 μL was added to the standard testing wells, sample diluents of 40 μL were added to sample wells, then 10 μL of the testing sample was added (the final sample was diluted to 5 folds), and then incubated at 37 °C for 30 minutes. Following incubation, the wells were centrifuged and washed with distilled water. The liquid was discarded from wells, followed by washing with buffer for 30 seconds then the well was drained (the step was repeated five times). To all wells, except blank, 50 μL of enzyme HRP-conjugate reagent was added, and repeat incubation and washing as mentioned before in previous steps.

The colour was generated by adding 50 μL of each Chromogen solution A and B was added to each well while avoiding the light. The wells were preserved for 15 minutes at 37 °C. Fifty μL of stop solution to each well was added to halt the reaction (the colour changed from blue to yellow). Within 15 minutes of administering the stop solution, the absorbance was read at 450 nm. The blank was considered as zero. The standard curve of the absorbance versus the concentration was generated using standard solutions.

3. 6. C-reactive protein measurement

The sensitive C-reactive protein levels were measured in blood samples using the i-CHROMA™ serum C-reactive protein analyser, BodyTech. The procedure was based on the manufacturer's instructions. Zero value was assigned to the control wells. Immediately after adding stop solution, the absorbance was read at 450 nm. To establish the concentration of test samples, standard solutions were employed to create a standard curve of absorbance versus concentration [7].

3. 7. Statistical analysis

The data for the test and control groups were analysed using t-tests; any significant differences in means were reported by carrying out a one-way ANOVA with Tukey's posthoc test using the Minitab®17 program. Differences were considered significant at P values less than 0.05 (two-sided confidence intervals).

3. 8. Ethical approval

Before participating in the experiment, all participants were required to sign a written informed consent form. All details of the experiment and its aim, expected effects and adverse effects (if any) of anthocyanin extract consumption were explained to all participants. The ethical agreement was approved by "The Ethical Committee of Scientific Research" in the College of Pharmacy/University of Babylon with a reference number for the research: (COP SEC 2023-C1 on 8/March/2022). In this work, all ethical concerns, including patient approval, sample col-

lection and sample destruction, have been carried out in accordance with the Code of Ethics of the World Medical Association, Declaration of Helsinki, version: 2013.

4. Results

4. 1. Blood pressure measurements

The mean blood pressure for the hypertensive group was measured at day zero and at day 30 of experiment for participants receiving the drug or the placebo. No significant differences ($P < 0.5$) were detected in the mean blood pressures of patients receiving anthocyanin capsules when compared with the control group. Although there was a slight elevation in diastolic levels at day 30, no significant differences in the mean blood pressure of patients receiving the extract were observed in comparison to the values at day zero (Table 1). This elevation may be due to individual minor factors such as stress and environmental changes.

Table 1
Systolic (S) and diastolic (D) blood pressure values for participants receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

Group (hypertensive)	Mean BP (S/D) \pm SD (S/D) in mmHg at day 0	Mean BP (S/D) \pm SD (S/D) in mmHg at day 30
Test group (Anthocyanin extract)	139.1/92.4 \pm \pm 25.7/43.2	138.2/93.9 \pm \pm 14.2/35.6
Control group (Placebo)	138.8/ 92.2 \pm \pm 26.1/42.9	141.6/91.3 \pm \pm 22.1/18.8

4. 2. Blood glucose level measurements

To examine the effect of using anthocyanin extract in lowering glucose levels of diabetic patients, the mean blood glucose levels of diabetic participants were measured before and after anthocyanin usage. The data for patients receiving placebo capsules were considered as control and used for comparison (Table 2). Similar to the hypertensive group, no significant reduction ($P < 0.5$) in blood glucose levels was detected in comparison with results prior to using the drug or patients receiving placebo.

Table 2
Blood glucose levels for participants receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

Group (Diabetic)	Mean blood glucose \pm SD in mg/dL at day 0	Mean blood glucose \pm SD in mg/dL at day 30
Test group (Anthocyanin extract)	154.6 \pm 49.1	161.2 \pm 32.3
Control group (Placebo)	155.2 \pm 48.8	150.1 \pm 45.8

4. 3. Total antioxidant capacity

A standard curve was produced using the series of standard solutions (Fig. 1). Later, (based on the test samples' corresponding absorbance), the standard curve was used to calculate the total reactive oxygen species (ROS) levels in each sample.

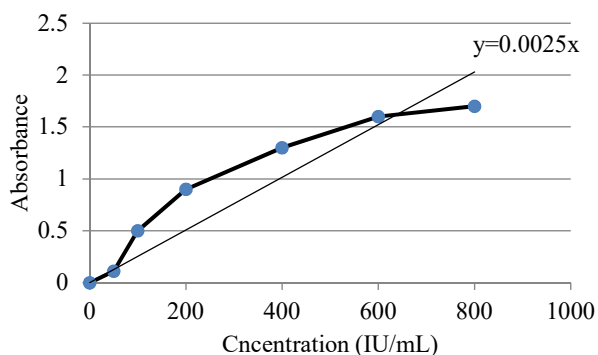


Fig. 1. Standard curve of total ROS generated by a series of standard solutions

The effect of anthocyanin ingestion on total ROS concentration in the hypertensive group is illustrated in Fig. 2. Patients who received the extract showed a significant lowering in total ROS concentrations when compared with day 0 of the experiment ($P<0.001$) and also when compared with the control groups. However, no significant difference ($P<0.05$) was detected when comparing the placebo group at day 30 with day 0. These results indicate that the anthocyanin extract consumption and due to its antioxidant effects resulted in reducing the total oxidative stress state in the investigated patients.

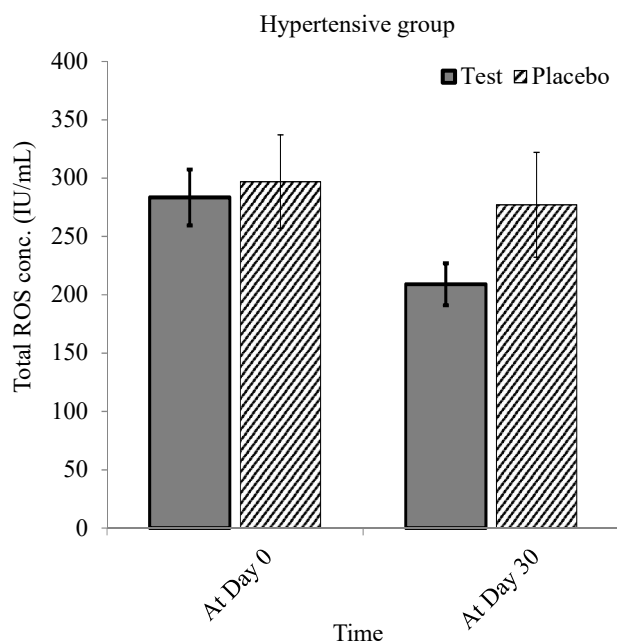


Fig. 2. Total ROS levels for hypertensive participants receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

The data for the effect of anthocyanin extract ingestion in terms of total ROS in diabetic groups are illustrated in Fig. 3. Similar decrease in total ROS caused by anthocyanin intake was also detected in the diabetic group, where after 30 days of receiving the drug, the total ROS was reduced to 204.6 IU/mL compared to 303.5 IU/mL prior to drug intake (baseline level) with P value of less than 0.001. However, for patients receiving a placebo, no significant difference was detected ($P<0.05$).

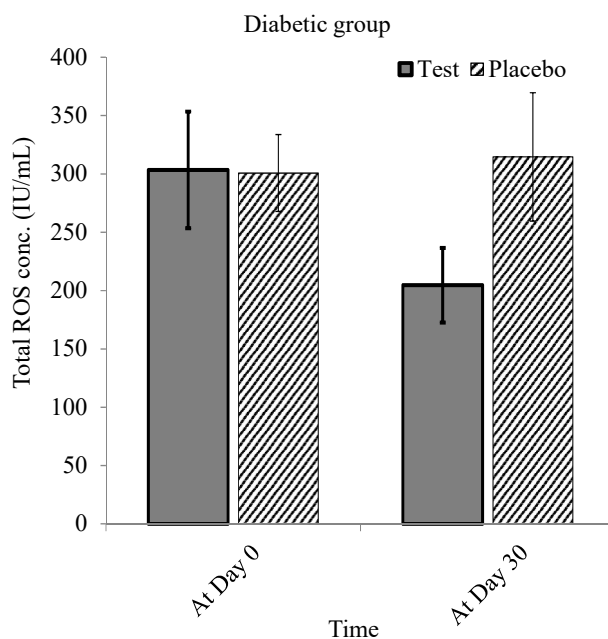


Fig. 3. Total ROS levels for diabetic participants receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

4. 4. Levels of C-reactive protein

For the hypertensive group, C-reactive proteins levels in participants who had received anthocyanin extract were compared with participants who received the placebo after 30 days of the experiment, and the results were further compared with the baseline levels (at day 0) (Fig. 4). Both the test and the control groups values were within the normal levels of C-reactive protein (less than 10 mg/L). However, a significant decrease ($P<0.01$) was observed in the test group (3.1 mg/L) in comparison to the control group (4.8 mg/L) or to the baseline levels (5.5 mg/L).

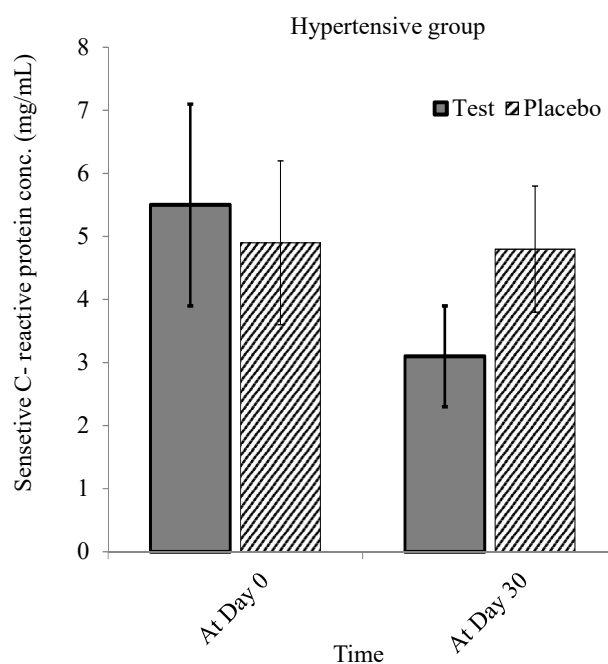


Fig. 4. Sensitive C-reactive proteins levels for the hypertensive group receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

Fig. 5 shows the baseline and the 30-day levels of C-reactive protein levels in the test and the placebo participants for the diabetic group. In both groups, the levels were within the normal range of C-reactive protein. Nevertheless, anthocyanin intake caused a significant ($P < 0.01$) lowering of C-reactive protein levels from 8.8 mg/L on Day 0 to 5.3 mg/L on Day 30. However, no such decrease was noticed in the placebo group.

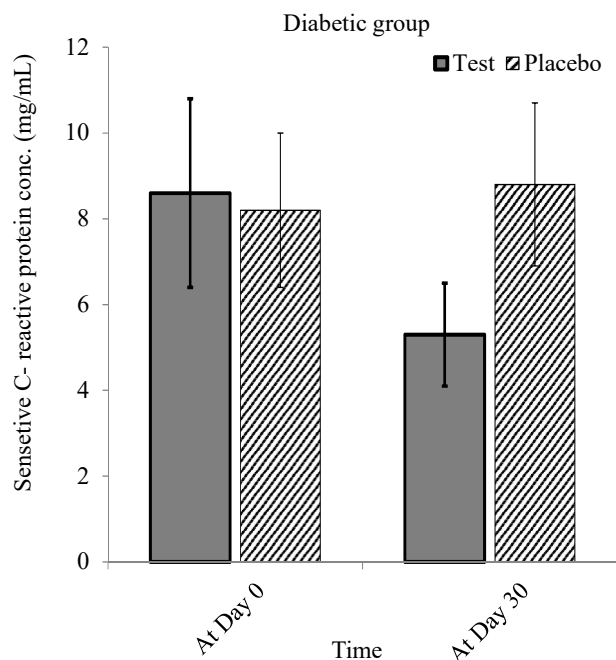


Fig. 5. Sensitive C-reactive proteins levels for the diabetic group receiving anthocyanin extract or placebo at day 0 and day 30. Values are expressed as mean \pm SD

6. Discussion

The vision-improving effect of anthocyanins is an interesting and important field of study, especially nowadays, where people are increasingly seeking healthier lifestyles and diets, with many of them preferring natural pharmaceutical materials rather than conventional chemical pharmaceuticals. Although it has been suggested that nutraceuticals (such as anthocyanin) are able to enhance general health, major research must be performed to illustrate such effects on specific disease conditions such as diabetes mellitus and hypertension. In addition to improving the status of oxidative stress, dietary antioxidants can also alter enzyme activity and biotransformation, reduce inflammation, stimulate the immune system, reduce platelet aggregation, modulate lipid (such as cholesterol) and hormone synthesis and metabolism, lower blood pressure, and have antibacterial and antiviral effects.

In our previous work, we used an *in vitro* model to examine the effect of delphinidin (a major constituent of anthocyanin extract) on the inflammatory status and found it decreased the expression of MCP-1 and CINC-1, two major cytokines markers [8]. That indicates the potential role of this extract to be examined further clinically in chronic diseases associated with inflammation in the present work.

Previous research showed that strict blood glucose control considerably reduces the clinical problems of

diabetes, but even the best blood glucose control could not totally prevent complications, indicating the need for new therapeutic approaches [9].

However, despite the potential effect of anthocyanin on reducing total oxidative stress status and inflammatory markers, no effect has been found on lowering blood glucose levels or blood pressure values, and this is inconsistent with other studies which highlighted the prophylactic effects of antioxidants rather than the pharmacological action. These agents could delay the progression of diseases by modulating numerous risk factors such as oxidative stress, hyperlipidemia and inflammation [6, 10]. It is noteworthy that the effect of starch was not taken into consideration in the placebo group on the 30th day of the study because the quantity ingested per day is most likely not to cause any changes in glycaemia.

The results showed that the consumption of anthocyanin extract in the enrolled participants reduced total oxidative stress levels and alleviated stress status in both diabetic and hypertensive groups compared to the control group (Fig. 2, 3). The ring orientation of anthocyanins is behind their capability to transfer electrons and donate protons, which in turn potentiate their antioxidant properties. The quantity and distribution of free hydroxyls in the vicinity of the pyrone ring are other important factors that affect the antioxidant activity [11].

Anthocyanins have demonstrated antidiabetic effects indirectly by their anti-obesity benefits through a variety of pathways, including limiting lipid absorption, controlling lipid metabolism, increasing energy expenditure, reducing food intake, and controlling gut microbiota, making them interesting candidates for alleviating complications in type 2 diabetes [12]. In the last decade, the involvement of oxidative stress in the development of a number of disease processes has been revealed. Such diseases may include cardiovascular disease, atherosclerosis, diabetes mellitus, arthritis and neurodegenerative disorders [12]. Such involvement is usually increased with age, where oxidative stress is thought to be a major deriving factor in explaining ageing theory and ageing-linked diseases [13]. Thus, measuring total oxidative stress values of human body fluids provides an essential tool to assess the biological redox status, disease progression and state and may illustrate the health-beneficial effects of consuming antioxidant extracts or an antioxidant-rich diet in humans.

The *ex vivo* methods of measuring the production of free radicals and total oxidative stress status in different body fluids are used in human studies to integrate the levels of ingested antioxidants (from food sources or supplements) with enhancement of the total body antioxidant state and disease state [14]. Published data clearly show that the intake of anthocyanins (either as in whole extract or its pure form) has marked antioxidant activity *in vitro*, often higher than other natural antioxidant materials [15]. There is evidence from previous epidemiological research that a high dietary intake of foods rich in flavonoids, especially anthocyanin, is associated with a lower incidence of some diseases, such as cancer and cardiovascular diseases [16–18].

Regarding the anti-inflammatory activities of anthocyanin extract in both test groups, the inflammation, which

was expressed by C-reactive protein levels, was found to be lower than that of the control (Fig. 4, 5). Previous related studies have revealed that high levels of C-reactive protein are accompanied by the risk of diabetes [19, 20]. Its gene expression is regulated by interleukin-6 and tumour necrosis factor- α . Since it is released by adipose tissues, obese individuals (a common feature in type 2 diabetes) usually have higher baseline C-reactive protein [21]. According to earlier research [22], adiponectin, as an anti-inflammatory cytokine substance, is formed and secreted by adipose tissues. Inverse relationships exist between adiponectin serum levels with dyslipidemia, obesity, insulin resistance and cardiovascular diseases. Reduced adiponectin or elevated leptin levels in Type 2 diabetes may worsen tissue inflammation and oxidative stress, which raises the risk of atherosclerotic disease [23]. Therefore this damaged response may be interrupted by anthocyanin.

Oxidative stress is considered a key player in several chronic diseases, and consumption of anthocyanin extract might mitigate the onset and progression of these diseases by counteracting the damage to biological molecules (such as lipids and DNA) due to oxidative stress [24]. Despite the fact that inflammation is deemed a normal physiological response, considering it a chronic condition or from a pathological perspective, it can pose considerable stress on the body.

Hence dispensation of anthocyanins present in fruits and vegetables may be a promising supplement for patients with chronic diseases such as diabetes mellitus and hypertension.

Research limitations. Unfortunately, some participants did not comply with the exact instructions required by the research, even some of them did not continue the treatment for the planned period, and therefore their results were excluded.

Prospects for further research. The extract shows a potential anti-inflammatory and antioxidant activity making it a promising substance to be tested with

inflammatory-underlined diseases such as rheumatoid arthritis and vasculitis.

6. Conclusion

In this study, we examined how would anthocyanin extract ingestion affects blood pressure and blood glucose levels in individuals who were already diagnosed with diabetes or hypertension. In both illness groups, the degree of change in the total antioxidant capacity and anti-inflammatory status following the extract administration was also examined.

Although the results did not show any physiological effect of anthocyanin consumption in lowering blood pressure levels or blood glucose levels in the tested participants, it clearly highlighted its significant effect in improving the oxidative stress status as well as reducing the inflammations. Such results attract attention to the expected role of these extracts in disease state and prophylactics, especially on regular and long-term use, especially in chronic diseases associated with high levels of inflammatory responses such as DM, arthritis and neurodegenerative disease.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

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