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Effects of sour cherry fruits on platelet aggregation and arterial blood pressure

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ABSTRACT

Background: The pivotal roles that platelet aggregation and hypertension play in the pathogenesis of ischemic disorders have emphasized the importance of antiplatelet and antihypertensive agents in the treatment of cardiovascular and cerebrovascular diseases, the leading causes of disability worldwide. Despite the abundance of these drug groups, finding new agents with fewer side effects and complications continues to be an important mission in modern medicine. To combat the adverse effects of manufactured medications, plants could be promising sources for new remedies. One such plant, the Sour Cherry, can serve as a source for new antiplatelet and antihypertensive medications considering its rich content of anthocyanins, flavonoids, and organic acids.

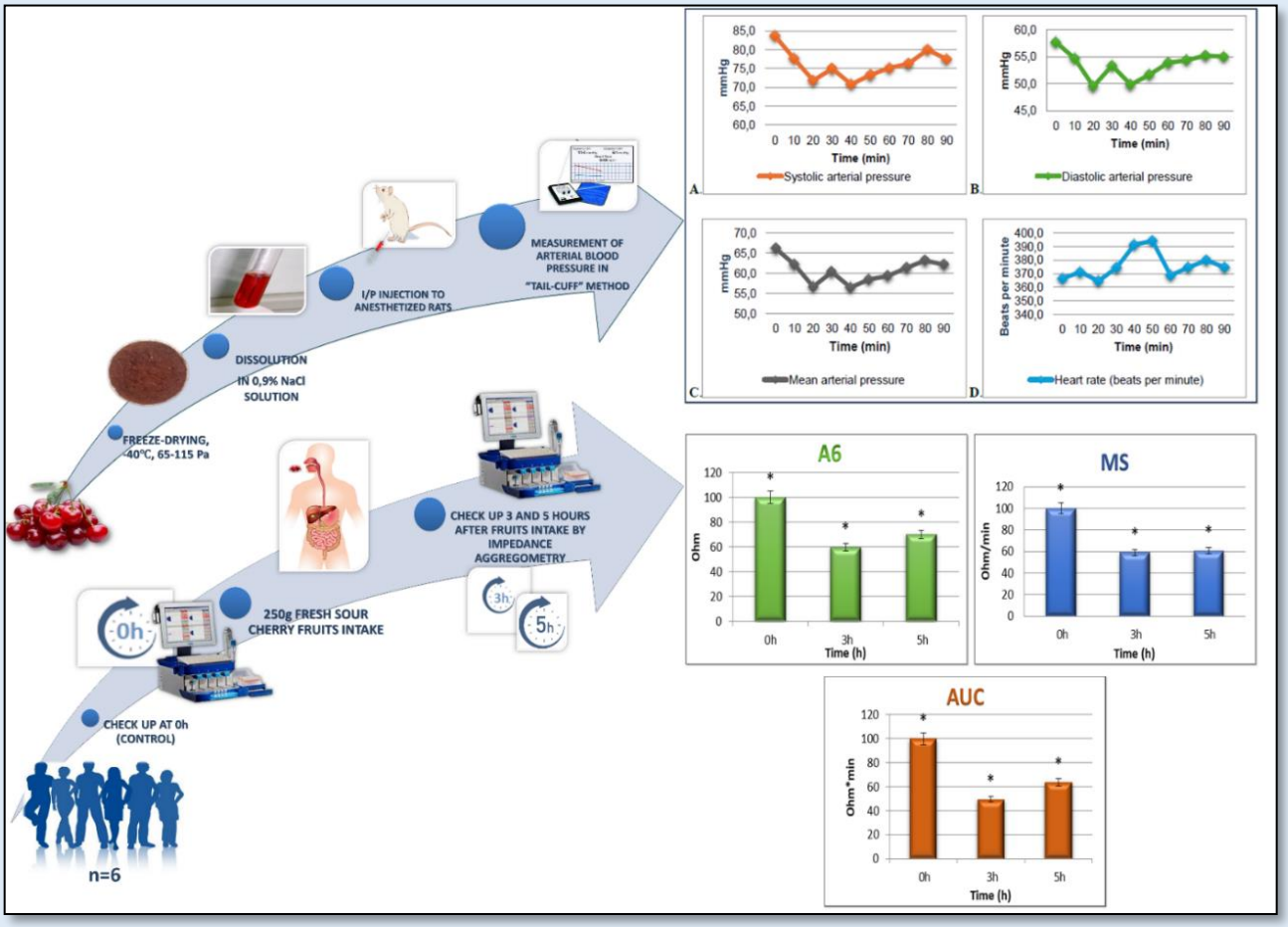
Objectives: The purpose of this study was to investigate the antiplatelet and antihypertensive effects of Armenian Sour Cherries.

Results: It has been revealed that Sour Cherries contain properties that can be incorporated into antiplatelet and antihypertensive remedies. Conducted observation shows that after 3 hours of Sour Cherry intake, the amplitude of aggregation (A6) was reduced by 40.2±17.21% ($p<0.05$), the maximal slope of aggregation by 41.1±14.6% ($p<0.05$,) and the area under the curve by 50.3±19.75% ($p<0.05$) in comparison to the negative control. Measuring the same indicators after 5 hours demonstrated that the effect of the Sour Cherry on the aggregation process was inferior compared to the 3rd hour data, remaining less than the same characteristics of the negative control. After 5 hours the reduction of aggregation amplitude, the maximum slope and area under the curve compared with the control, were 29.84±8.27% ($p<0.05$), 39.29 ±11.74% ($p<0.05$) and 36.18±19.13% ($p<0.05$), respectively.

The investigation of Sour Cherries' effects on animals' blood pressures demonstrates that intraperitoneal injection of freeze-dried Sour Cherry solution was accompanied by changes in blood pressure indicators and the animals' heart rates. Systolic blood pressure values after administration of Sour Cherry fruits began reducing from the 10th minute of the experiment and reached maximal reduction at the 40th minute by 15.3%. After the 40th minute, the tendency of recovery for systolic blood pressure values, which remained less than 0hour values even at 90th minute of the experiment, were registered. Maximum reduction (14.2 %) of diastolic blood pressure values takes place at the 20th minute and continues to be less than control values until the 90th minute of the experiment. Calculations of mean arterial pressure values demonstrated similar changes with the same tendency. Heart rate changes followed the fall of arterial pressure, increasing by 27.7 beats per minute at the 50th minute of the experiment.

Conclusion: The presented investigation proves Sour Cherry fruits as functional foods with antiplatelet and antihypertensive effects which opens up perspectives in the search for new, safe agents in the prevention and treatment of cardiovascular diseases and stroke based on functional food properties. This obtained data could serve as a platform for the development of a new dosage in the form of freeze-dried Sour Cherries with the possibility of a highly preserved content of biologically active substances.

Keywords: Sour cherry fruits, antiplatelet activity, antihypertensive action



INTRODUCTION

Platelets have a crucial role in the pathophysiological mechanisms of different disorders, especially in cardiovascular diseases and stroke [1], which, according to the last report of the World Heart Federation, caused up to 20.5 million deaths in 2023 [2] and are considered the leading causes of disability worldwide [3].

Mechanisms of cardiovascular pathology development, including endothelial dysfunction, ischemic cascade and thrombi formation, were predetermined targets for pharmacological approaches to ischemic disorders in which more importance is given to the correction of platelet dysfunction [4,5,6]. It is well known that platelets, besides their primary function of hemostasis regulation, play pivotal roles in inflammation, antimicrobial host defense, tumor growth and atherogenesis [7]. In the process of atherogenesis, platelets have dual actions. On the one hand, platelets mediate the adhesion of leukocytes to altered endothelium and provoke inflammation in the intimate layer of arteries; on the other hand, they become the main players in thrombi formation in end stages [8]. One of the main risk factors of ischemic diseases is hypertension which contributes to 48% for ischemic incidences. Due to this, one of the milestones in the treatment and prevention of ischemic disorders are antiplatelet and antihypertensive agents [9].

During the last decades, it has become clear that antiplatelet and antihypertensive drugs prolong life expectancy and prevent progression of ischemic diseases [10]. Unfortunately, side effects such as resistance, bleeding, and hemorrhagic disorders begin to develop with prolonged use of the mentioned drugs [11]. Similarly, side effects including electrolyte imbalance, acute kidney injury, and dry cough, have been recorded in association with antihypertensive drugs [12].

In this regard, despite the huge armory of antiplatelet drugs (COX-1 inhibitors, PDE inhibitors, GP IIb/IIIa blockers, ADP-blockers, TxA2 blockers and PgI2 analogues [13]) and antihypertensive drugs (Renin-angiotensin-aldosterone system (RAAS) blockers, beta-blockers, alpha-blockers, diuretics, calcium channel blockers, etc. [14]) the discovery of new, effective agents with fewer side effects caused by f the mentioned groups continues to be an important goal in modern medicine [15].

In view of these, plants could be promising sources for new remedies which is proven by the fact that about 80% of cardiovascular drugs have plant origins [16]. The cardiovascular activity of plants is based on their content of polyphenolic substances with a wide range of pharmacological activity including antiplatelet [17] and antihypertensive effects[18]. According to the literature, there are described cardioprotective effects of curcumin [19], antiplatelet,anti-hypertensive and antihyperlipideic effects of pomegranate [20,21,22], high antiplatelet activity of tomato [23], antioxidant activity of plants with high content of carotenoids, etc [24].

In search for plant sources for new antiplatelet and antihypertensive activities, our attention was focused on the Sour Cherry (Prunus cerasus) fruits which are characterized with rich content of anthocyanins, flavonoids [25], organic acids and melatonin and appear to be anti-inflammatory, antihyperlipidemic [26], sleep-regulating [27], uricosuric [28], antioxidative , etc [29].However, there is no data pertaining to antiplatelet effects of Sour Cherry fruits.

Based on the above-mentioned, it was investigated and scientifically proven the antiplatelet and antihypertensive activity of Sour Cherry fruits with an example of the Armenian Sour Cherry.

MATERIALS AND METHODS

Participants: Investigation was conducted with participation of 6 men and women from 38 to 68 years old. Fasting blood samples were collected from all participants at the start of the study (baseline, 0 hours for antiplatelet effect evaluation) for the initial assessment

of platelet function and profiles. Blood samples were collected after 3 and 5 hours of Sour Cherry intake to assess changes in platelet aggregation.

For the evaluation of the antiplatelet effect of Sour Cherries, participants consumed 250 grams (about 8.82 oz) of fresh Sour Cherry fruits on the day of the study. According to our previous investigation, the mentioned quantity of Sour Cherry fruits contains approximately 224 mg anthocyanins of cyanidin-3-glucoside equivalent. Considering the influence of other polyphenolic compounds contained in food on the results of the study, an appropriate diet with a minimum number of polyphenolic compounds was developed for the participants.

Animals: The antihypertensive activity of Sour Cherry fruits was studied in "tail-cuff" method on 6 inbred, white, male rats, weighing 200–240 g using CODA™ Monitor Single Channel Non-invasive Blood Pressure System (Kent Scientific, USA).

In order to minimize circadian influences on the animal response, the experiments were performed between 12 and 15 h at a laboratory room temperature of 22±1°C. Food and water were available *ad libitum*. Animals were kept in standard laboratory vivarium conditions in accordance with the PHS Guide for the Care and Use of Laboratory Animals.

Experiments were carried out under the urethane anesthesia (1.1g/kg dose, injected intraperitoneally) which provided reliable values in changes of blood pressure and heart rate, and has long duration of action and minimal effects on autonomic nervous system.

Antiplatelet activity evaluation: Investigation of Sour Cherry antiplatelet action was conducted using the method of impedance aggregometry using ROTEM® aggregometer. For the evaluation of platelet aggregation in whole blood was used ''Ar-tem®'' reagent - produced for ROTEM system, which activates arachidonic acid induced platelet aggregation. Prior to measurements, the blood and solvent (NaCl, 0.9%) were heated in specific cabins of the ROTEM module. For inducing aggregation, 150 µl blood and 20 µl diluents containing arachidonic acid were added. For the preparation of platelet aggregation-inducing solution arachidonic acid was dissolved in 20 µl diluents within 3 minutes. Before making the solution, arachidonic acid was kept at room temperature for 5 minutes. Blood samples were collected in citrate-containing tubes according to the demands of Biosafety in Microbiological and Biomedical Laboratories (U.S. Department of Health and Human Services, Public Health Service, 6th edition 2020).

To reduce the development of possible mistakes, this method assumes one-time usage of reagents with standardized volumes using a cuvette system supported with special electrodes, energized with a certain voltage, and stirring bar. The order of actions is controlled by an automated alarm system.

After 6 minutes of arachidonic acid addition, 3 different measurements took place:

-A6 (amplitude in 6 minutes), which reflects the measured impedance 6 minutes after starting the test. It is a measure for the extent of platelet aggregation and is expressed in Ohms (Ω).

-MS (maximum slope) shows the maximum slope to the aggregation graph.MS is a measure of the rate of aggregation. The unit of measure is Ohm (Ω)/min.

-AUC – is the area under the curve of aggregation from the start of the measurement until 6 minutes of runtime. As a measure unit, it uses Ohm (Ω)*min.

"Tail-cuff" method for arterial blood pressure measurement: Rat's arterial pressure was measured on the caudal artery under urethane anesthesia (1.1 g/kg, i/p). After anesthesia, a small, inflatable cuff is placed around the base of the rat's tail. A Volume Pressure Recording (VPR) sensor is placed distal to the cuff (further down the tail). The cuff is inflated to a pressure higher than the expected systolic blood

pressure to occlude the blood flow in the tail artery. The cuff is then slowly deflated. As the pressure decreases, blood flow returns, and the sensor detects the reappearance of the blood pulse. The pressure at which the first detectable pulse returns is recorded as the systolic blood pressure. Mean arterial pressure is calculated based on systolic and diastolic arterial pressure values. The temperature for the experiments was maintained constant at 30-32°C to eliminate the influence of differences of temperatures between rats' tails and environments.

For the evaluation of Sour Cherry fruits antihypertensive effect, measurements were taken every 10 minutes up to 90 minutes, starting immediately after i/p injection of freeze-dried Sour cherry fruit solution (0.5 g freeze-dried fruits in 0.5 ml saline).

Ethical considerations: Considering that for the study were used Sour Cherry fruits, which are the part of daily diet and venipuncture for the blood collection from the healthy adults, this study falls under the category of "minimal risk". Participants were given both written and verbal information about the study. They were also informed that participation was voluntary, and they could withdraw from participation at any time without any consequences.

These study protocols were approved by the Ethics Committee of the Science Department of Yerevan State Medical University after Mkhitar Heratsi.

Statistical analysis: Statistical analysis of the received data was performed by SPSS 20.0 using the student t-test to determine the significance of the observed differences between groups. A p-value of less than 0.05 was considered statistically significant. 0-hour results of aggregation and 0-minute results of blood pressure indicators served as negative controls.

RESULTS

Conducted experiments have evidently shown that Sour Cherry fruits have antiplatelet ability. Thus, after 3 hours of Sour Cerry fruits intake among participants, it was stated that there was a reduction in the amplitude of aggregation (A6), which was proved by the decrease of platelet impedance toward impulse passage between electrodes by 40.2±17.21% compared with the initial level ($p<0.05$). The mentioned indicator of platelet aggregation after 5 hours was a little bit increased compared with 3-hour data but remained lower than the control by 29.84±8.27% ($p<0.05$) (Figure 1A).

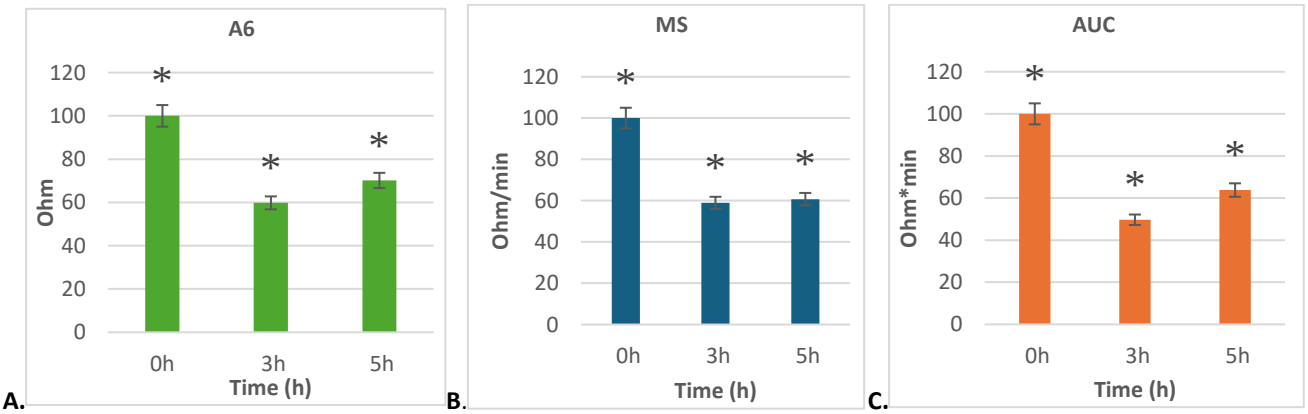


Figure 1. Effects of Sour cherry fruits on platelet aggregation indicators after 3 and 5 hours of Sour cherry fruits intake: A-changes of amplitude of aggregation (A6), B-changes of maximal slope of platelet aggregation (MS), C-changes of area under the curve of platelet aggregation (AUC), M±SD, n=6, *$p<0.05$.

Antiplatelet activity of Sour Cherry fruits was also detected by measuring the changes in aggregation rate, which is characterized by maximal slope. The mentioned indicator of platelet aggregation was decreased by 41.1±14.6% ($p<0.05$) compared to control. After 5 hours, the values of the maximum slope of platelet aggregation were lower by 39.29 ±11.74% ($p<0.05$), than the 0-hour values (Figure 1B).

More pronounced changes under the action of Sour Cherry fruits were registered in changes of area under the curve, which indicates that Sour Cherry fruits provide a reduction in platelet amount. As evident, the mean results of the conducted experiments (Figure 1C), the area under the curve was decreased by 50.3±19.75% ($p<0.05$). The duration of observation time until the 5 hours indicated that the number of platelets appeared to decrease, and at the end of the experiments this indicator was less than the control by 36.18±19.13% ($p<0.05$).

Investigation of the effects of Sour Cherry fruits on animal's blood pressure demonstrated that i/p injection of freeze-dried Sour Cherry solution was accompanied by changes in blood pressure indicators and the animals' heart rates. Data presented in Table 1. shows that systolic blood pressure values after action of freeze-dried Sour Cherry solution begin to reduce starting from the 10^{th} minute of experiment and reach maximal reduction at the 40^{th} minute by 15.3%. After the 40^{th} minute, t the tendency of recovery for systolic blood pressure values,which remained less than 0hour values even at 90^{th} minute of experiment, was registered (Figure 2A).

TABLE 1. Changes of systolic, diastolic, mean arterial pressures and heart rate after intraperitoneal injection of Sour cherry freeze-dried fruits solution to rats.

Time after injection	SBP (mmHg)	DBP (mmHg)	Mean arterial pressure (mmHg)	HR (beats per minute)
0min	83.7±10.5	57.7±10.4	66.2±10.0	366.5±46.0
10min	77.7±8.3	54.7±3.7	62.2±4.8	371.2±41.3
20min	71.8±10.7	49.5±11.1	56.7±10.4	364.5±28.8
30min	75.0±11.7	53.3±6.7	60.3±7.9	374.3±31.9
40min	70.8±9.4	49.8±2.8	56.5±4.9	391.5±42.6
50min	73.3±11.0	51.7±6.6	58.5±7.7	394.2±46.4
60min	75.2±11.8	53.8±11.1	59.3±11.8	368.7±23.2
70min	76.3±9.3	54.3±11.3	61.3±10.4	374.7±18.7
80min	80.0±11.3	55.2±8.5	63.2±9.0	379.8±15.2
90min	77.5±9.6	55.0±7.9	62.2±8.5	374.7±10.9

Registration of the maximum reduction (14.2 %) of diastolic blood pressure values takes place

at the 20^{th} min and continues to be less than the control values until the 90^{th} minute of the experiment (Figure 2B). Calculation of mean arterial pressure values demonstrated similar changes with the same tendency (Figure 2C). As evident from the data presented in Table 1, heart rate changes follow the fall in arterial pressure, increasing by 27.7 beats per minute at the 50^{th} minute of the experiment (Figure 2D).

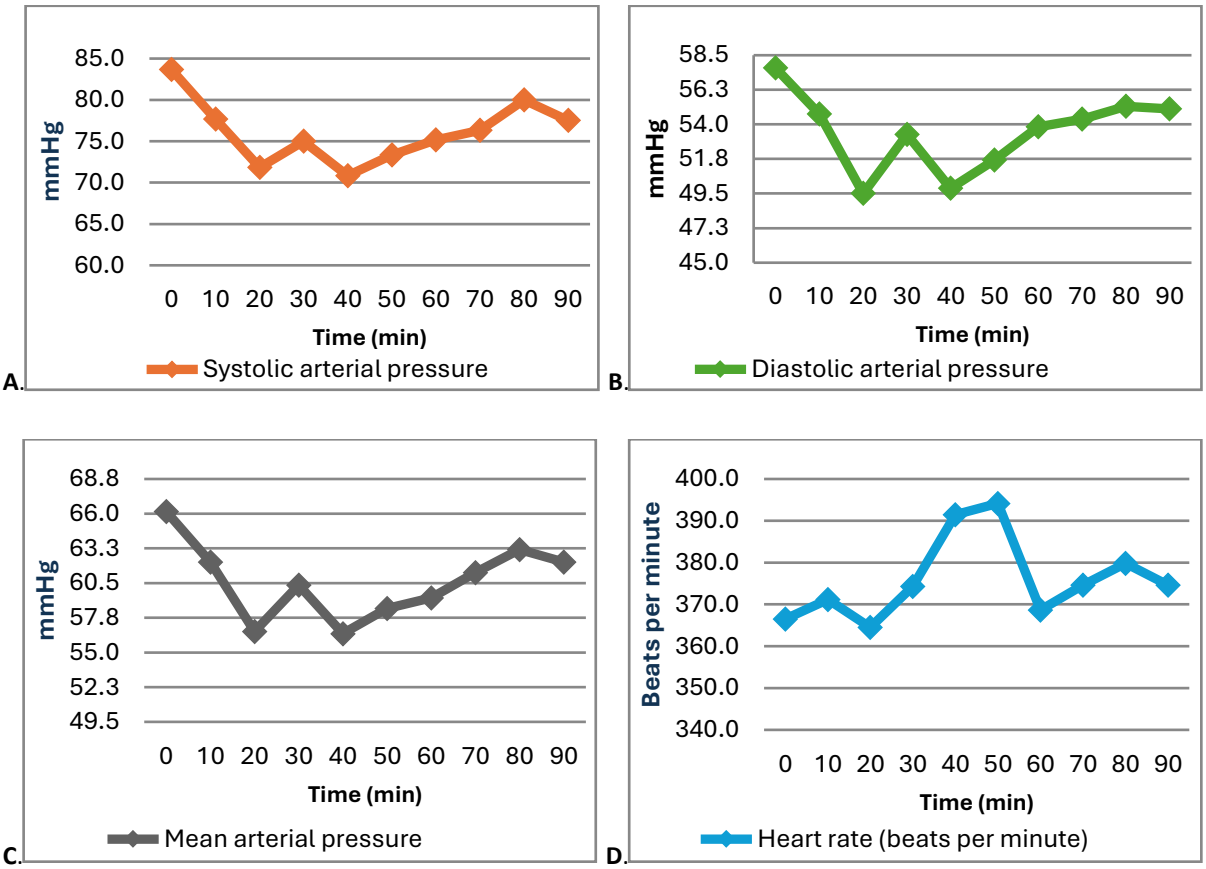


Figure 2. Changes of rats systolic (A), diastolic (B), mean arterial blood pressures (C) and heart rate (D) after the intraperitoneal injection of Sour cherry freeze-dried fruits solution. M±SD, n=6

DISCUSSION:

As is known, European guidelines on the prevention of cardiovascular diseases do not recommend aspirin for individuals who are free from cardiovascular diseases and are at low risk of these diseases due to the increased risk of major bleeding [30]. That is why the finding of new antiplatelet drugs with less side effects continues to remain as an important task of modern medicine. From this, promising drugs have been found to stem from plant origins, especially the water-soluble extract of tomatoes, specifically Fruitflow®, demonstrating high effectiveness as an antiplatelet agent [31].

For the finding of new and safe agents with natural origins, the Sour Cherry was chosen due to , the rich content of polyphenolic substances, organic acids and melatonin, possessing anti-inflammatory, antioxidant, sleep-regulating, and antihyperlipidemic effects. However, there is no data concerning the antiplatelet activity of Sour Cherry fruits.

Statistical analysis of the conducted experimental data confirms that Sour Cherry fruits possess antiplatelet activity which is displayed by their ability to decrease platelet impedance through a decrease of platelet amount, capacity and velocity of aggregation. The antiplatelet properties of Sour Cherry fruits were more prominent after 3 hours and kept their antiplatelet effect until 5 hours of fruit intake by volunteers.

The cardiovascular benefits of Sour Cherries were confirmed by an antihypertensive effect in animal models. Data obtained by non-invasive blood pressure measuring" tail-cuff'' method indicate a decrease in systolic and diastolic pressures between 20 and 40 minutes after administration, and levels were inferior to initial levels even at the 90th minute of observation along

with a slight rise in heart rate.

Thus, our experiments of fresh and freeze-dried Sour Cherry fruits' antiplatelet and antihypertensive activities justified our expectations in the search for effective and safe agents for the prevention and treatment of cardiovascular diseases and stroke based on its functional food properties. This obtained data could serve as a platform for the development of new dosages for forms of freeze-dried Sour Cherry fruits with a possibility of a highly preserved content of biologically active substances for supporting and encouraging patients with high blood pressure who seek natural dietary choices to enhance their treatment of antiplatelet and antihypertensive therapies.

List of Abbreviations: A6-amplitude of platelet aggregation; MS-maximal slope of platelet aggregation**;** AUC-area under the curve of platelet aggregation**;** SBP-systolic blood pressure**;** DBP-diastolic blood pressure**;** HR-heart rate.

Author's Contributions: All authors contributed to this study.

Competing Interests: The authors declare that they have no competing interests.

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