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Resveratrol; a Double-Edged Sword Antioxidant Agent for Preserving Platelet Cell Functions During Storage; Molecular Insights

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Abstract

Background: In the current study we have aimed to find the effects of Resveratrol treatment on platelet concentrates (PCs) at the dose dependent manner. We have also attempted to find the molecular mechanism of the effects.

Methods: The PCs, have received from Iranian blood transfusion organization (IBTO). Totally 10 PCs were studied. The PCs divided into 4 groups including untreated (control) and treated by different dose of Resveratrol; 10, 30 and 50 µM. Platelet aggregation and total reactive oxygen species (ROS) levels were evaluated at day 3 of PCs storage. In silico analysis was carried out to find out the potential involved mechanisms.

Results: The aggregation against collagen has fallen dramatically in all studied groups but at the same time, aggregation was significantly higher in the control versus treated groups ($p<0.05$). The inhibitory effect was dose dependent. The aggregation against Ristocetin did not significantly affect by Resveratrol treatment. The mean of total ROS significantly increased in all studied groups except those PCs treated with 10 µM of Resveratrol (P=0.9). The ROS level significantly increased with increasing Resveratrol concentration even more than control group (slope=11.6, P=0.0034). Resveratrol could potently interact with more than 15 different genes which, 10 of them enrolled in cellular regulation of the oxidative stress.

Conclusions: Our findings indicated that the Resveratrol affect the platelet aggregation at the dose dependent manner. Moreover, we have also found that the Resveratrol play as double-edged sword in the controlling oxidative state of the cells. Therefore, Using the optimal dose of Resveratrol is the great of importance.

Keywords: Aggregation, Oxidative stress, Platelet storage lesion, *Resveratrol*.

Introduction

Blood circulating platelets play an important role in homeostasis and thrombosis. Platelet transfusion is an important treatment strategy to prevent or treat bleeding in patients with thrombocytopenia and platelet dysfunction. Platelet concentrates (PCs) are prepared by apheresis or donated whole blood. There are two major procedures to prepared whole blood derived PCs including platelet-rich plasma derived PCs (PRP-PC) or buffy-coat derived PCs (BF-PC) (1, 2). The platelet product is stored for 5 days at 22-24 °C under gentle agitation to maintain cell functions (3).

Ideally, the transfused platelets do not have activation markers on their surface until destruction or clearance, unless they accumulate in a specific location due to vascular damage (4). Storage platelets, meanwhile, undergo severe biochemical, structural, and functional changes known as platelet storage lesions (PSL). Together, these changes reduce the efficacy and safety of

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platelet transfusions (5-7). These unwanted changes in platelet function cause complications associated with platelet transfusion, from a mild or relatively severe adverse reaction (fever, inflammation, and chills) to life-threatening complications (thrombosis, stroke, related lung injury) (8, 9). During storage, activated platelets secret prothrombotic and proinflammatory mediators, which in turn contribute to the complications of blood transfusion (8, 9). Various methods of platelet storage are currently being evaluated and researched, the most important of which are the search for platelet-preserving supplements, the production of storage bags with increased permeability to oxygen, and the storage of platelets at cold temperature (6, 10). Although some researchers have claimed to improve metabolic markers (pH, lactate, and glucose) and parameters related to platelet quality (mean volume, swearing and platelet deformation), these findings did not confirm the clinical efficacy and safety of these products (11). In addition, several reports have suggested that platelet longevity is regulated by apoptosis during storage. Although platelets are non-nucleated cells, they respond to apoptosis in response to stress when stored in the laboratory, resulting in depolarized mitochondrial membranes, caspase activation, and phosphatidylserine exposure (12). One of the ways to improve the quality of PCs is to use platelet additive solutions (PAS) that have been used since 1980 (13). For this reason, in this study, we looked at the effect of a natural compound called resveratrol at different concentrations on platelet function during storage (14).

Resveratrol, 3, 4', 5-Trihydroxy-trans-stilbene, is a natural polyphenol and a phytoalexin that protects plants from fungi in nature. It is found in small amounts in the skins of grapes, berries, peanuts, rhubarb roots and other plants (14). After discovering the effect of the French paradox (low prevalence of myocardial infarction in France despite high consumption of saturated fatty acids), this substance attracted of attraction by researchers (15). The effects of *Resveratrol* on the mechanisms involved in the development of cardiovascular disease have been extensively evaluated (16). Among the most important medicinal effects of this substance are its anti-atherosclerotic, anti-hypertensive, antioxidant, and anti-inflammatory properties. Recently, several studies have also evaluated the effects of *Resveratrol* on platelets and reported its reversible inhibitory effects on platelet aggregation thorough unknown mechanisms (17-20). In the current study we have aimed to find the effects of *Resveratrol* treatment on PCs function at the dose dependent manner. We have also attempted to find the molecular mechanism of the effects.

Materials and Methods

Ethical standards

All procedures have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent

Informed consent was signed prior to participation in the study.

PCs Preparation and storage

PC bags, prepared by platelet-rich plasma (PRP) method based on standard operating procedure (SOPs), have received from Iranian Blood Transfusion Organization (IBTO) (15). Briefly, whole blood was obtained by conventional phlebotomy in 450 ml bags containing 63 ml of adenine dextrose phosphate citrate solution (CPDA1) as an anticoagulant in triple blood bags (Maco Pharma, France). After that, the whole blood centrifuged at light spin and heavy spin, respectively to fraction it into poor platelet plasma, Pack cell and PRP-PCs. PCs stored at 20-24 °C under gentle agitation. This study was approved by the Research Ethics Committee of Higher Institute of Research and Medical Education of Blood Transfusion (IR.TMI.REC.1398.006). Informed consent was obtained from blood donors.

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Treatments and sampling

After receiving the PCs with similar blood groups, the bags were combined in pairs to provide enough volume. The combined bags are then divided into four equal parts; untreated (control group) and treated with 10, 30 and 50 µM of *Resveratrol*. All these PCs were stored in a plate incubator at 20-24 °C under continuously agitation for 3 days. Sterile sampling was performed on day 3.

Platelet Aggregometry assessment

Platelet aggregation test was performed by turbidimetric method using a aggregometer (Chronolog model 700 x, Havertown, Pennsylvania, USA). The aggregation against Collagen agonist at 2 µg / ml concentration and *Ristocetin* at 1.5 mg/ml concentration were evaluated. The results were reported as a percentage.

Reactive oxygen species (ROS) assessment

Total ROS concentrations in PCs were measured by ROS assay kit (Invitrogen, USA) according to manufacturer's instruction. In summary, 100,000 platelets per microliter were dissolved in the Tyrod buffer. Then 100 µl of this cell suspension was combined with 100 µl of the reagent and incubated for 60 minutes at 37 °C and 5% CO2. Then the Anti CD41 FITC conjugated was added and incubated for more 30 minutes. Finally, the ROS concentration was assessed by flow cytometry (Sysmex Partec) after gating platelets using CD 41 marker. Data were analyzed with FloMax software.

In silico analysis

To find the exact molecular mechanism of *Resveratrol* on the cells, the drug-gene interaction assessment was carried out by using the drug gene interaction database (20). The genes with high interaction scores submitted for functional network annotations by using the STRING database (20). At the end, genes enrolled in oxidative stress regulation pathways were identified.

Statistical analysis

The data were analyzed by descriptive statistics including mean, median, standard deviation, and frequency. Mean comparison between the groups have done by Tukey's multiple comparison test. The analysis of covariance (ANCOVA) was used to test for linear trend. P value less than 0.05 considered significant.

Results

Totally 10 PCs were studied. The mean PLT count and MPV before intervention were 1304±130 $\times 10^3/\mu l$ and 7.94±0.61 fl, respectively. The platelet aggregation against collagen and *Ristocetin* agonists before intervention were 76.6±6.02 % and 87.6±4.39 %, respectively.

At day 3, the aggregation against collagen has fallen dramatically in all studied groups. The reduction increased with increasing *Resveratrol* concentration. The aggregation against collagen was significantly higher in the control versus treated groups($p<0.05$). The inhibitory effect was dose dependent (Fig. 1). On the other hand, the aggregation against *Ristocetin* did not significantly affect by *Resveratrol* treatment (Fig. 2).

The mean total ROS level at baseline (day 0, before intervention) was 8.63±2.49. It is significantly increased in all studied groups except those PCs treated with 10uM *Resveratrol* (8.63 vs 9.83, P=0.9) (Fig. 3). Interestingly, the ROS level significantly increased with increasing *Resveratrol* concentration even more than control group (slope=11.6, P=0.0034) (Fig. 4).

The in-silico analysis has shown that the *Resveratrol* could potently interact with more than 15 different genes (Table 1). Interestingly, 10 out 15 were enrolled in cellular regulation of the oxidative stress (Table 2, Fig. 5).

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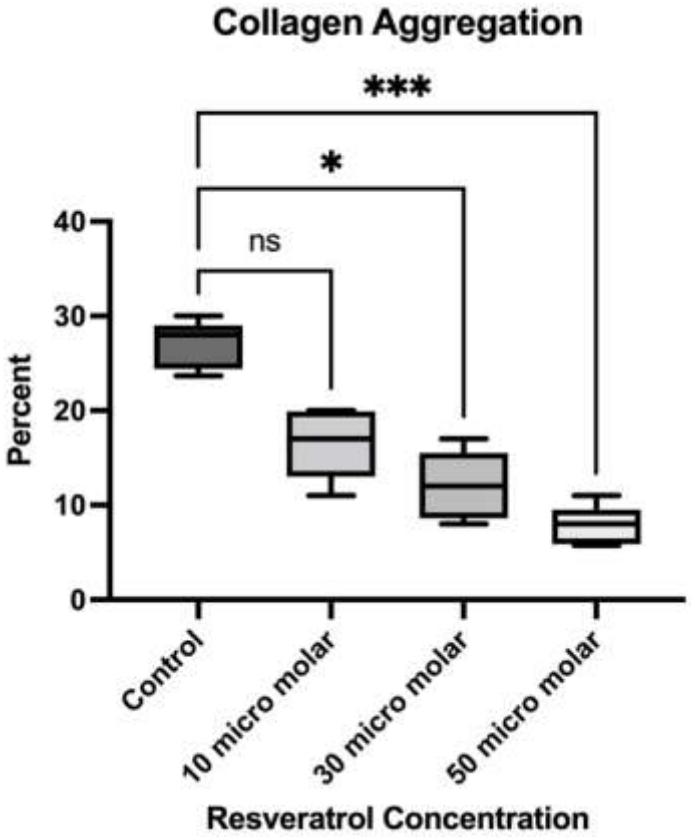

Fig. 1. Platelet aggregation at day 3 of PCs storage against collagen at different *Resveratrol* concentrations treatment compared to untreated PCs as control group. Abbreviations: *; P value less than 0.05, **; P value less than 0.01, ***; P value less than 0.001, Ns; Non- Significant.

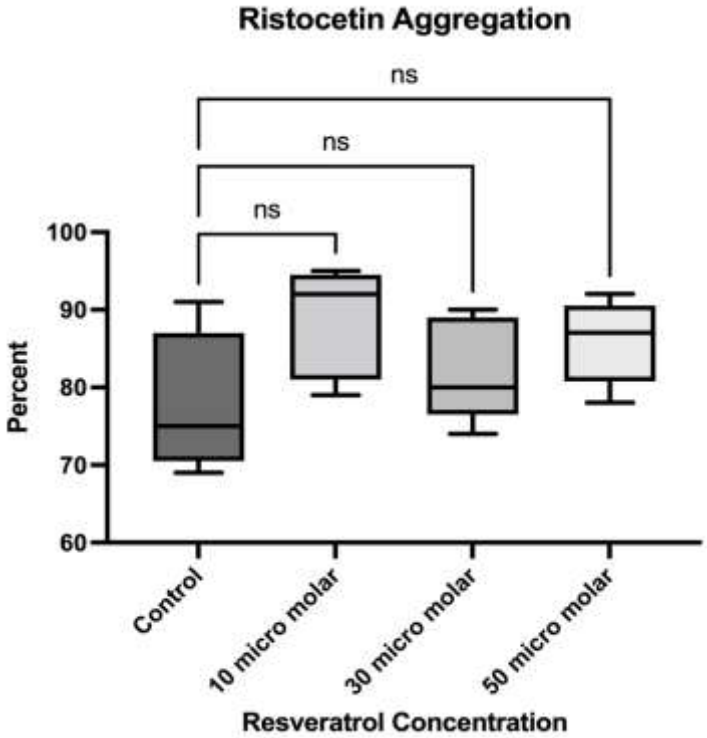

Fig. 2. Platelet aggregation at day 3 of PCs storage against *Ristocetin* agonist at different *Resveratrol* concentrations treatment compared to untreated PCs as control group. Abbreviations: *; P value less than 0.05, **; P value less than 0.01, ***; P value less than 0.001, Ns; Non- Significant.

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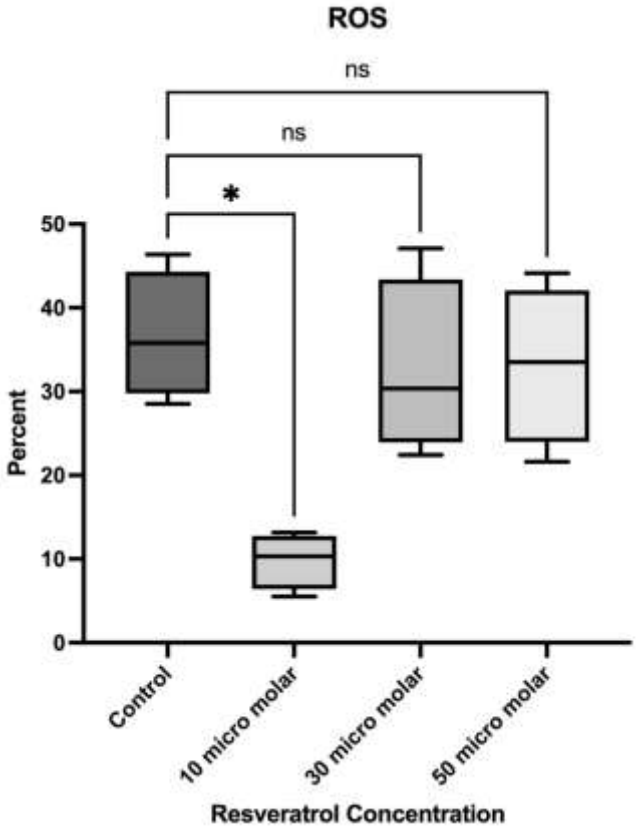

Fig. 3. Platelet ROS level at baseline (day 0, before intervention) and at day 3 of PCs storage at different *Resveratrol* concentrations treatment compared to untreated PCs as control group. Abbreviations: *; P value less than 0.05, **; P value less than 0.01, ***; P value less than 0.001, Ns; Non- Significant.

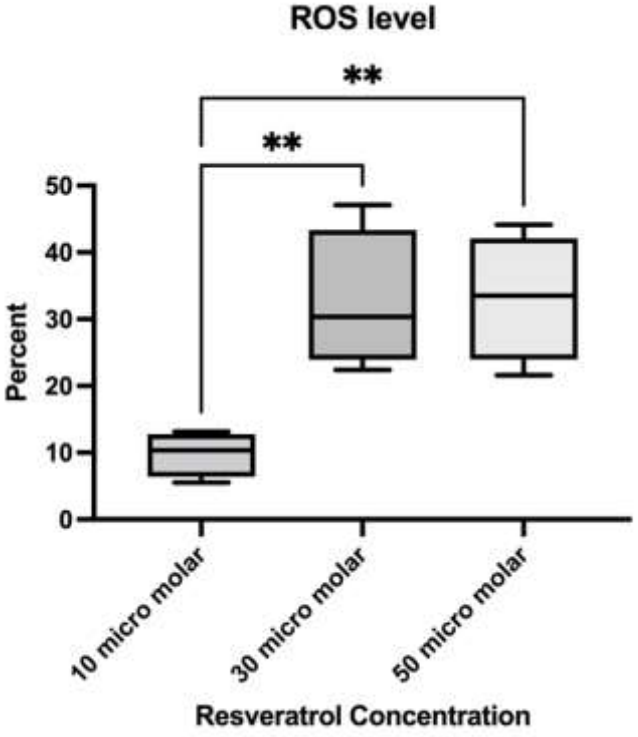

Fig. 4. *Resveratrol* dose dependent study on platelet ROS level. Abbreviations: *; P value less than 0.05, **; P value less than 0.01, ***; P value less than 0.001, Ns; Non- Significant.

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Table 1. *Resveratrol* Drug interaction.

Gene symbol	Gene Description	Interaction score	PMID
PECAM1	Platelet endothelial cell adhesion molecule	2.65	15041740
FOXO3	Forkhead box protein O3; Transcriptional activator which triggers apoptosis in the absence of survival factors, including neuronal cell death upon oxidative stress	1.33	17513867
Diablo	Diablo homolog, mitochondrial; Promotes apoptosis by activating caspases in the cytochrome c/Apaf-1/caspase-9 pathway.	0.99	15837718, 15469386
SLC2A3	Solute carrier family 2	0.88	11277764
RIPk1	Receptor-interacting serine/threonine-protein kinase 1	0.88	16116226
SIRT1	AD-dependent protein deacetylase sirtuin-1	0.31	23859249, 18046409 23316803, 23471411 23524286
PRKD1	Serine/threonine-protein kinase D1; Serine/threonine-protein kinase that converts transient diacylglycerol	0.29	11008129
HGF	Hepatocyte growth factor	0.22	15672869
APP	Amyloid-beta A4 protein; N-APP binds TNFRSF21 triggering caspase activation	0.13	23799643,17597573
PRKCA	Protein kinase C alpha type	0.12	21880495
IL1B	Interleukin-1 beta; Potent proinflammatory cytokine	0.07	16389574
SLC2A4	Solute carrier family 2, facilitated glucose transporter member 4	0.06	18065527
GSTP1	Glutathione S-transferase P	0.06	11279601
AKT1	RAC-alpha serine/threonine-protein kinase	0.05	17513867,24968355

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Table 2. Functional analysis of *Resveratrol* targeted genes.

GO-term	Description	Gene in network	Strength [Log10 (observed /expected)]	Node color in the network
GO:1905206	Positive regulation of hydrogen peroxide-induced cell death	**FOXO3, RIPK1**	**2.59**	
GO:1901298	Regulation of hydrogen peroxide-mediated programmed cell death	HGF, FOXO3	2.34	
GO:1903209	Positive regulation of oxidative stress-induced cell death	**FOXO3, RIPK1, APP**	2.24	
GO:1903205	Regulation of hydrogen peroxide-induced cell death	SIRT1, AKT1	2.11	
GO:1902176	Negative regulation of oxidative stress-induced intrinsic apoptotic signaling pathway	FOXO3, RIPK1, APP, HGF, AKT1, SIRT1	2.01	
GO:0032930	Positive regulation of superoxide anion generation	APP, GSTP1	2.01	
GO:1903201	Regulation of oxidative stress-induced cell death	SIRT1, AKT1, HGF	1.94	
GO:1903428	Positive regulation of reactive oxygen species biosynthetic process	FOXO3, RIPK1, HGF, AKT1, SIRT1, DIABLO, GSTP1, PRKD1	1.84	
GO:2000379	Positive regulation of reactive oxygen species metabolic process	AKT1, GSTP1, IL1B, FOXO3, APP, RIPK1	1.76	
GO:0006979	Response to oxidative stress	PRKD1, RIPK1, DIABLO, SIRT1, APP,GSTP1,AKT1	1.32	

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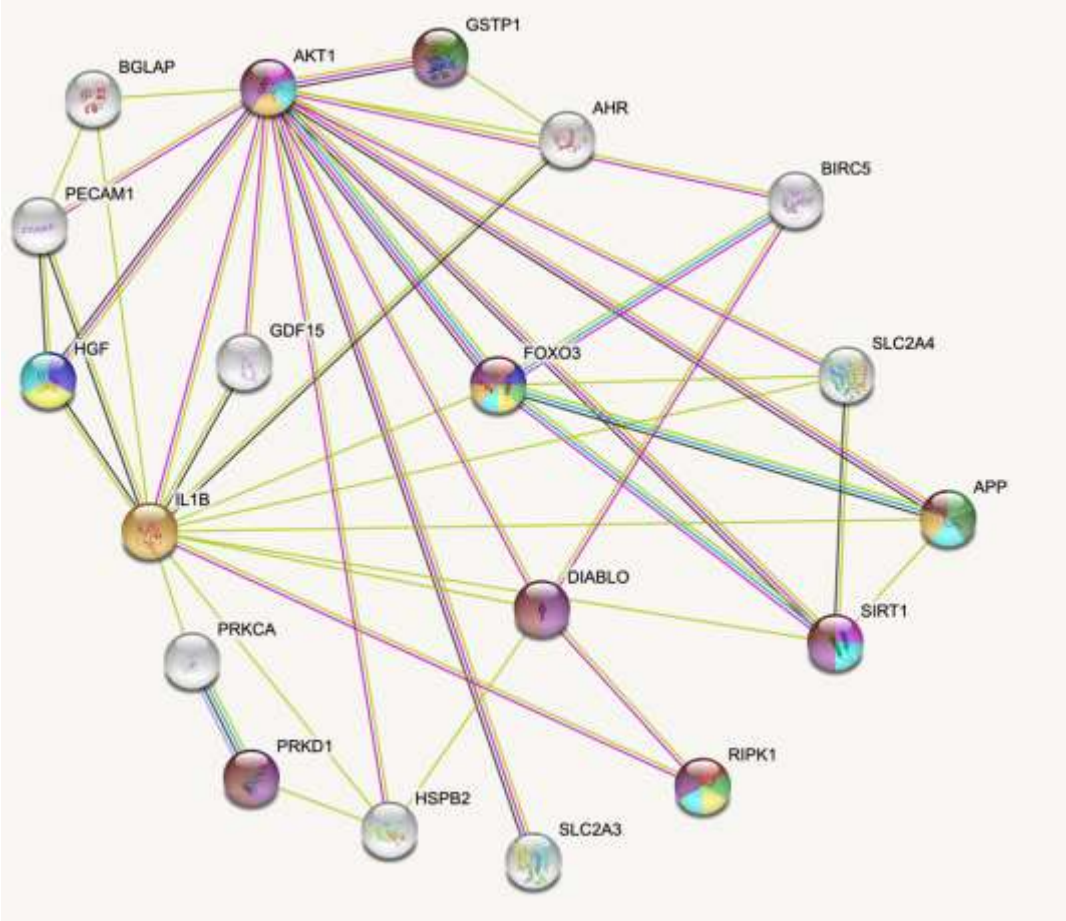

Fig. 5. Network analysis of *Resveratrol* targeted genes. *Node color code defined in the Table 2.

Discussion

Supplying platelet concentrates is one of the biggest challenges for blood transfusion organizations around the world. This is mainly due to the very short shelf life of the platelet product. On the other hand, providing a quality platelet product also faces many challenges. Platelet cells are inherently highly sensitive cells that easily activated under physical and chemical stress during storage or preparation, resulting in immediate clearance from the circulation following transfusion into the receptor. In the current study we have studied the effects of different doses of *Resveratrol* on the platelet function and oxidative state.

Our findings indicate that, despite to the *Ristocetin* agonist did not significantly affect by Resveratrol, the platelets aggregation against collagen agonist fallen dramatically after 3 days of PCs storage. The finding is in line with previous reports. Moroff et al. has shown the decreased response to collagen agonist during storage (23). In another study conducted by Fiedler et al. have also reported the marked losing response to collagen on day 4 storage (24). There are also some other reports in this regard (25-27). Platelet cells have two main collagen receptors including integrin alpha2beta1 (GPIba), main role in adhesion, and GPVI, responsible for signaling and activation (28). These two major receptors are shed from the platelet surface after platelet activation as well as shear stress. Hosseini et al. has shown that the GPVI receptor shed from the cells during storage and the shedding level from platelet surface has reverse significant correlation with collagen responsiveness (29, 30). In another study by Jamaat et al. has reported that the platelet surface expression of GPIba significantly decreased during storage (31). Therefore, it could be assumed that the PCs during preparation and

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storage get activated and start to shed collagen receptors. Decreasing platelet surface expression of GPIba and GPVI lead to irresponsiveness the collagen agonist. Moreover, the soluble GPIba and GPVI may also associate with PCs transfusion related life-threatening adverse events. But the question is what plays the most important role in secreting GPVI and GPIba receptors. It seems that the stresses applied to the product during preparation can be the most effective factor. However, further studies are needed to substantiate this claim.

Treatment of PCs with *Resveratrol* not only did not maintain a collagen response, but also showed dose-dependent aggregation inhibitory effects against collagen agonist. Interestingly, this inhibitory effect was not observed in relation to the *Ristocetin* agonist. Our findings are in line with previous studies (32-34). Shen et al. comprehensively studied the mechanism involved in the inhibition of collagen induced platelet activation. They have suggested three major mechanisms 1) p38 MAPK-cytosolic phospholipase A (2)-arachidonic acid-TxA(2)-[Ca(+2)]i cascade inhibition and 2) NO/cyclic GMP activation and hence 3) phospholipase C and/or PKC activation inhibition (34). On the other hand, to the best of our knowledge the direct effect of *Resveratrol* on *Ristocetin* responsiveness has evaluated in current study for the first time. *Ristocetin* bind to the GPIb on the thrombin site thorough von Willebrand factor activating. Energy inhibitor agents have not shown any negative effects on *Ristocetin*-induced platelet aggregation. This evidence suggests that despite other agonists, *Ristocetin* induced aggregation may not involve ATP dependent mechanisms (35).

Although *Resveratrol* at 10 μM was able to significantly control ROS levels, increasing its concentration inversely increased the concentration of reactive oxygen species. So, we have concluded that the *Resveratrol* at low concentration effectively decreased the oxidative state of platelet and in opposite at higher concentration led to ROS generation. Several studies had shown the anti-oxidative effects of *Resveratrol* on platelets (36-38). Moreover, in line with our findings, Bosutii et al. in a study on muscle cells have shown that the low *Resveratrol* doses attenuated the ROS generation, while high doses induce oxidative stress. They concluded the dose dependent effects of *Resveratrol* on the ROS level (38). Moreover, Lang et al. also has shown that the Resveratrol may promote apoptotic cell death thorough oxidative stress induction (39). To find the involved mechanisms we have in silico studied the gene targets of *Resveratrol*. It has found that, totally 15 genes potently interact with *Resveratrol* which 10 of them enrolled in regulation oxidative state. Among them, Forkhead transcription factors of the O class 3 (FOXO3), known as a key regulator of ROS and its activation reduce ROS level, is attenuate by Resveratrol (40, 41). Receptor Interacting Serine/Threonine Kinase 1(RIPK1), which also inhibits by Resveratrol play a vital role in blocking ROS accumulation (42, 43). Similarly, resveratrol could induce cell apoptosis via ROS generation by suppressing of AKT/PKB pathway (44). So, we have hypothesis that, the increased dose of *Resveratrol* could dysregulate the genes and thus disrupt the oxidative status of the cells. More experimental studies are needed to prove the hypothesis.

Taken together, our findings indicated that the *Resveratrol* affect the platelet aggregation at the dose dependent manner. Moreover, we have also found that the *Resveratrol* play as double-edged sword in the controlling oxidative state of the cells. Therefore, finding the optimal dose of *Resveratrol* is the great of importance. We did not experimentally assess the target genes, and this was the main limitation of our study.

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Conflict of interest
The authors declared no conflict of interest.

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