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Research Article

EFFECT OF RESVERATROL ON ADVERSE FUNCTIONS OF PLATELETS

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ABSTRACT

Atherothrombosis is a disorder which may lead to increased incidence of cardiovascular diseases. One of the causes for this disorder is platelets aggregation and adhesion. The objective of the present work was to study the effect of resveratrol (Resv) and clopidogrel(clopi) individually and in combination on inhibition of platelet aggregation and adhesion by *in vitro* and *in vivo* method. The platelet aggregation was measured by whole blood aggregometer (Chronolog Corporation) in 0.5 ml sample of PRP mixed with ADP by measuring infrared light transmission using different concentration of Resv and Clopi individually and in combination. Platelet adhesion was measured by Microplate reader, lab system (Merck pvt. Ltd.). Nitric oxide estimation was done by nitric oxide colorimetric estimation kit with retro orbital method using healthy male swiss albino rats. Resveratrol and clopidogrel at the effective concentration produced minimal platelet aggregation and adhesion effect, when combined together didn't show any synergistic or additive effect. There was no effect of resveratrol on clopidogrel or vice versa on their inhibitory effect. Both individually and in combination increased bioavaibility of nitric oxide revealed the significant ($P<0.05$). Since patients on antiplatelet therapy may consume beverages like grape juice, red wine, peanuts etc. which are rich sources of Resveratrol do not show any synergistic or additive effect on platelet function. But increased bioavaibility of nitric oxide which lead to adverse outcome.

Keywords: Resveratrol, Clopidogrel, platelets aggregation, platelets adhesion, nitric oxide

INTRODUCTION

Atherothrombosis is a global/systemic disorder affecting cerebrovascular, coronary and peripheral beds and which may lead to increased incidence of cardiovascular disease such as myocardial infarction, stroke, hypertension; etc. is partly attributed to the lifestyle, habits and diet of an individual. Rupture or erosion of an atherosclerotic plaque exposes the thrombogenic core of lesion and lead to adhesion, aggregation and thrombus formation. Intact circulation is essential for normal functioning of the tissues and organs. It is maintained by the mechanisms that exactly balance coagulant and anti-coagulant factors naturally present in the body. Both, genetic and drug factors can upset this balance leading either to excess bleeding or formation of clot within the body.

Platelets, which maintain the integrity of the circulation, are important in coagulation of blood. When they are activated they undergo a sequence of reaction that is essential for haemostasis. These is essential but are inappropriately trigged if the vessel wall is diseased, as in atherosclerosis leading to thrombosis and vascular insufficiency. Quite often the cause of life threatening myocardial infarction is coronary thrombosis secondarily atherosclerosis[1].

Platelets occupy a primary role in coronary artery disease, cerebrovascular disease, and peripheral vascular disease, which comprise the major causes of death and disability in the Western world. Medical science has witnessed exponential advances in the understanding of platelet physiology, molecular biology, and pharmacogenetics, a more thorough understanding of the role of the platelet in pathologic conditions involving haemostatic, atherothrombotic, and nonhemostatic disorders, and a greater appreciation of the clinical benefits and pharmacotherapy of antiplatelet agents [2].

Several drugs such as Clopidogrel, aspirin, ticlopidine, pyridamole, are prescribed to prevent/treat thrombosis. Among them Clopidogrel is found to be widely used in the treatment of thrombosis. Clopidogrel is believed to inhibit first line of treatment for thrombosis. clopidogrel is believed to inhibit ADP mediated actions which leads to platelet adhesion/aggregation and other activation processes[3]. Clopidogrel causes inhibition of platelet adhesion and aggregation to the expose endothelium thus Clopidogrel is found to be drug of choice in treatment of thrombosis [4].

Consumption of alcoholic beverage like wine and other like tea is a common practice amongst the population irrespective of their diet habits. Grape/Grape juice, red wine, green tea, peanuts, etc. are shown to contain significant amount of Resveratrol [5] a phytoalexin that is known to have wide range of biological activities including anti-inflammatory, anti-oxidant, vasodilator and anti-platelet [6].

A person who is on anti-platelet therapy if regularly consume Resveratrol rich beverages, an interaction could be excpected, leading to enhanced anticoagulant activity and suffer from excessive bleeding. Clopidogrel, a ADP release inhibitor not only prevent thrombus formation, but also used in coronary artery diseases and acute coronary syndrome[7].

Therefore the present study was planned to investigate the interaction of resveratrol and clopidogrel using healthy human

platelet rich plasma, in platelet aggregation and adhesion. And also effect on nitric oxide level was investigated in healthy male Swiss albino rats, by using resveratrol and clopidogrel.

MATERIALS AND METHODS

Chemicals: Resveratrol, Adenosine diphosphate, Bicinchonimic acd solution, L-nitro arginine methyl ester (L-name) were purchased from Sigma (Sigma-Aldrich USA). Clopidogrel (Sandoz Pvt. ltd. Thane INDIA), Bovine serum albumin (Dr, Reddy's Lab HYD, INDIA) were kindly donated. Nitric oxide colorimetric estimation kit (Cayman chemicals USA) all other common chemicals used were of laboratory grades.

Animals: Healthy male Swiss albino rats (150-200g) were used for the study. Rats were group housed in separate cages (six per cage). All animals were kept under standard12:12-h light/dark cycle (lights on 0700 h) at room temperature controlled environment with ad libitum access to rodent chow and tap water. All procedures were carried out under strict compliance with ethical principles and guidelines of the committee for the Purpose of control and Supervision of Experimental animals, Ministry of Environment and Forests, Government of India, New Delhi with approval no. 853/CPCSEA

Drug Solutions: Resveratrol was dissolved in 10% ethanol and clopidogrel was dissolved in normal saline.

Preparation of platelet rich plasma (PRP)

Blood from blood bank was collected into tubes containing 3.8% of sodium citrate. Immediately blood was centrifuged at 1000 x g for 20 min to obtain supernatant layer of PRP. After separation of PRP the tubes containing sediment were recentrifuged at 200 x g for 20 min to obtain supernatant layer of PPP. PRP and PPP prepared were used within 2 hours to perform the test [8].

In vitro platelet aggregation test

The whole blood aggregometer detects platelet aggregation in 0.5 ml sample of PRP by measuring infrared light transmission through the sample. A standard 10% to 90% span for PRP and PPP is established automatically on the aggregation channel of the strip chart recorder when the set aggregation base line button was depressed and released.

Test procedure

After opening heater block cover on the aggregometer, cuvette containing a 0.5 ml PPP sample was placed into the slot marked PPP. A magnetic stir bar was added to 0.5 ml of PRP cuvette placed into the slot marked PRP. After replacing cover on the aggregometer, aggregation baseline button was pressed for several seconds to allow the pen on the strip chart recorder aggregation channel to record aggregation channel to record a PPP baseline at 10% scale. When the button was released, the pen automatically moves to the 90% of scale and recorded PRP baseline. Heater block cover was re-opened after recording baseline for PRP and forcefully injected the ADP into cuvette, then cover was quickly closed to record platelet aggregation (till it was stabilized) on strip chart recorder. The procedure was repeated with PRP samples pretreated with drugs for 3 minutes to study the effect of various drugs [9].

Effect of various concentrations of resveratrol and clopidogrel on platelet aggregation individual

concentration of Resveratrol (5ug, 10ug, and 15ug/0.5mlPRP) and Clopidogrel (15uM, 30uM/0.5mlPRP) were added to the cuvette containing ADP individually and treated fourteen minutes to study the effect of various concentrations and traced the inhibition of platelet aggregation on strip chart.

Effect of various concentrations of Resveratrol and Clopidogrel on platelet aggregation in combination

concentration of Resveratrol and Clopidogrel are taken in combination (5ug+15uM, 15ug+15uM,/0.5mlPRP) were added to the cuvette containing ADP and treated for three minutes to study the effect of various concentrations and traced the inhibition of platelet aggregation on strip chart Platelet adhesion

Isolation of blood platelets: Human blood was collected in ACD solution (citric acid/citrate/dextrose; 5:1v/v), and platelet was isolated by differential centrifugation of blood (20 min. at 200g). Platelet rich was plasma was separated and centrifuged for 20 mins at 1000 x g to sediment platelets. The resulting pellets were suspended in Ca++/Mg++free tyrode solution and platelets were washed three times with the same buffer. Entire washing was carried out in plastic tubes and at room temperature. The platelet suspension was preincubuted at 37^0 C for 30 mins. With resveratrol at final concentration 25 ug/ml, 50ug/ml 75ug/ml and 100ug/ml. After Preincubation platelet were activated by Lipopolysacharide (LPS).

Platelet adhesion was determined according to Tuszynski and Murphy. Wells of 96-well micro titer dish were incubated for 2-3 hours with 50 ul/ml of ADP dissolved in phosphate buffer saline of Ph 7.5. The wells were aspirated, treated with 200 ul of PBS containing 1% BSA for 1 hour and then washed three times more with the 200 ul of PBS. Immediately after washing, the wells were supplemented with 50 ul of test agonist: LPS. Then 100 ul of platelet suspension were added to each well, and plates were incubated at 37^0 C for 1 hour. Non adherent cells were removed by aspiration. And wells were washed three times with 200ul of PBS. The total cell associated protein was determined by dissolving the attached blood platelet directly in the micro titer wells with 200ul of bicinchonimic acid (BCA) working solution, and incubated at 37^0 C for 60 min. plates were allowed to cool at room temperature, cover sheet were removed, and the absorbance of each well was determined at 560 nm with a micro titer plate reader[10]

The above mentioned procedure was followed when clopidogrel used individually at concentration 30uM, 60 uM, 90 uM, and 120uM/ml and in combination with Resveratrol (25ug Resv+ 30 uM Clopi, 25ug Resv +60 uM

Estimation of nitric oxide levels- *in-vivo* study

Animals were divided into five groups, 1) Saline treated (-ve control), 2) L-name treated (+ve control), 3) L-name+Resveratrol, 4) L-name+Clopidogrel, 5) L-name+Resveratrol clopidogrel. On the first day blood was taken out from rats by retro orbital method and plasma was separated. Estimation of nitric oxide was done by using nitric oxide colorimetric estimation kit as described earlier. Then immediately NOS inhibitor L-name (50mg/kg i.p.) was given to group 2, 3, 4 and resveratrol (20ug/kg i.p.) and clopidogrel (50mg/kg i.p.) were given to Group 3 and 4 for seven days and on seventh day again blood was withdrawn from rats by retro orbital method, and plasma was separated for estimation of

nitric oxide levels. NO estimation was done by using nitric oxide colorimetric estimation kit.

Statistical Analysis

Statistical analysis was carried out by using One-way analysis of variance followed by Neuman-keul's test for comparison between groups. $p<0.05$ was considered to be significant.

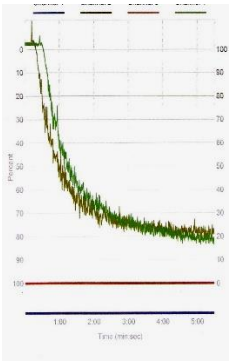
RESULTS

In-vitro study: platelet aggregation

10ug of ADP was selected for inducing the platelet aggregation in 0.5ml of PRP. The10 ug dose of ADP gives 83%of platelet aggregation and that was taken as 100% for further calculation (Figure1). Platelet aggregation induced by 10 ug of ADP in 0.5ml of PRP was studied by adding different concentration of Resveratrol. As shown in (Table1 and Figure 2) Resveratrol showed the dose dependent inhibition of platelet aggregation. Inhibition of platelet aggregation was 65%, 82%and 100% for 5ug, 10ug, and 15ug/0.5ml PRP of Resveratrol respectively.

Clopidogrel at different concentration inhibited platelet aggregation induced by 10 ug of ADP. As showed in (Table1 and Fig3) Clopidogrel at 15uM concentration inhibited platelet aggregation by 71% while at 30uM inhibited 100%. Clopidogrel also gives dose dependent effect.

In addition to study interaction of Resveratrol and Clopidogrel on platelet aggregation sub effective concentration of these drugs were added to 0.5 ml of PRP treated with ADP 10ug.The combination in concentration 5ug of Resveratrol and 15uM of Clopidogrel did not showed any synergistic or additive effect in inhibition of platelet aggregation (Table 1 and Figure 4)

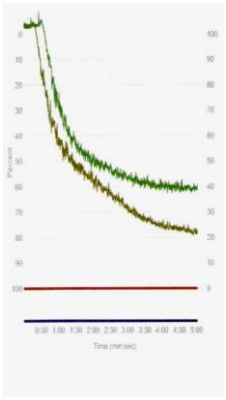


10ug ADP

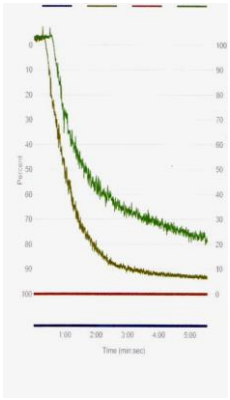
Figure 1: Recording of platelet aggregation by 10 ug ADP

Table 1 : Effect of different concentration of drug individually and in combination on inhibition of platelet aggregation

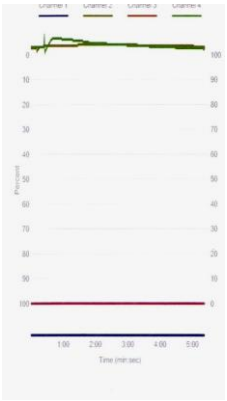
Drugs	Concentration Per 0.5 ML	% Aggregation Inhibition
Resveratrol	5 µg	65
Resveratrol	10 µg	82
Resveratrol	15 µg	100
Clopidogrel	15 µM	71
Clopidogrel	30 µM	100
Clopi+ Resv	15 µg+ 15 µM	54



5ug/0.5ml PRP



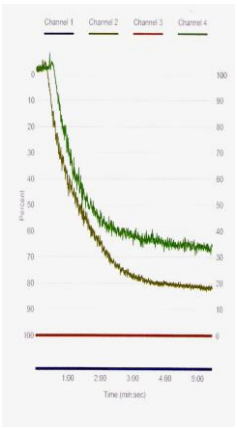
10ug/0.5ml PRP



15ug/0.5ml PRP

Figure 2: Strip chart tracing of inhibition on ADP induced platelet aggregation by different concentration of Resveratrol

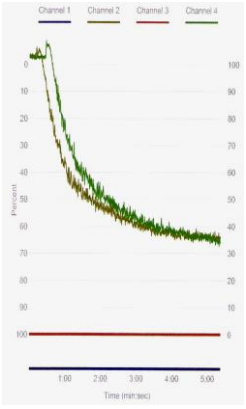
Note: 100%inhibition by 15 ug while 65% inhibition with 5ug of Resveratrol. Platelet aggregation induced by 10 ug of ADP in 0.5ml of PRP was studied by adding different concentration of Resveratrol. Inhibition of platelet aggregation was 65%, 82%and 100% for 5ug,10ug,and 15ug of Resveratrol respectively.



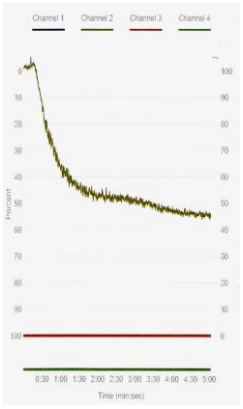
15uM/0.5ml PRP

30uM/0.5ml PRP

Figure 3: Strip chart tracing of inhibition on ADP induced platelet aggregation by different concentration of Clopidogrel.
Note: dose dependent inhibition by Clopidogre Clopidogrel at different concentration inhibited platelet aggregation induced by 10 ug of ADP. Clopidogrel at 15uM concentration inhibited platelet aggregation by 71% while at 30uM inhibited 100%.



5ug resv+15 uM clopi



15ug resv +15 uM clopi

Note: No synergistic or additive effect was seen after interaction.
Figure 4: Strip chart tracing of inhibition on ADP induced platelet aggregation by different concentration of Resveratrol and Clopidogrel

In addition to study interaction of Resveratrol and Clopidogrel on platelet aggregation sub effective concentration of these drugs were added to 0.5 ml of PRP treated with ADP 10ug.The combination in concentration 5ug of Resveratrol and 15uM of Clopidogrel did not showed any synergistic or additive effect in inhibition of platelet aggregation.

Platelet adhesion

The present study demonstrate that adhesion of platelet (Expressed as absorbance of cell attached protein) was stimulated when platelet were activated by LPS (lipopolysacharide). It had been noticed that preincubation of platelet with Resveratrol 25ug, 50ug, 75ug, 100ug had inhibitory effect on adhesion.

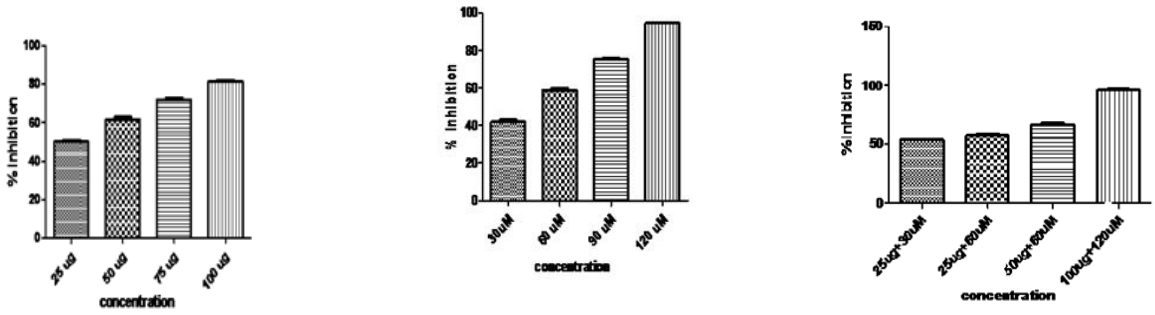
Maximum inhibitory effect of platelet adhesion was achieved by Resveratrol at the concentration of 100ug/ml (81%). Resveratrol gives the dose dependent inhibitory effect on platelet adhesion (Table 2 and Figure 5-A).

Also it had been noticed that Preincubation of Platelet with Clopidogrel 30uM, 60uM, 90uM, 120uM had inhibitory effect on adhesion. Maximum inhibitory effect of platelet adhesion was achieved by Clopidogrel at the concentration of 120uM/ml. The concentration of 120uM/ml gives 95% inhibition of platelet adhesion .Clopidogrel gives the dose dependent effect on platelet adhesion (Table 2 and Figure 5-B).

In order to study interaction of Resveratrol and Clopidogrel on platelet adhesion sub-effective concentration of these producing less inhibition were added in the plates containing platelets. The combination of 25ug Resveratrol and 30uM Clopidogrel produced 54% inhibition of platelet adhesion, indicating there was no synergistic or additive effect was seen between two (Table 2 and Figure 5-C).

Table: 2 Effect of various concentration of Resveratrol, Clopidogrel and Resv+Clopi on inhibition of platelet adhesion

Sr. No	Concentration			% inhibition of platelet adhesion		
	Resv (ug/ml)	Clopi uM/ml	resv+clopi (ug/ml)+ uM/ml	resv	clopi	resv+clopi
1	25	30	25+30	50±0.1	42±1	53.17±1.17
2	50	60	25+60	61.5±1.5	59.5±1	58±1
3	75	90	50+60	72±1	75.5±0.5	66.5±1.5
4	100	120	100+120	81.5±0.5	94.6±0.5	96±1



A (Resveratrol**)** B (Clopidogrel) C (Resv+Clopi)

Note: Dose dependent inhibition of platelet adhesion

Figure 5: Effect of Various concentrations of Resveratrol (A), Clopidogrel (B) and Resv+ Clopi (C) on inhibition of platelet adhesion

Maximum inhibitory effect of platelet adhesion was achieved by Resveratrol, Clopidogrel and the concentration of 100ug/ml (81%) and 120uM/ml (95%) respectively. and combination of 25ug Resveratrol and 30uM Clopidogrel produced 54% inhibition of platelet adhesion, indicating there was no synergistic or additive effect was seen between two.

***In-vivo* study**

Nitric oxide levels

The mean value 36.85+4.817uM and 43.84+3.574uM in groups treated with Resveratrol and Clopidogrel were significantly ($p<0.05$) increased as compared to19.12+1.87uM of positive controls (Table 3 and Figure 6)

The mean value of 65.07+6.027uM of Resveratrol and Clopidogrel combination treated group was not only higher than that of positive controls but also of negative controls indicating synergistic activity of these drugs (Table 3 and Figure 6).

Table 3: Effect of various drugs on nitric oxide levels expressed as nitrate+nitrite in (uM)

Control	L-name	Resv	Clop	Resv+clop
49.95	14.23	29.19	39.86	54.60
38.84	25.79	16.12	22.10	43.34
78.39	22.10	44.89	36.86	65.54
40.20	15.07	43.24	42.21	76.54
58.29	16.41	45.35	23.44	65.98
44.53	21.10	42.32	38.52	84.44
51.7±6.077	**19.12± 1.87#**	**36.85± 4.817***	**43.83± 3.574***	**65.07± 6.027*****

***p<0.001 when compared with positive control, * p<0.05when compared with negative control

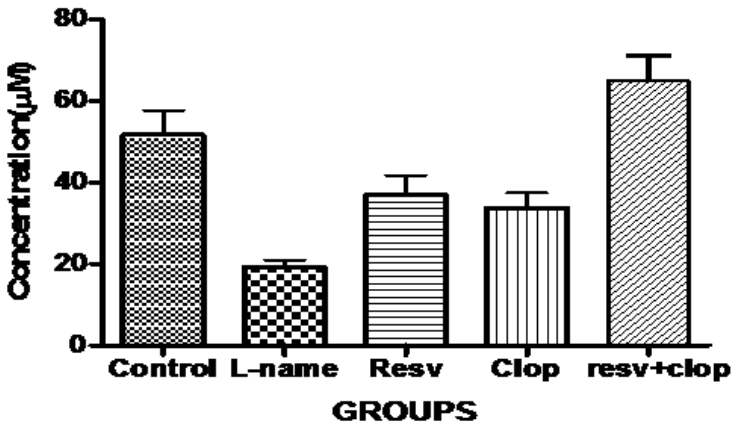


Figure 6: Effect of various drugs on NO levels

DISCUSSION

Cardiovascular pathologies such as atherosclerosis, arterial hypertension, and thrombosis lead to many complications like blood coagulation and platelet aggregation. Blood platelet plays an important role in process of hemostasis and thrombosis. After injury to blood vessel and in certain pathological conditions, blood platelets adhere to the exposed endothelial connective tissue (collagen in particular), aggregate, and release several biologically active substances. As mentioned in the objective of the study Resveratrol and Clopidogrel were investigated for their effect on platelet aggregation, Platelet adhesion and nitric oxide levels in plasma individually and in combination. The aggregation was induced by using potent agonist ADP (10ug/ml) in plasma. The finding of the present study clearly indicates that Resveratrol in concentration dependent manner inhibited platelet aggregation and also platelet adhesion and these findings agree with the earlier reports [11].

Clopidogrel similar to Resveratrol suppressed the platelet aggregation and platelet adhesion in concentration dependent manner and its antiplatelet activity has been reported earlier**.** Resveratrol and Clopidogrel at the effective concentration produced minimal platelet aggregation when combined together didn't show any synergistic or additive effect. Also when Resveratrol and Clopidogrel in concentration to produced minimal platelet adhesion when combined together, there was no synergistic or additive effect was observed. There was no effect of Resveratrol on Clopidogrel or vice versa on their inhibitory effect. Both Resveratrol and Clopidogrel individually and in combination increased bioavaibility of nitric oxide in animals after 7 days of treatment. Resveratrol and Clopidogrel has been reported to increased bioavailability of eNOS activity leading to increased bioavailability of nitric oxide [12]. Anti-platelet activity of Clopidogrel is said due to the inhibition of platelet aggregation by blocking the ADP receptors on platelets. Platelets are activated by factors like TXA2, ADP, collagen, 5HT, and thrombin which leads to increased expression of GPIIb/IIIa receptors causes fibrinogen binds to it and causes fibrin plug. Thus by blocking ADP receptor on platelet decreased platelet activation and aggregation.

However, ADP receptor as a site of action for Resveratrol seems to be unlikely, as the concentration of Resveratrol required to produce similar degree of effect is different than Clopidogrel. Inhibition of platelet aggregation and adhesion of Resveratrol and Clopidogrel appears to give in dose dependent manner. Similarly interaction of Resveratrol and Clopidogrel leading to increased nitric oxide bioavailability Indicated by (nitrite+ nitrate) appears to be pharmacodynamic in nature.

Similar interaction between Resveratrol and Clopidogrel (as observed in present study) are likely to be encountered in clinical practice, since patients on Clopidogrel therapy may consume beverages like grape juice, red wine, peanuts etc. which are reported to be rich sources of Resveratrol. It has been reported that red wine prepared from purple grape juice lowered cardiac mortality rate in French people and this protective activity has been attributed to resveratrol. Contribution of other proanthocyanidins like quercitin[7] cannot be ruled out for such cardioprotective activity.Proanthocynidin has been reported to possess remarkable free radical scavenging activit[13].

The dietary proanthocyanidins are likely to provide protection against cardiovascular diseases through there antioxidant activity and also through their anti-atherogenic activity.

It is likely that Resveratrol or Resveratrol rich dietary supplements could interact with other anti-platelet agents also, though there are very little reports of such interaction.

In clinical practice patients on Clopidogrel therapy are likely to consume the dietary supplements rich in Resveratrol that may lead to potential interaction leading to complication, if the findings of present study extrapolated to humans.

In clinical practice anti-platelet therapy is carefully titrated so as to avoid intravascular clotting without causing bleeding complication. Addition of any agent tha**t** interferes with the platelet activity is likely to upset this balance leading to complication either in the form of bleeding or intravascular clotting. The finding of the present study attempts to hypothesize that Resveratrol or Resveratrol rich dietary supplements have potential to interact with antiplatelet agents leading to modified therapeutic response. It is worthwhile to anticipate and investigate such possible interaction between Resveratrol rich dietary supplements and antiplatelet drugs in clinical practice.

CONCLUSION

Platelet aggregation and platelet adhesion related with cardiovascular diseases are corrected by prescribing the anti-platelet drugs. The findings of present study clearly demonstrate the anti-platelet activity of Resveratrol, which is a major constituent of grape juice and Clopidogrel (ADP release inhibitor) individually. When Resveratrol and Clopidogrel combined together for inhibition of platelet aggregation and platelet adhesion, there was no synergism or additive effect was seen. And the bioavailability of nitric oxide was seen to be increased when Resveratrol and Clopidogrel was given individually and in combination. Patient on antiplatelet therapy can likely to have such interaction with Resveratrol or Resveratrol rich dietary substances. Such interactions are of greatest importance in clinical practice as these interactions can lead to adverse outcome.

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