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Role of resveratrol in cardiovascular and associated diseases

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Abstract

Resveratrol is a potent bioactive compound found in fruits and taken as dietary supplements. Due to possessing multiple beneficial properties; anti-oxidant, anti-atherosclerosis, cardioprotective, anti-cholesterolemia and glucose regulation. It combats with globally high mortality and morbidity rate diseases. Resveratrol deals with cardiovascular disease and other associated diseases after the result of ROS accumulation. It seems successful in nutraceutical and pharmaceutical to prevent and treat cancer proliferation, diabetes, diabetic-cardiomyocyte, neuropathy, nephropathy and obesity.

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Introduction

Resveratrol belongs to polyphenol and non-flavonoid structure is present in grapes, barriers, peanuts and red wine. Resveratrol is a natural stilbene and a phytoestrogen that exhibit anti-oxidant, anti-inflammatory, cardio-protective and anti-cancer properties (Ko JH, *et al*., 2017). Due to its different bio-activities, it is approved to take as dietary supplementation. It is considered as efficiently beneficial to many disease handling. Resveratrol is absorbed precisely orally administration and completely absorbed in the intestine (Elshaer M, *et al*., 2018). Red wine contains resveratrol with different polyphenols. Many experimental trials have confirmed, phytochemical; resveratrol protects against heart failure, cancer and other associated diseases like diabetes-cardiac, cardio-oncology and obesity caused by oxidative stress or secondary disease function (Zordoky BN, Robertson IM, Dyck JR 2015) as they have become overwhelmed the global health (Abdelgawad IY, Grant MK, Zordoky BN 2019). A short term disclosure of resveratrol with high dosages shows extraordinary cardioprotective results (Ahmet I *et al*, Tae HJ, Lakatta EG, Talan M 2017). Furthermore, resveratrol is good for kidneys. Resveratrol plays a positive role in cardiovascular diseases and lowers down atherosclerosis as well.

Cancer, along with diabetes and CVD, is becoming a disease taking high mortality and morbidity across the world. There are restrictions in present chemotherapies due to the occurrence of resistance against the therapy. Many studies have shown resveratrol as an influential chemosensitizer agent (Mohammed S, Harikumar KB 2018). It belongs to the system of biopharmaceutical classification, as it has less water solubility and high-rise membrane permeability. Resveratrol is a phytoalexin polyphenol; produced in plants under stress conditions (Siddiqui IA, Sanna V, Ahmad N, Sechi M, Mukhtar H 2015). Resveratrol encapsulated with casein claimed remarkable oral availability of resveratrol. After oral intake, intestinal absorption can be enhanced by glycosylated PLGA NP of resveratrol. This compound acts as a chemo-preventive agent and increases bioavailability by 330%. Resveratrol blocks carcinogenesis at initial stages even with low dose concentration. It can change the gene expression that can rule cancer initiation and proliferation (Tabrez S, Jabir NR, Adhami VM, Khan MI, Moulay M, Kamal MA, Mukhtar H 2020). Therapies against cancer patients may cause toxicity in the cardiovascular system. Resveratrol manages the barrier that comes in cancer treatment, which is drug resistance. The ideal dose for resveratrol supplementation, however, may be less but Metabolic disturbance is a risk factor for multiple cancer types and reversal of metabolic disturbances by low-dose resveratrol may reduce cancer risk as well as improve cancer outcomes (Guthrie AR, Chow HH, Martinez JA 2017). The polyphenol resveratrol has antioxidant properties. The scientific literature indicates that there is a link between obesity, Diabetes Mellitus, Oxidative stress and cataract formation. Diabetes associated with CVD is more complicated (Yan F, Sun X, Xu C 2018). Long time hyperglycemia leads to the overproduction of reactive oxygen species in mitochondria. Resveratrol lowers the production of mitochondrial superoxide instead energizes biogenesis in mitochondria. Excessive oxidative stress may cause large-scale oxidative damage to proteins, DNA and lipids resulting in damaged cardiomyocyte functions including contractility, ion transport and calcium cycling that results in heart failure, fibrosis, cardiac hypertrophy. Meanwhile, oxidative stress dysfunctions NO; a vasoprotectant to endothelium. This compound increases the expression of various antioxidant enzymes. It has been shown that resveratrol has less direct scavenging activity rather it possesses gene regulatory property. Resveratrol has the ability to scavenge O_2 specially produced by xanthine (Xia N, Daiber A, Förstermann U, Li H 2017).

Mechanism of action against oxidative stress

Resveratrol disassociates Nrf2 from the cytoplasm and binds it where the transmission starts in the nucleus. Resveratrol also activates AMPK; AMP-activated protein kinase, that in terms promote SIRT

and FoxOs; forkhead box protein 01. AMPK stabilizes FoxOs structure. They produce antioxidant genes after transcription of FoxOs in the nucleus. SIRT; sirtuin1, also deacetylated PGC-1gama which facilitates antioxidant gene expression and reduce oxidative stress (Meng X, v 2020).

Recent study evidence showed that resveratrol improves cardiac-oxidative stress and myocardial dysfunctions in diabetes. In this experimental study diabetes-induced rats were given resveratrol supplements. The given dose was 50mg/kg/day, orally. And the duration of this treatment lasts 16 weeks. As a result of that trial, resveratrol faded diabetes-induced cardiac dysfunction and reduced hypertrophy was observed by increasing EF% ejection fraction, fraction shortening (Fang WJ, Wang CJ, He Y, Zhou YL, Peng XD, Liu SK 2018).

Table 1. The original evidence regarding the effect of resveratrol.

Sr.no	Subjects	Dosage	Duration	Outcome	References
1.	20 Rats	50mg/kg/day, orally	16 weeks	Improves cardiac-oxidative stress & myocardial dysfunctions in diabetes, and reduced hypertrophy	Fang WJ *et al.*, 2018
2.	36 T2DM older (above 49 years)	0, 75, 150, 300mg after interval of one week.	6 months	Improved metabolic & neurological system, lowest dose of resveratrol can enhance basal cerebral blood flow & associated improved learning	Wong RH *et al.*, 2016
3.	Group 1 (n=10), Group 2 (n=9), older participants	Group 1(300mg) Group 2 (1000mg)	90 days	Higher resveratrol dose increased CVD risk biomarkers i.e. oxidized low-density lipoprotein, soluble E-selectin-1 & soluble intracellular adhesion molecule-1 in older adults.	Mankowski RT *et al.*, 2020
4.	8-9 in each group, A was controlled group, B was diabetic group, C & D was resveratrol treatment group with different doses.	A was controlled group. B was diabetic group. C was 10 mg resveratrol, & D was 20 mg resveratrol treatment group.	4 weeks	Resveratrol supplementation administration showed antioxidant properties after T2DM.	Portillo MP *et al.*, 2019

In this study, the role of C-reactive protein (CRP) has been seen in randomized controlled meta-analysis studies. There was an eminent decrease in CRP with type 2 diabetes, took supplementation of resveratrol. As C-reactive protein (CPR), produced by liver cells, is associated with the inflammatory marker. It showed powerful preventive results on CRP in T2DM patients. It decreases the CRP level in people who were taking resveratrol supplements (Hosseini H, Koushki M, Khodabandehloo H, Fathi M, Panahi G, Teimouri M, Majidi Z, Meshkani R 2020).

In another experimental study, resveratrol improved the metabolic and neurological systems. It was a double-blind, placebo-controlled interventional study, in which 36 T2DM older (above 49 years) have participated. The dose was given 0, 75, 150, 300mg after one week. The duration of this study was 6 months. The study outcome suggested maximum improvement was observed with the lowest dose used and can enhance basal cerebral blood flow and associated improved learning 9 Wong RH, Nealon RS, Scholey 2016).

The present study is a pilot study in which analysis was performed on older participants. As older adults are more prone to CVD. Participants were randomly divided into two treatment groups. One treatment group had 10 participants (n=10) and a 300mg dose of resveratrol was given for 90 days. In the second treatment group1000mg dose was given to 9 participants (n=9). The trial was to study CVD risk biomarker i.e. oxidized low-density lipoprotein. As a result, the study showed a higher resveratrol dose of 1000 mg, increased CVD risk biomarkers i.e. oxidized low-density lipoprotein, soluble E-selectin-1 and soluble intracellular adhesion molecule-1 in older adults as compared to the lower dose treatment group (Mankowski RT, You L, Buford TW, Leeuwenburgh C, Manini TM, Schneider S, Qiu P, Anton SD 2020).

In a recent clinical study as discussed in table 1, rats have induced type 1 diabetes that resulted in oxidative stress. Rats were grouped in 4 experimental groups

with each 8- 9 sample size. A was a controlled group, B was a diabetic group, C was resveratrol 10 mg treatment group, D was 20 mg resveratrol, treatment group. The trial consumed 4 weeks. In this trial, oxidative stress markers (activity of superoxide dismutase, catalase and glutathione peroxide, sulfhydryl group, total oxidant status, soluble proteins) were assessed. The results claimed that the resveratrol supplementation administration showed antioxidant properties after T2DM (Portillo MP, Fernandez-Quintela A 2019).

In another study, resveratrol evident its eminent chemoprevention property by inhibition of multistage cancer development and its proliferation. But to attain its maximum therapeutic activity, nano-formation is used. As it increases its bioavailability and aqueous solubility. Resveratrol potential outcomes in intracellular signal transduction in carcinogenesis (Siddiqui IA, Sanna V, Ahmad N, Sechi M, Mukhtar H 2015). Regarding this pre-clinical data of experimental studies, dietary intake of resveratrol like other phytochemicals like curcumin and lycopene, are involved in immune system efficiency, apoptosis in transformed cells, make aware malignant cells to cancer killer cytotoxic T cells (Kotecha R, Takami A, Espinoza JL 2016; Tufail *et al* 2020).

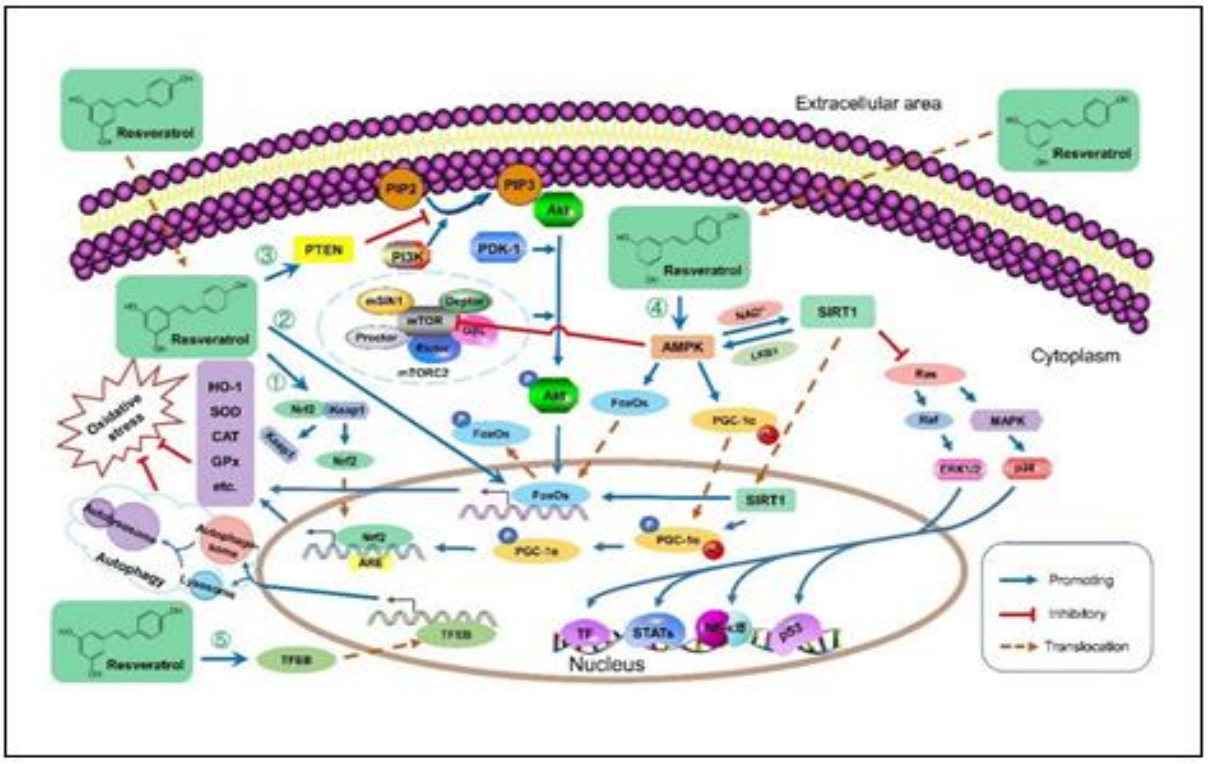

Fig. 1. Mechanism of action against oxidative stress.

This experimental study in animal models disclosed the unique antioxidant potent quality of resveratrol against diabetic cardiomyopathy. Chronic hyperglycemic condition mediates cardiac oxidative stress that leads to cardiac hypertrophy, fibrosis and apoptosis. Oral intake of resveratrol, for four months, enhanced the antioxidant superoxide dismutase enzyme by making left ventricular pressure better, in streptozotocin-nicotinamide experimental type-2 diabetic rats (Mohammadshahi M, Haidari F, Soufi FG 2014). Furthermore, diabetes also reflects many metabolic malformations. From the studies of different animal and human clinical trials, resveratrol depicted positive outcome against blood glucose level, insulin resistance, pancreatic beta-cells protection and secretion of insulin (Truong J, 2014).

Resveratrol has powerful anti-Atherosclerosis properties. In this meta-study, several trials resulted that resveratrol participates against plaque formation

by lowering the TG level, LDL and increasing the HDL level into the arteries. Atherosclerosis is a risk factor for CVDs. In rat studies, its anti-hypercholesterolemia was administered by its pravastatin effect, in the rats fed with high cholesterol diet.

Resveratrol is not fruitful to treat CVD patients in a single direction but importantly, it leaves its benefactor cardiovascular impact in diabetic patients. It was studied that in diabetic cardiomyopathy increased oxidative stress, increased apoptosis, diastolic dysfunction, cardiomyocyte hypertrophy happens as a secondary function. Resveratrol improved insulin signaling in rat models with the rise in SOD, p-eNOS, p-AKT. It has been seen in clinical trials that resveratrol is a dose-dependent phytochemical.

The anti-hypertensive effect of resveratrol (10-320mg/kg/day) has been demonstrated in several animal models. The lower dose did not affect B.P (Prasad K, 2012). In this study, different experimental and clinical trials were studied to know the functions of phytochemicals. Quercitin, Curcumin including resveratrol expressed beneficial results by reducing oxidative stress, lipogenesis and adipogenesis, and chronic inflammation.

In more, an analysis of experimental clinical studies revealed metabolic disorder; obesity control by resveratrol dietary supplementation. Resveratrol controls sirtuin-1 caloric restriction activity and lipid, glucose regulation (Aguirre L, Fernández-Quintela A, Arias N, Portillo MP 2014).

Conclusion

It can be concluded from the previous analysis and meta-analysis studies that a higher level of oxidants in the cell, let's move to the occurrence of primary causes of disease and secondary diseases. It was seen this important phytochemical, non-flavonoid, resveratrol plays a novel role in the treatment and prevention of diseases like cancer diabetes mellitus, cardiohypotrphy, CVD and its associated diseases. Resveratrol helps to stop the transcription of the gene that produces, an oxidant-producing enzyme in the cell and that is why resveratrol has taken attention to getting from food and dietary supplement as well. It gives beneficial results to major rising health problems.

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List of Abbreviations

AMP	Activated protein kinase
ATP	Adenosine triphosphate
CVD	Cardiovascular disease
CRP	C-reactive protein
FoxOs	forkhead box protein 01
HDL	High density lipoprotein
LDL	Low density lipoprotein
Nrf2	Nuclear related factor 2
PGC	Plant growth chamber
p-eNOS	Phosphorylation of endothelial nitric oxide synthase
PKB	Phosphoprotein kinase B
PLGA NP	Polylactic glycolic acid Nano particles
ROS	Reactive oxygen species
SIRT 1	Sirtuin-1
SOD	Superoxide dismutase
T2DM	Type 2 Diabetes Mellitus
TG	Triglyceride