Yeung, Cardiovasc Pharm Open Access 2017, 6:2
DOI: 10.4172/2329-6607.1000e134

Cardiovascular Pharmacology: Open Access

Editorial Open Access

Therapeutic Potential of Resveratrol for Cardiovascular Protection

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Received date: April 10, 2017; **Accepted date:** April 14, 2017; **Published date:** April 19, 2017

Introduction

Cardiovascular Disease (CVD) including stroke is one of the leading causes of death and disability worldwide and an enormous economic burden to our societies [1]. Based on the latest statistics for heart and stroke disease released by the American Heart Association in 2016, CVD is the leading global cause of death, accounting for more than 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. An estimated 83,600,000 adults in the United State (US) (>30%) have one or more types CVD of whom more than 90% have hypertension, 18% have Coronary Heart Disease (CHD), close to 10% have Myocardial Infarction (MI) and 8% have stroke. The total direct and indirect cost in the US alone for treatment of CVD (hospitalization, drugs, home healthcare, etc.) and loss of productivity and morbidity totalled more than $315 billion US per year [2]. While there was a decline in cardiovascular mortality reported in the American Heart Association 2014 update, the disease burden to society remains high [2,3]. Thus prevention by better diagnosis and treatment could provide a huge saving for the health care cost worldwide. Despite advancement in modern cardiovascular medicine, the prevalence of hypertension, Ischemic Heart Disease (IHD) and stroke is still on the rise, particularly in industrialized societies and in the elderly population, and finding an optimum drug therapy to slow disease progression remains a therapeutic challenge [4].

Natural Health Products (NHPs) are increasingly used in maintaining health, contributing to a healthy lifestyle, and as an alternative strategy for cardiovascular disease prevention [5]. Resveratrol is a natural health product found abundantly in grapes and red wine with anti-oxidant, anti-angiogenic, and anti-inflammatory properties. It has been linked to the well-known "French Paradox" in which drinking wine regularly can reduce the risk of developing cardiovascular, cerebrovascular and peripheral vascular disease and cancer [6-8]. Chemically, resveratrol is a natural polyphenolic compound (3,5,4'-trihydroxy-trans-stilbene) found in *Polygonum cuspidatum*, grapes, peanuts and berries, as well as in the processed food products, especially red wine. It is a pharmacologically active compound that interacts with multiple targets in different cardiovascular disease models to exert protective effects and reduction of cardiovascular risk factors [9]. While the mechanism of resveratrol for cardiovascular prevention is not fully understood, one likely mechanism which has attracted wide spread attention is its effect to upregulate Endothelial Nitric Oxide Synthase (eNOS), and scavenge free oxygen radicals which can limit the lipid peroxidation processes and prevent tissue damage [8]. Resveratrol has been shown to increase bioavailability of NO in Bovine Aortic Endothelial Cells (BAEC) under glucose-induced oxidative stress, probably by preserving the activity of Dimethyllarginine Dimethylaminohydrolase (DDAH), an enzyme that degrades an endogenous inhibitor of eNOS named Asymmetric Dimethylarginine (ADMA). Preclinical studies have also identified several molecular targets (e.g. SIRT-1, AMPK, Nrf2, NFkappaB, etc.) linking the effect of resveratrol to improved endothelial dysfunctions in cardiometabolic diseases [8,10].

There have been a number of studies demonstrating the beneficial effect of resveratrol on energy metabolism and autophagy in experimental animal models. For examples, it has been shown that resveratrol preserved mitochondrial morphology and cellular content of ATP, ADP and AMP in myocardium in an experimentally induced sepsis rat model [11]. On the other hand, it has been suggested that the cardio protective effect of resveratrol is, at least in part, attributed to preserving cellular autophagy which is an essential component of cardiomyocyte homeostasis and plays an important role in cell survival following cellular stress and starvation [12]. Dysregulation of autophagy in the cardiovascular system can lead to cardiac hypertrophy and failure, and eventually cell death. Moreover, resveratrol has been shown to protect against cardiotoxicity induced by doxorubicin which included reduction in tissue damage and cardiac enzyme activities in serum, preserving mitochondrial morphology and inherent anti-oxidant capacity [13].

Several clinical studies have recently shown the potential benefit from regular intake of resveratrol for cardiovascular prevention. For example, significant reduction in total cholesterol, systolic blood pressure, diastolic blood pressure, glucose, and insulin have been shown in obese subjects taking 300 mg or more of resveratrol per day [14]. There is also some evidence to suggest resveratrol may have therapeutic potential for management of congestive heart failure [15]. Other clinical studies have also demonstrated the beneficial effect of resveratrol for improving serum lipid profiles, attenuating atherosclerosis, lowering blood pressure, myocardial ischemia, and neuroprotection against stroke, although further and larger studies are needed to confirm these exploratory findings [8]. On the other hand there are also clinical studies challenging the beneficial effect of resveratrol to human health [16].

Although over 70% of resveratrol taken orally is readily absorbed across the gastrointestinal epithelium, the oral bioavailability is less than 1%, due to rapid and extensive first pass metabolism mainly by Phase II conjugation to form sulfate and glucuronide metabolites [17,18]. It is poorly water soluble and also unstable chemically, which requires advanced designer formulation such as micro- and nano-encapsulation using suitable carriers to improve oral delivery for systemic applications [17]. It is also a substrate of efflux transporters such as MRP2, MRP3, and ABCG2 which could further reduce its intracellular concentrations [19]. It is possible oral absorption of resveratrol from drinking wine which contains other natural products may be different from taking it as a food supplement.

In complementary medicine, resveratrol may enhance the therapeut ic effect of cardiovascular drugs and exercise. Although only limited

data are available, a number of studies have shown that resveratrol can potentiate the anti-hypertensive effect of typical vasodilators, and enhance the cardio protective effects of statins and other standard medications. While the beneficial effect of exercise on cardiovascular health is well documented [20], a synergy between exercise and resveratrol is less apparent. It has been shown in normal young rats that resveratrol not only complemented exercise, but also enhanced the beneficial effects of exercise on heart function in normal rats [21]. However, this complementary effect was not supported by a clinical study recently reported in which resveratrol blunted the beneficial effects of exercise on lowering blood pressure, and blood concentrations of several cardiovascular risk factors in elderly men [22]. Thus further studies using experimental animal models and clinical trials to assess the potential synergy between exercise and resveratrol are needed.

Summary

It is clear that resveratrol has therapeutic potential for cardiovascula r protection and prevention similar to other known natural anti-oxidants such as co-enzyme Q10 [23] and omega-3 fatty acid [24]. It may be used as an adjunct therapy for management of cardiometabolic diseases. However, it is not clear if taking resveratrol by drinking wine has the same effect as taking it as a dietary supplement. More research is also needed to determine its interaction with other drugs and natural health products and with life style factors such as exercise. Moreover it remains a pharmaceutical challenge to effectively deliver resveratrol systemically to increase its oral bioavailability.

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