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Opinion

The Grey Areas of Resveratrol Health Benefits

Anna Maria Posadino[1], Annalisa Cossu[1], Roberta Giordo[2] and Gianfranco Pintus[1,2,3]*

[1]*Department of Biomedical Sciences, School of Medicine, University of Sassari, CAP 07100, Sassari, Italy*

[2]*Biomedical Research Center, Qatar University, PO box 2714, Doha, Qatar*

[3]*Department of Biomedical Sciences, College of Health Sciences, Qatar University, PO box 2714, Doha, Qatar*

***Corresponding Author**: Gianfranco Pintus, Department of Biomedical Sciences, College of Health Sciences, Qatar University, Doha, Qatar.

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Due to a great variety of properties (e.g. anti-cancer, anti-diabetes, and neuroprotection), and among these a peculiar anti-aging [1] and cardiovascular protective action [2], Resveratrol (trans-3,4',5-trihydroxystilbene), the best-known antioxidant among red wine polyphenols, has been the subject of considerable research interest in the years . Some resveratrol features, including its capability of lengthening the life expectancy, make undoubtedly this molecule unique among the natural plant drugs and guarantee for the need of accurate clinical evaluations [3].

Resveratrol is proposed to possess multiple activities to pathways which have been genetically demonstrated to mediate longevity and health outcomes [1]. Although resveratrol has not yielded consistent results on longevity outcomes, it remains a highly researched phytochemical that may mediate disease risk or cellular/tissue health through other multiple effects [3,4]. Resveratrol antiaging effects were ascribed to its ability to activate sirtuins proteins, NAD^+-dependent de-acetylase involved in the regulation of metabolism, apoptosis, mitochondrial biogenesis, inflammation, fatty acid metabolism, and glucose homeostasis [3,5]. The identification of resveratrol as a strong sirtuins activator prompted studies and experimental observations that have demonstrated how this polyphenol can slow senescence in all the organisms investigated, including yeast, *Caenorhabditis elegans*, *Drosophila melanogaster* and the fish *Nothobranchius furzeri* [1]. Interestingly, in several experimental models, resveratrol induces the expression of genes similar to those induced by food deprivation, thus suggesting that resveratrol may modulate the aging process by mechanisms related to caloric restriction, possibly by the sirtuins activation [6]. Nevertheless, whether resveratrol can modulate human longevity remain an open question.

At the preclinical level, there are many studies demonstrating that resveratrol modifies various aspects of cardiometabolic health, including suppression of plaque formation [7], platelet aggregation [8], endothelial function [9], lipid metabolism [10], oxidative stress and inflammation [11,12]. Other cardiovascular benefits include an increase of NO production, down-regulation of vasoactive peptides, reduction of the LDL levels in the blood and inhibition of cyclooxygenase [13]. No definitive consensus has so far reached regarding the effects of resveratrol on metabolically compromised humans, where some reports have shown that resveratrol supplementation improves metabolic parameters, while other studies show no such benefits [14,15]. Therefore, whether Resveratrol may provide metabolic and cardiovascular benefit in human remain still an area of debate [5].

Whether data concerning clinical trials and in vivo experiments on natural antioxidants are so often controversial is an intriguing area of debate. Different studies report that for natural antioxidants such as resveratrol, the concentration will determine the overall effect [4,16]. Experiments performed on endothelial cells shown that, while low doses of natural antioxidants displayed an antioxidant effect, a modest increase in concentration induced an opposite result, ultimately inducing mitochondrial damage and cell death [17-19]. A similar behaviour has been reported with other antioxidant *in vitro* and *in vivo* experimental models [16,20-22], suggesting a dual role for natural antioxidants in regulating cell biology. Issues related to natural antioxidants controversial results may also be related to their dosage and bioavailability. Although concerns have been raised regarding that fact that in vitro toxic concentrations can be attained in vivo, there is

evidence suggesting that resveratrol can accumulate in specific compartments at relatively high concentrations. For example, after chronic consumption, resveratrol has been shown to be detectable in plasma up to 1 week after washout [23] and plasma peak concentrations of 32 and 8.1 μM have been reported in rodents [24,25]. Because of the lipophilic nature of most antioxidants, their tissue levels may provide a better indicator of the *in vivo* biologically active concentrations. In this regard, in rodents fed with dietary relevant doses, concentrations of resveratrol in tissues such as the heart, liver, and kidney have been found higher (~10 to 30 μM) than in plasma [26,27]. Also, it has been reported that plasmatic proteins may be natural polyphenols reservoirs *in vivo*, modulating their plasma concentration and delivery to specific organs and tissues [28-30]. Moreover, an increasing number of studies indicate that resveratrol metabolites half-life and concentration in plasma are ten times higher compared to that of the native compound [31] and whether these metabolites may function as a pool from which free resveratrol can be released locally in various tissues cannot be so far excluded. Since many studies indicate that natural antioxidants fail to protect against cardiovascular diseases or may accelerate their development [5,14,32], all the above-mentioned aspects might be relevant also in clinical practice. Indeed, evidence suggests that patients oxidant/antioxidant status need to be checked before undergoing high antioxidant supplementation [33-35]. In fact, despite present diffuse contradictions, it seems that at least individuals with unbalanced nutritional levels may benefit from an increased intake of dietary antioxidants or supplements [33-35].

According to the published data, it appears necessary to reconsider the beneficial role attributed to antioxidants and to resveratrol. In the light of the popularity of antioxidant-rich diets and therapeutic approaches aimed at reducing aging and cardiovascular risks, uncovering the optimal concentration threshold by which resveratrol can provide health benefits remains an aspect of paramount importance. Although resveratrol has proven to be great promise in the laboratory as both a lifespan and health span extending molecule, translating these findings to a clinical setting will require overcoming several challenges and obstacles. Nevertheless, several conclusions might be drawn, and they will possibly represent the starting points for novel investigations.

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