Advances in Traditional Medicine (2021) 21:1–14
https://doi.org/10.1007/s13596-020-00492-0

REVIEW

Effects of resveratrol on mitochondrial biogenesis and physiological diseases

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Received: 15 November 2019 / Accepted: 31 July 2020 / Published online: 25 August 2020

Abstract

Plants produce a number of biological active substances with healthy benefits. Resveratrol (3,5,4′-trihydroxystilbene), a polyphenol produced by plants has been associated with many health beneficial properties, including its ability to induce mitochondrial biogenesis and fight against health problems such as obesity, inflammation, heart diseases, cancers among others. Mitochondrial dysfunction is recognized as central to the pathogenesis and development of many diseases. Thus the present review describes how resveratrol (RSV) may counteract physiological and age-related diseases/disorders through its effect on mitochondrial biogenesis and function. In addition, we discuss the chemistry, main sources, and the doses of RSV shown in previous studies to be efficient for the prevention and treatment of different diseases. Through its ability to improve mitochondrial dysfunction, RSV can be used in the prevention and/or treatment of human physiological diseases. However, more research for optimal dose in a human scale is still relevant. This review brings new hope to the therapy of physiological diseases as it will provide useful future perspectives for the planning of clinical studies on RSV and mitochondrial dysfunction-related diseases.

Keywords Resveratrol · Mitochondrial biogenesis · Polyphenol · Antioxidant · Anti-inflammatory · Intracellular signalling

Introduction

Mitochondria are organelles responsible for several vital functions in our cells. Except for red blood cells, each of our cells has between 200 and 2000 mitochondria, and they are responsible for producing about 90 percent of the energy we use to live and grow (Siekevitz 1957). When these important structures fail, our cells produce less energy, which can injure and even cause cell death. Chronic fatigue and low-energy symptoms of many diseases can be attributed to mitochondrial dysfunction. Mitochondrial biogenesis is an increase in the cell's mitochondrial mass resulting from numerous interactions between information and constituents of nuclear origin, e1aborated by the cytoplasmic protein synthesis system, and components e1aborated within the mitochondria, by the intramitochondrial protein synthesis system (Fabian Sanchis-Gomar et al. 2014).

RSV is a plant polyphenolic micro-constituent with numerous protective potentials. It decreases mitochondrial superoxide anion generation by stimulating mitochondria biogenesis (Zhang et al. 2017). It has been previously demonstrated that oxidative stress and inflammation also contribute to premature aging and chronic diseases (Liguori et al. 2018). As an antioxidant, RSV provides the body with essential support to prevent, control, and repair oxidative stress induced by free radicals (Ning Xia et al. 2017). It also maintains levels of intracellular antioxidants, such as superoxide peroxidase (SOD), catalase, and glutathione reductase. This helps protect the mitochondria and tissues from the damaging effects of free radicals. (Leonard et al. 2003). RSV, with pleiotropic effects, has also the ability to activate sirtuin-1 (SIRT1); a protein that is associated with longevity (Lagouge et al. 2006). By activating SIRT1, resveratrol maintains the health and concentration of mitochondria. Besides oxidative damage, mitochondrial dysfunction also plays an important role in aging and disease (Amarendranath Choudhury

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et al. 2018). SIRT1 cooperates with the co-activator of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (PGC-1α) in promoting adaptation to caloric restriction (Krek 2006).

It increases the number and size of mitochondria in non-oxidative muscle fibers and increases their oxidative metabolism by transforming them into type 1 fibers, which probably explains the improvement in endurance (Muhammad and Allam 2018). The interest in using RSV as a bioactive compound was raised for the first time by a study conducted by Siemann and Creasy which has reported the presence of trans-resveratrol in red wine (Siemann 1992) but it has been long used in popular medicine as a treatment for hyperlipemia, arteriosclerosis, allergic diseases and inflammatory diseases (Yoshiyuki Kimura 1985). Until 2006, there was no study interested in the effect of RSV on mitochondrial biogenesis but in that year Lagouge et al. reported that RSV may improve mitochondrial function and protects against metabolic disease (Lagouge et al. 2006).

RSV also activates adenosine monophosphate-activated protein kinase (AMPK) (Timmers et al. 2011). Like SIRT1, AMPK regulates metabolism during energy stress to restore cellular homeostasis (Hardie et al. 2012). Thus, AMPK inhibits the anabolic pathways (synthesis of lipids, proteins, etc.) and activates catabolism (β-oxidation of fatty acids, autophagy, etc.). RSV activation of AMPK has been shown to result from direct inhibition of cyclic adenosine monophosphate (cAMP)-specific phosphodiesterases (PDE) (Park et al. 2012). Interestingly, several studies have revealed that activation of PGC-1α by SIRT1 (Canto et al. 2010; El-Khamisy et al. 2005), or inhibition of HIF-1α (hypoxia-inducible factor 1-alpha) by AMPK (Saiko et al. 2008) blocks aerobic glycolysis. Thus, it is tempting to think that the activation of the AMPK-SIRT1 axis by RSV induces metabolic reprogramming (Timmers et al. 2011; Wang et al. 2014).

RSV increases mitochondrial function by inducing the expression of genes controlling energy homeostasis, including PGC-1α, which in turn induces genes facilitating beta-oxidation of fatty acids and uncoupling protein 1 (UCP-1) mRNA, an uncoupling protein involved in the production of heat by brown adipose tissue (Lagouge et al. 2006). This proves the potential of RSV in the treatment of obesity and insulin resistance or at least reinforce resistance to weight gain and its related physiological imbalances. Thus, there is an evident compulsion for more clinical studies addressing the optimum doses of RSV for improving mitochondrial dysfunction and increasing mitochondrial biogenesis.

Applications of RSV in the treatment of physiological diseases have previously been presented by other authors (Catalgol et al. 2012; Rauf et al. 2017). Furthermore, some authors also focused on the effects of RSV on mitochondrial function (de Oliveira et al. 2016; Ning Xia et al. 2017) but did not detail their associations with different diseases and effective doses of RSV for their treatment.

In the present review, we discuss the effects of resveratrol on mitochondrial biogenesis and multiple diseases such as cancer, diabetes, obesity, CVDs, erectile dysfunction, neurodegenerative diseases, liver steatosis and Psoriasis that have been previously observed in animal and human studies. The solubility of RSV is very limited which may affect its bioavailability. Against this background, this review presented a different route of RSV administration and its efficacy to regulate and control various diseases. Additionally, the dose and time dependence effects were enumerated. The information provided in this review will help future researchers to plan and design preclinical and clinical studies on RSV and lifestyle or age-related diseases. At the conclusion, we supply hints for prospective directions of future resveratrol research.

Chemical structure of resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a polyphenolic compound synthesized by a varied assortment of plants (Saiko et al. 2008). In nature, it is found in two forms of isomers, these are cis-isomer and trans-isomer (Fig. 1), the trans-isomer has the greatest biological activity and is abundant (Vian et al. 2005). RSV is a very light-sensitive compound disposed to ultraviolet-induced isomerization, over 80% of the trans-resveratrol in solution is transformed to cis-isomer when exposed to UV light for an hour (Langkake 1976; Vian et al. 2005).

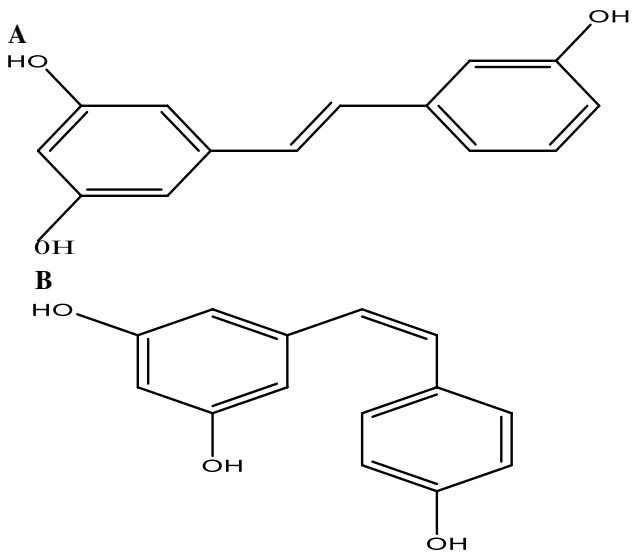

Fig. 1 Trans-3,5,4′- trihydroxystilbene (**a**) and cis-3,5,4′-trihydroxystilbene (**b**) structures

Sources of resveratrol

RSV was identified and isolated at the first time from the roots of white hellebore (*Veratrum grandiflorum O. Loes*) in 1940 (Baur and Sinclair 2006) and afterward, RSV has been found in a variety of plants species and foods these include grapes, peanuts, berries, cocoa, dates, groundnuts, tomatoes, pines among others (Counet et al. 2006). In grapes, particularly when affected by *Botrytis cinerea*, it is elaborated in the crust and its proportion is high just before the ripeness of the grapes (Jubilee and Stewart 2003). Accordingly, the highest amount of RSV is found in their crust and seeds (50–100 µg per gram) (Counet et al. 2006).

Table 1 Content of resveratrol in some food sources

Food source	Content of RSV
Peanuts	0.03–0.14 µg/g (Sanders et al. 2000)
Peanut shell	39.1 µg/g (Arslan and Yilmaz 2013)
Black mulberries	32.5 µg/g (Arslan and Yilmaz 2013)
Blueberries	0.24 µg/g (Wang et al. 2002)
Red grape seeds	0.35–237.8 µg/g (Wang et al. 2002)
Dry red grape berry skins	28.39 µg/g (Romero-Pérez et al. 2001)
Dry White grape berry skins	22.02 µg/g (Romero-Pérez et al. 2001)
Red grape berries	0.16–3.54 µg/g (Khurana et al. 2013)
Dates	3.0 µg/g (Sebastia et al. 2017)
White grape juice	0.03 mg/L (Romero-Perez et al. 1999)
Red grape juice	0.36 µg /g (Wang et al. 2002)
White wine	0.23 mg/L (Cvejic et al. 2010)
Rose wine	0.29 mg/L (Weiskirchen 2016)
Red wine	0.72–3.18 mg/L (Wang et al. 2002)
Hop	500 µg/L (Callemien et al. 2005)
Beers	1.34–77.0 µg/L (Chiva-Blanch et al. 2011)
Cherry seed	1.50 µg/g (Arslan and Yilmaz 2013)
Potato crust	0.25×10^{-4} µg/g (Arslan and Yilmaz 2013)
Cucumber skin	18.0 µg/g (Arslan and Yilmaz 2013)
Sunflower seeds	3.98 µg/g (Kisbenedek et al. 2014)
wild black mustard seeds	2.3 µg/g (Kisbenedek et al. 2014)
Almonds	1.76 µg/g (Kisbenedek et al. 2014)
Dark chocolate	0.350 µg/g (Hurst et al. 2008)
Milk chocolate	0.10 µg/g (Hurst et al. 2008)
Strawberry	0.2 µg/g (Sebastia et al. 2017)
Tomato	0.2–2.1 µg/g (Sebastia et al. 2017)
skin of tomato	19 µg /g dry weight (Ragab et al. 2006)
Itadori tea	974 µg /100 mL (Burns et al. 2002)

The concentrations of RSV vary significantly in comestible plants (Table 1). As an example, the level of RSV rises in the grapes affected by biotic and abiotic stresses, for example, bacteria, yeast, cold, or ultraviolet (UV) radiation (Weiskirchen 2016). The entire quantity of RSV consumed by humans might be augmented by more RSV-rich foods intake (e.g., red grapes, berries, itadori, peanuts) or their derivatives such as red wine, dried fruits, tea, jams, and juices.

Biological activities of resveratrol

Many researchers have reported that RSV has several biological activities (Fig. 2), comprising anti-oxidative, anti-diabetes, anti-aging, anti-cancer, anti-inflammatory cardioprotective activities, as well as other health benefits such as induction of apoptosis, mitochondrial biogenesis among others.

Anti-inflammatory effects of resveratrol

A number of human diseases are mainly due to chronic inflammation. The inflammatory progressions may cause mutations of DNA in cells through nitrosative or oxidative stress, which may affect normal functions of cells and hence result in inflammatory diseases (Sanchez-Fidalgo et al. 2010).

Recent studies have demonstrated the dynamic role of mitochondria in the regulation of inflammatory processes. Mitochondrial stress and the buildup of damaged and dysfunctional mitochondria caused by defects in the PTEN-induced kinase 1 (PINK1) or PARKIN genes mediated mitophagy may contribute to the pathology of mitochondria-induced inflammatory diseases such as Parkinson's disease (Newman and Shadel 2018; Sliter et al. 2018). In response to infection and stress, mitochondria release danger signals (mtDNA) in the cytoplasm that promote the formation and activation of nod-like receptor protein 3 (NLRP3) inflammasomes (inflammatory signaling platform), resulting in inflammation (Shimada et al. 2012; Zhang et al. 2010). Activation of inflammasomes by damaged mitochondria results in the caspase-1-dependent secretion of the inflammatory cytokines IL-1β and IL-18 (Nakahira et al. 2011).

In their experiment, Cui et al. have proven that RSV considerably repressed inflammation indicators, for example, inducible nitric oxide synthase (iNOS), tumor necrosis factor-α (TNF-α), and cyclooxygenase-2 (COX-2) (Cui et al. 2010). Sanchez-Fidalgo and co-workers' study was confirmed that its supplementation diminished chronic colonic inflammation by decreased proinflammatory cytokines, comprising prostaglandin E synthases-1 (PGES-1), interleukin-1 beta (IL-1b), IL-10, TNF-α, COX-2, and

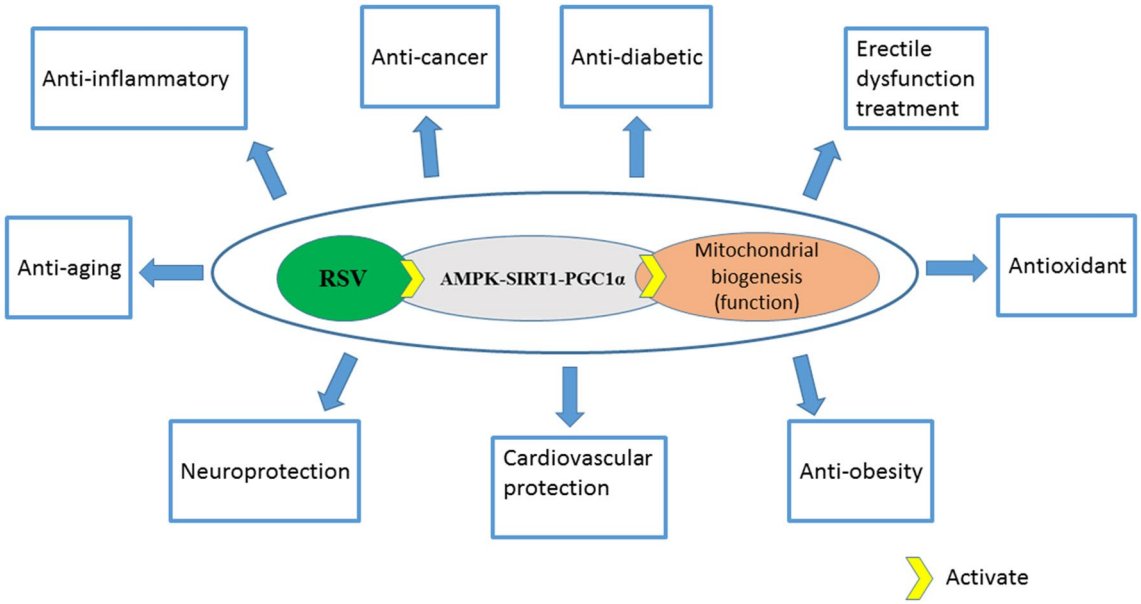

Fig. 2 Biological beneficial activities of resveratrol

iNOS, through reduction of the p38 MAP kinase (mitogen-activated protein kinases) signaling pathway (Sanchez-Fidalgo et al. 2010).

The potential of RSV in prevention and treatment of inflammatory and autoimmune diseases is elucidated by its ability to initiate apoptosis in activated T cells and downregulate IL-2, IL-9, IL-12, IL-17, TNF-α, interferon-g, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 alpha (Kjaer et al. 2015).

In recent years, the study conducted by Lee et al. (2015) recommended that RSV would rise apigenin (a strong anti-inflammation) bioavailability. Cotreatment of RSV and apigenin augmented the concentrations of plasma apigenin up to 2.39 times comparing to the group treated by apigenin only (Lee et al. 2015). Zhang et al. (2017) suggested that RSV can improve mitochondrial dysfunction through stimulation of mitochondrial biogenesis, improvement of energy homeostasis, and a decrease in oxidative damage (Zhang et al. 2017). Oxidative damage to cells (their membranes, lipids, enzymes, mitochondria, and DNA) affects the functions of tissues and organs, thus causing unwanted immune responses and inflammation (Lugrin et al. 2014).

Anti-cancer effects

A chemopreventive approach to cancer is a promising strategy in the control of the disease. The idea of chemoprevention is to stop, delay, or reverse the progression of malignant transformation of cells, through physiological mechanisms that do not affect the healthy cells (Sporn 2011). In this process, a particular interest is brought to phytochemical compounds. Their anti-carcinogenic effect is attributed to their anti-mutagenic, antioxidant, and anti-inflammatory properties (Catalgol et al. 2012).

During the process of tumorigenesis, mitochondria undergo a series of alterations that notably contribute to the metabolic reprogramming of cancer cells (Gogvadze et al. 2008). Reddivari et al. reported that two weeks of resveratrol-grapeseed extract (RSV-GSE) treatment resulted in suppression of Wnt/β-catenin signaling and elevation of mitochondrial-mediated apoptosis in colon cancer stem cells (Reddivari et al. 2016). RSV enhances mitochondrial functions via SIRT1 (Lagouge et al. 2006). When a calorie restriction SIRT1 is activated, it regulates the metabolism including mitophagy (Pietrocola et al. 2012), the process by which damaged mitochondria are destroyed.

Resveratrol activates SIRT1 via AMPK and in the same way as SIRT1, AMPK regulates metabolism during energy stress, to restore cellular homeostasis (Hardie et al. 2012; Park et al. 2012). AMPK inhibits anatomical pathways (synthesis of lipids, proteins, etc.) and activates catabolism (autophagy, beta-oxidation ...). It has been shown that the activation of AMPK by resveratrol is the result of direct inhibition of PDE specific for cAMP (Park et al. 2012). The rise in the cAMP level then induces a signaling cascade involving the exchange of protein directly activated by cAMP 1 (Epac1) and Ca^{2+}-calmodulin-dependent-protein kinase kinase beta (CamKKbeta). In increasing the NAD+/NADH ratio, AMPK activates SIRT1 which deacetylates and activates the PGC-1α, leading to an increase in oxidative phosphorylation and the synthesis of new mitochondria. Several studies have shown that the activation of PGC-1α

by the SIRT1 (Canto et al. 2010; El-Khamisy et al. 2005) or inhibition of hypoxia-inducible factor 1-alpha (HIF-1 alpha) by AMPK (Faubert et al. 2013) blocks aerobic glycolysis. It can thus be supposed that the activation of the AMPK-SIRT1 axis by RSV induces a metabolic reprogramming preventing tumor development. Recently a study conducted by Blanquer-Rossello et al. has described the ability of RSV to target cancer cell metabolism and enhance chemotherapy effects by promoting mitochondrial electron transport chain overload and, ultimately, increasing ROS production (Blanquer-Rossello et al. 2017).

Impact of resveratrol on obesity, diabetes and cardiovascular diseases

Obesity is a global societal health problem and it has been associated with high risks of contracting a number of diseases including type 2 diabetes and cardiovascular diseases. Its development has been strongly associated with mitochondrial imbalances (de Mello et al. 2018) which lead the development of many cardiac diseases such as Hypertension, ischemia-reperfusion injury, diabetes, cardiac hypertrophy, and heart failure and atherosclerosis, due to the uncontrolled production of ROS (Siasos et al. 2018).

Recent studies on obese animals showed that RSV treatment increased mitochondrial biogenesis and function, improvement of energy homeostasis, and a decrease in oxidative damage (de Oliveira et al. 2016; Zhang et al. 2017). These effects can be accredited to the activation of the AMPK/SIRT1/PGC-1α axis. It was confirmed that most cases of diabetes are due to oxidative stress caused especially by sedentary behavior and an undesirable eating routine. RSV counteract mitochondrial dysfunction by activating Nrf2 (nuclear respiratory factor 2) (Bonnefont-Rousselot 2016). RSV has been shown to activate Nrf2 in both mice heart (RSV at 10 mg/kg/day for 3 days before exposure to lipopolysaccharides (LPS)) and human neonatal cardiomyocyte (HCM) cells (that were treated with RSV at 3 μM for 4 h before exposure to LPS) (Enkui Hao et al. 2013).

Several human studies have demonstrated that RSV is effective for people with diabetes, overweight, and/or hypertension (Campbell et al. 2019; Sahebkar 2013). RSV restores blood sugar levels due to its ability to protect against high production of glucose in diabetic patients and eliminate free radicals, which can damage mitochondria (Naudi et al. 2012; Zhang et al. 2010). RSV promotes the loss of body fat and lowers cholesterol and triglyceride levels (Zhang et al. 2010). Treatment with RSV at concentrations of 30 mg/kg for 10 weeks significantly reduced body weight, liver weight, subcutaneous, and epididymal adipose tissue weight in obese mice (Chih-Chun Chang 2016). Mitochondrial dysfunction also plays an important role in the pathophysiology of cardiovascular diseases (Bayeva et al. 2013). In addition, RSV reduces the levels of different markers of risk of cardiovascular disease, which is particularly important with diabetes (Satya Dash 2013). A very recent study showed that RSV treatment (500 mg/day for 4 weeks) (Table 2) upregulated PPAR-γ and SIRT1 and had beneficial effects on total antioxidant capacity (TCA), high density lipoprotein-cholesterol (HDL-c) and malondialdehyde (MDA) levels in patients with T2DM, coronary artery disease, hyperlipidemia with other cardiovascular risks (Hoseini et al. 2019). A meta-analysis indicated that treatment with RSV (≥ 150 mg/day) lowered systolic blood pressure with no effect on diastolic blood pressure (Liu et al. 2015). Timmers et al. showed in 2011 that RSV mimics the effect of a low-calorie diet (Timmers et al. 2011) and thus facilitates weight loss. Thus RSV is an excellent solution even for people who cannot do physical exercises like those with a physical disability, heart disease, neurological problem, etc. and all too often suffer from overweight or diabetes.

Recently research findings demonstrated that RSV can control the development of T2DM via SIRT1 by regulating the expression of mitochondrial genes involving in biogenesis, β-cells differentiation, and lipid metabolism (Cao et al. 2018). Diao et al. revealed that RSV ameliorates mitochondrial function and consequently improves cardiac function in diabetic rats, and uncoupling protein 2 (UCP2) was involved in the protective effects of RSV on diabetic cardiomyopathy (DCM) (Diao et al. 2019).

The above results have proven that mitochondrial dysfunction was closely linked to the pathophysiology of T2DM and clarified the ability of RSV to prevent and control obesity, diabetes, and cardiovascular diseases.

Antioxidant effects of resveratrol

As described above, mitochondrial dysfunction arises as a consequence of the excessive production of ROS which oxidizes cellular lipids, proteins, and DNA (Esra Birben et al. 2012). One of the antioxidative effects of RSV is its ability to directly capture free radicals (scavenger effect of RSV) (Leonard et al. 2003).

In their study, Li et al. described that RSV induces the expression of mitochondrial genes and manganese superoxide dismutase (Mn-SOD) via SIRT1 and mitochondrial biogenesis signaling pathways, thus inhibits ROS production in cardiomyocytes (Li et al. 2013; Ning Xia et al. 2017).

RSV is capable to induce antioxidant enzymes such as Mn-SOD involved in the dismutation of the superoxide ion (O2, very reactive radical species) in oxygen and hydrogen peroxide (Campbell et al. 2019; Nakata et al. 2012). RSV can also prevent oxidation of low-density lipoprotein cholesterol (LDL-C) by chelating copper and capturing ROS (Andrea Markus 2008). The activity of deacetylase is required for the activation of the PGC-1α co-activator. Once activated,

Table 2 Effective doses of RSV for mitochondrial impairment-related diseases and /or disorders as demonstrated by previous animal and human studies

Disease or metabolic imbalances	Subjects	Dose of RSV	Effect of RSV	References
Inflammation and CVDs	Humans	0.025–0.1 mmol/L (incubated with blood platelets) for 2 min	Reduced carbonylation of proteins induced by $ONOO^-$ Scavenged $ONOO^-$	Olas et al. (2006)
Inflammation and CVD (atherosclerosis)	Human umbilical vein endothelial cells (HUVECs)	10 µM of RSV (incubated with endothelial cells) for 2 h	Attenuated endothelial inflammation by inducing autophagy which was mediated through the activation of the cAMP-PRKA-AMPK-SIRT1 signaling pathway Reduced TNFα-induced inflammation Increased microtubule-associated protein 1 light chain 3 β 2) expression	Chen et al. (2013)
Inflammation and Hepatic steatosis	Mice	30 mg/kg/d (orally) for 60 days	Inhibited over activation of NF-κB pathway and improved hepatic steatosis Increased the AMPKα phosphorylation and SIRT1 protein levels	Tian et al. (2016)
Psoriasis (localized and systemic low-grade inflammation)	Mice	400 mg/kg/d (orally) for 7 days	Diminished the severity of the psoriasis-like skin inflammation Increased expression of genes associated with retinoic acid stimulation Decreased mRNA levels of IL-17A and IL-19; both central in developing psoriasis	Kjaer et al. (2015)
Colon cancer	Mice	42 mg/kg/d (orally) for 2 weeks	Suppressed dextran sulfate sodium (DSS)-induced colitis Improved inflammation score Downregulated the percentage of neutrophils in the mesenteric lymph nodes and lamina propria Modulated CD3 + T cells that express TNF-α and IFN-γ Decreased inflammation of and inflammatory stress markers Decreased tumor multiplicity	Cui et al. (2010)

Table 2 (continued)

Disease or metabolic imbalances	Subjects	Dose of RSV	Effect of RSV	References
Obesity	Humans (obese)	150 mg/kg/d (orally) for 30 days	Reduced sleeping and resting metabolic rate Activated AMPK and increased SIRT1 and PGC-1a protein levels Increased citrate synthase activity without change in mitochondrial content Improved muscle mitochondrial respiration on a fatty acid-derived substrate Decreased intrahepatic lipid content, circulating glucose, TG, ALAT, plasma fatty acid, glycerol and inflammation markers Dropped systolic blood pressure	Timmers et al. (2011)
Obesity	Mice	30 mg/kg/d (orally) for 10 weeks	Attenuated HFD-induced obesity Mitigated weight augmentation of subcutaneous and epididymal adipose tissues Reduced liver weight Suppressed lipolysis in mature adipocytes	Chih-Chun Chang et al. (2016)
Obesity and T2DM	Wild-type C57BL/6J mice	400 mg/kg/d (orally) for 12 weeks	Activated AMPK Increased the metabolic rate Reduced fat mass Increased insulin sensitivity and glucose tolerance Increased mitochondrial biogenesis Increased physical endurance	Um et al. (2010)
T2DM	Sprague-Dawley rats	Administered once with 30 mg/kg (intragastrically)	Modulated the expression of SIRT1, PGC-1α and FOXO3a Promoted mitochondrial biogenesis Modulated lipid metabolism-associated and β-cell-associated genes	Cao et al. (2018)
T2DM and CVD	Humans (T2DM patients with CHD)	500 mg/kg/d (orally) for 4 weeks	Reduced fasting glucose, insulin, insulin resistance, total-/HDL-c ratio and MDA levels Increased insulin sensitivity, HDL-c levels and TAC Upregulated PPAR-γ and SIRT1	Hoseini et al. (2019)

Table 2 (continued)

Disease or metabolic imbalances	Subjects	Dose of RSV	Effect of RSV	References
Diabetic cardiomyopathy (DCM) and mitochondrial dysfunction and	Male Sprague-Dawley rats	10 mg/kg/d (orally) for 16 weeks	Ameliorated mitochondrial function Reduced the level of and LDL-c Reversed the impaired diastolic and systolic cardiac function Improved myocardial structural disorder and fibrosis Reserved mitochondrial membrane potential level Suppressed myocardial apoptosis Attenuated ROS generation Improved mitochondrial respiratory enzyme activities Increased the expression of UCP2	Diao et al. (2019)
Metabolic diseases (diabetes, CVDs, etc.)	Male Sprague-Dawley rats	100 mg/kg/d (orally) for 8 weeks	Ameliorated insulin sensitivity Improved SIRT3 expressions (keeping the balance between oxidative stress and antioxidant competence of subsarcolemmal mitochondria) Increased mitochondrial biogenesis and mtDNA content	Haohao et al. (2015)
CVD	Humans (42–80 year old, mean age 66.3 ± 8.9 years, 26 men, 14 women)	10 mg RES daily (capsule) for 3 months	Improved left ventricle diastolic function, endothelial function Lowered LDL-cholesterol level Protected against unfavourable hemorheological changes measured in patients with coronary artery disease	Magyar et al. (2012)
Oxidative stress, obesity and endotoxemia	Mice	100 mg/kg/d (orally) for 8 weeks	Increased GSH-Px, CAT, and SOD production Reduced MDA production Reduced LDL-c levels in HFD mice Restored the gut microbiota	Campbell et al. (2019)
Oxidative stress and Mitochondrial dysfunction	C57BL/6 male mice	0.06% RSV (orally) for 20 weeks	Stimulated mitochondrial biogenesis Restored mitochondrial functional activities of Tregs Prevented the development of oxidative stress and chronic inflammation	Wang et al. (2014)
Neurodegenerative diseases/ neuroinflammation (ischemic brain damage)	Adult male Wistar rats (290–330 g)	30 mg/kg/d (injected intraperitoneally) for 7 days prior to I/R induction	Decreased the global cerebral ischemia induced glial and JNK activation Decreased NF-κB, COX-2 and iNOS induced by Ischemia/Reperfusion	Simao et al. (2012)

Table 2 (continued)

Disease or metabolic imbalances	Subjects	Dose of RSV	Effect of RSV	References
Neurodegenerative diseases and Mitochondrial dysfunction	Sprague Dawley rats	100 µmol (microinjected bilaterally), at a volume of 150 nL on each side	Activated PGC-1α signaling pathway Increased mitochondrial biogenesis and function Reduced activated caspase-3 activity and attenuated neuronal cell damage in the hippocampus	Chuang et al. (2019)
Alzheimer's disease	Adult Wistar rats (250–300 g)	100 µM (incubated with synaptoneurosomes)	Decreased AA incorporation by about 50% into phospholipids of synaptoneurosomes membranes Prevented NO^- and cGMP-evoked inhibition of AA incorporation	Chalimoniuk et al. (2006)
Huntington's Disease	Male Wistar rats	5 and 10 mg/kg/d (orally) for a period of 8 days	Reversed 3-nitropropionic acid-induced motor and cognitive impairment Prevented the increase in MDA levels Decreased markers of oxidative stress	Puneet Kumar (2006)
Erectile dysfunction	Adult male Wistar rats (300–350 g)	10 mg/kg/d (intragastrically) for 4 weeks	Restored the endogenous GSH levels Decreased oxidative damage parameters in all studied tissues Increased the contractile response of the corpus cavernosum	Toklu (2010)
Mitochondrial dysfunction	Intrauterine growth retarded piglets	1.0 g/kg/d (orally) for 2 weeks (from 7 to 21 days of age)	Inhibited mitochondrial superoxide anion accumulation Increased complex III and MnSOD activities Ameliorated mitochondrial swelling and lipid peroxidation	Zhang et al. (2017)
Aging-associated decline of physical endurance and mitochondrial dysfunction	Mice (18 months old)	15 mg/kg/d (orally) and/or exercise trained for 4 weeks	Increased mitochondrial biogenesis and function Increased muscle PGC-1α mRNA expression and citrate synthase enzyme activity Improved aging-associated oxidative damage	Muhammad and Allam (2018)

UCP2 Mitochondrial uncoupling protein 2, *TG* triglyceride, *HDL-c* high density lipoprotein cholesterol, *PPAR-γ* peroxisome proliferator-activated receptor gamma, *TAC* total antioxidant capacity, *AA* arachidonic acid, *MDA* malondialdehyde, *GSH-Px* glutathione peroxidase, *CAT* catalase, *MnSOD* manganese superoxide dismutase, *HFD* high fat diet, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *DSS* dextran sulfate sodium, *IFN-γ* Interferon gamma, *JNK* c-Jun N-terminal kinases, *VLDL-c* very low density lipoprotein cholesterol, *T2DM* type 2 diabetes mellitus

PGC-1α may interact with transcription factors such as Nrf1/Nrf2 to induce transcription of antioxidant genes such as quinone oxidoreductase 1, γ-glutamylcysteine synthetase, or heme oxygenase-1 (Alissa and Ferns 2012). It has been shown that the exposure of blood platelets to oxidative stress, for example, the exposure of the cells to peroxynitrite (ONOO-), induces the inhibition of their essential activities (Pawel Nowak 2001). According to Olas and Wachowicz, the antioxidant effect of RSV is due to 4'-hydroxyl group but also of the meta configuration of the two hydroxyl groups of the first benzene group (Olas et al. 2006).

Briefly, RSV is an effective sensor of free radicals (ROS), a lipid peroxidation reducing agent, and an inhibitor of protein oxidation through regulating mitochondrial biogenesis.

Neuroprotective effects of resveratrol

RSV also appears as a neuroprotective agent because of its anti-inflammatory and antioxidant effects. Previous studies have shown that RSV can be used in treatment of neurodegenerative and neurological diseases and/or disorders (Parkinson's disease, Alzheimer disease, epilepsy, etc.) via promoting activation of AMPK and SIRT1 ensuing PGC-1α activation which lead to an increase of mitochondrial biogenesis and a decrease of ROS thus relieve mitochondrial dysfunction a characteristic of neurodegenerative diseases (Anna Ferretta et al. 2014; Chuang et al. 2019). Additionally, through AMPKα-SIRT1 activation, RSV decreases nuclear factor-κB (NF-κB) signaling (Tian et al. 2016). The activation of NF-κB in glial and immune cells initiates inflammatory processes thus RSV supplementation could decrease the inflammatory level (Tian et al. 2016; Vingtdeux et al. 2010).

RSV has been revealed to decrease plaque formation related to neurodegeneration (Karuppagounder et al. 2009). RSV has also been shown to significantly prevent intracerebroventricular streptozotocin (ICV)-induced cognitive impairment in rats (Monisha Sharma 2002). In rodent models with similar symptoms as those of Huntington's disease, RSV has expressively improved cognitive and motor impairment thanks to its inhibitory activity of COX-1 (Puneet Kumar 2006). Another study demonstrated that RSV prevents memory impairment induced by diabetes and the increase in Acetylcholinesterase (AChE) activity (Schmatz et al. 2009).

Resveratrol and erectile dysfunction

Erectile dysfunction (ED) is an inability to have and maintain an erection of sufficient quality to obtain satisfactory sexual activity. ED may be a reflection of a pathological condition, such as diabetes, a hormonal disease, a neurological disorder, a heart or vascular condition (Boydens et al. 2016). In addition, ED is common among heavy smokers, regular drug users and alcoholics (Zhong et al. 2019). RSV, due to its strong antioxidative effects, was able to preserve the important metabolic pathways involved in erectile function (Faid et al. 2015). Supplementation of RSV (10 mg/kg/day for 28 days) to nicotine-treated Wistar rats reversed contractile activity of the bladder and corpus cavernosum strips impairments (Toklu 2010). Other reports have shown that RSV downregulated the expression of PDE5, p53 and FOXO3a, which regulate apoptosis and oxidative stress and contrarily increased blood testosterone level, expression of nNOS, eNOS, cavernous cyclic guanosine monophosphate (cGMP) and SIRT1, an activator of mitochondrial biogenesis and thus, restored erectile function in experimental animals with diabetes (Bai and An 2015; Sener et al. 2018; Shin et al. 2008; Wen Yu et al. 2013). As we have described above, physiological diseases are closely linked to mitochondrial dysfunction. Therefore, supplementation with RSV may help not only to improve these pathologies but also erectile dysfunction as well as infertility.

Resveratrol, sirtuins and aging

Throughout aging, the decline of mitochondrial activity may impair the production of adequate adenosine triphosphate (ATP) for homeostasis, eventually initiating apoptosis (Biala et al. 2015), involving to the beginning and progression of aging and aging-related disorders. Mitochondrial dysfunction results in the decline of mitochondrial biogenesis and is expected to be the main cause of aging (Lopez-Lluch et al. 2008). Researchers demonstrated that RSV has a lifespan extension potential in various animal models (Kasiotis et al. 2013). An experiment carried by Muhammad and Allam (2018) demonstrated that RSV supplementation increased the endurance of aged mice in comparison with the aged control group (Muhammad and Allam 2018).

The anti-aging activity of resveratrol is clarified by its action on SIRT1 a molecule of longevity that can reverse the decline of mitochondrial biogenesis that occurs in senescent cells (Lagouge et al. 2006). The sirtuins are NAD-dependent deacetylase proteins able to modulate the transcriptional activity of many genes. Some of the best-characterized effects of SIRT1 include increased oxidative stress resistance and altered metabolism mediated by changes in the activity of the transcriptional factor FOXO (Anne Brunet 2004), suppression of NF-κB-dependent inflammatory responses (Fan Yeung et al. 2004) and the promotion of gluconeogenesis, fatty acid oxidation and mitochondrial biogenesis, through PGC-1α (Lagouge et al. 2006). According to Zhang et al. (2017), the treatment of intrauterine growth retarded suckling piglets with RSV increased hepatic SIRT1 activity, aided by increased NAD + concentration. Moreover, PGC-1α mRNA and its protein levels were significantly induced upon resveratrol administration. This was resembled

by the increased mRNA abundance of downstream target genes associated with mitochondrial biogenesis (Zhang et al. 2017). The activation of SIRT1 by RSV is substrate-dependent and many of its effects are consistent with the modulation of its target on genes (Purushotham et al. 2009). As described above resveratrol may grant various health benefits that may increase longevity to mammals and humans.

Conclusion

Resveratrol has been shown to improve mitochondrial function and prevention and/or treatment human physiological diseases through its ability to activate AMPK, PGC-1α, and SIRT1, the main drivers of mitochondrial biogenesis. One of the ways used to deal with the consequences of high-fat diet intake such as diabetes, obesity, cardiovascular diseases among others is to exercise regularly and confine the intake of calories which would result in a reduction in endoplasmic reticulum stress. In this review, we have described how RSV seems to mimic numerous biochemical effects of restriction of calories. Interestingly, several studies have shown that activation of PGC-1α by SIRT1 blocks aerobic glycolysis. Thus, the activation of the AMPK-PGC-1α-SIRT1 by RSV may induce metabolic reprogramming hence preventing or improving metabolic diseases. However, the research for the "optimal dose" is still relevant. Resveratrol has multiple action targets and beneficial effects that are however controversial in some studies. Most of the recent studies have been done on cell cultures or animal models but very little on a human scale. The very low bioavailability of resveratrol taken orally is one of the major limiting factors. Therefore, future clinical trials and meta-analyses should focus on obtaining more accurate and consensual data on resveratrol.

Acknowledgements This review was supported State Key Laboratory of Food Science and Technology, Jiangsu, P.R. China, and National First-class discipline program of Food Science and Technology (JUFSTR201180201) and Collaborative Innovation Center of Food Safety and Quality Control in Jiangsu Province, Jiangnan University.

Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest Angelo Uriho has no conflict of interest. Xue Tang has no conflict of interest. Guowei Le has no conflict of interest. Shaojun Yang has no conflict of interest. Yves Harimana has no conflict of interest. Steven Papy Ishimwe has no conflict of interest. Lu Yiping has no conflict of interest. Kai Zhang has no conflict of interest. Shuhua Ma has no conflict of interest. Bertrand Muhoza has no conflict of interest.

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