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Review Article

Trans-Resveratrol in Pregnancy, SCD and Woman's Health

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Abstract

Resveratrol is a common phytochemical found in an abundance in nutritious and wholesome foods and thus has always likely been part of the human diet for many centuries. As such, resveratrol may contribute to the success of the French Paradox, where the inclusion of red wines is a familiar dietary addition and is associated with reduced incidence of cardiovascular disease. The primary metabolic action of resveratrol and related phenolic compounds likely rests in its potential antioxidant activity, being able to quench reactive free radicals (ROS) and other inflammatory activities in peripheral tissues. Wholesome foods are an established contributor to healthy benefits, sometimes attributed to the ratio of dietary fibers to macronutrient intake being consumed, with glycemic index also a significant factor. Resveratrol has been suggested as an adjunct in the clinical management of numerous metabolic disorders, including diabetes, obesity, hypertension, pre-eclampsia, and sickle cell disease among others associated with chronic inflammation. Thus, the purpose of this review is to examine the safety and efficacy of resveratrol in pregnancy. The results indicate that resveratrol is likely a safe and effective adjunct in treating the hypoxia and chronic inflammation of pregnancy, in addition to its applications in various hemoglobinopathies including sickle cell disease by inducing increased production of sickle-resistant fetal hemoglobin (HbF) in addition to reducing the magnitude of chronic inflammation, while enhancing oxygen delivery to peripheral tissues via actions of fetal hemoglobin. Thus, RSV may also be able to partially correct the effects linked to the globin chain imbalance in SCD patients, while at the same time facilitating oxygen transport to myoglobin in peripheral tissues due to a more favorable oxygen-delivering capacity than is observed in adult hemoglobin. The purpose of this paper is to review the biochemical, pharmacologic and potential toxicologic aspects of trans-resveratrol administration as an adjunct in the treatment of hemoglobinopathies including SCD during pregnancy.

Keywords: Resveratrol; Hydroxyurea; Sickle Cell Disease; Sickle Cell Anemia; Antioxidants; Sirtuins

Introduction

Pregnancy imposes an additional challenge to oxygen transport and delivery individuals especially women suffering from β-thalassemia and sickle cell disease (SCD) and their omorbidities [1-4]. The medical issues that impinge on pregnancy outcomes include both the comorbidity of anemia (SCA) that often accompanies the disorders, in addition to the increased oxygen demands of gestation which may induce hypoxemia and sickle cell crises requiring hospitalization or blood transfusions following a vascular occlusive event (VOE) or vascular occlusive crises (VOC) [5]. The events may occur frequently, from an occasional to up to 10 or so per year, and typically require emergency treatment due to the severe pain induced by the vascular occlusive event and resulting tissue hypoxia where they occur [6,7]. While various opiates including morphine, fentanyl, and others are often administered to ameliorate the severe pain of SCD-linked vascular crises, such treatments

must be used with caution during pregnancy over concerns for the fetal and maternal well-being [5]. The frequency of potential opiate use places SCD patients at a higher risk of developing an opioid use disorder (OUD) due to the chronic pain associated with the condition and the subsequent need for opioid pain management. Although the risk for OUD may still be relatively small and not significantly higher than in other chronic pain conditions, it should not be overlooked [6]. Indeed, in animal studies, opiate use during gestation has been shown to induce DNA fragmentation defects in the brain tissues of offspring following opiate exposure during gestation. As an alternative approach In SCD, hydroxyurea (HU), a ribonucleotide reductase inhibitor and fetal hemoglobin (HbF) inducer, is often prescribed as the drug of first choice in treating the disorder in otherwise healthy, non-pregnant adults [6,7]. The efficacy of HU in the management of thalassemia and SCD is generally attributed to its limited ability to boost the levels of fetal hemoglobin (Hb F, $\alpha 2\gamma 2$) in RBCs, suppress the contributions of HbS, and thus provide a partially protective mechanism for the sickle reaction which ultimately damages the blood vessels [6,8,9]. Thus, HbS is contributory to the major pathophysiologic clinical signs and symptoms and decreased lifespan associated with the SCD disorder [4,5]. The administration of HU prior to conception and during pregnancy however remains controversial due to potential adverse teratogenic or other metabolic effects on the developing fetus. The controversy occurs due to an elevated risk for decreased maternal fecundity and compromised pregnancy outcomes associated with HU use prior to and during pregnancy although heritable deleterious effects in offspring are rare.[10] Nonetheless, HU, like many pharmaceuticals that have not undergone controlled, double-blind clinical human trials during pregnancy, is generally not recommended for use immediately prior to or during gestation out of a caution for safety for the unborn [6,7,10].

In the heritable disorder of SCD, an epigenetic-mediated substitution of valine for glutamate in the β-globin subunit of hemoglobin occurs to form sickle cell hemoglobin (HbS) [4]. This single amino acid substitution results in the transition from a hydrophilic, negatively charged peptide of hemoglobin A to a neutral, hydrophobic protein now containing the neutral amino acid valine, forming the HbS variant while also impacting oxygen saturation and transport characteristics. The amino acid change in charge structure can result in the abnormal polymerization of the HbS-β-chain when forming deoxy-HbS during periods of high oxygen demand by peripheral tissues. This action precipitates the sickling intracellular polymerization reaction in HbS erythrocytes. In addition, the HbS sickle cells also have a greater tendency for intravascular aggregation when converted to the deoxy-HbS during deoxygenation and oxygen, transfer and storage to intracellular myoglobin, necessary for supporting cellular respiration [4,511]. Because hemoglobin oxygen saturation curve for HbF falls to the left of HbA, it facilitates the ready donation of the oxygen moiety to myoglobin throughout the entire range of SpO2 saturation, sparing the deoxygenation of HbS which falls far to the right of HbF [1,11,12]. This difference in the hemoglobin O2 saturation curve thereby enables HbF to become more fully oxygenated than HbA or HbS at lower partial pressures of oxygen, decreasing the magnitude and preponderance of deoxy-HbS linked sickle cell vascular damage. The mitochondrial and cellular redox rection is similar to that which occurs in fullerenes and complex graphene structures [13]. This HbF protects not only the unborn during gestation for several months of extrauterine life during which time the HbF containing cells survive, but when introduced into adult circulation can also minimize the damaging impact of HbS moieties that remain available [12]. Hemoglobin has four oxygen binding sites, one for each heme group, allowing it to carry up to four oxygen molecules [1,4,11,12]. The binding of oxygen to hemoglobin is an allosteric, cooperative process, generating a sigmoid-shaped curve, as the binding or donation of one oxygen molecule progressively increases the affinity of the remaining binding sites for oxygen [5]. In contrast, tissue myoglobin is a monomer with a hyperbolic curve, avidly binding and storing only one molecule of oxygen, and resulting in a near linear saturation further to the left of HbF at all pO2 concentrations that are compatible with life. Myoglobin of both maternal and fetal systems can become 50% saturated with oxygen at partial pressures of oxygen at only 2 mm (~ 1-2 torr) of Hg pressure and ~75% saturated at only 4 to 5 mm of Hg partial pressure and readily donate its oxygen to cellular processes under virtually all conditions of oxygen availability [4]. This process is crucial for efficient oxygen delivery to and CO2 transport away from tissues and to support cellular respiration. The curve of both HbF and HbA and of myoglobin of the oxygen saturation profile for hemoglobin is depicted in Figure 1 below, depicting the phenomenon. Oxygen diffuses down a pressure gradient from a relatively high level (21.2 kPa (159 mmHg) at sea level) in inspired air, to progressively lower partial pressure levels as it descends to the alveolus in the respiratory tract, where the alveolar gas, the arterial blood, capillaries and finally the cell/mitochondria occur, and where the lowest pO_2 level occurs. (1 – 1.5 kPa; 7.5 – 11.5 mmHg, < 5 torr) [1,4,11].

The affinity for oxygen binding and transport in erythrocytes is also impacted by the presence of 2,3-bisohosphoglycerate, formed as a normal byproduct of glycolysis via the Rapoport-Luebering shunt, and providing additional control over oxygen delivery to peripheral tissues [1,4]. The 2,3-BPG binds to hemoglobin receptor domains and results in proportionate decreases in hemoglobin oxygen affinity. Higher levels of BPG are generally found in situations with low oxygen availability including high altitude environments, environmental impact of repeated noxious gas exposure including smoking, or in chronic lung diseases such as COPD in addition to progressive greater oxygen demands of late pregnancy [1]. Because HbF has a higher affinity for BPG compared with HbA, this phenomenon contributes to its ability to unload oxygen in fetal or adult tissues more efficiently. Myoglobin lacks a 2,3-DPG binding domain and thus does not bind to 2,3-BPG like hemoglobin does [1,4]. Instead, myoglobin has a higher affinity for oxygen and acts as an oxygen reservoir in muscle tissues, allowing efficient oxygen transfer from hemoglobin in the blood to the muscles during periods of high demand and during virtually all conditions of SpO2 availability consistent with survival. Myoglobin is a monomer compared to hemoglobin which is made of four heme subunits, each capable of cooperatively binding a single oxygen. Myoglobin consists of non-polar amino acids at the core of the globulin peptide, where the single heme monomer is non-covalently bonded with the surrounding polypeptide of myoglobin, and lacks a 2,3-DPG binding domain, which enables it to bind oxygen with great affinity, demonstrating a hyperbolic saturation curve. Thus myoglobin has a substantially higher affinity for oxygen saturation than hemoglobin and lacks oxygen- cooperative binding and discharge of oxygen throughout a broad range of SpO2 availability. In addition, the presence of myoglobin in blood is a likely indication of muscle damage, where the majority of myoglobin occurs and may transiently appear following VOC related events [5,7].

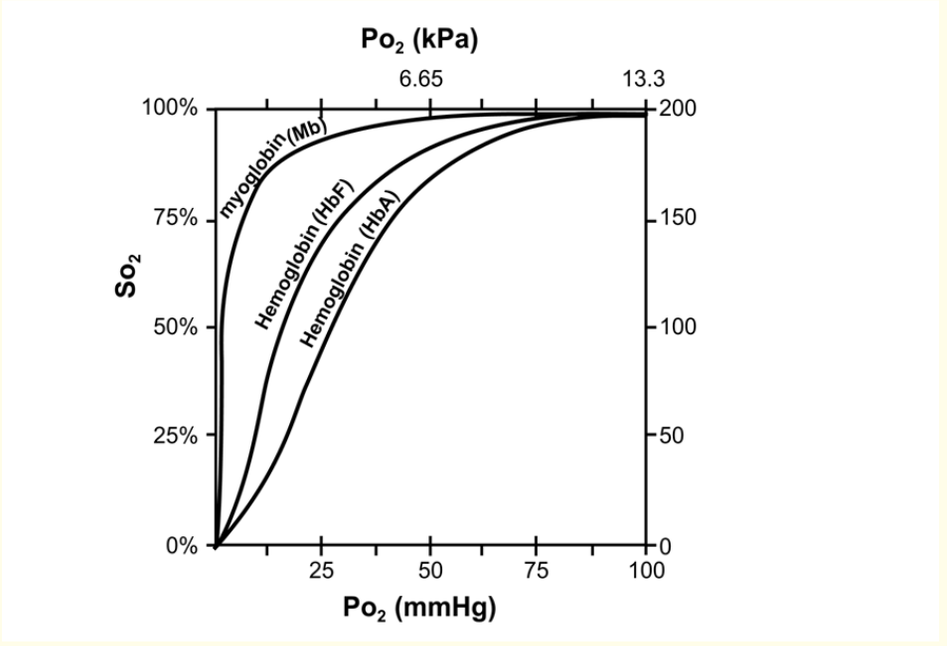

Figure 1: PO2 = partial pressure of oxygen in mm of Hg; SpO2 (SO2) is percent of hemoglobin saturation; k]Kp O2 = kilopascals; can be converted into kilopascals by dividing mm Hg by 7.5; Factors that can move the saturation curve for HbA and HbF to the left include an increase in pH, decrease in pCO2, decreases in 2,3-DPG, decreases in temperature, and an increase in the percent of HbF in blood (Haldane effect). The curve of myglobin is virtually unaffected by the changes that impact HbA and HbF since it lacks a 2,3-DPG binding domain. Pregnancy increases 2,3-DPG from the third month of gestation onward thereby slightly moving the curves to the right (Modified from references 1,8).

Relative Hypoxia in pregnancy

Hypoxia is a common and severe stress to an organism's homeostatic mechanisms, and hypoxia during gestation is associated with significantly increased incidence of maternal complications of preeclampsia. This condition can adversely impact the fetal development, facilitate excess ROS development, and subsequent risk for cardiovascular and metabolic diseases of both mother and child [3,14]. Multiple factors contribute to hypoxia and ROS during pregnancy, including both environmental, nutritional, and metabolic factors [4,5]. Hypoxia can increase the formation of reactive oxygen species (ROS), which can become detrimental to many cellular processes if left untreated. Preeclampsia, gestational diabetes, hypertension, and intrauterine fetal growth restriction (IUGR, FGR) are some of the most common pregnancy complications worldwide, affecting 5–10% of pregnancy outcomes [1-3,14]. Hypoxia is commonly due to hormonal and environmental effects on vascular function which restrict blood flow to the peripheral tissues including the umbilical circulation, restricting both delivery of oxygen, essential nutrients and energy to the developing fetus [11]. Thus, hypoxia is linked to intrauterine growth retardation (IUGR), defined clinically as a live neonatal weight of less than 5.5 pounds at birth. Efforts to improve peripheral circulation, including adequate blood pressure control and cessation of smoking when present also typically improve umbilical circulation, with corresponding improvements in fetoplacental oxygen and nutrient delivery, minimize hypoxia-mediated ROS generation and improve neonatal weights. It is now recognized that environmental altitude, smoking, and nutritional factors all contribute to fetal growth and development, impacting fetal substrate availability and metabolism, and to final neonatal weight and impact variable metabolic consequences depending on the stage of pregnancy in which the insults occur. High fat, caloric dense maternal diets typically result in a greater fetal mass and predispose both mother and their offspring with a greater lifetime predisposition of obesity, hypertension, diabetes and metabolic syndrome. Unacclimatized residing at higher altitudes can also result in decreased neonatal weights, secondary to the reduced pO2 in ambient air as the altitude increases [5,11]. It is now recognized that preeclampsia is thought to originate in the placenta vasculature, with an initial pre-onset during the early weeks of pregnancy that may become compromised by excess ROS generation [3,14]. Indeed, both preeclampsia and FGR/IUGR originate from the placenta due to uteroplacental dysfunction conferred by gestational hypoxia and nutrient availability [1,11,14]. Gestational hypoxia is associated with overproduction in reactive oxygen species (ROS) in the placenta, leading to oxidative stress which impact the spiral arteries where substrate transfer is mediated [5,14]. As mentioned above, preeclampsia and fetal growth restriction (FGR) are two most common pregnancy complications worldwide, affecting 5–10% of pregnancy, often with dire outcomes [14].

Resveratrol

Resveratrol occurs as a naturally occurring hormetic phytochemical in numerous wholesome foods and beverages and is readily available in supplement form, where it occurs as a glycophytochemical and in both cis- and trans- free forms [15,16]. Thus, it has likely been a part of the human diet since the beginning of time, since humans became omnivorous. By obtaining energy and nutrients including phytonutrients from both plant and animal matter, omnivores digest carbohydrates, protein, and lipids, into absorbable moieties, and metabolize the nutrients and energy obtained into useable nutrients to sustain life [4,5]. Non-animal sources of nutrients also provide variable proportions of dietary fibers, most of which undergo limited metabolism by colonic microbiota while providing physiologically important bulk to the luminal contents. Vegetable sources are rich sources of numerous antioxidant compounds including resveratrol, depicted in Figure 2 below. Once absorbed, antioxidants can quench reactive oxygen species (ROS) and free radicals, which if left unchecked can damage membranes and contribute to numerous pathophysiologic comorbidities including cardiovascular and other debilitating diseases [15-19]. In pregnancy, the prevalence of chronic inflammatory state can easily become increased, due to the gradual development of a state of oxygen deprivation especially during later states of fetal development when the energy requirements and oxygen demands of the fetus become increased and pulmonary capacity of the mom may become compromised due to the upward peritoneal volume displacement by the expanding uterus [3,20,21].

Hypoxia contributes to increased generation of ROS during gestation and may contribute to the onset and further development of preeclampsia [14]. The antioxidant mechanism of action of resveratrol occurs via several mechanisms, including donation of a hydrogen atom or a proton and an electron to an ROS, including superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($\cdot OH$), and singlet oxygen, thereby stabilizing the noxious species and decreasing ROS damage to tissues. On an epigenetic level, Resveratrol can activate the Nrf2 pathway, a key regulator of antioxidant response, in addition to influencing the expression of other antioxidant enzymes including superoxide dismutase (SOD) and catalase (CAT), the combined

impact is to further enhance the body's antioxidant defense system [22]. With respect to longevity, resveratrol also epigenetically activates the sirtuin compound Sirt1 associated with healthy aging, along with the direct antioxidant actions [23-25]. Beneficial metabolic actions include improving glucose metabolism, blood pressure control, and improved vascular circulation and substrate delivery of the umbilical blood supply, ultimately decreasing the potential of development of IUGR. While the hormetic actions of resveratrol have been demonstrated at higher concentrations *in vitro*, the limited solubility in plasma and tissues likely prevent the potentially deleterious effect in clinical studies [26-32]. The consideration of resveratrol in pregnancy is important because the compound readily crosses the placental barrier and can thus potentially impact metabolism and gestational outcome of both mother and child during pregnancy [3]. The chemical structure of both the *cis*- and *trans*- forms of resveratrol are depicted in Figure 2 below (REF).

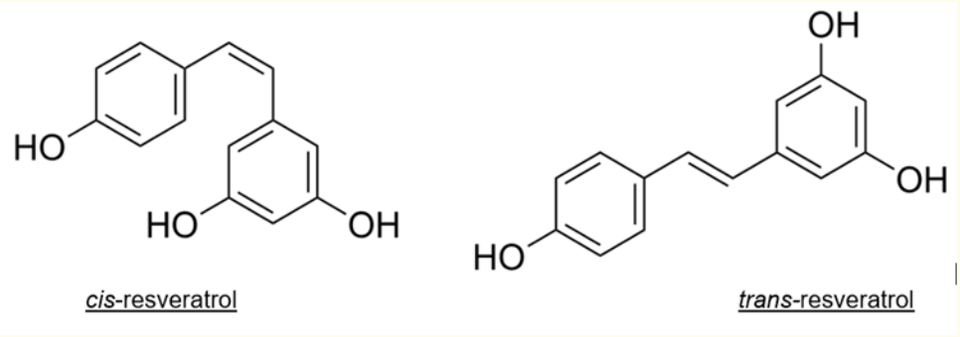

Figure 2: Chemical structures of cis- ((Z)-resveratrol, left structure) and trans-resveratrol ((E)-resveratrol, structure. Preferred IUPAC name is: 5-[(E)-2-(4-Hydroxyphenyl)ethen-1-yl]benzene-1,3-diol. Other common names include trans-resveratrol, cis-resveratrol, trans-3,5,4'-trihydroxystilbene; 3,4'5-Stilbenetriol; (E)-5-(p-Hyroxystyryl)resorcinol, and (E)-5-(4-hydroxystyryl)benzene-1,3-diol [5,6,10].

Discussion

The development of SCD occurs due to a single amino acid substitution (Val for Glu) in the β-subunit of hemoglobin A (HbA) to form SCD-hemoglobin (HbS), and which changes the β-peptide from a hydrophilic, negatively charged glutamic acid to a hydrophobic, neutral valine moiety [11,12]. While two gene-editing clinical protocols have recently been approved by the FDA for the treatment of the genetic disorders of SCD and β-thalassemia in non-pregnant adults, they remain cost prohibitive and not currently amenable to wise spread implementation [37]. The Casgevy and Lyfgenia protocols utilize CRISPR gene editing-based and vector technology to introduce normal beta-globin subunit within hemoglobin, caused by a specific mutation in the *HBB* gene, where a single amino acid substitution replaces glutamic acid with valine at position 6 of the beta-globin chain, with or without supplementation by additional Nrf2 enhancers [38]. Upon successful correction, the gene editing therapies can increase the hemopoietic production of HbF and normal HbA and decrease the production of HbS in human trials, producing similar but more long lasting resolution that RSV or HU. Both gene editing protocols have reported an approximate 90% effectiveness in clinical trials albeit with some as yet unresolved side effects in some subjects, and which could likely be improved with concurrent administration of the Nrf2 stimulator dimethyl fumarate to further improve antioxidant activity [38]. Thus, although available, at present they could not be widely implemented on a global basis due to cost and the individualization of patient selection. Widespread addressing the needs of SCD and SDA patients may be best achieved via an easy to administer, more cost-effective approach such as RSV, typically administered in an oral capsule form that can be mass produced and distributed in a pharmaceutical grade and potentially offers such an option. SCD represents a serious complication of normal pregnancy with few successful treatments, as the change in amino acid charge alters the protein's hydrophobic structure and function. When present, it can result in the abnormal polymerization to form deoxy-HbS and sickling, particularly during physiologic processes that incur high oxygen demand including later stages of gestation and partuition [12]. The disorder of SCD currently affects approximately 100,000 individuals in the USA, mostly African American or those bearing African-American heritage [32,33]. As a heritable

disorder, it has no readily available current curative therapeutic option, and reportedly affects 1 in 365 African-Americans born in the USA [32,33]. Hydroxyurea is currently the primary pharmaceutical used to treat SCD, where it is attributed to an induction and reactivation of the formation of fetal hemoglobin formation (HbF), a form of hemoglobin that does not undergo the sickling reaction and which can also more efficiently transport oxygen to needed tissues without undergoing the sickling reaction [8,9]. Both the HU and resveratrol agents primarily works in SCD by increasing fetal hemoglobin (HbF) production, improving red blood cell flexibility and decreasing the potential for erythrocyte aggregation. Both compounds accomplish this by inhibiting the enzyme called ribonucleotide reductase, which contributes to an essential role involved in DNA synthesis and epigenetic expression of hematopoiesis during cellular erythrocyte replication [8,12]. This inhibition increases stress on the bone marrow, prompting it to produce more fetal hemoglobin (HbF; Hb F,α2γ2) in response, and proportionately less HbA (Hb α2β2) and HbS. The HbF oxygen saturation curve falls to the left of the adult hemoglobin saturation curve and is equally proficient in transporting oxygen but more effective in discharging the oxygen to needed tissues. Thus, the efficacy of HU and resveratrol in the management of thalassemia and SCD is generally attributed to its limited ability to boost the levels of fetal hemoglobin (Hb F, α2γ2) in RBCs, and provide a partially protective mechanism to essentially bypass or minimize the sickle reaction which ultimately damages the blood vessels, and their progressive comorbidities associated with the SCD disorder. Resveratrol, as a normal healthful phytochemical of numerous commonly consumed fruits and vegetables, has likely been a constituent of the diet of humans for many decades, and with nominal patterns of consumption, is not known to pose a health hazard to mother or fetus during gestation [3,9,29,31]. The antioxidant functions have been reported to improve glucose tolerance, reduce the magnitude of insulin resistance, increase the expression of the antiaging epigenetic silent factor Sirt1, reduce the rate of telomere shortening, and promote longevity. In *in vitro* studies, resveratrol can induce hormetic effects, but adverse effects of higher dosages have not been observed in humans [31-36]. Thus, supplementation with RSV as a natural product already present in limited quantities in most diets [39], is proposed as a useful adjunct to HU in the clinical management of SCD including during woman's overall health and during pregnancy.

Conclusions

The application of natural products have long been used in the treatment of illness and disease, many of which formed the industrial inspiration to develop from pharmacognosy into active pharmaceuticals [39]. The incorporation of resveratrol during maintenance of women's health, including during pregnancy and certain thalassemia conditions are discussed. In addition, its use during SCD as an adjunct or therapeutic replacement for hydroxyurea is proposed. Resveratrol has likely always been a healthy phytochemical constituent of the human diet and is not known to adversely interfere with normal physiologic growth and development of the fetus, or to contribute to pathophysiologic comorbidities attributed to SCD in man and animals. In addition to stimulating the formation of sickle-resistant fetal hemoglobin (HbF) in pregnant and nonpregnant adults and which aids in oxygen delivery to myoglobin in peripheral tissues, resveratrol is also an active scavenger of free radicals, known to contribute to the etiology and manifestations of preeclampsia and gestational diabetes, common adverse conditions of human pregnancy. Because of its broader scope and mechanism of actions, it offers distinct advantages over hydroxyurea, often prescribed for hemoglobinopathy disorders. Moreover, the applications of resveratrol for addressing the chronic inflammation that contributes to the manifestations of cardiovascular disease and metabolic syndrome has long been proposed as an adjunct in decreasing the proliferation of pathophysiologic ROS that contribute to the progression of those disorders. Thus, in the present review, RSV may also be able to partially correct the effects linked to the globin chain imbalance in SCD patients, while at the same time facilitating oxygen transport to myoglobin in peripheral tissues due to a more favorable oxygen-delivering capacity to myoglobin than is observed from typical adult hemoglobin (HbA). Because the administration of hydroxyurea is not highly recommended during pregnancy due to uncertain potential effects on the offspring, resveratrol is proposed as an alternative healthy adjunct to promote the resurgence of fetal hemoglobin production, in addition to providing vital antioxidant functions which are associated with improvements in numerous metabolic, cardiovascular, and other benefits to health and longevity. Thus, consumption of resveratrol as a natural product, whether as a supplement or in com-

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