IJCIM
International Journal of Complementary and Internal Medicine

REVIEW ARTICLE

Effects of the Phytopolyphenol Resveratrol as a Therapeutic Adjunct in Sickle Cell Disease (SCD) and β-thalassemia Management

Orien L Tulp,[1,2,3,4] Syed A A Rizvi,[1,6] Uzoamaka Nwokorie,[1,5] George P Einstein[1,2]

[1]University of Science Arts and Technology, Montserrat, Colleges of Medicine and Graduate Studies
[2]The Einstein Medical Institute, North Palm Beach Florida
[3]East West College of Natural Medicine, Sarasota FL
[4]Universidad de Sevilla, Seville, Spain
[5]National Hospital, Abuja Nigeria
[6]Larkin Hospital, Miami FL USA

Corresponding Author: Orien L Tulp, Professor of Medicine and Graduate Studies, University of Science Arts and technology, Montserrat, British West Indies, PO Box 506, MSR1110; East West College of Natural Medicine, Sarasota, FL USA. 34234, and Universidad de Sevilla, Seville, Spain, 41004. E-mail: o.tulp@usat.edu, otulp@myewcnm.org

Received: July 03, 2025 **Published:** July 22, 2025

Citation: Tulp OL. Can trans-3'5'4-trihydroxystilbene (resveratrol) become an effective adjunct in the treatment of sickle cell disease? Int J Complement Intern Med. 2025;6(3):399–408. DOI: 10.58349/IJCIM.3.6.2025.00156

Abstract

Sickle Cell Disease (SCD) and β-thalassemia are among the most common forms of hemoglobinopathy and life-threatening genetic diseases worldwide, necessitating the need for more effective and cost-effective therapies to treat these disorders. SCD occurs due to a single amino acid substitution of Valine for Glutamic acid in the β-chain subunit to form the sickle cell (HbS) variant. Hydroxyurea (HU) is currently the only disease modifying drug approved for SCD, while advances in gene editing processes have also recently been introduced but their clinical use is not yet widely therapeutically available. HU is a ribonucleotide reductase inhibitor and fetal hemoglobin (Hb F; α2γ2) inducer that can reduce the clinical symptoms and frequency of hospitalizations for SCD, but it falls short of being a curative therapy and must be continued indefinitely in SCD patients. 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, α2γ2) in RBCs, and provide a partially protective mechanism for the sickle reaction which ultimately damages the blood vessels, thereby contributory to the major pathophysiologic clinical signs and symptoms and decreased lifespan associated with the SCD disorder. Thus, we propose that partial amelioration of SCD hemoglobin (HbS) with fetal hemoglobin via pharmacologic effects of trans-resveratrol (RSV), a naturally occurring phytochemical, may become a benefit to the patient since HbF is not susceptible to the disordered intracellular VO2-linked

hemoglobin (HbS) polymerization often referred to as the sickling reaction during HbS deoxygenation. Accordingly, RSV would thereby limit the subsequent vessel damage due to small vessel occlusion which occurs due to HbS and thus should be able to improve patient outcomes by reducing the magnitude of ROS damage in addition to diminishing the ratio of cells that are susceptible to sickling reactions vs. the sickle-protected fetal-hemoglobin containing cells. In addition, RSV may also provide beneficial impacts on the sickle cell anemia (SCA) by prolonging erytrocyte survival that typically accompanies the disorder. 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. Thus, in conclusion, RSV may be a useful and cost-effective phytochemical adjunct in the treatment of SCD and β-thalassemia, the two major heritable hemoglobinopathies of humans.

Keywords: resveratrol, hydroxyurea, sickle cell disease, antioxidants, sirtuins, Nrf2 Activation

Introduction

The naturally occurring dietary polyphenol resveratrol (cis- or trans-3'5'4-trihydroxystilbene; RSV) depicted in Figure 1 below has been postulated to induce fetal hemoglobin production via a biochemical mechanism similar to that induced by hydroxyurea (HU) in addition to contributing antioxidant actions to reduce the magnitude of inflammatory reactive oxygen species (ROS) generation. The polyphenol stilbenoid resveratrol (3,4',5 trihydoxystilbene) is a naturally occurring compound in numerous edible foods of plant origin. Resveratrol was first identified over 85 years ago by Takaoka (1939) from Veratrum grandiflorum and has now been isolated from over 70 additional plant and yeast species.[1,2] Resveratrol has been found to be highly concentrated in the skin of red grapes and has been proposed to contribute to the 'French or Mediterranean paradox' where robust consumption of red wine and grape juice have been associated with a lesser prevalence of heart disease.[3,4] Lesser concentrations of resveratrol have been found in numerous other natural sources of nutritious foodstuffs including white grapes, blueberries, pomegranates, grapefruits, tea, nuts, and numerous edible berries. Resveratrol and other antioxidants have also been isolated from dark chocolate in varying concentrations, also suggestive of healthful benefits for aa variety of medical conditions.[1] In nature, resveratrol typically exists as cis and trans isomers (Figure 1), but the trans isomer is the predominant and most widely studied form.[5,6] In clinical studies the trans- isomer has been reported to exert the most potent therapeutic benefits. This phenomena is likely at least in part to the lower steric hindrance induced on the compound from the chemical nature of the functional groups of the side chain structures.[5–8] The trans form of RSV can be obtained via recombinant chemical reconfigurations from the extracts of Saccharomyces cerevisiae yeast, and is commonly used in the food and cosmetic industries both as a food supplement or as a cosmetic ingredient.[9,10] Isomerization back to the cis from the trans form can occur when the RSV is inadvertently exposed to excess heat, light, or ultraviolet radiation during manufacture, processing or inappropriate storage thereby decreasing its therapeutic efficacy.[8–11] The purpose of this paper is to review the biochemical, pharmacologic and significant toxicologic aspects of trans-resveratrol administration as an adjunct therapeutic medicinal in the treatment of SCD and hemoglobinopathies.

Proposed biochemical mechanism of action in SCD

The epigenetic progression of SCD in adolescents and adults occurs due to an amino acid substitution (Val for Glu) in the β-subunit of hemoglobin A (HbA). This epigenetic amino acid substitution results in the pathophysiologic formation of SCD-hemoglobin (HbS), and which functionally converts the β-peptide from a hydrophilic, negatively charged glutamic acid moiety to a hydrophobic, valine carrying a neutral charge.[11,12] Thus, the change in amino acid charge alters the protein's hydrophobic structure and function and can result in the abnormal polymerization to form deoxy-HbS and sickling, particularly during physiologic processes that incur high oxygen demand.[12] The disorder currently affects approximately 100,000 individuals in the USA, mostly African American or bearing African-American heritage. As a genetically inherited disorder, it has minimal curative therapeutic option readily available for global applications. The disorder has been reported to affects 1 in 365 African-Americans born in the USA.[14,15] Hydroxyurea is currently the primary pharmaceutical agent used to treat SCD worldwide. Its beneficial actions are attributed to an induction and reactivation of the formation of fetal hemoglobin formation (HbF) in adults. HbF is a form of hemoglobin that normally only occurs only during human gestation, and that does not undergo the sickling reaction, and which permits the HbF to efficiently transport oxygen to needed tissues during fetal growth and development.[16] The agent primarily works in adult SCD by also increasing fetal hemoglobin (HbF) production. This effect improves red blood cell flexibility and decreases the potential for erythrocyte aggregation and microvascular occlusion. It does this by suppressing an enzyme called ribonucleotide reductase, which contributes to

an essential role involved in DNA synthesis and epigenetic expression of hematopoiesis during cellular erythrocyte replication.[12,13] This resveratrol induced enzymatic inhibition impacts greater stress on the bone marrow, resulting in prompting it to produce more fetal hemoglobin (HbF; Hb F,α2γ2) and proportionately replace HbA (Hb α2β2) and HbS production. In addition, SIRT1 expression protects against cellular apoptosis by promoting cellular autophagy via actions on the *Bcl-2* gene, a member of the Bcl-2 gene family, important in intracellular regulation of apoptosis, functionally critical for cell survival mechanisms.[43] Thus, as an apoptotic-related gene, the *Bcl-2* gene family plays an important role in regulating apoptosis and cell survival. Bcl-2 proteins mainly affix to the outer membrane of the mitochondria, where they exert their anti-apoptotic effects by inhibiting the release of cytochrome C and hydrolytic caspases into the cytosol. The contrary effect of this is exhibited by the pro-apoptotic protein Bax, and modulating the ratio of the apoptotic regulatory factors.[44]

Because the HbF oxygen saturation curve falls leftward of the adult hemoglobin saturation curve, it demonstrates an equal or greater proficiency to transport oxygen to fetal tissues during gestation and early postnatal growth.[12,13] Both HbF and HbA resist sickling and thus decrease the risk of sickle cell aggregates on vascular occlusion events and subsequent anoxic-linked pathophysiology, erythrocyte lysis, and sickle cell anemia (SCA). Additionally, hydroxyurea may affect red blood cell adhesion factors and reduce inflammation, further contributing to its overall benefits.[15,16] Because resveratrol functions in an analogous manner to hydroxyurea in the red bone marrow, it results in producing both DNA stress-related HbF formation in red blood cells in both *in vitro* and *in vivo* applications. In addition, HbF adds beneficial antioxidant functions capable of decreasing inflammatory ROS activity in peripheral tissues including the cardiovascular epithelium and other tissues during aerobic and anaerobic substrate metabolism. Resveratrol results in only minimal tissue concentrations following typical clinical dosages commonly administered, but the polyphenol still demonstrates a broad range of therapeutic efficacy with minimal intracellular concentrations, in addition to a virtual absence of evidence of potential toxicity.[17,18]

Overview of preclinical resveratrol studies

The human erythroleukemic K562 cell line has been used in *in vitro* preclinical studies, and have suggested that RSV can induce fetal hemoglobin production in a more robust manner than HU.[19] Dose-dependent erythroid differentiation and hemoglobin production can be induced in the human erythroleukemic K562 cell line by both resveratrol and hydroxyurea, where RSV at 50 μmol/L induced a higher hemoglobin production than hydroxyurea at 500 μmol/L.[19]

However, double blind clinical studies designed to confirm the therapeutic efficacy and effectiveness of RSV are limited and results somewhat conflicting. The differences are likely due to differential experimental conditions, different dosages employed, genetic variations, and metabolic differences in the subject populations selected, and differences in the duration of treatments among other factors including potential dose related hormetic effects of RSV.[19–22] In a recent case study, the authors sought to evaluate the clinical efficacy and safety of RSV in managing SCD compared to HU.[6] Unfortunately, the study remains incomplete due to interruption by the recent pandemic with only one subject completing the ESV trial. However, in that single subject, administered at a dosage of 1000 mg/day, p.o., prevented a recurrence of symptoms, hospitalizations or blood transfusions for over a year. In the interim, a systematic literature review with pre-defined eligibility criteria including RSV, HbF and clinical outcomes was conducted in peer-reviewed, published full-text articles investigating RSV in the management of SCD. To be eligible for inclusion, studies were required to report explicitly, including participants diagnosed with β-thalassemia or SCD anemia or cultured cells with the SCD or thalassemia disease and where HU was included in a control group. The analysis included thalassemia, RSV dosage, duration of treatment, and outcome, including evidence of fetal hemoglobin induction and antioxidant ROS activity. Additionally, the referenced pilot study of RSV in the management of adults with SCD who received treatment at National Hospital Abuja, Nigeria, was attempted but interrupted prematurely due to the COVID 19 pandemic.[6] In that case study, a single 23-yearold female SCD patient who completed the study and who had been taking trans-resveratrol [1000mg daily p.o.] for more than 6 years was reported. Outcome variables evaluated included the number of hospitalization episodes for pain crisis, the clinical need for blood transfusion due to anemia, RBC indices, or other factors, and included possible side effects of the resveratrol. During the taking of RSV, no hospitalizations or acute episodes were reported, and hematologic indicies also remained within normal ranges. The proportion of HbF vs HbA was not reported, and no clinical evidence of RSV toxicology was noted. Thus, the early results of this metanalysis review suggested that RSV may be as clinically effective as HU in inducing production of fetal hemoglobin in adult SCD patients and reducing hospital treatment days post RSV treatment.

Currently, there are 4 four primary treatment and curative therapies that have shown great potential and have currently been introduced to prevent and treat acute and chronic complications in SCD. These include hydroxyurea (HU) and blood transfusions, in addition to life-style modifications to minimize situations of oxidative stress are the most commonly well-established disease-modifying therapies in current use to prevent and treat complications associated with SCD.[13] Other innovative but lesser used therapies include stem cell transplantation or the allogeneic hematopoietic stem cell transplant (HSCT) procedure. Also, recently developed CRISPER gene editing repair technology has been introduced, in attempt to correct the globin dysfunction of HbS. Both gene editing approaches have recently been granted initial approval by the FDA in the United States.[41,42] Thus, the individualized, investigational gene therapy methods are the only known potential curative therapies that currently exist to resolve the pathophysiologic symptoms of SCD. To date however, reports of effective CRISPR attempts at gene therapy are limited but gaining traction with satisfactory early results. The results of this study indicate that RSV is an effective inducer of fetal hemoglobin production in adults and children and shows promise as a cost-effective and useful adjunct for the treatment of hemoglobinopathies including SCD and thalassemia. Its ready availability and ease of oral administration may offer significant benefits to global populations where thalassemias including SCD are endemic.[6] Moreover, at nominal dosages of less than 1,000 mg/day (~ 20 mg/kg BW) in adults, reported adverse events are exceedingly rare.[23]

Overview of Bioavailability, Dose Responses and Molecular Pharmacokinetics of Resveratrol

The *in vivo* pharmacokinetics of resveratrol typically have been demonstrated to be relatively poor in man and animals at least in part due to its limited water solubility as an organic compound.[24] One reason for the pharmacokinetics in humans may occur because although RSV is highly absorbed when administered orally (~70%), it's systemic uptake and bioavailability in peripheral tissues is limited (~0.5% of the administered dose).[28] Once RSV is absorbed and enters the circulation, it readily binds to plasma proteins where it may be transported in lipoprotein lipid fractions in circulation, which also contribute to an extension of its biological half-life as only the free fraction undergoes cellular absorption.[23–26] Once absorbed, RSV can undergo first pass, Phase II glucuronidation and sulfate conjugation, increasing plasma solubility and renal clearance. Residual luminal RSV is readily metabolized by colonic microbiota, that can also generate additional potentially pharmacologically active moieties.[25,26] Among those moieties, the glucose-conjugate of resveratrol piceid is a also found in plants and fruits, and also undergoes luminal and tissue uptake with similar pharmaceutic effects to that of molecular parent resveratrol.[27] In addition, RSV also demonstrates biphasic hormetic dose-dependent effects *in vitro* and has been postulated to exert similar hormetic effects *in vivo*. RSV is stable at acidic pHs but as noted above, becomes less stable at alkaline pHs. Thus, gastric acidifying agents including ascorbic acid may help to preserve potential biological activity via enhancing its water solubility. In contrast, while antacids and other alkalizing agents including gastric H2 inhibitor agents may alter the charge and structural configuration of the polyphenol moiety thereby decreasing its potential luminal bioavailability in the gastrointestinal environment. Because the compound is subject to light and thermal degradation, it is best stored and administered in light protected, cool or room temperature environments to best preserve its optimal biological activity and longevity during manufacture and preclinical storage.[11,18,21]

Multiple inflammatory reactive oxygen species (ROS) are often a significant contributing factor to the development of a sickle cell VOC event requiring hospitalization and pain control therapy. Thus, factors that can reduce the magnitude of inflammation are useful adjuncts in reducing the frequency and magnitude of such episodes. RSV behaves physiologically as an hormetic antioxidant against cellular ROS formation at low tissue concentrations. Accordingly, anti-ROS therapies may potentially protect tissues from excessive ROS mediated oxidative stress and oxidation linked DNA damage, and improve survival.[1,2] In contrast, at high *in vitro* concentrations, resveratrol can act as a pro-oxidant thereby promoting DNA damage while increasing the potential magnitude oxidative stress and potentially become additive to the development of harmful, reactive oxygen species (ROS). At the greater clinical dosages surveyed however, the evidence reported in *in vitro* studies remains unconfirmed. Low and high RSV concentrations *in vivo* however may contribute to beneficial effects as a chemoprotective nature and may be beneficial in the treatment of cancer via direct cytotoxic effects. Because RSV has been reported to produce biphasic, hormetic dose-related effects, it may contribute

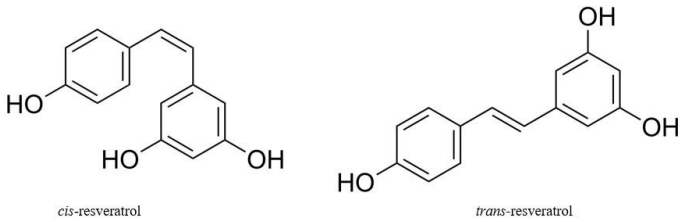

Figure 1. Chemical structures of *cis*- ((*Z*)-resveratrol, left structure) and *trans*-resveratrol ((*E*)-resveratrol, structure. Preferred IUPAC name is: 5-[(E)-2-(4-Hydroxyphenyl)ethen-1-yl]benzene-1,3-diol. Other common names include trans-resveratrol, cis-resveratrol, trans-3,5,4'- truhydroxystilbene;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

to cardioprotective antioxidant effects at lower dosages, and prooxidant effects at higher dosages typically beyond 1000 mg/day in adult humans. RSV is stable at acidic pHs but becomes less stable at alkaline pHs. Thus, gastric acidifying agents including ascorbic acid may help to preserve its biological activity during luminal absorption, while alkalizing agents including antacids and gastric H2 inhibitor agents may decrease its bioavailability.[11,18,21] In addition, Nrf2 activators including dimethyl fumarate (DMF), has shown promise in reducing inflammation and vaso-occlusion in SCD in animal studies, and could potentially complement the effects of therapeutic measures by providing ancillary chemoprotection against adverse oxidative stress and secondary inflammatory processes.[41]

Resveratrol, like many organic moieties and compinds, is readily lipid soluble. Thus, because of its lipid solubility, tissue uptake may be enhanced in the presence of micronized, lipid, or liposome-based forms of RSV.[27–30] The liver metabolizes RSV via phase II enzymes, thereby producing more water soluble sulfated and glucoronate forms. The more water soluble conjugates may be readily excreted by the kidneys. At nominal dosages, RSV toxicity is uncommon, while greater doses of up to 5 grams/day have been reported to result in reversible gastrointestinal discomfort upon dosage reduction. In *in vitro* studies, toxicity has also been demonstrated to DNA and other cytotoxic effects noted, but corresponding effects have not been noted in clinical observations.[22,23] Indeed, RSV has been found to clinically be useful to help to control adverse ROS related symptoms in pre-eclampsia and eclampsia during pregnancy.[31] The agent impacts the cell cycle differentially by suppressing the p-53 and S-phase activity of the cell cycle. As such, it thereby modulates the progress of cellular replication and apoptosis which at least in theory, can reduce the rate of new tumor growth while potentially increasing its direct impact on tumor cell cytotoxicity. The biochemical actions are consistent with ameliorative, anti-ROS actions and processes of electron scavenging and improving mitochondrial respiration, analogous to that which occurs with fullerene compounds.[32,33] While no studies appear to have clearly demonstrated to promote an extension of longevity, RSV administration has been shown to increase generation of Sirt1 in a manner analogous to that which occurs during caloric restriction, and the contributes to the epigenetic modulation aspects of thyroid hormone activation and carbohydrate metabolism.[34,35] Sirt1 is a silent cellular-based biological transfer factor that has been reported to function as an antiaging factor that may impact secondary effects on cellular metabolism and respiration, and is associated with longevity during aging in man and animals.[35,36] Unabsorbed RSV can enter the colon and undergo additional metabolism by colonic microbiota to multiple compounds, some of which may also impart physiological activity, and which can potentially modulate the presence of microbial balance and colonic health.[25,26]

The RSV has long been proposed as a useful cardioprotective agent, although supportive clinical studies have yielded variable results likely due to multiple factors including diet, environmental conditions, comorbidities, and heritable elements that also impact healthy aging and longevity.[37–39] The antioxidant effects on lipid metabolism and oxidation have been proposed to reduce the rate of progression of atherosclerotic development in cardiovascular tissues, while in larger doses, RSV can induce prooxidant responses in the same tissues, thus theoretically potentially accelerating the progression of cardiovascular disorders at the higher dosages. Application of RSV in larger daily dosages up to ~ 1000 mg/day has demonstrated beneficial effects in patients suffering

with sickle cell disease (SCD).[6] In SCD, RSV suppresses the pathophysiologic polymerization of HbS heme proteins. In normal adults, approximately 97-99% occurs as HbA (α2β2) and the remaining 1-3 % as HbA2 (α2δ2), thus the addition of HbF decreases the potential for sickle cell formation during painful episodes of hypoxia and oxidative stress.

In this context, RSV has been proposed as a useful adjunct in the clinical treatment and management of SCD, where it would be predicted to reduce the incidence of acute SCD episodes, microvascular damage, need for blood transfusions, intensity and duration pain medications, and overall frequency of hospitalizations.

The presence of HbF during fetal life protects fetal tissues from the sickle reaction. During fetal life, the oxygen saturation curve falls leftward of HbA, thereby facilitating an enhancement of oxygen delivery to the fetus, ensuring fetal oxygen demands can be met. .Thus, HbF while sparing the fetus from the sickle response that is unique to hemoglobin S (HbS). In addition, RSV and HU both stimulate increased recruitment of fetal hemoglobin formation in the maternal compartment (HbF: α2γ2), HbF is normally only present during gestation and occurs in progressively decreasing amounts of HbF α2γ2 as erythrocytes age and are gradually replenished with HbA containing erythrocytes during the first 4 months of life. As the proportion of HbF to HbA or HbS erythrocytes increases in the adult or maternal compartment, it results in gradually moving the oxygen saturation curve further to the left in a manner similar to that which occurs during gestation, thereby improving oxygen delivery to peripheral tissues while exhibiting dose-related protection from the sickling process common to adult hemoglobin Hb A (α2β2) and HbS during physiologic episodes of greater oxygen demand.[40]

Discussion

Because SCD is an heritable disorder, pharmacologic remedies fail to generate fully curative effects. Recently, two epigenetic, gene-editing clinical protocols have been approved by the FDA following reports of clinical success for the treatment of the genetic disorders of SCD and β-thalassemia. Casgevy and Lyfgenia protocols utilize CRISPR gene editing-based and vector technology to introduce biologically normal β-globulin peptides, and to improve the hemopoietic production of HbF while decreasing the production of HbS. In the initial controlled human trials, both protocols have reported an approximate 90% or greater effectiveness in the clinical trials, albeit with some as yet unresolved side effects in a limited number of subjects, all of whom had confirmed SCD well into adulthood.[42] Thus, although technically available at present, formidable individual costs and gene-editing availability resources, the gene editing process could not yet be widely implemented on a global basis due to cost and the individualization of patient selection processes cited.[42] Wide spread addressing the needs of SCD patients may be best achieved via an easy to administer, more cost effective approach. RSV is typically administered as an oral capsule formulation, and can be mass-produced and distributed in a high-purity pharmaceutical grade. This oral encapsulation of RSV potentially offers such an option for broad distribution with cost effective monitoring. The effects of RSV on contributing to an amelioration of the frequency of painful symptoms of SCD likely occur to its ability to induce a reintroduction of fetal hemoglobin (HbF), in combination with anti-oxidant actions to decrease the magnitude of inflammatory ROS symptoms. In addition, the increase in HbF physiologically shifts the hemoglobin oxygen saturation leftward, in closer proximity to tissue myoglobin, and thus RSV contributes to a facilitation of more efficient oxygen delivery to the peripheral tissues, both during and independent of gestational effects. As the oxygen hemoglobin saturation curve moves leftward, it thus spares the oxidative impact of SCD hemoglobin (HbS) and subsequent polymerization effects of deoxyHbS during episodes of higher peripheral oxygen demand in peripheral tissues, since the oxygen saturation curve for HbS falls to the right of HbF, more distant from that of myoglobin.

RSV occurs in numerous natural products including wine, berries and other delectable, edible foodstuffs, thus like other phytonutrients and phytochemicals, it has likely always formed part of the human diet albeit in more limited quantities when consumed in typical wholesome meals. The toxicity profile of RSV at nominal clinical dosages commonly administered has not been reported. While dosages of 5 grams/day or more likely exceed gastrointestinal luminal uptake capacity for RSV, such large dosages have been reported to induce easily reversible gastrointestinal discomfort upon dose reduction or discontinuation. The adverse symptoms are likely secondary to osmotic or colonic microbiota actions that may generate excess acid or gas formation. In several *in vitro* studies RSV was shown to generate hormetic effects, where it is a beneficial antioxidant at lower dosage concentrations. Only in *in vitro* studies, RSV has been shown to exhibits prooxidant actions at higher concentrations. Tissue accumulations *in vivo* are limited however, seldom exceeding 0.5% of the ingested dose. Free plasma RSV readily undergoes hepatic Phase

II conjugation reactions to form sulfate and glucuronide conjugates, thereby increasing the plasma solubility and efficiency of renal clearance while decreasing the risk of adverse reactions. Moreover, luminal colonic microbiota may generate additional physiologically active metabolites of piceid and RSV that may further augment the antioxidant actions of the phytochemical.

The use of hydroxyurea remains the standard pharmaceutical approach to ameliorating the symptoms of SCD and appears to function in a biochemical manner similar to RSV, and resulting in clinical outcomes that are remarkably similar in both RSV and HU. RSV is a common phytochemical already present in variable amounts in wholesome fresh foods and commonly consumed worldwide since the beginnings of human existence. However, to ensure adequacy and constancy in natural sources of pieceid and RSV, a more concentrated form of RSV is highly desirable, and would facilitate better dietary control in addition to more predictable clinical outcomes. Since SCD is a heritable disorder, with no currently known curative therapy, the more practical approach is to treat it symptomatically to minimize or prevent episodic crises, likely improving the lifespan and quality of life of those individuals impacted by the disorder. The incidence of SCD and sickle cell anemia (SCA) that often results from the primary disorder is a global healthcare issue, and impacts a significant burden on the health care resources of many counties. While cost effective prevention of recurrence of SCD crises is preferable to hospitalizations and to the progression of SCD-related comorbidities, the local economic burden may be formidable for many individuals and their community health care resources. It is proposed that these benefits can likely be achieved with more widespread application and incorporation of maintenance RSV Phyto therapeutics in the global management of this disorder and its devastating comorbidities.

Summary

The ease of administration of RSV supports cost effective and clinically improved outcomes in patients with the heritable hematologic disorders of sickle cell disease (SCD) and the commonly associated comorbidities including sickle cell anemia (SCA) linked to the genetic disorder. As such, RSV offers economic and therapeutic advantages over other pharmacotherapeutic or gene-editing solutions as options for the treatment of SCD and its comorbidities. The phytochemical is widely distributed in numerous foods including grapes, berries and other desirable edibles and their juices, and thus has always likely been an obligatory and healthful component of the human diet. Luminal absorption is enhanced by the normal acidic properties of the gastric environment throughout much of the life cycle, diminishing only in later stages of aging. The effect of the gastric acidity due to HCl production would likely preserve the redox state and isomeric trans-configuration of the phytochemical. In contrast, alkaline conditions induced by gastric antacids, H2 blockers, or functions of aging may contribute to degradation including conversion to the less active cis-stereo configuration of the RSV moiety. The trans-configuration exerts the greatest pharmacological activity, and despite the limited tissue concentrations attained during the hours immediately following oral administration, produces significant beneficial effects. Pieceid, a naturally occurring glucose conjugate of RSV also demonstrates equally effective phyto-therapeutic effects. In addition, several luminal metabolites of RSV have also demonstrated varying levels of effectiveness in generating HbF and are likely additive to the overall clinical effectiveness of RSV administration following colonic microbiota actions, and may be contributory to the primary RSV effects, especially when supraphysiologic doses are administered.[7,8]

The proposed mechanism of action of RSV is presumed to be linked to its antioxidant activity, in addition to its ability to induce renewed biosynthesis of fetal hemoglobin (HbF), with contributes its favored oxygen saturation curve to the left of that of adult hemoglobin (HbA) or sickle cell hemoglobin (HbS). Because HbF diminishes the potential for HbS-mediated polymerization, erythrocyte aggregation and small vessel occlusion become decreased. The ease of administration of RSV makes it an attractive and cost-effective substitute for hydroxyurea (HU), currently the only approved pharmaceutical agent to treat the condition, which has few other available therapeutic options. If left untreated, SCD typically results in a 20% decrease in projected longevity of affected individuals, and in a significant long term strain on available community health care resources in many localities. The disorder is prevalent among individuals of African, Middle Eastern or Asian descent, who make up the vast majority of cases in the USA and abroad. Toxicity od RSV is virtually nil at moderate dosages that induce favorable biological responses, due to its rapid Phase-II conjugation and renal clearance within a few hours of administration.

In contrast when administered at extreme dosages, transient reversible gastrointestinal discomfort is the primary side effect noted. The colonic microbiota also contributes an ancillary role in RSV Phyto therapeutics, as some of the intestinally generated metabolites also appear to augment the primary RSV responses. Thus, RSV may be a useful and cost-effective phytochemical adjunct in the treatment of SCD and β-thalassemia, the two major heritable hemoglobinopathies.

Acknowledgement

The author thanks the University of Science Arts and Technology for the resources to prepare this manuscript, and the animal care staff for assistance with animal husbandry and experimental protocols.

Disclaimer (Artificial Intelligence)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-toimage generators have been used during the writing or editing of this manuscript.

Consent

It is not applicable.

Ethical Approval

The study was approved by the Institutional Animal Care and Use Committee of USAT.

Competing Interests

Author has declared that no competing interests exist.

Disclosures

The authors have no disclosures.

References

1. Takaoka M. Resveratrol, a new phenolic compound, from Veratrum grandiflorum. *J Chem Soc Jpn.* 1939;60:1090–1100.
2. Detampel P, Beck M, Krahenbuhl S, et al. Drug interaction potential of resveratrol. *Drug Metab Rev.* 2012;44(3):253–265.
3. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet*. 1992;339(8808):1523–1526.
4. Weiskirchen S, Weiskirchen R. Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy? *Adv Nutr Int Rev J.* 2016;7(4):706–718.
5. Camont L, Cottart CH, Rhayem Y, et al. Simple spectrophotometric assessment of the trans-/cis-resveratrol ratio in aqueous solutions. *Analytica Chimica Acta*. 634(1):121–128.
6. Uzoamaka Nwokorie, George P Einstein, Orien L Tulp. Use of trans3'5'4-trihydroxystilbene (Resveratrol) as an adjunct in the treatment of Sickle Cell Disease. *FASEB Journal.* 2021;35(S1).
7. Cardile V, Chillemi R, Lombardo L, et al. Antiproliferative activity of methylated analogues of E- and Z-resveratrol. *Z Nat C J Biosci.* 2007;62:189–195.
8. Nawaz W, Zhou Z, Deng S, et al. Therapeutic Versatility of Resveratrol Derivatives. *Nutrients.* 2017;9:1188.
9. Li M, Kildegaard KR, Chen Y, et al. De novo production of resveratrol from glucose or ethanol by engineered Saccharomyces cerevisiae. *Metab Eng.* 2015;32:1–11.
10. Chen X, He H, Wang G, et al. Stereospecific determination of cis- and trans-resveratrol in rat plasma by HPLC: application to pharmacokinetic studies. *Biomed. Chromatogr.* 2007;21(3):257–265.
11. Colica C, Milanović M, Milić N, et al. A Systematic Review on Natural Antioxidant Properties of Resveratrol. *Nat Prod Commun.* 2018;13.
12. Devlin TM. Textbook of Biochemistry with clinical correlations, 7th edn. ISBN: 978-0-470-28173-4. 2010.
13. Localzo J, Harrison TR. Harrison's Principles of Internal Medicine. 21st edn. (IBSN-10.1264268505: IBSN 13-978-1264268504. Publisher: McGraw Hill. NY. 2022.
14. Kayle M, Blewer AL Pan W, et al. Morbidity and Mortality Weekly Report (MMWR): Birth Prevalence of Sickle Cell Disease and CountyLevel Social Vulnerability — Sickle Cell Data Collection Program, 11 States, 2016–2020. 2024;73(12);248–254.
15. Agrawal RK, Patel RK, Shah V, et al. Hydroxyurea in Sickle Cell Disease: Drug Review. *Indian J* Hematol *Blood Transfus*. 2013;30(2):91–96.
16. Bo S, Ciccone G, Castiglione A, et al. Anti-inflammatory and antioxidant effects of resveratrol in healthy smokers a randomized, double-blind, placebo-controlled, cross-over trial. *Curr Med Chem.* 2013;20:1323– 1331.
17. Pannu N, Bhatnagar A. Resveratrol: From enhanced biosynthesis and bioavailability to multitargeting chronic diseases. *Biomed Pharm.* 2019;109:2237–2251.
18. Rodrigue CM, Arous N, Bachir D, et al. Resveratrol, a natural dietary phytoalexin, possesses similar properties to hydroxyurea towards erythroid differentiation. *Br J Haematol*. 2001;113(2):500–507.
19. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: The in vivo evidence. *Nat Rev Drug Discov.* 2006;5:493–506.
20. Cottart CH, Nivet-Antoine V, Laguillier-Morizot C, et al. Resveratrol bioavailability and toxicity in humans. *Mol Nutr Food Res.* 2010;54:7–16.
21. Salehi B, Mishra AP, Nigam M, et al. Resveratrol: A Double-Edged Sword in Health Benefits. *Biomedicines.* 2018;6(3):91.
22. Shaito A, Posafino AM, Younes N, et al. Potential Adverse Effects of Resveratrol: A Literature Review. *Int J Mol Sci*. 2020;21(6):2084.
23. Walle T, Hsieh F, Delegge MH, et al. High Absorption but Very Low Bioavailability of Oral Resveratrol in Humans. *Drug Metab Dispos*. 2004;32(12):1377–1382.
24. Zhang B, Xu Y, Lv H, et al. Intestinal pharmacokinetics of resveratrol and regulatory effects of resveratrol metabolites on gut barrier and gut microbiota. *Food Chemistry*. 2021;357;129532.
25. Springer M, Moco S. Resveratrol and Its Human Metabolites—Effects on Metabolic Health and Obesity. *Nutrients*. 2019;11;11(1):143.
26. Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv Drug Deliv Rev.* 2002;54(Suppl. 1):S131–155.
27. Intagliata S, Modica MN, Santagati LM, et al. Strategies to Improve Resveratrol Systemic and Topical Bioavailability: An Update. *Antioxid (Basel)* 2019;8(8):244.
28. Wan S, Zhang L, Quan Y, et al. Resveratrol-loaded PLGA nanoparticles: Enhanced stability, solubility and bioactivity of resveratrol for nonalcoholic fatty liver disease therapy. *R Soc Open Sci.* 2018;5(11):181457.
29. Howells LM, Berry DP, Elliott PJ, et al. Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases--safety, pharmacokinetics, and pharmacodynamics. *Cancer Prev Res.* 2011;4(9):1419–1425.
30. Ramli I, Posadino AM, Giordo R, et al. Effect of Resveratrol on Pregnancy, Prenatal Complications and Pregnancy-Associated Structure Alterations. *Antioxidants (Basel).* 2023;;12(2):341.

31. Mizuguchi Y, Hatakeyama H, Sueoka K, et al. Low dose resveratrol ameliorates mitochondrial respiratory dysfunction and enhances cellular reprogramming. *Mitochondrion.* 2017;34:43–48.
32. Bourassa DJ, Tulp OL, Einstein GP. Electron Scavenging not Free Radical Scavenging by Fullereen Materials Protects Against Mitochondrial Oxidative Stress in Complex Organisms. *ECPharmacology and Toxicology*. 2020;8(6)::61–67.
33. Longo VD, Kennedy BK. Sirtuins in aging and age-related disease. *Cell*. 2006;126(2):257–268.
34. Tulp, OL. Effect of aging and obesity on parameters of insulin, T4/T3 ratios, metabolic rates, sirtuins and longevity in congenic LA/Ntul//-cp rats. *Suntext review of medical and clinical research*. 2024;5(4):212:1–9.
35. Cote CD. Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. *Nat Med.* 2015;21(5):498–505.
36. Wong RH, Nealon RS, Scholey A, et al. Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus. *Nutr Metab Cardiovasc Dis.* 2016;26(5):393–399.
37. Galiniak S, Aebisher D, Bartusik-Aebisher D. Health benefits of resveratrol administration. *Acta Biochim Pol.* 2019;66(1):13–21.
38. Berman AY, Motechin RA, Wiesenfeld MY, et al. The therapeutic potential of resveratrol: a review of clinical trials. *Npj Precis Oncol.* 2017;1:35.
39. Tulp OL, Rizvi AA, Einstein GP. *Low dose biophotonic treatment enhances oxygen saturation and hematologic parameters*. Ch 11 in: Achievements and Challenges of Medicine and Medical Science. IBSN 978-93-48388-45-2. 2024.
40. Manai F, Amadio M. Dimethyl Fumarate Triggers the Antioxidant Defense System in Human Retinal Endothelial Cells through Nrf2 Activation. *Antioxidants (Basel).* 2022;11(10):1924.
41. FDA Newsroom. *FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease*. 2023.
42. Ren Q, Hu Z, Jiang Y, et al. SIRT1 Protects Against Apoptosis by Promoting Autophagy in the Oxygen Glucose Deprivation/ReperfusionInduced Injury. *Front Neurol*. 2019;10:1289.
43. Anvekar RA, Asciolla JJ, Missert DJ, et al. Born to be alive: a role for the BCL-2 family in melanoma tumor cell survival, apoptosis, and treatment. *Front Oncol*. 2011;1(34):34.