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The effectiveness of resveratrol in the management of childhood obesity

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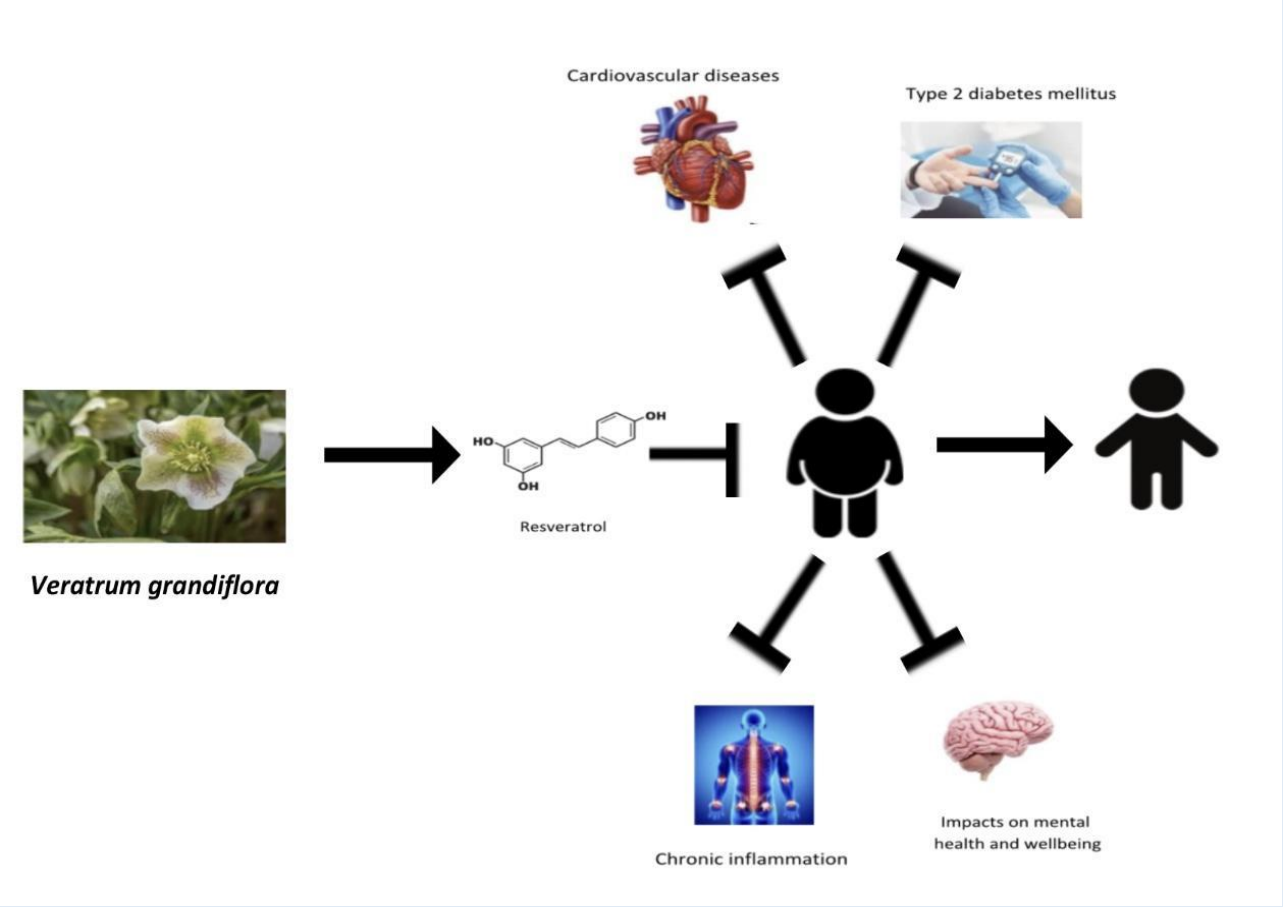
ABSTRACT

Our review is focused on examining whether or not resveratrol is effective in managing and treating childhood obesity based on its beneficial health effects, while also discussing the progress made in developing functional food products containing resveratrol. Resveratrol is a natural phenolic compound found in the *Veratrum grandiflorum* and is known for its antioxidant properties. Resveratrol can be found in various foods like berries, grapes, pistachios, dark chocolate, peanut skins, soybeans, and pomegranates. Studies evaluating the effectiveness of resveratrol in the management and treatment of childhood obesity have been conducted both in animals and humans. Through numerous mechanisms, such as activation of AMPK, increasing lipolysis, decreasing leptin levels and leptin/soluble leptin receptor (sOB-R) ratio, managing embryonic oxidative stress biomarkers, and reducing body weight and adiposity in offspring, resveratrol has been shown to be effective in ameliorating symptoms of obesity. Thus far, researchers have established both a goal to be accomplished (treatment and management of childhood obesity) and a bioactive compound (resveratrol) to accomplish that goal, as well as appropriate dosages and times of consumption for preclinical trials, mechanisms of action, and relevant biomarkers of resveratrol. These findings have been used to conduct various preclinical trials to test the efficacy and safety of resveratrol both in vivo and on animals. To our knowledge, the following steps have not yet been completed and are required for future research; 1) clinical trials involving resveratrol supplementation to establish safety, appropriate dosage, and time of consumption in humans, 2) creation of a specialized label for resveratrol functional food products, 3) publications submitted to open access, peer-reviewed journals, 4) approval by a reliable governmental agency, 5) official establishment of the product, and 6) epidemiological studies and after-market research conducted following release of the functional food product to the general public.

Keywords: Resveratrol, Obesity, Childhood, Maternal, Cardiovascular, Diabetes, Inflammation.



Graphical Abstract: Effects of resveratrol on managing childhood obesity

INTRODUCTION

Obesity is growing at alarmingly rapid rates both within the United States and globally, contributing to its classification as the "obesity epidemic" [1-5]. In the years between 1975 and 2016 alone, obesity in individuals aged 5-19 years increased from just 4% to an astounding 18% across the globe, with the vast majority residing in well-developed nations [8]. As of 2017, it is estimated that roughly 30% of the world's population, equating to about 2 billion individuals of all ages, have an excess of body weight, classifying themselves as either overweight or obese [2]. It has been predicted that the obesity epidemic is likely perpetuated by a society that encourages sedentary behaviors and superfluous food consumption [4,8-9]. In addition to the societal behaviors and attitudes that keep this epidemic at the forefront of health issues, obesity is also believed to be the result of environmental, genetic, and in-utero factors as well [1].

Obesity is classified as an excess in body weight, measured on the body mass index (BMI) scale, which demonstrates the ratio of body weight in kilograms (kg)

to height in meters (m) squared [1-6]. A BMI of 30kg/m^2 or greater classifies one as obese and is associated with increased risk for comorbidities and death [3]. Within the larger umbrella of obesity exist three subcategories – Class I, Class II, and Class III, with Class III obesity reaching BMI values of 40 kg/m^2 or greater [3,7]. Although obesity can affect an individual at any stage of life, childhood obesity and the detrimental impacts that accompany it have the ability to adversely transform the health outcomes of children well into adulthood. Children with obesity experience a fivefold increase in the risk of being obese during adulthood when compared with their non-obese peers, in addition to lofty medical costs and other comorbidities including cardiometabolic risk, diabetes, metabolic syndrome, and premature death [10-11]. Over the last 30 years, the incidence of childhood obesity has significantly increased among children and adolescents, making childhood obesity a cause for concern among the American population [11].

Along with the various increases in health risk for obese children, both throughout childhood and into adulthood, comes psychological consequences as well [10]. Many children with obesity experience bullying and stigmatization due to their weight, resulting in behaviors like social isolation, limited physical activity, and feelings of depression, anxiety, and shame [10]. In order to thoroughly understand childhood obesity and the multifactorial influences that accompany it, it is important to examine its genetic determinants. Numerous factors may contribute to the phenotype that is obesity in children, such as race/ethnicity, socioeconomic status, food insecurity, and geographic location, as well as genetic pre-exposure, as is the case in Prader-Willi and Alstrom syndromes [12-13].

In recent years, there has been growing interest in the use of bioactive compounds and functional foods for the treatment of obesity, and more specifically, childhood obesity [14]. According to the Functional Food Center, functional foods refer to "natural or processed foods that contain biologically active compounds, which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral disease and manage their symptoms" [15]. Of the numerous bioactive compounds found within functional foods, resveratrol has been studied for its potential health benefits and disease prevention/management abilities [16-19]. Resveratrol, found to be produced by plants, is a natural phenolic substance that has anti-oxidizing abilities, as well as the potential for the improvement and management of various cardiovascular and insulin-dependent conditions [20-21].

A keen interest in functional foods, and resveratrol in particular, have led researchers to begin studying it for the treatment and management of various chronic conditions. Many studies have been conducted evaluating the beneficial effects of resveratrol in areas like neurocognitive functioning, hepatic steatosis, and medulloblastoma (MB) treatment [22-24]. Several additional studies, discussed shortly, have examined the effects of resveratrol on childhood obesity, both through direct and maternal supplementation [20-21,25-27]. Our literature review's objective is to look at previous and current research to evaluate the effectiveness of resveratrol in the management of childhood obesity. This is significant in the sense that improvements in childhood obesity through resveratrol supplementation have the potential to manage the rapidly growing obesity epidemic.

METHODOLOGY

A literature review of published studies regarding the effectiveness of resveratrol treatment in managing

childhood obesity was conducted electronically using PubMed®, ScienceDirect, and the Functional Food Center's journal database [www.ffhjd.com]. These databases were chosen based on the large number of items housed within them which are of relevance to our literature review. 67 review and research articles were included, published between 1998 and 2023, as the last 25 years have marked a period of immense growth and recognition of resveratrol in research and literature. Articles provided objective, scientific information and findings on resveratrol and its possible effects on the management of obesity and/or childhood obesity. Inclusion criteria for articles consisted of those demonstrating physiologic and biochemical mechanisms of resveratrol and those linking resveratrol to chronic disease outcomes. Exclusion criteria included review articles and research studies conducted or published before 1998 and those that do not examine resveratrol through the scope of disease outcomes. Keywords for the search included resveratrol, obesity, childhood, maternal, cardiovascular, diabetes, and inflammation.

RESVERATROL

Resveratrol is a natural phenolic substance that is found in plants, specifically *Veratrum grandiflorum*, otherwise known as white hellebore plants [20-21,28]. The antioxidant properties, as well as mechanisms for controlling mitochondrial dysfunction, angiogenesis, oxidative stress, inflammation, and apoptosis, build a relatively strong case for resveratrol as a method of management of several chronic conditions, including childhood obesity [20,28]. Resveratrol can be found in many dietary sources like peanut skins, berries such as blueberries, mulberries, bilberries, cranberries, and red grapes, soybeans, pomegranates, dark chocolate, and pistachios [28].

Impacts on Cardiovascular Health*:* Among the various benefits of resveratrol that have been observed are cardioprotective effects. Cardiovascular diseases are extremely common comorbidities, as roughly 30% of coronary heart disease (CHD) and 60% of hypertensive disease can be traced to obesity [1,29]. Visceral adipose tissue (VAT) can be considered both the root of and an indicator of cardiometabolic disease, linking the prevalence of obesity with cardiovascular diseases [3]. In particular, childhood obesity is highly correlated with the incidence of cardiovascular conditions such as ischemic heart disease, stroke, and other cardiac pathologies [29].

Resveratrol has been shown to induce nitric oxide synthase (NOS), which favors vasodilation and is responsible for synthesizing nitric oxide (NO) in the body [20,28]. NO plays crucial roles in vasodilation, improving cardiac outcomes and functioning [30]. Vasodilation, or relaxation of arteries, increases blood flow, resulting in decreases in blood pressure, while vasoconstriction decreases blood flow through arteries, increasing blood pressure and potentially leading to hypertension [20,31]. By increasing NOS, and subsequently NO production, resveratrol functions as an antioxidant in the heart after ischemic events and reduces oxidative stress [20].

Resveratrol also induces angiogenesis, an essential process for growth and oxygen and nutrient delivery in which new blood vessels are formed [32]. An interesting property of resveratrol is its multifaceted effects, as can be seen with angiogenesis [20]. Angiogenesis can be halted if concentrations of resveratrol are too high, however, at low enough concentrations, resveratrol stimulates angiogenesis and allows cardiovascular functioning to thrive [20].

In addition to inducing NOS and angiogenesis, resveratrol has the ability to improve post-ischemic cardiac outcomes by increasing the expression of GLUT-4, the primary glucose transporter of the heart [20,33]. Moreover, GLUT-4 expression is increased by resveratrol

while concurrently reducing cardiac apoptosis and endothelin production [20]. This ability to reduce endothelin is essential in resveratrol's mechanism to improve post-ischemic cardiac outcomes, since endothelin regulates blood pressure within the endothelium through vasoconstriction [20,34].

Along with improving post-ischemic cardiac outcomes by increasing GLUT-4 expression, resveratrol also does this by reducing the incidence of ventricular fibrillation and infarct size [20]. Ventricular fibrillation is considered a medical emergency and refers to an abnormal heart rhythm in which blood does not pump to the entire body [35]. The ability of resveratrol to reduce, and ideally eliminate, episodes of ventricular fibrillation in ischemic-reperfused hearts points to its great potential in serving as a method of treatment and management of obesity and its comorbidities. Resveratrol also decreases infarct sizes, in other words, the extent of damage to tissues from lack of blood flow [20,36].

In a study conducted by Hao et al. examining the effects of resveratrol on sepsis-related myocardial injury, resveratrol was shown to be protective against oxidative stress in cardiomyocytes [37]. Human primary cardiomyocytes were cultured and treated with lipopolysaccharide (LPS) for 24 hours, either with or without resveratrol [37]. After careful examination, it was found that resveratrol treatment at 3μM resulted in excellent protection against cell death [37]. Additionally, the incidence of apoptotic and necrotic cells was dramatically decreased in cells treated with resveratrol when compared to cells that were not [37]. The findings of Hao et al., along with resveratrol's ability to induce both NOS and angiogenesis, improve post-ischemic cardiac outcomes through increasing GLUT-4, and decrease ventricular fibrillation and infarct size, strongly support the case for resveratrol's ability to improve cardiovascular functioning [20,28,37].

Another study conducted in 2010 by Toklu et al. evaluated the effectiveness of resveratrol on multiple cardiovascular markers, such as blood pressure, aortic hypercontractility, left ventricular functioning, and oxidative injury in hypertensive rats [17,38]. Hypertensive rats were treated with resveratrol for 6 weeks and monitored for changes in the measures of cardiovascular functioning [17,38]. Researchers discovered that resveratrol treatment in the hypertensive rats significantly lowered blood pressure, and thus, improved overall cardiac health [17,38]. In addition to decreases in blood pressure, resveratrol intervention also showed reductions in oxidative damage, supporting claims for resveratrol's antioxidant capabilities [17,38].

Impacts on Diabetes: Commonly existing alongside obesity, not only does diabetes pose its own set of health risks but is also places individuals at a much greater risk of developing additional comorbidities like cardiovascular diseases, as previously mentioned [3]. The development of diabetes, specifically type 2 diabetes mellitus, is largely driven by obesity through elevated levels of VAT [3]. Numerous characteristics of obesity are believed to be attributed to type 2 diabetes mellitus, including large amounts of VAT and excessive levels of dietary glucose [3,20]. Regardless of BMI, obesity poses a much greater risk for developing diabetes, and it is estimated that among individuals with type 2 diabetes mellitus, 37% experienced metabolic syndrome, as opposed to only 4% of individuals without it [2].

To target insulin resistance in individuals with type 2 diabetes mellitus, resveratrol's primary mechanism is acting as an antioxidant to gather and dispose of reactive oxygen species (ROS) [20]. Oxidative damage caused by ROS is likely a result of elevated blood glucose levels, also measured as HbA1c [20,39]. Although many possible reasons exist for why an individual might receive an

HbA1c test, one of the most frequent for those under 45 years of age is increased risk due to overweight or obesity [39].

In a study conducted by Breen et al., researchers were able to demonstrate that glucose uptake in skeletal muscle, independent of translocation of glucose transporters like GLUT-4, can be increased with resveratrol treatment [20,40]. Researchers tested the effects of various resveratrol concentrations on glucose uptake in skeletal muscle tissue by incubating L6 myotubes and found an optimal concentration for incubating to be around 100µM [40]. Interestingly, as incubation concentrations of resveratrol were raised above the optimal 100µM, glucose uptake began to plateau, signifying a maximum capacity for glucose uptake by resveratrol [40]. Regardless, the data collected by Breen et al. point to resveratrol's ability to enhance skeletal muscle glucose uptake without translocating key glucose transporters like GLUT-4 [20,40].

An additional study conducted in 2012 by Bhatt et al. examined the effects of resveratrol on specific diabetic markers such as glycemic control [17,41]. Participants were either provided with hypoglycemic agents alone, or hypoglycemic agents in conjunction with 250 mg/d of resveratrol [17,41]. HbA1c, along with other measurements, were documented after 3 months [17,41]. Researchers uncovered those participants receiving both the hypoglycemic agent and resveratrol experienced major decreases in HbA1c when compared to participants receiving the hypoglycemic agent alone [17,41]. The findings of Bhatt et al. are important in understanding the effects of resveratrol on HbA1c in individuals with type 2 diabetes mellitus, as a large portion of individuals experiencing type 2 diabetes mellitus are also obese [3,20,40].

Another study, conducted by Zarei et al. also proved resveratrol to be successful in decreasing blood glucose in rats with type 2 diabetes mellitus [28,42]. In an attempt to investigate the effects of resveratrol on apelin gene expression in diabetic rats, researchers found increases in insulin as a result of decreases in blood glucose [28,42]. In rats with the most significant reductions in blood glucose levels, concentrations of resveratrol administered were between 5-10 mg/kg/d [42]. The results of Zarei et al. provide more support for the claim that resveratrol has hypoglycemic effects on individuals with type 2 diabetes mellitus by reducing HbA1c levels, in addition to enhancing skeletal muscle glucose uptake as evidenced by Breen et al. [28,40,42].

Impacts on Inflammation: Inflammation is one of the major symptoms that is associated with obesity and its comorbidities, and adipose tissue is believed to be a decisive regulator [20]. Because of this, it is no wonder why inflammation is observed in many chronic health conditions, including diabetes and cardiovascular diseases [20,43]. Among the variety of adverse health outcomes that individuals with obesity experience are endothelial dysfunction, insulin resistance, and cardiovascular problems [20].

In order to directly target inflammation related to chronic conditions such as obesity, resveratrol inhibits both the excretion and gene transcription of monocyte chemo-attractant protein (MCP-1) [20]. MCP-1 is an essential chemokine that regulates movement and penetration of monocytes, which are required for the body to respond to inflammation [44]. Due to MCP-1's ability to influence, and possibly increase inflammatory responses, its inhibition by resveratrol is a potential mechanism for bypassing inflammatory responses in the body altogether [20,44].

In addition to inhibiting MCP-1, resveratrol also reverses the excretion of atherogenic adipokines [20]. Adipokines, released by adipose tissue, play important

roles in the accumulation of lipids, progression of atherosclerosis, and inflammation [45]. This can especially be seen in individuals with inflammation as a result of obesity and its complications. In reversing the excretion of atherogenic adipokines, resveratrol also diminishes the magnitude of atherosclerotic plaques and lesions [20].

A study conducted by Sharma et al. aimed to examine the effects of resveratrol on oxidative stress and renal functioning in diabetic rats [20,46]. During the first 4 weeks of the study, rats were administered a single 65 mg/kg dose of streptozotocin to induce diabetes, and between weeks 4-6, were administered one of four treatments – control, diabetic, and diabetic with either 5 mg/kg or 10 mg/kg oral resveratrol supplementation [46]. Researchers found that after 6 weeks, rats treated with resveratrol experienced drastically lower levels of oxidative stress and renal dysfunction than those that were not [46]. The data collected by Sharma et al. shows diabetes significantly affects renal functioning and oxidative stress, but resveratrol treatment could mitigate these outcomes [20,46].

Impacts on Obesity: As mentioned previously, with obesity comes numerous coexisting conditions like cardiovascular diseases, inflammation, and diabetes, among others [1,3,20,28-29,43]. Various animal studies have reported that resveratrol has similar effects to energy restriction in terms of reducing weight and triglyceride (TG) aggregation in hepatocytes [20,47-50]. The proposed mechanism of resveratrol on weight loss and TG reductions is thought to be through directly targeting adipocytes [20]. In addition to targeting adipocytes, resveratrol also increases lipolysis, in other words, the breaking down of triglycerides for storage as fatty acids, further contributing to reductions in triglycerides [21]. By reducing the size of adipocytes and the amount of fat that is able to build up in the abdomen, resveratrol is able to mimic the effects of energy restriction [20-21].

Another possible mechanism of resveratrol in managing obesity is through the activation of AMP-activated protein kinase (AMPK) [21]. AMPK is a protein kinase pathway in the liver and skeletal muscle [21,40]. When AMPK is activated in the liver, both fatty acid and TG synthesis are decreased, allowing resveratrol to induce weight loss through lipolysis [20-21]. On the other hand, when AMPK is activated in skeletal muscle, glucose uptake improves, regardless of insulin status [21]. These outcomes show that resveratrol could correct lipid profiles and increase glucose utilization, which proves to be extremely beneficial in the management and treatment of obesity [21].

A study conducted by Le Duc et al. aimed to answer the question of whether lipid accumulation can be well understood through the examination of lipomas [51]. During the study, 15 participants had their lipomas surgically removed and histologically evaluated for adipocyte size and distribution, in addition to numerous other analyses [51]. Through the examination of the data collected during this study, it has been proposed that resveratrol's ability to decrease lipid buildup is due to reductions in fat formation, as well as weakened viability of cells [28,51].

Another study, conducted by Zou et al., concluded that resveratrol improves markers of brown fat formation, as opposed to white fat formation [28,52]. Brown adipose tissue, also known as brown fat, is a unique category of fat in the body that is responsible for producing heat through the burning of calories [53]. Although labeled as "fat", brown adipose tissue has tremendous potential for managing and treating metabolic disorders due to its fuel burning capacity [53]. By activating AMPKα1, a subunit of AMPK, resveratrol increases brown fat formation, as well as energy and heat

expenditure in mouse adipocytes [28,52].

Dolinsky et al. conducted a study that posed the question of whether or not resveratrol is capable of preventing the detrimental impacts of intrauterine growth restriction (IUGR) [21]. In the study, one of two different environmental conditions were administered to pregnant rats in the third trimester – a controlled, normoxic environment with 21% O_2, or a hypoxic environment with 11.5% O_2 to achieve IUGR [21]. Following this, male offspring were assigned a high-fat diet, either with or without the supplementation of resveratrol [21]. After 9 weeks of intervention, researchers found that offspring on the high fat diet with resveratrol supplementation experienced reduced abdominal fat when compared to offspring that did not receive resveratrol [21]. After close examination, researchers suggested that this is possible due to resveratrol's ability to redistribute fat to areas of the body other than the abdomen while simultaneously reducing the diameter of adipocytes [21].

THE EFFECTS OF RESVERATROL ON CHILDHOOD OBESITY

Effects of Maternal Resveratrol Consumption on Offspring*:* Although obesity is a multifaceted condition, the root cause of obesity in many individuals can be traced back to long before they were even conceived [1,4,8-9,25]. According to what is known as the Developmental Origins of Health and Disease Theory (DOHaD), environmental exposures during critical developmental stages can influence the health status of offspring later in life [54,56]. This is especially true for maternal nutrition before and during pregnancy, as well as during lactation [25]. Well-established evidence exists proving correlations between gestational obesity and adiposity in offspring, as well as correlations between maternal micronutrient deficiencies and adverse health outcomes in offspring during childhood [25]. In addition, many animal studies have shown a higher prevalence of obesity in offspring as a result of maternal obesity and overnutrition [25,55-56].

If poor maternal health status and malnutrition can negatively influence health outcomes of offspring, then correlating these factors might have the opposite, favorable effect [25]. Bioactive compounds, such as resveratrol, can easily pass through the placenta and be transferred from mother to fetus during pregnancy, presenting beneficial effects, even in-utero [25]. The effects of maternal bioactive compound consumption on offspring have become a topic of growing interest, and resveratrol is just one of the compounds that are being examined.

Maternal Resveratrol Consumption and Leptin in Animal Studies: Several studies have looked at the effects of maternal resveratrol consumption and leptin in offspring [25,57-58]. Adipose tissues release leptin to signal satiety to balance sensations of hunger and fullness [59]. Oftentimes, individuals with obesity experience what is known as leptin resistance, in which the brainstem and hypothalamus fail to recognize this hormone, resulting in a lack of fullness, constant hunger, increased food intake, and/or decreased adiposity [59]. By examining the effects of maternal resveratrol intake on leptin in offspring, researchers can decide whether a definitive correlation exists between the two.

In a study conducted by Tsai et al., Sprague-Dawley (SD) rats were administered one of four diets – maternal control diet/postnatal control diet (CC), maternal high-fat diet/postnatal control diet (HC), maternal control diet with resveratrol/postnatal control diet (CRC), and maternal high-fat diet with resveratrol/postnatal control diet (HRC) – to examine the effects of maternal resveratrol intake on high fat diets and obesity in offspring [57]. Each month, the body weight for each rat was measured until the rats reached 4 months of age

[57]. After the 4-month mark, the rats were euthanized, and adipose tissues were collected for histological examination [57].

Researchers were able to conclude that rats receiving HC intervention exhibited much higher levels of plasma leptin when compared to those receiving the CC and HRC interventions, indicating that maternal high-fat diets result in decreased levels of plasma leptin in offspring [57]. In addition, the ratio of leptin to soluble leptin receptor (sOB-R) serves as an indicator for leptin resistance, and therefore, a higher ratio indicates an excess of leptin and not enough receptors [57]. Researchers were able to determine that a maternal high-fat diet was significantly correlated with higher leptin/sOB-R ratio, indicating that in-utero exposure to a high-fat diet predisposes offspring to insulin resistance ($p = 0.037$) [57].

Although offspring receiving the maternal high-fat diet with resveratrol also experienced higher ratios than those receiving the maternal control diets, this value was not found to be statistically significant [57]. However, statistically significant results show a positive correlation between body weight and levels of plasma leptin ($p < 0.001$) [57]. Researchers discovered that maternal resveratrol treatment, in both the high-fat and control diets, resulted in lower body weights among the offspring ($p = 0.011$) [57]. Due to the correlation between body weight and plasma leptin levels, researchers were able to draw the conclusion that maternal resveratrol intake results in lower body weights in offspring, leading to lower leptin levels and therefore, decreased leptin/sOB-R ratios, indicating a reduced risk for insulin resistance and obesity [57].

Another study conducted by Liu et al. evaluated the effects of maternal resveratrol consumption on offspring of maternal and postnatal high-fat diets [58]. Similar to Tsai et al., Liu et al. administered either a high-fat/high sucrose (HFHS) diet or control diet to Sprague-Dawley (SD) dams for 8 weeks [58]. After mating, 3 male offspring were selected from each litter and provided a control of HFHS diet until about 4 months of age [58]. Offspring were then categorized into one of five groups – maternal control diet/postnatal control diet (CC), maternal control diet/postnatal HFHS diet (CH), maternal HFHS diet/postnatal control diet (HC), maternal HFHS diet/postnatal HFHS diet (HH), and maternal HFHS diet with the addition of resveratrol/postnatal control diet (HRH) [58].

Researchers found that plasma leptin levels were substantially elevated in offspring receiving a high-fat/high sucrose diet, both pre- and postnatally ($p < 0.001$) [58]. Maternal resveratrol treatment (HRH), even with a high-fat/high sucrose diet, was shown to effectively lower leptin levels experienced by offspring of the HH group [58]. The HH intervention group had plasma leptin levels of 39.16 ng/mL ± 3.81, whereas the HRH intervention group's plasma leptin levels were less than half of that, at only 18.12 ng/mL ± 2.26 ($p < 0.001$) [58]. The same trend holds true for the leptin/sOB-R ratio, as the HH intervention group's ratio was 8.57 ± 1.35, while the ratio of the HRH intervention group was just 4.73 ± 0.82 ($p = 0.049$) [58]. These results show that maternal resveratrol intake is effective in decreasing both plasma leptin levels and leptin/sOB-R ratios in offspring [58].

Maternal Resveratrol Consumption and Oxidative Stress in Animal Studies: Oxidative stress is present in individuals exhibiting many of the comorbid conditions that exist with obesity, such as cardiovascular diseases, diabetes, and chronic inflammation [20]. Since one of the

promising capabilities of resveratrol is to decrease oxidative stress, researchers have begun investigating the potential of maternal resveratrol consumption to ameliorate oxidative stress in offspring [20,28,60]. When a disproportion of ROS exists in cells and tissues in the body, oxidative stress occurs [61]. A variety of environmental factors can contribute to the development of oxidative stress, including pollution, radiation, UV, and xenobiotics [61]. Over time, oxidative stress can have many harmful effects on the body by damaging cells and causing inflammation and dysfunction of key molecules [61].

Singh et al. conducted a study in which the goal was to determine whether resveratrol has the ability to prevent oxidative stress and apoptosis resulting from diabetes in dams [60]. Researchers examined pregnant rats in one of four categories – control (C), control with resveratrol (CR), diabetic (D), and diabetic with resveratrol (DR) [60]. Upon examination of the embryos after 10 days of resveratrol treatment, researchers discovered regulation of lipid peroxidation ($p = 0.0165$), total thiol levels ($p = 0.003$), and glutathione (GSH) levels ($p = 0.012$), all of which are known to be common biomarkers of oxidative stress in the body [60]. These results indicate that maternal resveratrol consumption was effective in managing embryonic oxidative stress through a number of different measures [60].

Maternal Resveratrol Consumption and Adiposity in Animal Studies: In the Liu et al., study conducted on SD rats, there were also significant results indicating reduced lipogenesis and adiposity as a result of maternal resveratrol consumption [58]. Body weight and adipose tissue in the offspring was significantly lowered in those exposed to maternal resveratrol intake when compared with those that were not ($p < 0.001$) [58]. In offspring exposed to a high-fat maternal diet without resveratrol treatment, body weight was recorded to be 858.79g ± 27.56g, whereas body weight in offspring exposed to maternal resveratrol was just 685.86g ± 23.95g ($p < 0.001$) [58]. In addition, the weight of total adipose tissue for the offspring in the HH group was 165.97g ± 9.75g, versus only 108.07g ± 8.64g in the HRH group ($p < 0.001$) [58]. These results suggest that maternal resveratrol treatment, even in conjunction with a high-fat diet, has positive effects on body weight and adiposity in offspring [58].

In another study, conducted by Ros et al., Wistar rats were given either a low-fat or high-fat diet, and half of each group was also administered resveratrol through their drinking water [62]. The objective of this study was to determine whether or not maternal resveratrol intake is effective in improving malnutrition in offspring [62]. Upon examination of the results, researchers came across some interesting findings. While maternal resveratrol consumption resulted in significant decreases in body weight of pups from mothers fed high-fat diets, it also shows increases in body weight of pups from mothers fed low-fat diets, with results only being statistically significant in female pups (males: $p < 0.05$, females: $p < 0.0001$; females < 0.05) [62]. Additionally, resveratrol was proven to substantially decrease amounts of visceral adipose tissue (VAT) in females from mothers fed high-fat diets ($p < 0.0001$) [62]. Evidence from this study shows that maternal resveratrol consumption is effective in reducing body weight and VAT in offspring exposed to maternal high-fat diets in-utero, further supporting the claim that maternal resveratrol might be an effective method for preventing childhood obesity [62].

Table 1. Studies published examining the relationship between maternal resveratrol consumption and effects on offspring that influence obesity.

Study	Supplement	N	Participants	Duration	Outcome(s)
Maternal Resveratrol Treatment Re-Programs and Maternal High-Fat Diet-Induced Retroperitoneal Adiposity in Male Offspring [Tsai et al.] [57]	Maternal HF diet (58% fat) with resveratrol (50 mg/L) via water	52 total	Male SD rats from 3 weeks to 4 months of age	6 months	Significantly lower leptin/sOB-R ratio, when compared to HC, and lower body weights among HRC
Resveratrol intake during pregnancy and lactation re-programs adiposity and ameliorates leptin resistance in male progeny induced by maternal high-fat/high sucrose plus postnatal high-fat/high sucrose diets via fat metabolism regulation. [Liu et al.] [58]	Maternal HFHS diet (35.8g% fat, 35.5g% carbohydrate) plus resveratrol treatment (50 mg/L dissolved in 30 mL 20% 2-Hydroxypropyl-β-cyclodextrin solution and dispensed into 1L by distilled water)	50-60 total	Male SD rats from birth to 4 months of age	6 months	Significantly lower leptin levels, leptin/sOB-R ratio, body weight, and adipose tissue weight among HRH
Resveratrol prevents embryonic oxidative stress and apoptosis associated with diabetic embryopathy, and improves glucose and lipid profile of diabetic dam [Singh et al.] [60]	Maternal resveratrol treatment (100 mg/kg b. wt. dissolved in water) for 10 days	153 total	60 day old female SD rats	10 days	Improvements in regulation of lipid peroxidation, total thiol levels, GSH levels, and HNE levels with maternal resveratrol treatment
Resveratrol Intake During Pregnancy and Lactation Modulates the Early Metabolic Effects of Maternal Nutrition Differently in Male and Female Offspring [Ros et al.] [62]	Maternal HF diet (61.6% fat) with resveratrol treatment (2.0-2.5 mg/kg/d dissolved in 0.5% ethanol)	32 total	Male and female Wistar rats from birth to 21 days old	8 weeks	Significant decreases in body weight and VAT among HFD + R

Effects of Direct Resveratrol Consumption on Childhood Obesity: While maternal resveratrol consumption has shown to be effective in the treatment of obesity as a result of maternal behaviors, limited research exists investigating the effects of resveratrol consumption on childhood obesity postnatally [21,57-58,60,62-63,66-68]. It is important to understand how both maternal and direct resveratrol consumption affect offspring, as nutrition during critical developmental stages, both gestational and postnatal, can have lasting impacts on health later in life [54].

Resveratrol Consumption and Oxidative Stress in Animal Studies: In a study conducted by Shah et al., researchers examined the ways in which resveratrol consumption in rat offspring inhibits metabolic and cardiovascular complications [63]. Rat offspring were predisposed in-utero to either a normoxic or hypoxic

environment and fed a high fat diet, either with or without resveratrol supplementation from age 3-12 weeks [63]. At 12 weeks of age, the offspring were measured for body composition, metabolic functioning, as well as other cardiac assessments [63]. After close examination, researchers observed that levels of oxidative stress following cardiac ischemia-reperfusion (I/R) injury were substantially higher in offspring exposed to hypoxic environments in-utero than those exposed to normoxic environments [63]. However, the oxidative stress in offspring exposed to hypoxic environments in-utero was found to be ameliorated with resveratrol supplementation [63]. In both male and female offspring, resveratrol supplementation nearly halved oxidative stress levels after exposure to hypoxia in-utero ($p < 0.05$) [63].

Hypoxia in-utero limits the amount of oxygen available for the fetus, resulting in impaired intrauterine growth and decreased development and can also predispose the fetus to future metabolic diseases [63-65]. Oxidative stress, along with numerous other metabolic conditions, are extremely prevalent in individuals with obesity, including childhood obesity [10-11,20,28]. Although in some cases, it is nearly impossible to control in-utero environmental conditions, bioactive compounds like resveratrol can be utilized after birth to reverse the effects of hypoxia and the risk of future metabolic consequences [63].

Another study, conducted by Tain et al., aimed to determine whether or not hypertension as a result of maternal and postnatal high-fat diets can be inhibited with resveratrol treatment [66]. Researchers administered either control or high-fructose diets to female SD rats during pregnancy and lactation [66]. Afterwards, male offspring were gathered and categorized into one of five intervention groups – maternal normal diet/post-weaning normal diet (ND/ND), maternal normal diet/post-weaning high-fructose diet (ND/NF), maternal high-fructose diet/post-weaning normal diet (HF/ND), maternal high-fructose diet/post-weaning high-fructose diet (HF/HF), and maternal high-fructose diet/post-weaning high-fructose diet with resveratrol (HF/HF+Resveratrol) – from 3 weeks until 3 months of age [66].

Researchers observed that a high-fructose diet administered both during gestation and post-weaning resulted in hypertension, as well as oxidative stress, in offspring [66]. When comparing the measurements from offspring that were fed high-fructose diets without resveratrol to the ones with resveratrol, it was apparent that resveratrol supplementation significantly decreased oxidative stress ($p < 0.005$), in addition to several other biomarkers [66]. The data collected from Tain et al. demonstrate that supplementation with resveratrol in offspring fed high-fructose diets is effective in reducing oxidative stress [66].

Wong et al. also reports significant findings, supporting resveratrol's capabilities in reducing oxidative stress in F2 generation mice [67]. Resveratrol was provided to F2 hybrid mice via drinking water at concentrations of approximately 1.50 to 2.27 mg/kg of body weight [67]. Researchers measured levels of several biomarkers of oxidative stress in offspring receiving resveratrol versus age-matched offspring that were not, including 8-hydroxy-2'-deoxyguanosine (8OHdG) ($P < 0.05$, $p < 0.01$), 8-isoprostane (8-Iso-$PGF_2\alpha$) ($p < 0.05$, $p < 0.01$), and protein carbonyl content ($p < 0.05$) [67]. They found that although markers of oxidative stress in offspring worsened with age, resveratrol supplementation for 6 to 12 months was able to alleviate these effects, showing both baseline and age-dependent decreases [67]. Findings from this study suggest that resveratrol supplementation in offspring is effective in

reducing biomarkers of oxidative stress, both from baseline measures and as offspring age [67].

Resveratrol Consumption and Adiposity in Animal Studies: In the previously mentioned study from Dolinsky et al., a question was posed of whether or not the effects of intrauterine growth restriction (IUGR) can be prevented with resveratrol treatment in rat offspring [21]. Researchers documented that after 9 weeks of intervention, offspring receiving a high-fat diet with the supplementation of resveratrol showed decreased abdominal adiposity when compared to offspring that were not supplemented with resveratrol [21]. Levels of intra-abdominal fat were lower in offspring receiving a high-fat diet supplemented with resveratrol, regardless of IUGR ($p < 0.05$) [21].

Although similar reductions in intra-abdominal fat were seen among offspring, both control and IUGR offspring experienced greater decreases in intra-abdominal fat as a percentage of total body weight than the control offspring ($p < 0.05$) [21]. These findings demonstrate that resveratrol supplementation is effective in reducing adiposity in offspring born IUGR, which proves critical in evaluating the mechanisms involved in childhood obesity [21]. As previously discussed, hypoxia and other suboptimal in-utero conditions can result in IUGR in offspring, predisposing them to future metabolic disorders [63-65].

Not only did Shah et al. have significant findings linking resveratrol supplementation to improvements in oxidative stress, but they also have linked resveratrol to reductions in adiposity as well, specifically in females [63]. While no significant results have been recorded with males, Shah et al. found that resveratrol treatment was effective in reducing body weight in females exposed to hypoxia ($p < 0.05$) [63]. Specifically, greater amounts of the body weight that was gained at or beyond the 10-week mark was eliminated with the supplementation of resveratrol [63]. Reductions in body weight were observed in female offspring receiving resveratrol, despite the same level of food intake, signifying the effectiveness of resveratrol in managing adiposity, at least in female offspring, exposed to in-utero hypoxia [63]. Because these results were only statistically significant in female offspring, further research is needed to prove these points, however, these data still offer a strong foundation for the evaluation of resveratrol for the reduction of body weight in offspring [63].

Supportive Micronutrient Treatment in Human Studies: A study conducted by Pecoraro et al. investigated the effects of a combination supportive treatment containing resveratrol, curcumin, zinc, magnesium, selenium, and vitamin D on childhood overweight and obesity [68]. During the study, 48 participants aged 6-17 years with a BMI greater than the 95th percentile were administered either the supportive treatment or a placebo over the course of 6 months [68]. Measurements of endothelial function were assessed at baseline, 3 months, and 6 months [68]. After 6 months, researchers observed significant delta flow (DF) improvements in both the supportive treatment and the placebo ($p < 0.001$) [68]. Between the 3-month and 6-month period, DF changes in the heat provocation test (HPT) were observed ($p < 0.05$), indicating improvements in endothelial function [68]. In addition, there was also a correlation found between BMI and DF at the 6-month mark ($p < 0.05$), showing that as DF increases, BMI increases [68]. This correlation proves that, despite increases in BMI among participants, the supportive treatment was successful in improving endothelial functioning [68]. The data from this study support the hypothesis that resveratrol, in conjunction with various other vitamins, minerals, and bioactive compounds, is effective for the treatment of endothelial function in childhood obesity [68].

Table 2. Studies published examining the relationship between direct resveratrol consumption and effects on childhood obesity.

Study	Supplement	N	Participants	Duration	Outcome(s)
Effects of resveratrol on metabolic and cardiovascular function in male and female adult offspring exposed to prenatal hypoxia and a high-fat diet [Shah et al.] [63]	In-utero hypoxia (11% oxygen concentration) and resveratrol treatment (4 g/kg or roughly 10-20 µmol/L)	20 total	Male and female SD rats from 3 weeks to 3 months of age	4 months	Significant decreases in levels of oxidative stress and reduced body weights in females among hypoxia-HF + resveratrol
Resveratrol Prevents the Development of Hypertension Programmed by Maternal Plus Post-Weaning High-Fructose Consumption through Modulation of Oxidative Stress, Nutrient-Sensing Signals, and Gut Mictobiota [Tain et al.] [66]	Maternal HF diet (66.7% carbohydrate), and HF post-weaning diet (66.7% carbohydrate) plus resveratrol treatment (50 mg/L dissolved in ethanol and diluted with water twice weekly)	40 total	Male SD rats from 3 weeks to 3 months of age	15 weeks	Significant decreases in levels of oxidative stress among HF/HF+ Resveratrol
Elevation of oxidative-damage biomarkers during aging in F2 hybrid mice: Protection by chronic oral intake of resveratrol [Wong et al.] [67]	Resveratrol treatment (14.09 mg/L daily via drinking water)	66 total	F2 hybrid four-way cross mice, either of 6 months, 12 months, or 24 months of age	Either 6 or 12 months	Significant decreases in 8OHdG, 8-Iso-$PGF_2\alpha$, and protein carbonyl content
Continued Postnatal Administration of Resveratrol Prevents Diet-Induced Metabolic Syndrome in Offspring Born Growth Restricted [Dolinsky et al.] [21]	IUGR (11.5% oxygen concentration) with resveratrol treatment (4 g/kg or roughly 10-20 µmol/L)	72 total	Male rats from 3 weeks to 3 months	13 weeks	Significant reductions in abdominal fat, both on its own and as a percentage of total body weight among IUGR HF-R
Supportive treatment of vascular dysfunction in pediatric subjects with obesity: the OBELIX study [Pecoraro et al.] [68]	Supportive treatment of vitamin D3 (25.00 µg), folic acid (90.00 µg), selenium (55.00 µg), magnesium (300.00 mg), zinc (7.00 mg), curcumin (Meriva®) (100.00 mg), Polygonum dry extract (20.41 mg, of which 20.00mg is resveratrol), and Soy dry extract (37.50 mg)	48 total	Children aged 6-17 years with BMI higher than the 95th percentile for age	6 months	Significant DF improvements for HPT and correlation between increased DF and decreased BMI

ALLOMETRIC SCALING OF RESVERATROL

A Potential Model for Optimal Resveratrol Dosage in Humans: Despite the various resveratrol concentrations utilized in the preceding studies, a review published by Smoliga and Blanchard in 2017 attempts to develop an allometric scaling model for resveratrol usage [69]. Due to the inconsistencies in resveratrol doses among studies, Smoliga and Blanchard deduced a Cmax for 100 mg/kg of oral resveratrol.

According to this model, the Cmax for 100 mg/kg resveratrol supplementation in a human weighing 70 kg would be 921 ng/mL [69]. However, due to the various limitations in the data available, this model is suspected to have marked error [69]. Despite the considerable risk of error in this model, the work done by Smoliga and Blanchard is significant in beginning to evaluate appropriate resveratrol doses in humans, in order to both continue conducting more human studies and successfully identify resveratrol's role in functional foods [69].

Limitations of Allometric Scaling: Despite the great potential of the allometric scaling model proposed by Smoliga and Blanchard, there are several limitations that exist, one of which being that few studies have demonstrated similar resveratrol dosages across species [69]. The wide variability in resveratrol dosages greatly limits the ability to compile these findings to formulate an ideal dosage for this model [69]. Although Smoliga and Blanchard attempted to overcome this limitation by estimating a Cmax for a hypothetical dosage on a curve, this is still a hypothetical calculation [69].

Another limitation of the allometric model proposed by Smoliga and Blanchard is the fact that data from only two species (dogs and humans) were able to be utilized due to lack of data from other species [69]. Not only does this limitation have the potential to impact the accuracy of the model, since only dog and human subjects were utilized, but it also limits the generalizability of the model to be used on other species such as rats [69]. Further research is required to establish an optimal resveratrol dosage in human subjects.

POSSIBLE IMPLICATIONS OF RESVERATROL TREATMENT

Resveratrol Treatment and Kidney Toxicity: Although several animal and human studies have shown the many beneficial effects of resveratrol treatment on childhood obesity, there are also possible implications to take into consideration when evaluating its effectiveness [20]. Existing evidence shows associations between resveratrol supplementation and increases in DNA and protein carbonyl damage in the kidneys [20,67]. Because of resveratrol's ability to form interconnected metabolites, such as sulfates and other methylated substances, supplementation carries with it a risk of kidney toxicity [20].

In a study conducted by Crowell et al., rats were administered resveratrol in doses of 0, 300, 1,000, or 3,000 mg/kg of body weight on a daily basis [72]. After 28 days, researchers collected blood samples and conducted histological examinations of all body tissues [72]. Among rats receiving 3,000 mg/kg of resveratrol each day, researchers observed a much greater incidence of nephrotoxicity and higher kidney weights [72]. In particular, serum blood urea nitrogen (BUN) was measured at 20.3 mg/dL in rats receiving 3,000 mg/kg of resveratrol, versus just 15,8 mg/dL in the control group ($p < 0.05$) [72]. Additionally, creatinine levels were measured at 0.50 mg/dL in rats receiving 3,000 mg/kg of resveratrol, while in the control group, they were only 0.37 mg/dL ($p < 0.05$) [72].

Serum BUN tests offer information that is crucial to assessing and understanding how well one's kidneys are

functioning [73]. After the kidneys decompose proteins in the body, they excrete ammonia, which contains nitrogen [73]. Free nitrogen in the body blends with other elements, like oxygen, carbon, and hydrogen, to form a substance known as urea, which travels into the kidneys [73]. An obvious indicator that the kidneys are not working properly is the inability to filter out urea, shown through a serum BUN test [73].

In addition to serum BUN, creatinine can also serve as an indicator of kidney functioning [74]. Creatinine is a waste product that's presence depends on one's age, gender, race/ethnicity, and body size, along with other factors [74]. Because the kidneys also work to filter creatinine out of the body, higher creatinine levels are another signal of kidney dysfunction [74]. Examining these two markers of kidney dysfunction in rats was key in this study to determine whether or not resveratrol can cause adverse effects in the kidneys [72]. Although many studies have shown resveratrol to be effective in treating childhood obesity and its possible comorbidities, it is important to evaluate all potential risks [21,57-58,60,62-63,66-68,72].

CONCLUSION

Among the many proposed mechanisms for the management and treatment of childhood obesity is a natural phenolic substance known as resveratrol [20,28]. Resveratrol has been shown to be effective in improving the symptoms and biomarkers of obesity, and researchers suspect that possible mechanisms include activating AMPK and increasing lipolysis [20,28]. Maternal resveratrol consumption has proven effective in decreasing body weight, adiposity (VAT), leptin levels, and leptin/sOB-R ratios in offspring, as well as managing embryonic oxidative stress [57-58,60,62]. Direct resveratrol consumption has shown similar results, including reducing levels of oxidative stress and adiposity in offspring exposed to hypoxia and/or high-fat diets in-utero, and improving endothelial function when combined with other vitamins, minerals, and bioactive compounds [21,67-68]. Resveratrol has also been found to ameliorate symptoms of some of the most prevalent comorbidities of obesity, due to its cardioprotective, anti-diabetic, and anti-inflammatory properties [20,28].

In the various preclinical trials that were examined in our review, several consistent findings were made, regarding both the effects of maternal resveratrol consumption on offspring and direct resveratrol consumption. Our findings indicate significant outcomes of maternal resveratrol consumption, in conjunction with high-fat diets, on offspring through numerous biomarkers, including leptins/sOB-R ratios, decreased body weight, and decreased adiposity [57-58,62]. Additionally, findings also demonstrate that indicators of oxidative stress among offspring were significantly reduced in the presence of maternal resveratrol supplementation [60]. Observed biomarkers that showed substantial improvements include lipid peroxidation, total thiol levels, GSH, and HNE levels [60]. Not only do our findings signify effectiveness of maternal resveratrol consumption on biomarkers in offspring, but they also demonstrate that direct resveratrol supplementation in offspring also yields significant results.

In offspring consuming high-fat diets, resveratrol supplementation was effective in decreasing indicators of both oxidative stress and body weight in females [63,66]. In addition, direct resveratrol consumption via drinking water also yielded similar results, reducing biomarkers of oxidative stress, including 8OHdG, 8-Iso-$PGF_2\alpha$, and protein carbonyl content [67]. Direct resveratrol supplementation in intrauterine growth restricted (IUGR) offspring also produced significant reductions in abdominal fat, both on its own and as a percentage of total body weight [21]. Our findings also indicate that resveratrol in supportive micronutrient

treatments (along with vitamin D3, folic acid, selenium, magnesium, zinc, curcumin, polygonum dry extract, and soy dry extract) is effective in improving DF and BMI [68].

The findings of the numerous studies we have reviewed contribute significantly to understanding of resveratrol's effectiveness in managing childhood obesity by highlighting the specific effects and mechanisms of both in-utero and direct resveratrol supplementation. These results can be used to establish more detailed correlations between resveratrol as a bioactive substance and the management of childhood obesity, among other chronic diseases. In order to continue furthering our knowledge of resveratrol as a functional food and investigate its effectiveness in the management of childhood obesity, we must conduct more studies on the direct effects of resveratrol consumption on children, as well as longitudinal studies on the long-term effects and/or consequences of resveratrol supplementation in childhood. These study designs will help researchers gain a better understanding of all the potential benefits, and possibly risks as well.

Limitations: While the studies collected in this literature review demonstrate significant findings for the potential of resveratrol in managing childhood obesity, several limitations exist when extrapolating findings from animal studies to humans. One of the most obvious limitations lies in the biological differences between humans and animals. Although animal studies have been extremely groundbreaking in research, there are countless physiological and genetic differences that affect the way that drugs, nutrients, and other compounds metabolize in the body. The metabolic pathways and mechanisms of resveratrol in rats have the potential to be different from that of humans, resulting in decreased ability to translate findings over to humans.

In regard to the biological differences between animals and humans, lifespan is also an important limitation to consider. Since animals experience a drastically shorter lifespan on average than humans do, resveratrol supplementation can only be examined over a relatively short time period. Not being able to collect long-term data on resveratrol supplementation greatly limits our ability to translate these findings over to humans, since humans might be exposed to resveratrol over the course of years, not just weeks or months.

Additionally, experimental conditions are likely to differ drastically from real-world conditions, resulting in decreased generalizability of findings. Animals under tightly regulated controls in a laboratory do not experience the same environmental influences that humans in the real world do, such as lifestyle behaviors, stress, climate differences, among many others.

Along with the several limitations of extrapolating findings from animal studies to humans, there are also ethical considerations needed when working with animals in a laboratory. Complying with ethical regulations ensures the fair and humane treatment of the animals being handled, but unfortunately limits the amounts and types of data that can be collected, as certain experiments are deemed unethical in animal models. Due to the several limitations that exist surrounding the use of animal studies, cautious interpretation of findings is essential.

The Functional Food Center defines functional foods as "natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms" [15]. The Functional Food Center's step-by-step process demonstrates the development process of

functional food products (Table 3) [76]. The first two steps in this 17-step process involve establishing the goal of the functional food product, as well as identifying the specific bioactive compound(s) that will accomplish this desired goal [76]. In this case, resveratrol has been proven to have numerous health benefits, including cardioprotective, anti-diabetic, anti-inflammatory, and antioxidant properties, making it an effective bioactive compound in the overall goal of managing childhood obesity [20,28]. Steps 3 and 4 focus on establishing both appropriate dosages and timing of consumption of the bioactive compound(s) [76].

After careful examination of various studies utilized in this review, our findings show that resveratrol dosage varies across studies and depends on a number of factors including weight and species. In addition to resveratrol dosage, the timing of resveratrol consumption also varies widely across studies, with some studies administering resveratrol on a daily basis and others providing just one consumption period. Steps 5 and 6 focus on determining specific pathways and mechanisms of the proposed bioactive compound(s), as well as relevant biomarkers to base results off [76]. A number of pathways and mechanisms for resveratrol have been proposed, including activating AMPK and increasing lipolysis [20,28]. In order to assess whether or not resveratrol is effective in targeting these pathways, relevant biomarkers have been examined by researchers including body weight, adiposity (VAT), leptin levels, leptin/sOB-R ratios, and levels of oxidative stress [21,57-58,60,62,67-68].

Once steps 1-6 have been completed, step 7 begins to focus specifically on the functional food product itself, establishing a food vehicle for the chosen bioactive compound(s) [76]. Resveratrol is a naturally occurring phenolic substance that is found in various foods like peanut skins, blueberries, mulberries, billberries, cranberries, red grapes, soybeans, pomegranates, dark chocolate, and pistachios [28]. Since these foods already are natural carriers of resveratrol, they would be excellent food vehicles for additional resveratrol supplementation as functional food products in the future. However, the trials examined in our review have only tested resveratrol supplementation in the form of resveratrol extracts.

Steps 8 and 9 emphasize the need for preclinical and clinical trials to assess the efficacy, safety, dosage, and timing of consumption for the chosen bioactive compound(s) [76]. There is interesting information about the usage of resveratrol for various purposes such as hepatic steatosis, glioblastoma, medulloblastoma, glucose tolerance, hepatocellular carcinoma, and various others [23-24,77-79]. These studies have all been preclinical trials, being conducted either in vivo or with animals [23-24,77-79]. A trial was conducted by Shibayama et al. on concentrated Kurozu with resveratrol supplementation in mice with hepatic steatosis [23]. Not only were significant results uncovered of resveratrol's ability to reduce hepatic steatosis onset, but researchers also proposed a potential pathway and mechanism of action taken by resveratrol (activation of AMPK) [23]. By examining the results from preclinical trials like this one, researchers can better determine the goals and parameters of clinical trials in order to establish safe and appropriate resveratrol dosages and times of consumption.

While significant findings have been made in these studies regarding resveratrol's effectiveness on specific biomarkers, as well as its efficacy and safety in humans,

much work continues to be needed in order to classify resveratrol-containing foods as functional food products. The next step in this process is to conduct more clinical trials with resveratrol to test not only its efficacy and safety in humans, but also its appropriate dosage and time of consumption. Once more clinical trials are conducted, step 10 involves creating a specified label for instructions on the correct usage of the product [76]. In addition to the proper dosage and timing for consumption, the label would also inform consumers of the various health benefits of the bioactive compound(s) [76]. Ideally, this label would include information about resveratrol's cardioprotective, anti-diabetic, anti-inflammatory, and antioxidant properties, as well as its appropriate dosage and time of consumption, which can be narrowed down with more clinical trials [20,28,69].

Step 11 requires all publications of the proposed bioactive compound(s) and functional food product(s) to be submitted to preferably open access, peer-reviewed journals, and step 12 emphasizes properly educating the public [76]. After steps 11 and 12 are completed, step 13 involves seeking approval from the FDA, and other trustworthy government agencies, to get the desired functional food product(s) officially established as such (step 14) [76]. Step 15 involves receiving the basic, level C, functional food classification by releasing the product to the public market [76]. To receive the optimal level of functional food product classification (level A), functional food products must first undergo epidemiological studies to reach level B (step 16), and finally, undergo after-market research to reach level A (step 17) [76].

For the future development of functional food products containing resveratrol as the bioactive compound, these steps need to be completed. As previously stated, the first step in accomplishing this would be to advance the research being done on resveratrol supplementation from preclinical to clinical trials, to assess the safety, correct dosage, and time of consumption for humans. Once this step of the process is completed successfully, a specific label can be created for resveratrol-containing functional food products (step 10) and be marketed to the public (step 11). Although there is still much work that must be done to establish functional food products with resveratrol, significant findings have already been made in terms of identifying specific pathways, mechanisms, and relevant biomarkers of resveratrol, as well as numerous preclinical trials.

Table 3. Steps for developing functional food products proposed by the Functional Food Center [76]

Step Number	Description of Steps to Create Functional Food Products
1	Establishes a goal of the functional food product
2	Determines relevant bioactive compound(s)
3	Establishes the appropriate dosage of bioactive compound(s)
4	Establishes the appropriate time of consumption of bioactive compound(s)
5	Determines the specific pathway and mechanism of action
6	Establishes relevant biomarker(s)
7	Chooses an appropriate food vehicle for bioactive compound(s)
8	Provides preclinical trials on efficacy and safety

Step Number	Description of Steps to Create Functional Food Products
9	Provides clinical trials for dosage, time of consumption, efficacy, and safety
10	Creates a special label that informs consumers of the most effective way to consume the product
11	Publications are submitted to peer-reviewed journals, preferably in open access
12	Educates the general public
13	Sends information to credible governmental agencies, such as the FDA, for approval
14	Official establishment of the accredited functional food product
15	Release the functional food product to the market (Receive the basic category (level C))
16	Provides epidemiological studies (Reapply for the approval for a new category (level B))
17	Provides after-market research (Reapply for the approval for a new category (level A))

Food products containing resveratrol provide numerous health benefits, such as cardiovascular protection, as well as anti-diabetic, anti-inflammatory, and antioxidant properties [20,28]. Future research on the optimal dosage and timing for consumption of resveratrol will prove beneficial in the creation of resveratrol-containing foods as functional food products. In a clinical setting, resveratrol supplementation has the potential to serve as an early lifestyle/nutritional intervention before more intense methods are resorted to, such as weight loss regimens and medications for children. Despite its great potential, challenges still exist in the logistics of resveratrol supplementation for children in terms of exact dosage, timing of consumption, and the monitoring of potential side effects. While resveratrol has shown promise in managing the symptoms of childhood obesity, proper nutrition and physical activity should always be advised.

The Novelty of This Work: Our article investigated the beneficial health effects of resveratrol on childhood obesity and its comorbidities. By evaluating various preclinical trials utilizing resveratrol, we have established relevant biomarkers, as well as the proposed pathways and mechanisms of resveratrol. For resveratrol-containing foods to continue through the process to becoming functional food products, more clinical trials are needed, in addition to label making, approval by a reliable government agency, and release of the product to the general public, with both epidemiological studies and after-market research following. In this article we evaluated data related to the effectiveness of resveratrol in the management of childhood obesity by using steps for developing functional food products proposed by the Functional Food Center [76].

List of Abbreviations: BMI: body mass index, MB: medulloblastoma, CHD: coronary heart disease, VAT: visceral adipose tissue, NOS: nitric oxide synthase, NO: nitric oxide, ROS: reactive oxygen species, MCP-1: monocyte chemoattractant protein-1, TG: triglyceride, AMPK: AMP-activated protein kinase, IUGR: intrauterine growth restricted, DOHaD: Developmental Origins of Health and Disease, SD: Sprague-Dawley, sOB/R: soluble leptin receptor, I/R: ischemia-reperfusion, 8OHdG: 8-hydroxy-2'-deoxyguanosine, 8-Iso-$PGF_2\alpha$: 8-Isoprostane, DF: delta flow, BUN: blood urea nitrogen, LPS: lipopolysaccharide

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