



# Transforming Women's Health with Resveratrol

## A Closer Look at Clinical Research

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### Introduction

As more women seek natural, preventive approaches to manage the range of physiological changes and challenges they experience throughout their lifetime, nutraceuticals are emerging as valuable tools for maintaining an active, healthy lifestyle.

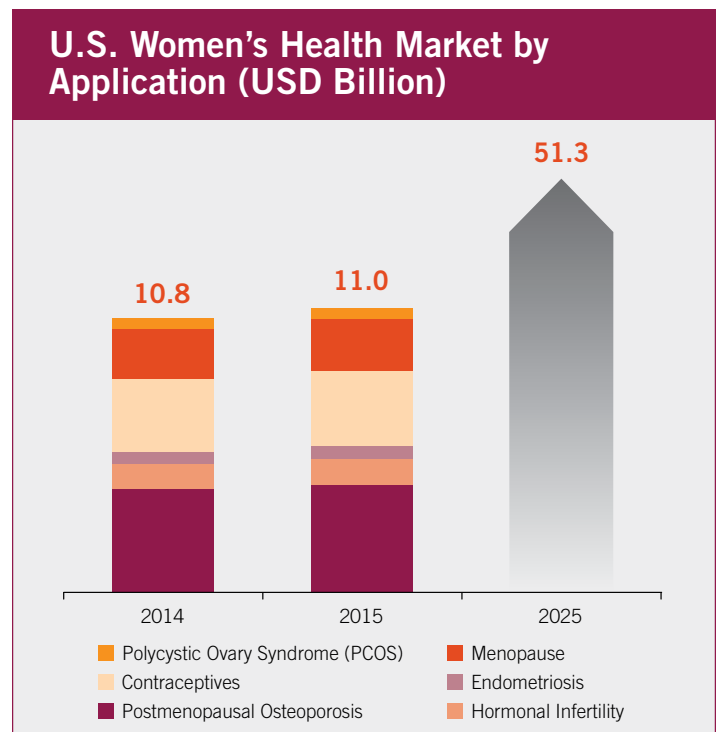
nutritional gaps (34%) and bone health (31%). Tied at 27%, women also ranked energy, immune health and healthy aging as the top reasons they take supplements.

**The global women's health market is expected to reach USD 51.3 billion by 2025.**  
Grand View Research 2017

Women aged 55+ are expected to account for nearly 40% of the 18+ female population in the U.S. by 2019. As the aging female demographic grows, so will a need for products targeting the concerns of older women, including supplements supporting bone health, pre and post-menopause, muscle function and blood homeostasis. Emerging health categories for women include a focus on 'beauty-from-within' skincare products and cognitive function supplements, which are both gaining momentum in this category.

**29% of respondents from a survey of 1,039 women ranked menopause as a top health issue for them, or someone close to them**  
Mintel

A consumer survey by the Council for Responsible Nutrition (2015) found the top concerns among female supplement users included overall wellness (56%), filling



Source: Grand View Research October 2017

In this white paper we take an in-depth look at the clinical studies supporting the essential role resveratrol could play in the growing women's health category.

## Resveratrol, a Unique Ingredient for Healthy Aging in Women

Resveratrol (a.k.a. *trans*-resveratrol or 3, 4', 5-trihydroxystilbene) is a natural phytoalexin compound, found in red grape skin, Japanese knotweed, peanuts, blueberries, and some other berries<sup>1</sup>. In nature it is produced by some plants in response to stress, injury, infection or ultraviolet (UV)-irradiation<sup>2</sup>. In humans, resveratrol has raised attention not only for being a very effective antioxidant<sup>3</sup> but also for exhibiting a number of complementary functions on cellular and systemic levels, leading to a plethora of beneficial health effects<sup>4</sup>. These additional advanced complimentary functions are what sets resveratrol apart from ingredients that function mainly as antioxidants.

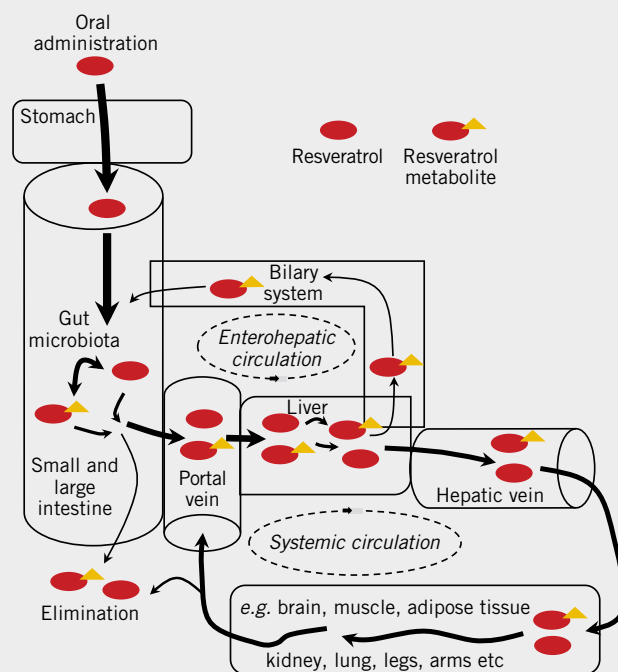
In the mid-1990s, resveratrol was brought into the spotlight as the main polyphenol in red wine, in the context of the French paradox - the apparent contradiction between the French having a low rate of cardiovascular diseases despite having a diet rich in saturated fats, including the consumption of large amounts of alcohol and cigarette smoking. It was hypothesized that the benefits for the French were due, at least in part, to their consumption of moderate amounts of red wine that contained 1 to 2 mg of resveratrol per 8 ounces<sup>5</sup>. Since then, scientific interest in this polyphenol has increased exponentially. By 1996, there were 46 scientific papers on resveratrol, increasing to over 1,300 by 2006 and to more than 11,300 by the end of 2018<sup>6</sup>. Today, resveratrol is globally recognized for its beneficial effects on, amongst others, cardiovascular health<sup>7</sup>, blood glucose control<sup>8</sup>, bone health<sup>9,10</sup>, memory<sup>11</sup> and skin health<sup>12</sup>. Resveratrol is therefore widely used as a key ingredient to promote healthy aging.

## Understanding the Mechanism of Action

The mechanisms by which resveratrol achieves such a wide range of benefits is still not fully understood and under current investigation<sup>13</sup>. It has been shown that resveratrol, like most polyphenols, is rapidly metabolized in the intestine and the liver after oral intake to its glucuronide or sulfate derivatives, leading to relatively low plasma concentrations

of free resveratrol<sup>14</sup>. However, repeated or prolonged dosing is suggested to result in enterohepatic recirculation<sup>15</sup>, leading to higher plasma and tissue levels of resveratrol and its key metabolites (see Figure 1). A relatively low dose of 25 mg is enough to result in a plasma concentration of total resveratrol (including its metabolites) of about 2  $\mu$ M after 60 minutes<sup>16</sup>. Moreover, certain resveratrol metabolites seem to serve as an intracellular pool for resveratrol regeneration, possibly allowing higher local concentrations and leading to positive cellular effects<sup>17,18</sup>. As a result, resveratrol and its metabolites appear to be present in all tissues, even crossing the blood-brain barrier and having potential beneficial effects on the central nervous system<sup>19,20</sup>.

Figure 1.



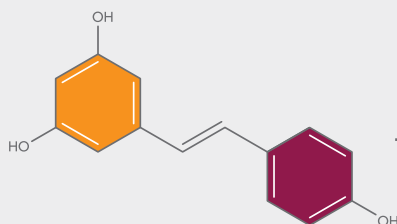
**Figure 1. Schematic illustration of resveratrol metabolism after oral administration.** Resveratrol passes the stomach and enters the intestinal tract where it is absorbed and enters the portal vein, metabolized by enzymes from the gut microbiota or eliminated from the system. By biotransformation in the liver, resveratrol gets conjugated with sulfate and glucuronide groups and enters back into the intestine through the enterohepatic cycle or enters the systemic circulation via the hepatic vein to be available for tissue and organs like muscle, brain and adipose tissue etc.

Illustration derived from Roberts *et al.*, 2014<sup>21</sup>

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Figure 2.



**trans-resveratrol**  
(3,5,4'-trihydroxy-trans stilbene)

Physico-chemical property  
(e.g. Polyphenol with 3 OH-groups)

Protein modulating function (e.g.  
AMPK↑, SIRT1↑, SOD↑, GPx↑,  
NFκB↓, CAT↑, COX-2↓, EGFR2↓,  
eNOS↑, m-TOR↓, NOX↓, Nrf2↑,  
p53↑, PGC-1↑, STAT3↑, VEGF↓,  
VCAM1↓)

- Adipogenesis↓
- Antibacterial activity↑
- Autophagy↑
- Beneficial gut microbiota↑
- Blood flow↑
- Blood glucose↓
- Blood pressure↓
- Bone mineral density↑
- Cardiac dysfunction↓
- Cell cycle regulation↑
- Cellular energy↑
- Cerebrovascular responsiveness↑
- Cholesterol and triglycerides↓
- Cognitive decline↓
- DNA repair↑
- Fat oxidation↑
- Halitosis↓
- Inflammation↓
- Insulin resistance↓
- Mitochondrial biogenesis↑
- Muscle fatigue↓
- Neuron survival↑
- Oxidative stress↓
- Periodontitis↓

**Figure 2. Beneficial health effects of resveratrol.**

The physical chemical feature and protein modulating function of resveratrol involved in regulating stressors, cell cycle and longevity as well as cellular energy homeostasis. Stated list of proteins regulated by resveratrol is not comprehensive. Adenosine monophosphate activated protein kinase (AMPK), sirtuin 1 (SIRT1), superoxide dismutase (SOD), glutathione peroxidase (GPx), nuclear factor kappa B (NF-κB), catalase (CAT), cyclooxygenase (COX), endothelial growth factor receptor (EGFR), endothelial nitric oxide synthase (eNOS), mammalian target of rapamycin (mTOR), nicotinamide adenine dinucleotide phosphate oxidase (NOX), nuclear factor-E2-related factor (Nrf), tumor protein 53 (p53), peroxisome proliferator activated receptor-gamma coactivator (PGC), signal transducer and activator of transcription (STAT), vascular endothelial growth factor (VEGF), vascular cell adhesion protein 1 (VCAM-1).

Effect is indicated by ↓: reduction; ↑: induction.

Resveratrol effects on protein regulation are adopted from Tomé-Carneiro *et al.*, 2013<sup>36</sup>

In order to contribute to the understanding of the mechanisms through which resveratrol exerts its biological effects, it is critical to review the direct molecular targets of resveratrol<sup>22-24</sup>. Among these targets include enzymes involved in inflammation, adipogenesis, apoptosis, DNA repair, autophagy, regulation of cellular energy, regulation of gene expression, and stress response at the cellular level (see Figure 2). Importantly, several of the molecular targets of resveratrol seem to interact with each other and trigger a cellular response similar to calorie restriction<sup>22,25</sup>.

Calorie restriction has been shown to have a lengthening effect on the lifespan of a number of species ranging from yeast<sup>26</sup> to dogs<sup>27</sup> to primates<sup>28</sup> and to ameliorate multiple age-related diseases such as type 2 diabetes, cardiovascular disease, and cancer<sup>29</sup>. Many of the effects of both calorie restriction and resveratrol are mediated by the activation of a histone deacetylase enzyme called SIRT1<sup>30</sup> and through

the AMP-activated protein kinase (AMPK) pathway and its role on maintaining a proper mitochondrial function<sup>31</sup>.

Relevant to the potential benefits of resveratrol is how different foods/supplements affect the gut biota, especially those promoting increased growth of favorable microbes in the gut. Resveratrol and other polyphenols have been suggested to inhibit pathogenic bacteria while stimulating the growth of beneficial bacteria, exerting prebiotic-like effects<sup>32,33</sup>. Importantly, recent publications show that some of the effects of resveratrol including reduced atherosclerosis<sup>34</sup> and improved glucose homeostasis<sup>35</sup> occur via gut microbiota alteration. This opens the door to the possibility that other health benefits attributed to the oral intake of resveratrol could also be mediated by gut microbiota alteration and provides a possible new explanation for the so-called resveratrol paradox (i.e. low bioavailability but high bioactivity)<sup>36</sup>.

## Managing the Menopausal Transition and Afterwards

At the beginning of the 20th century, the life expectancy of a female born in the USA was barely 50 years. This number has increased steadily and in 1960 a woman's life expectancy reached 73 years. A female born today could easily expect to blow out 80 candles<sup>37</sup>. However, the increase in life expectancy has not been accompanied by a similar increase in the age of menopause onset<sup>38</sup>. Therefore, women may live as many years post-menopausal as they do during child bearing years. Consequentially, there is a rise in the need for physical and dietary interventions that help postmenopausal women to properly manage the changes that their body and metabolism experience, and thereby allow them to feel, look and perform better for much longer.

**Every day, an estimated 6,000 American women reach menopause - that is approximately 2 million a year.**

North American Menopause Society (NAMS)

An active lifestyle and exercise have been proven to be key for the maintenance of long and stimulating lives after going through the menopausal transition<sup>39</sup>. A healthy diet also plays an important role in the management of peri- and postmenopausal-associated conditions<sup>40</sup>. Among the dietary interventions supporting healthy aging in women are polyphenols such as resveratrol, soy isoflavones, green tea flavonoids, and others, which have gained traction in the past two decades<sup>40</sup>.

As we age, our bodies experience gradual changes and decline in many systems and processes. Most of these changes are not gender-specific but, in some cases, these changes are more of a concern to women than to men. Examples of such conditions could be the imbalance of sex steroid hormone levels or the decrease of bone density that accompany menopause<sup>41</sup>. Moreover, peri- and postmenopausal women often suffer with mood changes, including depression, increased pain and lowered sexual desire and activity<sup>41</sup>. Other, less gender-specific issues that are also of concern for peri- and postmenopausal women are the loss of skin elasticity and the appearance of

wrinkles and age spots on the skin<sup>42</sup>, the progressive loss of skeletal muscle mass and function (sarcopenia)<sup>43,44</sup> and the increased risk of cardiovascular and metabolic diseases<sup>45</sup>. Fortunately, in the past couple of decades, awareness of these changes has increased and, in parallel, new nutritional strategies to help manage them have emerged<sup>40</sup>. Among these, the inclusion of resveratrol in the diet has been suggested as an effective way to tackle some of these menopause-related conditions. It has been suggested that the antiaging effects of resveratrol could be due to several related mechanisms, including its antioxidant, anti-inflammation and chemo-preventive<sup>46</sup> properties, as well as resveratrol's potential role as a phytoestrogen<sup>47</sup>.

## Clinical Studies on Resveratrol for Women's Health and Menopause

The health benefits of resveratrol in humans are supported by over 150 clinical studies<sup>6</sup> published to date. The present document is a review of the published clinical studies that investigate the benefits of resveratrol supplementation in conditions and concerns related to women's health and aging, including:

- Maintenance of a good hormonal balance
- Bone density (osteoporosis) and joint health (osteoarthritis)
- Muscle function (sarcopenia)
- Skin health using oral supplements and topical applications
- Blood homeostasis
- Cognitive performance
- Quality of life (vitality, mood, perception of pain)

In clinical research, randomized controlled trials (RCTs) are considered the best way to study the safety and efficacy of new treatments. Most of the articles described in this review are randomized, double-blind, placebo-controlled human clinical trials, the "gold-standard" for clinical research<sup>37</sup>.



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Table 1. Studies on Resveratrol for Women's Health and Menopause.

Health indication	Reference	Study participants	Intervention each day	Length of trial	Study focus	Main Result
Hormonal imbalance	Bazzan <i>et al.</i> , 2013 <sup>50</sup>	76 women	Supplement containing resveratrol and other elements	196 ± 175 days	Changes on 2-Hydroxyestrone (2-HE) and 16 $\alpha$ -Hydroxyestrone (16 $\alpha$ -HE) as associated with cancer risk	Treatment improved the 2-HE level and 2-HE/16 $\alpha$ -HE ratio
	Chow <i>et al.</i> , 2014 <sup>51</sup>	40 obese (BMI $\geq$ 25 kg/m <sup>2</sup> ) postmenopausal women	Resveratrol	12 weeks	Change in sex steroid hormone levels	Treatment improved estrogen metabolism and sex steroid hormone binding globulin level
Bone health and joint health (osteoporosis and osteoarthritis)	Ornstrup <i>et al.</i> , 2014 <sup>9</sup>	74 middle-aged adults with metabolic syndrome	Veri-te™ resveratrol or placebo	16 weeks	Bone alkaline phosphatase (BAP), bone mineral density	BAP and bone mineral density increased dose dependently with Veri-te™ resveratrol
	Poulsen <i>et al.</i> , 2014 <sup>10</sup>	24 obese adults	Veri-te™ resveratrol or placebo	4 weeks	Levels of BAP	Resveratrol increased plasma levels of BAP
	Marouf <i>et al.</i> , 2018 <sup>52</sup>	110 older adults with mild osteoarthritis	Resveratrol + meloxicam or placebo	12 weeks	Inflammation biomarkers	Treatment decreased the production of inflammatory markers serum C-reactive protein (hs-CRP), interleukin-6 (IL-6) (B) and tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )
	Khojah <i>et al.</i> , 2018 <sup>53</sup>	100 older adults	Resveratrol or placebo	12 weeks	Effects on biochemical markers in rheumatoid arthritis	Treatment lowered inflammation biomarkers and disease activity score assessment for 28 joints
Muscle function (sarcopenia)	Alway <i>et al.</i> , 2017 <sup>54</sup>	30 older adults	Resveratrol + exercise or placebo + exercise	12 weeks	Mitochondrial density, muscle fatigue resistance and cardiovascular function	Exercise + resveratrol improved mitochondrial density and muscle fatigue resistance greater than exercise alone
	Most <i>et al.</i> , 2017 <sup>56</sup>	37 overweight and obese subjects	Resveratrol + epigallocatechin-3-gallate or placebo	12 weeks	Microbiota composition in feces, fat oxidation and skeletal muscle mitochondrial oxidative capacity	Supplementation increased skeletal muscle mitochondrial oxidative capacity
	Polley <i>et al.</i> , 2016 <sup>55</sup>	16 healthy young adults	Resveratrol + piperine + exercise or placebo + exercise	4 weeks	Skeletal muscle mitochondrial capacity	Treatment increased skeletal muscle mitochondrial capacity
Skin Health	Buonocore <i>et al.</i> , 2012 <sup>57</sup>	50 adults	Supplement containing resveratrol or placebo	60 days	Oxidative stress, skin moisturization and elasticity, intensity of age spots and others	Treatment increased antioxidant capacity, improved skin moisturization and elasticity, and diminished skin roughness, depth of wrinkles and intensity of age spots
	Fabbrocini <i>et al.</i> , 2011 <sup>58</sup>	20 young adults affected by acne vulgaris	Gel containing resveratrol (topical application) or placebo	60 days	Global Acne Grading System (GAGS) score and area of microcomedones	Improved GAGS score by 53.75% and reduced area of microcomedones by 66.7%
	Mayano-Mendez <i>et al.</i> , 2014 <sup>58</sup>	8 older women	Cream containing resveratrol or placebo	30 days	Visible improvement of skin health and clinical conditions	Treatment enhanced skin hydration, elasticity and colorimetry of about 20.53%, 49.70% and 6.17%
Blood homeostasis	Malvasi <i>et al.</i> , 2017 <sup>65</sup>	110 overweight pregnant women	Supplement containing resveratrol or placebo	60 days	Total cholesterol, LDL, HDL, triglycerides and glucose levels	All blood chemistry parameters improved compared to placebo
	Zern <i>et al.</i> , 2005 <sup>64</sup>	24 pre- and 20 postmenopausal women	Lyophilized grape powder containing resveratrol or placebo	8 weeks	Levels of plasma lipids and glucose. Biomarkers for oxidative stress and inflammation	Treatment beneficially effected risk factors for coronary heart disease
Cognitive Performance	Evans <i>et al.</i> , 2017 <sup>62</sup>	80 healthy postmenopausal women	Resveratrol or placebo	14 weeks	Cerebrovascular function and cognitive performance	Resveratrol optimized brain blood flow and cognitive performance
Quality of life (QoL)	Caruso <i>et al.</i> , 2017 <sup>60</sup>	60 perimenopausal women having vasomotor symptoms	Supplement containing resveratrol or placebo	24 weeks	Menopause symptoms, quality of life, sexual function and sexual distress	Menopause symptoms, quality of life and sexual activity improved
	Davinelli <i>et al.</i> , 2017 <sup>61</sup>	60 recently menopausal women	Supplement containing resveratrol or placebo	12 weeks	Severity of menopause-related complaints, depression and sleep quality	Treatment improved vaginal dryness, heart discomfort, sexual problems, depression, and sleep quality
	Wong, <i>et al.</i> , 2017 <sup>63</sup>	80 postmenopausal women	Resveratrol or placebo	14 weeks	Cerebrovascular function, perception of pain, sleep quality, depressive symptoms and mood states	Resveratrol improved total well- being and cerebrovascular function

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18 published RCTs were selected to represent the benefits of resveratrol supplementation on women's health and menopause (see Table 1 above). Studies investigating the effects of resveratrol-containing supplements were also taken into account.

The cohort chosen for many of the studies has been exclusively composed of women – menopausal or not. However, some studies including male or mixed subjects are also covered as the study conditions fit the focus of this review and the conclusions would be transferable to females. For example, osteoporosis caused by metabolic syndrome or by menopause can be assumed to have very similar origins (i.e. low levels of sex hormones). This is also supported by extensive research in different animal models of osteoporosis<sup>48,49</sup>.

**Results indicate that resveratrol supplementation contributes to the maintenance of optimum levels of sex steroid hormones<sup>50,51</sup>, good bone mineral density<sup>9,10</sup>, joint and cartilage health<sup>52,53</sup> and mitochondrial density in skeletal muscle, as well as improved muscle fatigue resistance<sup>54-56</sup>. Resveratrol also decreases skin wrinkling and age spots<sup>57,58</sup>, reduces acne<sup>59</sup>, improves several mood parameters leading to a better general well-being and sexual activity, and reduces the perception of pain<sup>60-63</sup>. Finally, under certain conditions, the intake of resveratrol or resveratrol-containing supplements improves several metabolic parameters and blood homeostasis, including cholesterol and glucose plasma levels, and reduces markers of inflammation<sup>64,65</sup>.**

## Resveratrol Supply Chain Considerations

All resveratrol treatments were generally well tolerated and adverse events such as gastrointestinal symptoms including nausea and diarrhea have been reported after ingesting a dose of > 2.5 g per day resveratrol only<sup>66</sup>. It is believed that the origin of resveratrol plays a dominant role in this perspective. In fact, plant-derived resveratrol often contains emodin, an anthraquinone derivative with laxative properties which requires an elaborate chromatographic separation technique for its removal due to its structural similarity to resveratrol<sup>67</sup>. Additionally, soil-born contaminants such as polycyclic aromatic hydrocarbons, pesticides and herbicides might also be detected in resveratrol extracted from plants. The result is that resveratrol products on the market do not always contain the amount and quality of contaminant-free resveratrol as indicated on the label and therefore careful selection is key<sup>68</sup>. An innovative new source of resveratrol made through a yeast fermentation process by Evolva has eliminated these concerns, as Veri-te™ resveratrol is guaranteed to be contaminant-free.

## Conclusions

While resveratrol protects plants from harsh conditions in nature, it has garnered attention in human health as a very effective antioxidant<sup>3</sup>. However, what makes resveratrol unique compared to other antioxidants is its effect on complementary functions at the cellular and systemic level, leading to beneficial health effects<sup>4</sup>. The present research suggests that the effects of resveratrol on women's overall health is promising for a wide range of health indications as outlined in this paper.

This review for women's health draws on over 150 clinical studies<sup>6</sup> published to date. Eighteen published RCTs were specifically selected to demonstrate the effect of resveratrol supplementation on women's health and menopause.

The review focuses on the benefits of resveratrol supplementation in conditions and concerns related to women's health and aging, including: hormonal balance, bone density and joint health, muscle function, skin health using oral supplements and topical applications, blood homeostasis and cognitive performance.

When selecting a resveratrol supply, there are several important factors to consider, such as purity and potential contaminants, reliability and sustainability of the source, clinical trial support, manufacturing standards, and certifications that may be required for the end product.

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