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Longitudinal Safety Analysis of Chronic Resveratrol Supplementation: A Critical Review of the Interaction between Thyroid, Bone and Iron Metabolism

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Abstract: *Objective:* Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a natural polyphenol that has been found to have the effects of anti-aging, anti-inflammation, and metabolism. However, there are still no long-term safety data for resveratrol, so in this review, its effects on thyroid function, bone mineral density, and iron metabolism, etc., will be examined to explore its long-term safety and how its pharmacological properties may affect health in various ways. *Methods:* In April 2026, PubMed, EMBASE, Cochrane Library, and Web of Science were used for the search. The long-term safety, thyroid function, bone health, and iron metabolism of preclinical and clinical studies were also examined. *Results:* Generally speaking, the short-term clinical trials have demonstrated good tolerance; however, animal studies have shown that it may affect the activity of thyroid peroxidase, bone remodeling, and iron chelation. *Conclusion:* It is not yet known whether the results will help treat the disease in the long run; therefore, at present, this evidence cannot be applied. More good clinical trials need to be carried out to determine the impact on thyroid function, bone health, and iron homeostasis.

Keywords: Resveratrol; Long-term safety; Thyroid function; Bone mineral density; Iron metabolism

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1. Introduction

Resveratrol is a naturally occurring stilbene polyphenol in grapes, peanuts, berries, and some medicinal plants; it is often named after resveratrol. Based on the "French paradox" hypothesis, resveratrol has been extensively studied for its antioxidant, anti-inflammatory, cardioprotective, neuroprotective, and metabolic effects, and it is thought to be mediated by the SIRT1, AMPK, and NF-κB signaling pathways [1–6].

Although there may be some benefits, no long-term safety data for resveratrol have been gathered yet.

Natural products are generally believed to be safe, but this belief is not always supported by clinical data [7–8]. Another reason for the poor oral bioavailability is fast first-pass metabolism; therefore, it was proposed that a high-dose formulation should be used to reduce the total amount of substance available in the body and improve safety [9–10].

Resveratrol has some biological effects that could be detrimental in the long run. It is a metal chelator that can bind iron and may affect the amount of iron in the body; given that it has the same structure as phytoestrogens, it could also disrupt endocrine function and the hypothalamic-pituitary-thyroid axis. Based on the above research, it is known that resveratrol is safe for the thyroid, bones, and metals in the body over a long period.

2. Pharmacokinetic considerations in chronic use

2.1. Absorption and first-pass metabolism

Resveratrol has very poor oral bioavailability (less than 1%) because of the first-pass effect in the intestine and liver. UDP-glucuronosyltransferases and sulfotransferases can increase the amount of glucuronide and sulfate conjugates. These metabolites are still biologically active and may be different from the parent compound. Resveratrol-3-O-sulfate can inhibit thyroid peroxidase in vitro, and it is suspected that its metabolites may change the endocrine function after a long time.

2.2. Systemic exposure and tissue distribution

Resveratrol concentration in the circulation is relatively low; therefore, it may not reach tissues effectively. After oral administration of 25 mg, the maximum plasma concentration is generally 1–5 ng/mL, and a gram dose will have much higher levels. Based on animal and human studies, resveratrol and its metabolites are more concentrated in the liver, kidney, and intestine, and the local concentration may be higher than that in the blood. The tissue distribution of such tissues may have long-term adverse effects on thyroid function and iron metabolism.

2.3. Formulation effects on exposure

A good form can help the body absorb it. Micronized preparations have a relatively higher concentration in the blood than the old ones, and when taken with piperine, they can be absorbed better due to a decrease in glucuronidation. Therefore, people taking the same labeled dose will have different amounts of systemic exposure and thus cannot be safely studied for a long time.

3. Thyroid function: An under-researched link

3.1. Mechanistic basis of thyroid interference

The thyroid is a possible target of resveratrol, but there is currently little evidence. Therefore, the reasons put forward so far are inhibition of thyroid peroxidase (TPO), changes in deiodinase activity, and disorders of the hypothalamic-pituitary-thyroid (HPT) axis.

TPO is needed for the production of thyroid hormones. Resveratrol can reduce the activity of TPO in vitro, and its 3-O-sulfate metabolite is even more inhibitory; therefore, it is proposed that this metabolite may also have endocrine-modulating effects after prolonged consumption. Resveratrol can also reduce the activity

of type I deiodinase (DIO1); therefore, it may change the peripheral conversion of T4 to T3 and affect the balance of thyroid hormones.

3.2. Preclinical evidence

Resveratrol may have some effect on the thyroid gland in the animal kingdom at high concentrations. After 90 days in rats, a high dose of resveratrol lowered circulating T3 and T4 and raised TSH, and there was a reduction in the size and colloid density of thyroid follicles. Another study found that after a long time, the expression of sodium-iodide symporter (NIS) and TPO was reduced; therefore, there may be a decline in thyroid hormone production. Although the above results indicate that there are multiple mechanisms by which the thyroid is damaged, they may not apply to people because the amount administered in animals was too large.

3.3. Human data and clinical relevance

There is no clinical data. Turner and others did not find an increase in TSH in healthy older adults after the intake of resveratrol in a randomized study. However, thyroid function was not the main subject of this paper, and free T3 and free T4 were not used.

Subclinical hypothyroidism is relatively frequent and has been linked to many problems in the heart and metabolism. A small increase or decrease in the amount of thyroid hormone can also cause symptoms in some people. However, there has been no good, long-term clinical study investigating the effect of resveratrol on thyroid function. In the future, TSH, free T3, free T4, and thyroid autoantibodies will be added to better determine the endocrine condition.

4. Bone health: A double-edged sword

4.1. The complex biology of resveratrol–bone interactions

Resveratrol may have some good and bad effects on the bones at different doses and under different conditions of the body. Bone remodeling is a result of the difference in formation and resorption by osteoblasts and osteoclasts. Resveratrol can promote the differentiation of osteoblasts by activating SIRT1 and increasing osteogenic markers, and it can reduce the formation of osteoclasts through the inhibition of RANKL/NF-κB.

4.2. Beneficial effects in preclinical models

Most animal studies have shown that resveratrol is protective of bone. Resveratrol can help to maintain the bone density of ovariectomized rats by promoting the formation of new bone cells (osteoblasts) and inhibiting the degradation of existing bone, thus regulating the microarchitecture of trabecular bone. Meta-analysis of the 18 animal studies has also shown that there are considerable improvements in bone mineral density and bone strength; however, due to different dosages, treatment times, experimental models, etc., there is significant heterogeneity.

4.3. Possible adverse effects and fluctuations in the population

Despite its potential benefits, resveratrol may also exert adverse skeletal effects under certain conditions. As a phytoestrogen with preferential binding to estrogen receptor β (ERβ), its biological effects may vary

according to sex and hormonal status. In male rats, high-dose resveratrol reduced bone mineral density and mechanical strength, possibly through excessive SIRT1 activation disrupting normal bone remodeling (**Figure 1**).

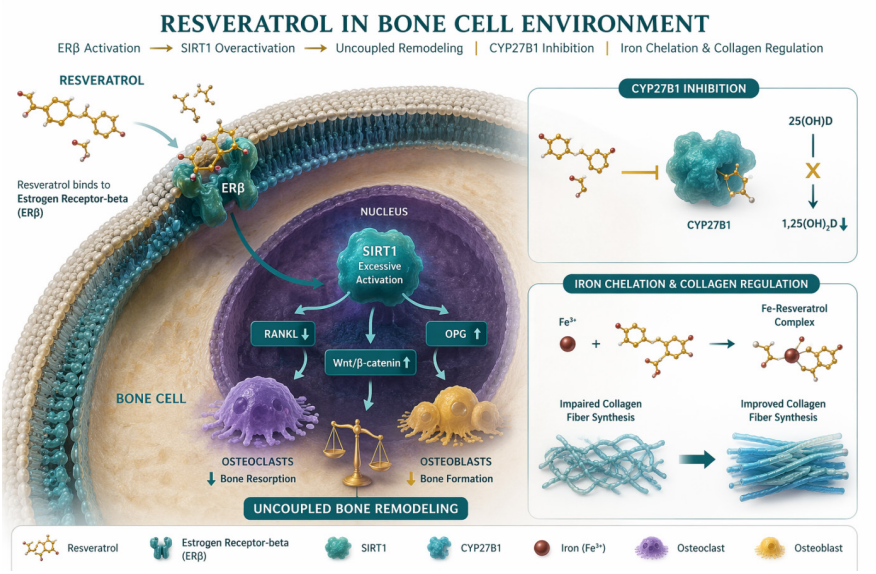

Figure 1. Resveratrol in bone cell environment

Resveratrol can also inhibit CYP27B1 and reduce the activation of vitamin D and calcium absorption (**Figure 2**). It is also possible that the iron-chelating effect will reduce the production of collagen and interfere with the mineralization of the bone matrix over time due to several factors.

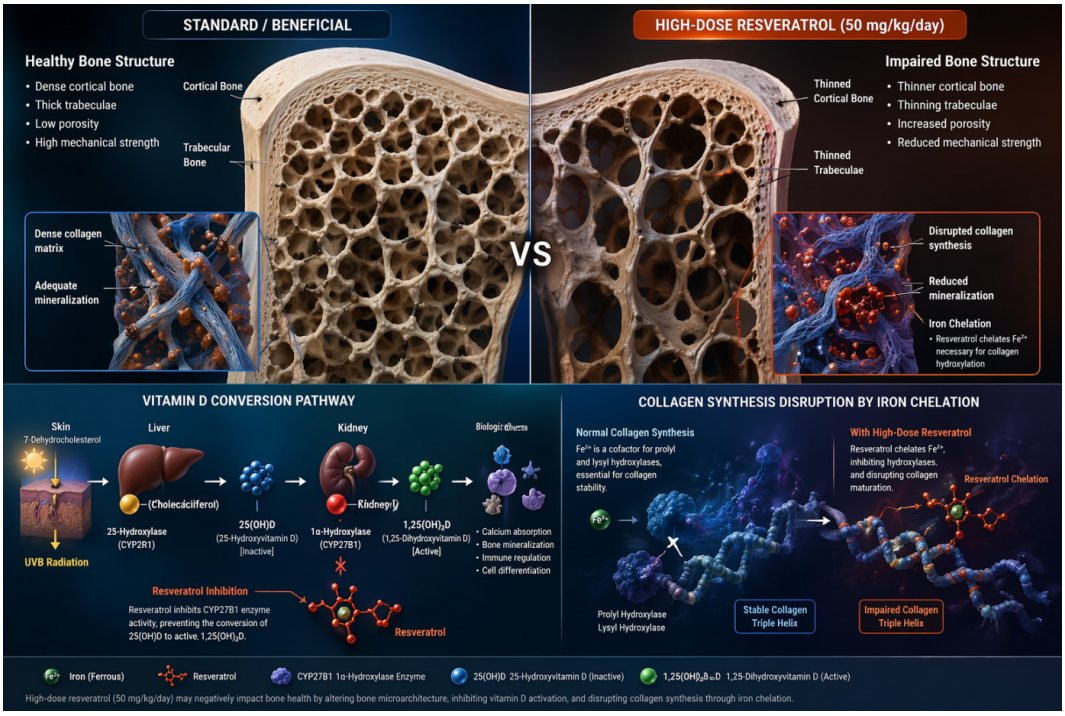

Figure 2. Dose-dependent effects of resveratrol on bone structure

4.4. Limitations of clinical evidence

The clinical data do not agree. According to the results of the RESHAW study, after one year of adding resveratrol, the overall bone mineral density of postmenopausal women did not show a significant increase; only in the group with reduced insulin resistance was a relatively small increase observed. Another 6-month follow-up of the healthy men did not show any changes in bone density or bone turnover markers. Different doses, formulations, subjects, and different periods of treatment may be the reasons for the differing results. Importantly, no randomized trials have evaluated bone health after one year or more, so researchers do not know about its long-term effect on bones.

5. Iron metabolism and chelation problems

5.1. Mechanism of iron chelation

People with some blood diseases use iron chelation to cleanse the blood naturally. Toxic iron levels are reduced in people with hereditary hemochromatosis. Patients with thalassemia also use it to remove excess iron accumulation. Vital organs will not be permanently damaged by iron deposits, and daily supplements may cause nutrient deficiency in healthy people. Prolonged use of the extract has lowered the amount of iron in the body. Low mineral content is associated with severe tiredness and dizziness. Anemia is the result of this prolonged loss of minerals; Resveratrol forms oxygen pairs on a ring to bind iron. Often, it is compared with the clinical drug deferoxamine. Molecular “hooks” are very good at grasping minerals strongly. The reason for its good binding properties is the specific chemical structure.

Resveratrol tightly binds iron in the presence of water in the lab. The combination of light and electrical means was used to measure it. Changes in color, light absorption, and behavior of metal ions can be observed with instruments, and at physiological pH, two molecules of resveratrol bind one Fe^{3+} ion. The Ligand/metal ratio is 2:1. The reported conditional stability constant is about log K’$_{18}$.5. It is a relatively stable form of iron binding.

The same complexes are still in the reduced form. This is the special situation of biology; therefore, there is often a chemical reduction. It indicates that the iron in resveratrol may be less available for the body in its usual form. Direct effects on the whole-body iron status have not yet been determined in humans.

5.2. Preclinical data on iron depletion

Animal studies have found that resveratrol affects iron metabolism. Sanchis and others have been carrying out experiments on rats for more than 90 days. The daily amount of food for the animals is 100 mg/kg. Some indicators have changed after the treatment.

Serum ferritin was 30 percent lower than that in the untreated group. Ferritin is used by the body to store iron. A drop in ferritin indicates less iron. Hematocrit was also slightly lower and had dropped by about 3–4 percent. It shows how many red blood cells are in the body. A small number indicates that there is little iron for making blood. Resveratrol reduced the amount of iron in the liver by about 25 percent. Hepcidin is a hormone that regulates iron in the body, so it changed as well. Its expression was reduced at the level of genetic information and at the level of proteins. Hepcidin normally keeps iron within the cells. Hepcidin reduces the level of iron in the blood by downregulating it. At the same time, the reduction in stored iron and circulating ferritin also shows that there is a net loss of body iron; this may be due to the compound directly binding iron in the gut and inhibiting its absorption.

Resveratrol has also been applied to some illnesses separately. Franco and others have used mice with β-thalassemia, an inherited blood disease. Patients have iron overload for this reason. They have insufficient red blood cell production and thus absorb too much iron. The Number of blood transfusions is too high. Too much iron is harmful to the liver and heart, etc. Resveratrol ameliorated the animals' anemia. It promoted the proper development of young red blood cells. There was a reduction in oxidative stress. As a result, both the liver and the heart had decreased iron content. These organs are the first to be affected by iron toxicity in thalassemia. The results show that resveratrol can bind iron in the body of a living organism; it is not only in test tubes. It is to be expected that, with an increase in red blood cells, the amount of iron in organs will decrease simultaneously.

5.3. Clinical significance and vulnerable populations

It has clinical significance, but the human data have not been collected yet. About 3%–5% of adults are iron deficient but not anemic. It has been associated with cognitive impairment, loss of physical function, and an increased risk of infection; low ferritin levels in the presence of normal hemoglobin are often the initial signs. A ferritin level of less than 30 ng/mL is frequently regarded as a sign of mild iron deficiency.

This may be the case with prolonged use of resveratrol.

5.3.1. Premenopausal women

Menstruation causes more iron loss, and about 10–15 percent of premenopausal women are iron-deficient.

5.3.2. Vegetarians/Vegans

The absorption rate of non-heme iron from plants is low, and resveratrol may also reduce its absorption.

5.3.3. Endurance athletes

Prone to deficiency of foot-strike hemolysis and increased iron turnover

5.3.4. Patients with subclinical inflammation are more susceptible to harm from the inflammation

Inflammation increases hepcidin, and it is unknown whether this increases the iron-repressing effect of resveratrol.

5.4. Gaps in evidence from human studies

Scientists do not know how long the effects of resveratrol on iron will last. Most of the human trials are only 4–12 weeks long. These short studies rarely have all the iron panels. One study had a 12-month follow-up. Only whole blood counts were recorded. Vital signs of the patient were not taken.

Resveratrol has the property of metal chelation. It forms an iron-ion complex, Fe^{2+}, in the gut. Therefore, it will not enter the blood circulation. After a long time, the body will gradually lose some minerals. Clinically speaking, people generally care more about their heart and life. Nutritional side effects have received little attention.

Iron deficiency is often asymptomatic. Compensatory Changes are the body's ways of dealing with problems. Hemoglobin is in the normal range for a long time. Meanwhile, internal iron stores are steadily exhausted. Functional impairment begins before a doctor is aware of anemia. There will be less cognitive ability and energy. The problems have appeared, but the blood test is still normal.

6. Current deficiencies of clinical trials

6.1. The duration paradox

Most people take resveratrol supplements for long-term maintenance, not treatment. However, the clinical data are mostly from a short time. Ramírez-Garza and others have organized and meta-analyzed the results of the 29 randomized controlled trials in about 1,493 people. The median length of the study was only 8 weeks, and 90% of the trials were shorter than six months.

It is not a problem of safety. There are many changes in the body, such as hormone fluctuations, tissue recovery, and a lack of nutrients, that may take a long time to show. Thyroid disorders, bone loss, and iron deficiency will not be evident after a short time. Therefore, the short-term study may be wrongly regarded as safe in the long run.

6.2. Heterogeneous endpoints and weakness of safety analysis

The current literature has many different endpoints and tests. Most meta-analyses have still focused on the effect on the cardiovascular system, blood sugar, and inflammation. Safety reports are usually shorter. Usually, it is based on adverse event reports and general tests of liver enzymes, kidney function, and blood count.

There are relatively few particular safety checks. Most of the trials do not have thyroid markers, bone density tests, or iron tests. Therefore, it is not expected that the body will change gradually over time. The size of the sample is too small to see the effect. For example, about 100 people may be too few to detect a small increase in TSH or ferritin in a clinical trial. There will be some small modifications in the future.

6.3. Critical analysis of meta-analyses

Most meta-analyses have indicated that resveratrol is generally safe in people. Do not assume that is the end of all safety checks. Most of the available trials were short, and the safety results are not well-known. Ramírez-Garza and others have found that the upper limit is 5 g/day. The minor adverse reactions of the stomach were the most frequent. However, in the review, it was also mentioned that long-term safety studies are needed. Therefore, the Scope of Application for the Dose Finder is relatively limited.

Yadegar and others have also had the same worries about older adults, but the review could not combine the safety results. The studies had different reporting, so they could not be compared. The authors put forward that more studies should be conducted on the long-term effects and safety of RSV.

The deeper problem is what many trials did not investigate. Short follow-up is only one part of the evidence gap. If the study does not have thyroid tests, researchers do not know the person's thyroid status. If it does not list bone density, then bone health will be unknown. It is the same for iron status. Unreported harm is not the same as demonstrated safety.

7. Conclusion

Based on the above analysis, researchers do not know much about the long-term safety of resveratrol supplements. Studies have been carried out in a short period of time, and most people are used to them, but research prior to clinical trials is lacking.

It can be seen from the above that resveratrol modifies the function of the thyroid gland and bone-building activity, as well as iron regulation in the body; it does this via many different biological pathways. No one has really figured out if these results would be applicable to people taking it for a long time, because there are just not enough good long-term studies that have had many participants and closely observed all possible

safety issues. Currently, researchers do not have sufficient safety information for people who take high doses of natural products such as this for an extended period. The effects of resveratrol on the thyroid and iron are not well-known; however, given that it has been taken for a long time, people are concerned about this. Since millions of people around the world have started taking resveratrol supplements in their daily lives, and they often take a higher dose than what has been tested in clinical trials or for how long these studies have been conducted, there is still a lack of reliable safety data, which is a significant problem for public health.

Long-term safety of high-dose resveratrol supplements is not yet known. Uncertainties are relatively large in the function of the thyroid gland, bone health, iron metabolism, etc., so well-designed randomized controlled trials should be started as soon as possible.

Clinicians need to inform patients that the long-term risk profile is not yet known, and as a new type of supplement, regulators will likely increase supervision of it; although some people have shown interest in the possible health benefits of this supplement, safety must still be ensured, and prospective, long-term studies are needed before any claims about benefits based on harm reduction can be made.

Disclosure statement

The authors declare no conflict of interest.

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