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Clinical trials of resveratrol efficacy and safety

Klinička ispitivanja efikasnosti i bezbednosti resveratrola

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Introduction

Trans-resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a phytoalexin class of stilbene, phenolic compound from non-flavonoid group. Plants produce it in response to fungal infections (*Botrytis cinerea, Plasmopara viticola*, etc.) and other stress factors such as ultraviolet (UV) radiation, ozone, heavy metal ions, mechanical injury to plant tissues, or frost [1]. It was first detected in 1940 from the root of white *Veratrum grandiflorum*, and since then until today, its derivatives (glycosides and oligomers) have been isolated and identified in over 70 plant species [2]. The well-known source of this compound in the human diet is certainly wine [3–5]. In traditional Asian medicine, white *Veratrum* root has been used for many purposes, such as for treating atherosclerosis, cough, asthma, hypertension, and cancer [6]. Numerous *in vitro* and preclinical animal studies have demonstrated the ability of trans-resveratrol to exhibit a wide range of potential benefits for human health, such as antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antidiabetic, and anticancer activity [7–14].

We presented the available data on the most significant clinical trials of resveratrol's biological effects and evaluated its efficacy in humans. Resveratrol studies were found via a search of the PubMed, Web of Science, and SCOPUS databases using "resveratrol" and "clinical trial" as keywords. The search was limited to studies published between 2010–2019 reporting on cardioprotective activity, circulatory function, metabolism, and anticancer activity of resveratrol. These conditions were selected due to the fact that most of the clinical trials were conducted in these treatment areas. Unregistered clinical trials, trials without clear and specific end-point outcomes, and clinical trials focusing solely on general pharmacokinetics of resveratrol were excluded.

Studies related to cardioprotective activity

In their study, Bo et al. [15] examined the beneficial effects of resveratrol on markers of inflammation and oxidative stress in smokers (Table 1). A study of 50 healthy smokers who received 500 mg of resveratrol daily for 30 days was randomized, double-blind, and crossover. The results showed that resveratrol significantly decreased C-reactive protein (CRP) and triacylglycerol concentrations while the total antioxidant status was increased by 74.2 μmol/L. Concentrations of uric acid, glucose, insulin, cholesterol, and liver enzymes, as well as weight and blood pressure values, did not change significantly. Due to the demonstrated anti-inflammatory, antioxidant, and hypotriglyceridemic effects, resveratrol supplementation may be beneficial for reducing cardiovascular risk in healthy smokers.

In a much longer study of one year, Tome-Carneiro et al. [16] examined the effect of resveratrol-enriched grape supplementation on the inflammatory and fibrinolytic status of high-risk cardiovascular subjects receiving statins for primary prevention. A randomized, triple-blind, parallel, placebo-controlled study included 75 subjects divided into 3 groups. The resveratrol group received 8 mg of resveratrol for the first 6 months and twice the dose for the next 6 months. In the resveratrol-enriched grape supplement group, a highly-sensitive CRP (-26%), tumor necrosis factor (TNF) α (-19.8%), plasminogen activator inhibitor type 1 (-16.8%),

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Table 1

Clinical trials of resveratrol

Subjects	Daily resveratrol dosage/length of trial	Biomarker changes	Effect	Ref.
50 healthy smokers	500 mg /30 days	↓ CRP and triacylglycerol concentrations; ↑ the total antioxidant status	Beneficial	15
75 high-risk cardiovascular subjects receiving statins for primary prevention	8 mg/first 6 months 16 mg/next 6 months	↓ highly-sensitive CRP, TNF-α, PAI-1, IL-6/IL-10; ↑ anti-inflammatory IL-10	Beneficial	16
166 patients with stable angina pectoris	Group I: 20 mg, Group II: 20 mg + 112 mg of calcium fructoborate, Group III: 112 mg of calcium fructoborate; 60 days	↓ highly-sensitive CRP, N-terminal prohormone of brain natriuretic peptide	Beneficial	17
40 patients who have suffered a heart attack	10 mg/3 months	Improved left ventricular diastolic function and endothelial function; ↓LDL cholesterol	Beneficial	18
75 subjects receiving statins for primary prevention of cardiovascular disease	8 mg/6 months	↓LDL cholesterol, ApoB, and oxidized LDL cholesterol; no changes in hepatic, renal, and thyroid function	Beneficial	19
71 patients with dyslipidemia	100 mg/2 months	↓Total cholesterol and triacylglycerol concentrations; no significant differences in HDL- and LDL-cholesterol concentrations	Beneficial	20
28 obese subjects	75 mg/6 weeks	↑ Flow-mediated dilation; unchanged blood pressure and arterial compliance	Beneficial	25
22 healthy subjects	250 or 500 mg/single doses	Dose-dependent increase in cerebral blood flow (measured via total hemoglobin concentration); no significant change in cognitive function	Beneficial	26
66 patients with type 2 diabetes	1,000 mg/45 days	↓ Systolic blood pressure, blood glucose, hemoglobin A1c, insulin and insulin resistance; ↑ HDL cholesterol; unchanged markers of liver and renal function	Beneficial	27
24 obese men	1,500 mg/4 weeks	No effect on blood pressure, ectopic or visceral lipid content, inflammatory and metabolic biomarkers	None	30
29 postmenopausal women with normal glucose tolerance	75 mg/4 weeks	Unchanged plasma lipids, inflammation markers, and insulin sensitivity of the liver, skeletal muscle, and adipose tissue	None	31
28 obese men (11 Caucasians and 17 non-Caucasians)	2,000 mg/30 days	Significant improvement in insulin resistance and glucose homeostasis only in Caucasians	Beneficial	32
39 adult women with increased risk of breast cancer	50 mg/12 weeks	↓ Methylation of tumor suppressor gene RASSF-1α	Beneficial	33
9 patients with colorectal cancer and hepatic metastases	5,000 mg of micronized resveratrol SRT501/2 weeks prior to surgery	↑ Cleaved caspase-3, a marker of apoptosis, in malignant hepatic tissue	Beneficial, well-tolerated	34
24 patients with relapsed and/or refractory multiple myeloma	5,000 mg of micronized resveratrol SRT501 with or without bortezomib/~4 months	Not available	Severe adverse events: Nephro-toxicity to renal failure	35

interleukin (IL)-6/IL-10 (-24%) were significantly decreased, while anti-inflammatory IL-10 (+19.8%) was significantly increased compared to placebo and the resveratrol-free supplementation group. Adiponectin was increased by 6.5%, while soluble intercellular adhesion molecule-1 decreased by 5.7%. No adverse effects were reported. The results of the study indicated that one year of resveratrol-enriched grape supplementation could improve the anti-inflammatory and

fibrinolytic status of patients receiving statins for primary prevention of cardiovascular disease and thus be used together for better effect.

By enrolling a larger number of subjects, Militaru et al. [17] conducted a randomized, double-blind, controlled, parallel study of 166 patients with stable angina pectoris for 60 days, divided into three groups. The group I received resveratrol (20 mg/day), the group II was a combination of resveratrol and calcium fructoborate, and the group III only had calcium fructoborate (112 mg/day). Biomarkers of inflammation, markers of left ventricular function, and lipid markers were measured. The results showed that there was a significant decrease in a highly-sensitive CRP in all three groups, but the largest decrease was in the group III (39.7%). On the other hand, the marker of left ventricular function (N-terminal prohormone of brain natriuretic peptide) was decreased by 59.7% (the group I) and 52.6% (the group III), while the combination of resveratrol and calcium fructoborate (the group II) was the most effective (65.5%). This combination significantly reduced the weekly frequency of angina attacks and, by that, improved the quality of life of the respondents. Lipid markers changed only slightly from baseline values.

Through a randomized, double-blind placebo-controlled study, Magyar et al. [18] investigated the cardioprotective effects of resveratrol in patients who have suffered a heart attack. The subjects (n = 40) were divided into two groups, where one group received 10 mg of resveratrol for three months and the other one placebo. The results demonstrated that resveratrol improved left ventricular diastolic function as well as endothelial function, lowered low density lipoprotein (LDL) cholesterol, and protected patients with coronary artery disease from adverse hemorheological changes.

In a randomized, triple-blind, placebo-controlled study, Tome-Carneiro et al. [19] included 75 subjects receiving statins for primary prevention of cardiovascular disease. Their aim was to investigate a 6-month-effect of grape supplementation containing 8 mg of resveratrol on oxidized LDL cholesterol, Apolipoprotein B (ApoB), and serum lipids. Compared to the placebo group, LDL cholesterol (-4.5%), ApoB (-9.8%), and oxidized LDL cholesterol (-20%) decreased significantly. No changes in hepatic, renal, or thyroid function were observed. No adverse effects were reported in any of the subjects. Thus, the resveratrol-enriched grape extract may have the effect of reducing atherogenic markers and exerting cardioprotective activity [19].

In a randomized, double-blind, placebo-controlled clinical trial from 2019, Simental-Mendia and Guerrero-Romero [20] examined the effect of resveratrol on the lipid status of men and women (n = 71) with dyslipidemia at a dose of 100 mg daily for two months. As an outcome, resveratrol supplementation significantly reduced total cholesterol (-19.2) and triacylglycerol (-33.3) levels compared to the placebo group, whereas there were no significant differences for high density lipoprotein (HDL) and LDL cholesterol.

In 2013, Sahebkar [21] conducted a systematic review and meta-analysis of seven randomized, controlled studies in order to investigate the effects of resveratrol supplementation on plasma lipids. This meta-analysis included 282 subjects (141 in each group). The results demonstrated that resveratrol supplementation had no significant effects on any of the lipid parameters: total cholesterol (-8.70%), LDL cholesterol (-3.22%), HDL cholesterol (-0.26%), and triacylglycerols (-4.30%). The obtained results were robust against the sensitivity of the analysis and did not depend on the dose of resveratrol, the time of supplementation, or the cardiovascular risk of the study population. The results indicated that other mechanisms, other than hypolipidemic, are responsible for the cardioprotective properties of resveratrol. A more recent systematic review and meta-analysis from 2018 included twenty-one randomized clinical trials and provided the same results, with the only difference that a statistically significant difference occurred for triacylglycerol levels. However, after eliminating only one study from the meta-analysis, this significance was also lost [22].

In a new systematic review and meta-analysis of 17 randomized, controlled clinical trials from 2019, Fogacci et al. [23] compared the impact of resveratrol administration on human blood pressure. The results showed that resveratrol supplementation did not significantly affect systolic or diastolic blood pressure. However, administration of higher doses of resveratrol ($\geq$ 300 mg daily) significantly reduced systolic blood pressure in diabetic patients and thus exhibited cardioprotective activity.

Studies related to circulatory function

Wong et al. [24] demonstrated earlier, acute, dose-dependent, flow-mediated dilation (FMD) of the brachial artery after the administration of resveratrol in mildly hypertensive, obese subjects. Resveratrol supplementation also showed an acute increase in cerebral blood flow without affecting cognition. This time, the study was conducted to evaluate the effects of chronic resveratrol supplementation on flow-mediated dilatation and cognitive performance (Table 1). Obese but otherwise healthy subjects (n = 28) were randomized into two groups. In a double-blind, crossover study, one group received 75 mg per day of encapsulated resveratrol and the other one placebo for 6 weeks. The results showed that resveratrol supplementation for 6 weeks was well-tolerated and resulted in a 23% increase in flow-mediated dilation compared with the placebo group. A single dose of resveratrol (75 mg) followed by chronic resveratrol supplementation resulted in a 35% stronger acute FMD response than placebo supplementation. On the other hand, blood pressure and arterial compliance remained unchanged. In conclusion, chronic resveratrol supplementation has the potential to maintain the healthy circulatory function of obese subjects [25].

Through a randomized, double-blind, crossover investigation, Kennedy et al. [26] evaluated the impact of resveratrol on cognitive performance and localized cerebral blood flow. Healthy volunteers (n = 22) received a placebo or two different single doses of resveratrol (250 or 500 mg).

Administration of resveratrol led to a dose-dependent increase in cerebral blood flow, which was measured via total hemoglobin concentration. After the administration of both doses of resveratrol, there was also an increase in deoxyhemoglobin. However, the cognitive function of subjects did not change significantly.

Studies on metabolism

Through a randomized placebo-controlled double-blind, parallel study, Movahed et al. [27] examined the efficacy of resveratrol on lowering blood glucose levels in the presence of standard antidiabetic drugs (Table 1). The study included 66 patients with type 2 diabetes who received resveratrol supplementation (1 g/day) for 45 days and the placebo (control) group. The results showed that resveratrol treatment significantly reduced systolic blood pressure, blood glucose, hemoglobin A1c, insulin, and insulin resistance, while HDL cholesterol was significantly increased compared with the placebo group. Markers of liver and renal function remained unchanged. No significant changes in body weight and body composition occurred. This study showed that resveratrol supplementation could exert potent antidiabetic activity in patients with type 2 diabetes, unlike previous reports that showed only mild effects on hyperglycemia and hyperinsulinemia [28, 29].

However, Poulsen et al. [30] obtained different results after conducting a randomized, double-blind, placebo-controlled study involving 24 obese but otherwise healthy men. Subjects were given 500 mg of resveratrol three times a day for four weeks. The results demonstrated that endogenous glucose production, turnover, and oxidation remained unchanged, whereas insulin sensitivity slightly decreased in both groups. Supplementation with resveratrol had no effect on blood pressure, ectopic or visceral lipid content, as well as inflammatory and metabolic biomarkers.

Another study that also did not have positive results was conducted by Yoshino et al. [31]. In a randomized, double-blind, placebo-controlled study, 29 postmenopausal women with normal glucose tolerance received 75 mg of resveratrol a day for four weeks. Although resveratrol supplementation led to an increase in resveratrol concentration in plasma, plasma lipids and inflammation markers remained unchanged. There was also no increase in insulin sensitivity of the liver, skeletal muscle, and adipose tissue. Therefore, resveratrol supplementation in this study did not exhibit beneficial metabolic effects in postmenopausal women with normal glucose tolerance.

An interesting pilot study from 2019 was conducted by Walker et al. [32], and it included 28 obese men with metabolic syndrome. The subjects (11 Caucasians and 17 non-Caucasians) received orally 2 g of resveratrol/day (in two daily doses) or a placebo over 30 days. The results showed that resveratrol supplementation led to a significant improvement in insulin resistance and glucose homeostasis, but only in Caucasians. These different reactions between members of different races are due to their differences in the gut microflora, where resveratrol in the case of Caucasians reduced the diversity of gut microflora and increased the number of microbe *Akkermansia muciniphila*, which has been shown to have beneficial effects on obesity and diabetes in experimental animals. As this was a pilot trial, more people should be included before reaching conclusions.

Studies on anti-cancer activity

Zhu et al. [33] conducted a randomized, double-blind study of 39 adult women with an increased risk of breast cancer. For 12 weeks, one group received a placebo, and other two groups received resveratrol. One of the two groups got 5 mg and the other 50 mg of resveratrol. The obtained results provided new insights into the effects of resveratrol, which included a decrease in the methylation of tumor suppressor gene RASSF-1α with an increase in serum resveratrol levels.

In 2011, Howells et al. [34] conducted the first phase of a randomized, double-blind study with the micronized resveratrol SRT501, whose micronization improved the absorption and thus the bioavailability of resveratrol. SRT501 was given to patients with colorectal cancer and hepatic metastases at a dose of 5 g daily for 14 days. The aim of the study was to evaluate the safety, pharmacokinetics, and pharmacodynamics of this resveratrol formulation. The obtained results led to the following conclusions: daily use of SRT501 for 14 was well-tolerated in patients with colorectal cancer; C_{max} for SRT501 was significantly higher compared to equivalent doses of non-micronized resveratrol; ingestion provided measurable concentrations in tissue distant from the gastrointestinal tract (specifically in the liver), which led to a significant pharmacological effect (significant increase in cleaved caspase-3, a marker of apoptosis, in malignant hepatic tissue).

A year later, in the second phase of the clinical study, the same form of micronized resveratrol SRT501 was given to patients with relapsed and/or refractory multiple myeloma (n = 24), where a severe adverse event for SRT501 was observed – nephrotoxicity to renal failure. Since this adverse event was not recorded in the first phase of the clinical study in patients with colorectal cancer, this is considered an adverse event only for patients with multiple myeloma [35]. New large-scale studies are required to assess the use and safety of resveratrol as a chemoprotective or chemotherapeutic agent.

Evaluation of resveratrol efficacy in humans

The results of clinical efficacy of resveratrol indicate that resveratrol may have beneficial cardioprotective effects in smokers [15], persons with stable angina pectoris [17], persons who have suffered from a heart attack [18], and persons who already receive statins for the primary prevention of cardiovascular disease [16, 19]. In addition, resveratrol can improve circulatory function [24–26] and glucose metabolism [27], while anticancer activity in humans remains poorly investigated [33, 34]. These studies were not patient-oriented but

mainly focused on changes in some biochemical parameters that are indicators of the existence or severity of diseases.

Some studies gave conflicting results, such as whether resveratrol supplementation changes inflammatory or metabolic biomarkers. Reasons for obtaining inconsistent results may be differences in the characteristics of the involved patients, the dose of resveratrol, as well as the duration of supplementation [36]. One of the biggest challenges in evaluating resveratrol efficacy in clinical studies is the fact that regarding its very low bioavailability, there is a wide range of used doses (from 5 mg to 5 g). Furthermore, some supplements contain additional components with a presumed synergistic effect where synergism is reflected by increasing the bioavailability or bioactivity of resveratrol, such as the resveratrol/calcium fructoborate combination [17]. These synergistic components may also influence the results, and their relative individual contribution is still unknown [37].

What undoubtedly encourages future clinical trials of resveratrol is that its administration at a dose of 5 g/day for one month is safe and well-tolerated [38].

Conclusion

The results of clinical trials suggest that resveratrol may exert some beneficial effects on human health. However, important questions such as the dose and length of a treatment that would make the most of resveratrol potential remain unsolved. It is expected that future extensive and better-designed clinical trials will give answers to these challenges.

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