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Please cite this article **CLINICAL TRIALS OF RESVERATROL EFFICACY AND SAFETY**

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UDC:

DOI: https://doi.org/10.2298/VSP201126006C

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
CLINICAL TRIALS OF RESVERATROL EFFICACY AND SAFETY

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Abstract

Trans-resveratrol is a phytoalexin from the stilbene class, polyphenolic compound from non-flavonoid group. In vitro and animal studies have shown that trans-resveratrol may exert a wide range of potential beneficial effects to human health, which involves antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anti-diabetic and anti-cancer activity. The objective of this paper was to summarize available data concerning the most important clinical trials focused on resveratrol biological effects.

The results of clinical trials indicate that resveratrol has potential cardioprotective activity in patients with increased risk of cardiovascular disease. It can also have positive effect on the circulatory function and exert anti-diabetic activity in humans, while the anti-cancer activity is still insufficiently tested. Some issues remain unsolved, such as the dose and length of treatment that would maximize the potential of resveratrol. It is expected that future, better designed and more extensive clinical trials will provide additional information related to this topic.

Key words: resveratrol, biological activity, clinical trial.

Apstrakt

Trans-resveratrol je fitoaleksin klase stilbena, polifenolnih jedinjenja iz grupe neflavonoida. In vitro ispitivanja, kao i ispitivanja na životinjama pokazala su da trans-resveratrol ispoljava širok dijapazon potencijalnih blagotvornih delovanja po zdravlje ljudi, kao što su antioksidantno, antiinflamatorno, kardioprotektivno, neuroprotektivno, antidijabetesko i antikancerogeno delovanje. Cilj rada je pregled dostupnih podataka najznačajnijih kliničkih ispitivanja biološkog dejstva resveratrola.

Rezultati pomenutih ispitivanja ukazuju na to da resveratrol ima potencijalno kardioprotektivno delovanje kod osoba sa povećanim rizikom od kardiovaskularnih bolesti.
Takođe, može pozitivno uticati na cirkulatornu funkciju i ispoljiti antidijabetsko delovanje, dok je antikancerogena aktivnost i dalje nedovoljno ispitana. Ipak, pitanja, kao što je doza ili dužina tretmana koji bi maksimalno iskoristili potencijal resveratrola, ostaju nerešena. Očekuje se da buduća, bolje dizajnirana i opsežnija klinička ispitivanja daju detaljnije informacije vezane za ovu temu.

**Ključne reči: resveratrol, biološka dejstva, klinička ispitivanja.**

**Introduction**

*Trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilben) is a phytoalexin class of stilbene, phenolic compound from non-flavonoid group. Plants produce it in a response to fungal infections (*Botritis cinerea, Plasmospora viticola*, etc.) and other stress factors such as UV radiation, ozone, heavy metal ions, mechanical injury to plant tissues or frost. 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. The well-known source of this compound in human diet is certainly wine. In traditional Asian medicine, white *Veratrum* root has been used for many purposes, such as treatment of atherosclerosis, cough, asthma, hypertension and cancer. 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 anti-oxidant, anti-inflammatory, cardioprotective, neuroprotective, anti-diabetic and anti-cancer activity. The aim of this study is to review the available data on the most significant clinical trials of resveratrol biological effects and to evaluate its efficacy in humans. Resveratrol studies were found via search of the PubMed, Web of Science and SCOPUS databases using "resveratrol" and "clinical trial" as key words. The search was limited to studies published between 2010-2019 reporting on cardioprotective activity, circulatory function, metabolism.
and anti-cancer 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**

Bo and colleagues in their study (Table 1) examined the beneficial effects of resveratrol on markers of inflammation and oxidative stress in smokers. A study of 50 healthy smokers who received 500 mg of resveratrol daily for 30 days was randomized, double-blind, 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, anti-oxidant and hypotriglyceridemic effects, it is possible that resveratrol supplementation may have a beneficial effect on reducing cardiovascular risk in healthy smokers\(^\text{15}\).

In a much longer study of one year, Tome-Carneiro et al.\(^\text{16}\) 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%), IL-6/IL-10 (-24%) were significantly decreased, while anti-inflammatory IL-10 (+19.8%) was significantly increased in comparison with 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 indicate that one year of the resveratrol-enriched grape supplementation can improve the inflammatory and fibrinolytic status of patients receiving statins for primary prevention of cardiovascular disease, and thus can be used together for better effect.

By enrolling a larger number of subjects, Militaru and colleagues conducted a randomized, double-blind, controlled, parallel study of 166 patients with stable angina pectoris for 60 days, which were divided into three groups. The group I received resveratrol (20 mg/day), group II a combination of resveratrol and calcium fructoborate, and group III only 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 C-reactive protein in all three groups, but the largest decrease was in 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% (group I) and 52.6% (group III), while the combination of resveratrol and calcium fructoborate (group II) was the most effective (65.5%). This combination reduced significantly weekly frequency of angina attacks and by that improved the quality of life of the respondents. Lipid markers changed only slightly from baseline values 17.

Through a randomized, double-blind placebo-controlled study, Magyar et al. 18 investigated 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 other one placebo. The results demonstrated that resveratrol improved left ventricular diastolic function as well as endothelial function,
lowered 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. included 75 subjects receiving statins for primary prevention of cardiovascular disease. Their aim was to investigate the 6-months effect of grape supplementation containing 8 mg of resveratrol on oxidized LDL-cholesterol, Apolipoprotein B (ApoB) and serum lipids. In comparison with the placebo group, LDL-cholesterol (4.5%), ApoB (9.8%) and oxidized LDL-cholesterol (20%) decreased significantly. No changes in hepatic, renal, and thyroid function were observed. No adverse effects were reported in any of the subjects. Thus, 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 in comparison with the placebo group, whereas there were no significant differences for HDL- and LDL-cholesterol.

In 2013, Sahebkar 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 indicate that other mechanisms, other than hypolipidemic, are responsible for the cardioprotective properties of resveratrol \(^1\). 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 \(^2\).

In a new systematic review and meta-analysis of 17 randomized, controlled clinical trials from 2019, Fogacci et al. \(^3\) 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 and colleagues demonstrated earlier, acute, dose-dependent, flow-mediated dilation (FMD) of the brachial artery after administration of resveratrol in mildly hypertensive, obese subjects. Resveratrol supplementation has also shown an acute increase in cerebral blood flow without affecting cognition \(^4\). This time, the study (Table 1) was conducted to evaluate the effects of chronic resveratrol supplementation on flow-mediated dilation and cognitive performance. Obese but otherwise healthy subjects (\(n = 28\)) were randomized within 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 in comparison 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 healthy circulatory function of obese subjects 25.

Through a randomized, double-blind, crossover investigation, Kennedy and colleagues 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 administration of both doses of resveratrol, there was an increase in deoxyhemoglobin, too. However, cognitive function of subjects did not change significantly 26.

**Studies on metabolism**

Through a randomized placebo-controlled double-blind, parallel study (Table 1), Movahed et al. 27 examined the efficacy of resveratrol on lowering blood glucose levels in the presence of standard antidiabetic drugs. The study included 66 patients with type 2 diabetes who received resveratrol supplementation (1g/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 in comparison 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 may exert
potent antidiabetic activity in patients with type 2 diabetes, unlike previous reports that showed only mild effects on hyperglycemia and hyperinsulinemia.\textsuperscript{28, 29}

However, Poulsen and colleagues 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 daily 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 on inflammatory and metabolic biomarkers.\textsuperscript{30}

Another study that also did not have positive results was conducted by Yoshino et al.\textsuperscript{31} In a randomized, double-blind, placebo-controlled study, 29 postmenopausal women with normal glucose tolerance received 75 mg of resveratrol daily 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 and colleagues and included 28 obese men with metabolic syndrome. 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 case of Caucasians reduced 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 and colleagues conducted a randomized, double-blind study of 39 adult women with increased risk of breast cancer. For 12 weeks, one group received a placebo, the other group 5 mg, and the third group 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. 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*\textsubscript{max} for SRT501 was significantly higher compared to equivalent doses of non-micronized resveratrol and ingestion provided measurable concentrations in tissue distant from GIT (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 severe adverse event for SRT501 was observed - nephrotoxicity to renal failure. As this adverse event was not recorded in the first phase of the clinical study in
patients with colorectal cancer, this is considered to be an adverse event only for patients with multiple myeloma. For assessing the use and safety of resveratrol as a chemoprotective or chemotherapeutic agent, new large-scale studies are required.

**Evaluation of resveratrol efficacy in humans**

The results of clinical efficacy of resveratrol indicate that resveratrol may have beneficial cardioprotective effects in smokers, persons with stable angina pectoris, persons who have suffered a heart attack, and persons who already receive statins for the primary prevention of cardiovascular disease. In addition, resveratrol can improve circulatory function and glucose metabolism, while anti-cancer activity in humans remains poorly investigated. 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 or not 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. One of the biggest challenges in evaluating resveratrol efficacy in clinical studies is that regarding its very low bioavailability there is a wide range of used doses (from 5 mg to 5 g). In addition, 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. These synergistic components may also influence the results and their relative individual contribution is still unknown.
What really 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  

**Conclusion**

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

**Acknowledgements**

This work was supported by the Ministry of Education, Science and Technological Development of Republic of Serbia (Project No. TR31020).

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Table 1

Clinical trials of Resveratrol

| Subjects                          | Daily Resveratrol | 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 | 8 mg/first 6 months | ↓ highly-sensitive CRP, TNF-α, PAI-1, IL-6/IL-10; ↑ anti-inflammatory IL-10 | Beneficial   | 16.  |
| 166 patients with stable angina | Group I: 20 mg, Group II: 20 mg + 112 mg of calcium fructoborate, Group III: 112 mg of calcium fructoborate; 60 | ↓ highly-sensitive CRP, N-terminal prohormone of brain natriuretic peptide | Beneficial   | 17.  |
| Patients/Subjects | Dose | Effect | Conclusion |
|------------------|------|--------|------------|
| 40 patients who have suffered a heart attack | 10 mg/3 months | Improved left ventricular diastolic function and endothelial function; ↓ LDL-cholesterol | Beneficial |
| 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 |
| 71 patients with dyslipidemia | 100 mg/2 months | ↓ total cholesterol and triacylglycerol concentrations; no significant differences in HDL- and LDL-cholesterol concentrations | Beneficial |
| 28 obese subjects | 75 mg/6 weeks | ↑ flow-mediated dilation; unchanged blood pressure and arterial compliance | Beneficial |
| 22 healthy subjects | 250 or 500 mg/ single doses | Dose-dependent increase in cerebral blood flow (measured via | Beneficial |
total hemoglobin concentration);
no significant change in cognitive
function

66 patients with type 2 diabetes
1000 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 1500 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 2000 mg/30 days Significant improvement in insulin
resistance and glucose homeostasis
Beneficial 32.
(11 Caucasians
and 17 non-
only in Caucasians
| Intervention                                      | Duration       | Effect                                   | Adverse Events |
|--------------------------------------------------|----------------|------------------------------------------|----------------|
| 39 adult women with increased risk of breast cancer | 50 mg/12 weeks | ↓ methylation of tumor suppressor gene RASSF-1α | Beneficial     |
| 9 patients with colorectal cancer and hepatic metastases | 5000 mg of micronized resveratrol SRT501/2 weeks prior to surgery | ↑ cleaved caspase-3, a marker of apoptosis, in malignant hepatic tissue | Beneficial, well tolerated |
| 24 patients with relapsed and/or refractory multiple myeloma | 5000 mg of micronized resveratrol SRT501 with or without bortezomib/~4 months | not available | Severe nephro-toxicity to renal failure | adverse events: |