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## **Tyrosol and Hydroxytyrosol: Their Role in Cardioprotection**

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## **Abstract**

**Introduction:** In recent years, research has focused on identifying and studying natural bioactive compounds that may have potential implications in the prevention and treatment of cardiovascular diseases. Phenolic ingredients such as Tyrosol and hydroxytyrosol, found in olive oil, attract particular attention due to their potential cardioprotective properties. The aim of this study is to provide a comprehensive research review of the current knowledge of the cardioprotective effects of tyrosol and hydroxytyrosol, highlighting their potential health benefits and identifying research gaps for future research.

**Aim:** The aim of this study is to investigate the cardioprotective effect of phenolic compounds found in olive oil, such as tyrosol and hydroxytyrosol, which is an important health care problem due to the prevalence of deaths caused by cardiovascular diseases. The aim of the study is to understand the effectiveness of natural ingredients in the prevention and treatment of cardiovascular diseases and to learn the specific effects of these compounds, which may contribute to the development of new therapeutic and preventive strategies and improve the quality of life of patients.

**Review methods:** A non-systematic review of the scientific literature was carried out according to the following keywords: Tyrosol, hydroxytyrosol, cardioprotection, cardiovascular diseases, olive oil cardioprotective role, geriatric patients, elderly people. PubMed was searched and 34 sources published up to 2023 were analysed. It was done to ensure that the knowledge contained in this article includes the most up-to-date information.

**Abbreviated description of the state of knowledge:** Tyrosol and hydroxytyrosol, prominent in olive oil, are studied for their potential cardioprotective properties. Linked to a Mediterranean diet, these compounds show promise in reducing cardiovascular disease risk. They counter oxidative stress, improve lipid profiles, and modulate inflammatory processes. Clinical studies suggest their positive impact, with tyrosol also explored as a potential anticoagulant. Ongoing research aims to uncover optimal doses and mechanisms, highlighting their significance in cardiovascular health.

**Conclusions:** Tyrosol and hydroxytyrosol, found in olive oil, show promise in cardioprotection by combating oxidative stress, improving lipid profiles, and modulating inflammation. Clinical studies suggest their positive impact on cardiovascular health. Tyrosol has potential as an anticoagulant and exhibits antioxidant effects. These compounds present a

compelling avenue for future therapeutic interventions, with emphasis on understanding mechanisms and optimizing supplementation.

**Keywords:** Tyrosol, hydroxytyrosol, cardioprotection, cardiovascular diseases, olive oil cardioprotective role

## **Introduction**

In recent years, scientists have focused on identifying and studying natural bioactive compounds that may play a key role in the prevention and treatment of cardiovascular diseases. Among these compounds, particular interest has been shown in tyrosol and hydroxytyrosol, phenolic components of olive oil, known for their potential cardioprotective properties [1, 2].

Cardiovascular diseases (CVD) remain the leading cause of death worldwide [3], and their incidence is closely linked to risk factors such as hypertension, hyperlipidemia, diabetes, and obesity [4]. The introduction of lifestyle changes and the adoption of a diet rich in bioactive compounds, such as those present in the Mediterranean dietary pattern, have been identified as an effective approach to reducing the risk of CVD [1, 2].

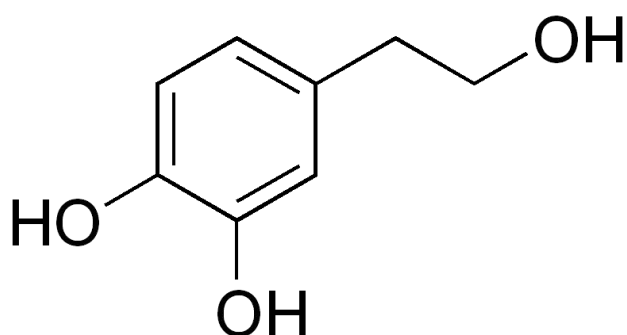
This work aims to provide a holistic view of the current state of knowledge regarding the role of tyrosol and hydroxytyrosol in cardioprotection, highlighting their potential health benefits and identifying gaps in research that require further exploration. In the context of growing interest in using natural components for the prevention and treatment of cardiovascular diseases, understanding the specific actions of these compounds may contribute to the development of new therapeutic and preventative strategies.

## **Tyrosol and Hydroxytyrosol - Characteristics and Sources**

Hydroxytyrosol (HTY) is an amphipathic phenol with a molecular weight of 154.16 g/mol, characterized by a phenylethyl alcohol structure. In the nomenclature of the

International Union of Pure and Applied Chemistry (IUPAC), it is also known as 3,4-dihydroxyphenylethanol (DOPET), 3,4-dihydroxyphenylethanol (3,4-DHPEA), or 4-(2-hydroxyethyl)-1,2-benzenediol [5, 6] (Fig.1). The primary sources are olives and olive oil [7, 8]. Over the last decade, it has been established that hydroxytyrosol (HT) is also present in both red and white wines, with higher concentrations in red wines. However, the levels of this compound in wines are lower than those typically found in extra virgin olive oil and olive leaf extracts [5, 9] (Table 1).

*Fig. 1. Hydroxytyrosol structure.*

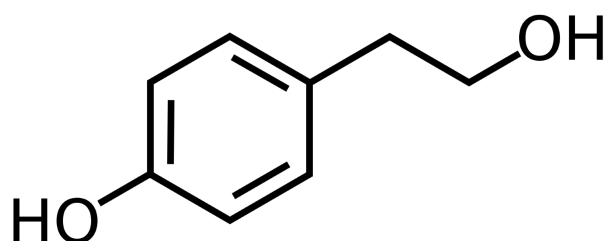


*Table 1. Average concentration of HTY in different foods.*

Food	HTY average content
Olive oil	24,2-614.5 mg/kg
Age red wine	20 mg/l
Olive tree leaves	12 mg/g
Red wine	3 mg/l
White wine	2 mg/l

Tyrosol (Tyr) - tyrosol [4-(2-hydroxyethyl)phenol] (Figure 2) is a phenolic compound with a simple structure (molecular weight 138.16 g/mol [10]) that occurs naturally and is also produced in the human body [11]. Similar to HTY, olive oil and wine are the main dietary sources of Tyr, although Tyr is also found in other alcohols such as beer and vermouth [1, 12, 13, 14]. Studies by Romero, C. & Brenes, M. indicate that the content of Tyr in extra virgin olive oils ranges from 40 to 180 mg/kg oil [15]. In a study conducted by Lucci, P. et al., the tyrosol content varied from 43 to 68 mg/kg oil [16].

*Fig. 2. Tyrosol structure*



### **Cardioprotective Mechanisms**

#### **Antioxidant Properties**

Oxidative stress forms the basis for many diseases, including neurological disorders such as Parkinson's disease, cardiovascular diseases, and diabetes. Additionally a connection has been established between oxidative stress and the processes of the development and progression of cancer [17]. Research reports that polyphenols found in extra virgin olive oil (EVOO) protect DNA from oxidative stress, inhibit mitochondrial dysfunction and alleviate lipid peroxidation by neutralizing free radicals. This results in maintaining endogenous antioxidant stability [18]. The beneficial impact of olive oil on the circulatory system is mainly attributed to the presence of two phenolic compounds: oleuropein (OLE) and hydroxytyrosol (HT). These substances exhibit antioxidant activity as well as the ability to reduce platelet aggregation and monocyte adhesion, thereby reducing cardiotoxicity [19]. In a molecular context OLE and HT, owing to their catechol structure, exhibit antioxidant activity in various ways: by scavenging peroxide radicals and interrupting peroxidative chain reactions, as well as acting as metal chelators [18].

## **Improvement of Lipid Profile**

The report examining the impact of olive oil on lipid profile indicates that regular consumption of at least two tablespoons of extra virgin olive oil may have a beneficial effect on the lipid profile by reducing the levels of low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL) levels. In the case of higher daily consumption, even greater benefits for the circulatory system can be observed. It is important to choose EVOO that is rich in phenols, as they are responsible for delivering a greater number of health benefits [20]. The effect of tyrosol on lipid profiles in streptozotocin-induced diabetic rats was investigated. The results of the observations revealed significant changes in biochemical parameters. Tyrosol has a positive impact on the lipid profile, with a significant reduction observed in total serum cholesterol, LDL, and very low-density lipoprotein (VLDL) levels. Additionally, the level of HDL significantly increased after tyrosol therapy. Furthermore, there was a significant decrease in serum glucose levels [21]. Despite the potentially favorable impact on the lipid profile of EVOO, it is recommended to avoid excessive consumption of fats, even those derived from olive oil. Current research does not allow for a clear determination of what level of olive oil consumption may be considered harmful. Such an assessment will depend, among other factors, on an individual's dietary habits, especially in the context of the profile of fats consumed [22].

## **Anti-inflammatory action**

Aging is a multifactorial process, with a constant component being the progressive oxidative and inflammatory processes [23]. During the aging process, a decrease in the activity of nuclear factor erythroid 2-related factor (Nrf-2) is observed, accompanied by an increase in the activity of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) system, promoting the inflammatory process. Nrf-2 is the main regulator of the xenobiotic-activated receptor (XAR). Its role is to activate the antioxidant response element (ARE) [24]. Its activity increases during disruptions in redox processes and inflammatory states. Additionally, it is involved in apoptotic processes, metabolism, and cell proliferation [25]. NF- $\kappa$ B, on the other hand, is a protein complex acting as a transcription factor. It is responsible for cytokine production and cell survival [14]. NF- $\kappa$ B mediates the stimulation of the release of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6 in monocytes/macrophages and through cytokines, promotes the differentiation of Th17

lymphocytes [26]. Polyphenols found in Extra Virgin Olive Oil (EVOO), mainly tyrosol and hydroxytyrosol, can modulate the inflammatory process by interfering with intracellular signaling pathways associated with NF- $\kappa$ B and Nrf-2. Their main role is to stimulate the increase in Nrf-2 activity, leading to a simultaneous decrease in NF- $\kappa$ B activity [23].

Recent studies show that consuming a Mediterranean diet rich in phenols found in olive oil reduces postprandial inflammatory response associated with lipopolysaccharides (LPS) in serum, which are components of the outer membrane of Gram-negative bacteria. It is crucial to emphasize that EVOO reduces postprandial expression of pro-inflammatory cytokines and activation of the nuclear factor NF- $\kappa$ B in peripheral blood mononuclear cells. This is key because an increase in the activity of mononuclear cells is observed in metabolic syndrome or obesity, which present an inflammatory component [27]. Metabolic syndrome itself and obesity as one of the components of metabolic syndrome are direct risk factors for cardiovascular disease. There is strong evidence to suggest that hydroxytyrosol plays a crucial inhibitory role in the development of cardiovascular disease. Hydroxytyrosol suppresses macrophage activation and inhibits endothelial dysfunction. This leads to a reduction in cholesterol oxidation in low-density lipoproteins (LDL) and a decrease in chronic inflammation and platelet aggregation. In a study on rats given hydroxytyrosol, a decrease in CRP, IL-6, TNF $\alpha$ , and IL-1 $\beta$  in serum was observed [28]. Both TNF- $\alpha$  and IL-1 $\beta$  directly activate the production of IL-6. IL-1 $\beta$  increases the expression of COX-2, the main enzyme involved in prostaglandin synthesis, stimulating the synthesis of PGE2 and PCD2. These products play a significant role in inflammatory processes as mediators of the inflammatory response [29, 30]. The presence of chronic inflammatory reactions should therefore become a key point of therapeutic interventions, as it affects the development of cardiovascular disease and its consequences. As indicated by the above research, the use of EVOO has a beneficial impact on modulating the inflammatory response, demonstrating significant cardioprotective effects [31].

### **Clinical Trials**

In recent years, several clinical studies have been conducted to assess the impact of tyrosol and hydroxytyrosol on human health. The results of these studies are promising, suggesting that these compounds may indeed contribute to cardioprotection. However, further research is needed to better understand the mechanisms of action of these compounds and to determine the optimal doses and duration of supplementation.



Clinical studies on the use of tyrosol as a new antioxidant and a new type of anticoagulant are relatively new and limited. Since 1976, only 18 papers have been published on PubMed, with only 11 scientific papers published in the last 10 years specifically related to research on this compound.

Tyrosol has been investigated for its potential use as a longer half-life anticoagulant with greater bioavailability than traditionally used heparins. The sulfated polymer of tyrosol has shown better water solubility, potentially allowing for broader applications of this polyphenol. In vitro studies have demonstrated a proven anticoagulant effect. Clinical studies on OligoTyrS I, a tyrosol derivative with a sulfate phenolic group, have shown both antioxidant and anticoagulant effects, which may be utilized in the future for conditions such as myocardial ischemia. Additionally, a 2021 study demonstrated that tyrosol and its derivatives do not interfere with the activity of factor Xa and IIa, thereby not significantly affecting the common coagulation pathway. The favorable anticoagulant effect does not substantially disrupt the hemostasis process [32].

A study from 2019 aimed to demonstrate the conversion rate of tyrosol to hydroxytyrosol by CYP2A6 and CYP2D6 enzymes. Red wine consumption showed the highest increase in the total recovered TYR. Analysis revealed a significant difference in the conversion rate based on gender, genetics, and the type of alcohol consumed. The experiment demonstrated that the presence of alcohol is a key factor influencing the bioavailability of tyrosol, and it may also be associated with changes in dopamine metabolism after alcohol consumption, resulting in the formation of hydroxytyrosol through metabolic transformations [33].

Another randomized, crossover, controlled experiment in 2019 showed that tyrosol undergoes biotransformation in the human body to hydroxytyrosol. The OHTyr form is responsible for improving endothelial function, increasing HDL concentration, and antithrombin III in the plasma. Furthermore, a reduction in homocysteine concentration, which can damage the endothelium, and a decrease in endothelin-1 concentration, which causes vessel constriction and plays a role in vascular hemostasis, were observed. The study revealed that the biotransformation of Tyr to OHTyr is modified by genetic polymorphisms CYP2A6/CYP2D6, so some individuals may derive greater benefits from the biological activities of these antioxidants [34].

The most valuable clinical studies in this area have been conducted in the last few years. The obtained results encourage further experiments on the biological activity and the potential use of tyrosol in cardioprotection. It is essential to further investigate individual differences affecting tyrosol metabolism, such as gender, the influence of genetic factors, and the type of food consumed, on the final concentrations of metabolites in individual subjects. Interactions with food and drugs are also significant, as well as the possibilities of supplementing this component in the diet in the absence of contraindications.

### **Conclusion:**

The cardioprotective potential of tyrosol and hydroxytyrosol found in olive oil, were investigated. these bioactive compounds are relevance in preventing cardiovascular diseases (CVD) and highlights their sources, structures, and impact on oxidative stress, lipid profiles, and inflammatory processes. The benefits of a Mediterranean diet rich in these compounds are emphasized, especially in reducing postprandial inflammatory reactions. Clinical studies suggest promising cardioprotective results, and ongoing research is aimed at understanding the mechanisms, optimal doses and duration of supplementation. Tyrosol also has potential as an antioxidant and anticoagulant, and recent studies indicate its positive effect on endothelial function. However, more research is needed on individual differences, interactions with food and drugs, and safe supplementation.

### **Author's contribution**

Conceptualization: Cezary Guzowski, Joanna Murawska, Karolina Winiarek, Martyna Michalska; Methodology: Cezary Guzowski;

Software: not applicable;

Verification: Karolina Winiarek, Martyna Michalska;

Formal analysis: Cezary Guzowski, Joanna Anna Murawska;

Research: Cezary Guzowski, Joanna Anna Murawska, Karolina Winiarek, Martyna Michalska, Aleksandra Czernicka;

Resources: Cezary Guzowski, Joanna Anna Murawska, Karolina Winiarek, Martyna Michalska, Aleksandra Czernicka;

Writing - rough preparation: Cezary Guzowski;

Writing - review and editing, Cezary Guzowski, Joanna Anna Murawska, Karolina Winiarek, Martyna Michalska, Aleksandra Czernicka

Visualization: Karolina Winiarek;

Supervision, Martyna Michalska;

Project administration, Cezary Guzowski;

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