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Red Wine: Poison or the Secret to Eternal Youth?

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ABSTRACT
Introduction: Red wine has been the subject of extensive research due to its complex polyphenolic composition and potential health effects on the human body. This review examines the cardioprotective effects of red wine, highlighting the role of polyphenols in promoting cardiovascular health, increasing insulin sensitivity, and offering protective benefits against type 2 diabetes and neurodegenerative diseases. Despite these potential benefits, red wine consumption is also associated with several adverse effects, including liver damage, headaches, and increased risk of depression. This duality highlights the importance of moderation in alcohol consumption..
Aim: Review and presentation of the current state of knowledge on the effects of red wine on the human body, with particular emphasis on the impact on the pathogenesis of cardiovascular diseases, which are the most common cause of death in the world.
Material and methods. Analysis of the studies available on open access sources at PubMed, Google Scholar, National Library of Medicine and Coachrane. The research was conducted through word analysis key words such as: " red wine", „polyphenols", „resveratrol". Selection criteria for articles included consideration of their title, abstract, and publication date, with a focus on English-language publications.
Conclusion and Results: A review article shows that moderate red wine consumption is associated with several potential health benefits, including cardioprotective effects attributed to polyphenols, improved insulin sensitivity in preventing type 2 diabetes, and possible neuroprotective properties against neurodegenerative diseases. However, these benefits must be weighed against the significant risks associated with alcohol consumption, including liver damage, increased incidence of headaches, and potential exacerbation of mental health problems such as depression.
It is important to emphasize that the amount of red wine consumed is key. While moderate consumption—defined as one glass per day for women and up to two for men—may provide protective benefits, excessive consumption may lead to adverse health effects. Furthermore, individual variability in response to alcohol suggests that dietary recommendations should be personalized, taking into account genetic, lifestyle, and health factors.
Given the complexity of the relationship between red wine and health, further research is needed to clarify the mechanisms at play and identify populations that may benefit the most. Ultimately, a holistic approach to health—including a balanced diet, regular physical activity,

and psychosocial well-being—remains essential. Red wine can be part of a healthy lifestyle for some, but it should not replace overall healthy living practices.

Keywords: red wine, polyphenols, resveratrol, cardioprotective effect,

Abbreviations: catalase (CAT), superoxide dismutase 2 (SOD2), glutathione peroxidase 1 (GPX1), ferric-reducing antioxidant capacity (FRAP), de-alcoholized red wine (DRW), red wine (RW), cell adhesion molecules (CAMs), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), C-reactive protein (CRP), endothelial nitric oxide synthase (eNOS), nitric oxide (NO), homeostasis model assessment of insulin resistance (HOMA-IR), sirtuins (SIRT), aldehyde dehydrogenase 2 (ALDH2), alcohol-related liver diseases (ALD), non-alcoholic fatty liver disease (NAFLD),

INTRODUCTION

Nourishing habits remain a cornerstone in the realm of contemporary medicine. In the 20th century, researchers launched a deep dive into the effects of diet and lifestyle on overall population health. Among the standout studies was a 1992 investigation by French epidemiologists Renauld and De Lorgeril, which explored the diets of French, British, and Northern European populations [1]. Remarkably, despite comparable intakes of saturated fats, cholesterol, and smoking habits across these groups, the French showcased notably lower rates of mortality from coronary heart disease. This intriguing discrepancy, now famously dubbed the “French Paradox,” has been intricately linked to the Mediterranean lifestyle and the cherished tradition of enjoying red wine in southern European cultures. While the methodology employed by the French researchers has sparked its share of debate, their findings have inspired a wave of scientific inquiry into the effects of red wine on our health.

STATE OF KNOWLEDGE

From a chemical perspective, wine is a captivating blend of multiple components, birthed from a two-step fermentation process involving grapes and the magical touch of yeast [2], [3]. The end result is a delightful concoction primarily made up of water, ethanol, sugars, and polyphenols—those intriguing compounds that lend a tantalizing bitterness to its aftertaste [4]. The unique profile of each wine is shaped by a symphony of factors, including grape variety, soil composition, climate, maceration techniques, and fermentation conditions [5].

Treasured Elements

The rich source of polyphenols in wine comes from the seeds and skins of grapes (Vitis vinifera) [6]. Interestingly, red wine boasts a phenolic content of about 1 mg/L, surpassing that of many fruits and vegetables [7]. Among these compounds, two main groups stand out: flavonoids, known for their metal-chelating abilities and prowess in reducing free radicals, and non-flavonoid compounds [8]. In the realm of red wine, flavonoids reign supreme, featuring notable players like anthocyanins, procyanidins, and flavonols.

One of the most extensively studied non-flavonoids is resveratrol (3,5,4′-trihydroxystilbene), which boasts an average concentration of about 7 mg/L in red wine [9]. A wealth of research highlights its remarkable antioxidant, anti-inflammatory, cardioprotective, and neuroprotective properties. Despite its many health benefits, resveratrol faces challenges due to its low bioavailability, poor solubility in water, and rapid breakdown by the intestinal microbiome, leading to limited absorption when taken orally [10]. Another noteworthy compound is polydatin, a derivative of resveratrol that exhibits enhanced anti-inflammatory and antioxidant effects [11], [12]. Studies have indicated that polydatin can modulate signaling pathways involved in carcinogenesis, showing promise as a therapeutic agent in the fight against various cancers, including laryngeal cancer, nasopharyngeal cancer, and glioblastoma multiforme [13], [14], [15], [16].

One familiar ingredient often found on wine labels is sulfur dioxide. This common preservative plays a crucial role in maintaining wine quality by preventing the breakdown of antioxidants through the inhibition of polyphenol oxidase activity [17]. However, it's important to note that many individuals may not tolerate sulfur dioxide well; its consumption can lead to symptoms such as abdominal pain, diarrhea, hives, and in some cases, anaphylaxis [18]. Consequently, the maximum allowable concentration of sulfur dioxide in red wine is set at 150 mg/L [19].

The Alcoholic Aspect

Despite the abundance of antioxidants in red wine, it is primarily an alcoholic beverage, with ethanol content typically ranging from 9% to 15% by volume [20]. In the United States, a standard drink is defined as a 5-ounce glass of wine (equivalent to approximately one alcoholic beverage), which contains around 14 grams of pure alkohol [21]. The Dietary Guidelines for Americans recommend limiting alcohol intake to no more than two drinks per day for men and one for women [22]. Hence, moderation is key in alcohol consumption. Long-term studies examining the effects of moderate red wine consumption have not revealed significant negative impacts on mortality, suggesting that, when enjoyed responsibly, red wine can fit within a balanced life style [23].

Effects on the cardiovascular system

In the world's most affluent nations, cardiovascular disease reigns as the leading cause of mortality. As red wine is rich in antioxidants, researchers embarked on an exploration of its impact on the bloodstream. A comprehensive review of 19 studies revealed an intriguing uptick in the expression of vital enzymes, including catalase (CAT), superoxide dismutase 2 (SOD2), and glutathione peroxidase 1 (GPX1), all of which play crucial roles in neutralizing harmful free radicals [24]. Additionally, polyphenols found in red wine have demonstrated the ability to suppress the postprandial release of NF-κB, a transcription factor that sets off inflammatory signaling cascades [25].

A key indicator reflecting the drink's beneficial properties is the antioxidant capacity of the plasma, assessed through the ferric-reducing antioxidant capacity (FRAP) assay. In a compelling experiment, de-alcoholized red wine (DRW) was pitted against regular red wine (RW) devoid of polyphenols [26]. Surprisingly, both varieties showcased comparably high FRAP values. Furthermore, consumption of polyphenol-free wine led to an uptick in plasma urates—robust antioxidants in their own right. This finding suggests the presence of two distinct mechanisms that contribute to the enhancement of FRAP.

A crucial facet of this discussion is the impact of red wine's constituents on the progression of atherosclerosis. Endothelial damage serves as a catalyst for the pathological processes that pave the way for this condition [27]. During this cascade, there is a surge in the release of cell adhesion molecules (CAMs) and an uptick in the production of inflammatory mediators by monocytes, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [28]. Remarkably, moderate alcohol consumption has been shown to thwart this damaging sequence of events [29]. It is important to note that the research focused on a healthy population, excluding individuals with pre-existing risk factors for atherosclerosis.

Another remarkable player in wine's heart-healthy arsenal is flavan-3-ols, with the standout stars being epicatechin and catechin—the crucial building blocks of proanthocyanidins [30]. On average, red wine boasts a flavan-3-ol content ranging from 50 to 120 mg/l, with some vintage treasures shining even brighter at levels soaring up to 1000 mg/l [31], [32]. Research by McCullough et al. reveals that a diet rich in these flavonoids can significantly cut the risk of death from coronary heart disease [33]. As for how this magic happens? It appears that flavan-3-ols turbocharge the activity of endothelial nitric oxide synthase (eNOS), leading to a delightful increase in the production of nitric oxide (NO)—a mighty vasodilator—and a reduction in harmful superoxide free radicals [34],[35].

Considering the inductive effect of dyslipidemia on the development of atherosclerosis, the relationship between red wine consumption and lipid metabolism was investigated. Da Luz et al. showed that the group consuming moderate amounts of red wine had significantly higher HDL levels compared to abstainers [36]. In a similar study, alcohol consumption correlated with increased levels of HDL-C, apolipoprotein A1 and adiponectin, which indicates an additional protective effect [37]. The subject was deepened by Marques-Vidal, who showed that it is alcohol, not polyphenols, that increase HDL levels [38].

In an enlightening study led by Magyar, a group of 40 patients living with stable coronary artery disease showcased the heart-healthy benefits of resveratrol found in wine [39]. The findings were encouraging: participants experienced a notable drop in LDL cholesterol, along with significant enhancements in endothelial function and the diastolic performance of the left ventricle.

Influence on carbohydrate metabolism

Red wine isn't just a delightful indulgence; it also has intriguing implications for carbohydrate metabolism. Type 2 diabetes often leads to chronic inflammation in the body, but fear not—red wine's potent antioxidants may help combat this issue. One standout compound, resveratrol, activates a group of proteins known as sirtuins (SIRT), which play a crucial role in regulating carbohydrate balance and the development of atherosclerosis [40].

Research by D'Onofrio shines a light on the link between elevated SIRT levels and their protective role against endothelial damage typically seen in diabetes [41]. It's worth to note that SIRT1 receptors are plentiful in neurons of the central nervous system, which oversee blood glucose regulation. In a study involving obese mice with diabetes, a daily infusion of 79.2 ng of resveratrol showed remarkable results [42]. Continued activation of SIRT1 not only reduced insulin resistance but also helped restore normal blood sugar levels.

Tackling insulin resistance remains a significant therapeutic hurdle. To delve deeper into the effects of red wine, researchers conducted randomized studies comparing red wine, de-alcoholized red wine, and gin on glucose metabolism and lipid profiles [43]. The study, involving 67 men at high cardiovascular risk, spanned four weeks, during which participants received either red wine (30 g of alcohol daily), an equal amount of de-alcoholized red wine, or gin (30 g alcohol daily) in a random sequence. At the study's outset and after each intervention, critical markers like fasting glucose, insulin levels, insulin resistance (HOMA-IR), plasma lipoproteins, apolipoproteins, and adipokines were meticulously measured. Results revealed that both red wine and its de-alcoholized counterpart lowered plasma insulin levels and improved HOMA-IR scores. Notably, red wine led to a decrease in Lipoprotein(a) and an uptick in beneficial HDL cholesterol, along with apolipoproteins A-I and A-II. This research not only underscores the beneficial effects of antioxidants on carbohydrate metabolism but also paints a compelling picture of red wine as a not-so-guilty pleasure with potential health perks.

A study led by Brasnyó explored the powerful impact of resveratrol on insulin resistance [44]. Nineteen participants—men, specifically—took part in a four-week randomized trial designed to uncover how this compound could potentially influence metabolic health. The participants were split into two groups: one group received a daily dose of resveratrol (5 mg twice daily), while the other served as a placebo group. Before kicking off the study and again after the second and fourth weeks, researchers diligently assessed insulin resistance, oxidative stress levels, and phosphorylated protein kinase B (AKT), a protein crucial for inhibiting glycogen synthesis. By the end of the study, results revealed a remarkable decline in insulin resistance within the resveratrol group, alongside a noteworthy increase in AKT levels.

Further emphasizing the relationship between alcohol consumption and metabolic health, a meta-analysis was conducted, including data from 20 studies encompassing over 477,200 individuals of both sexes [45]. This extensive research aimed to unravel the dose-response dynamics between alcohol intake and the risk of developing type 2 diabetes. Astonishingly, it was found that moderate alcohol consumers exhibited a significantly lower risk of type 2 diabetes compared to those who abstained entirely. The analysis identified an optimal preventive alcohol intake, which stood at 22 grams per day for men and 24 grams for women. On the flip side, it also shed light on harmful alcohol thresholds—60 grams per day for men and 50 grams for women. Ultimately, this comprehensive study underscores alcohol's protective effects against type 2 diabetes, suggesting that factors beyond just polyphenols, such as the alcohol content itself, may play a vital role in metabolic well-being.

Red wine's impact on the liver

The impact of red wine on liver health hinges on both the quantity of alcohol consumed and its rich array of bioactive compounds, notably polyphenols like resveratrol. Renowned for its abundance of polyphenols, red wine boasts a cocktail of beneficial compounds, including resveratrol, anthocyanins, and catechins, all of which work to combat oxidative stress. These powerful agents may help curb liver fat accumulation and bolster antioxidant defenses, enhancing the activity of enzymes like superoxide dismutase and glutathione peroxidase [46]. Research involving animals has revealed that red wine infused with polyphenol extracts can significantly reduce inflammation and liver damage sparked by high-fat diets or excessive ethanol consumption. In contrast to pure ethanol, red wine tends to inflict less oxidative damage on liver cells—a protective effect largely attributed to its polyphenolic content [47].

However, it's crucial to note that excessive intake of any alcoholic beverage, including red wine, can pave the way to alcohol-related liver diseases (ALD), such as steatosis, hepatitis, and cirrhosis. High alcohol consumption triggers oxidative stress and inflammation, which can threaten liver health. While moderate red wine consumption may offer a silver lining by potentially decreasing insulin resistance and tackling non-alcoholic fatty liver disease (NAFLD), it's worth considering that elevated levels of resveratrol or other components could intensify liver damage in certain circumstances when combined with alcohol [48].

The effect of red wine on the mind

Unfortunately, red wine is not a cure-all. What's more, it has very harmful effects when consumed in excessive quantities. The influence of red wine on mental well-being is a fascinating topic, particularly when it comes to its unique effects compared to other alcoholic beverages. One common complaint associated with red wine is the occurrence of headaches, often tied to the inhibition of the enzyme ALDH2. This enzyme plays a crucial role in metabolizing acetaldehyde—a byproduct of alcohol consumption. When ALDH2 activity is impaired, acetaldehyde can accumulate in the body, leading to symptoms such as flushing and headaches. Interestingly, red wine's high quercetin content, especially in the form of quercetin-3-glucuronide, has been identified as a potential inhibitor of ALDH2, which may further elevate acetaldehyde levels in sensitive individuals [49].

In an intriguing study conducted in a Lisbon wine bar, researchers explored how moderate consumption of red wine (approximately 40.98 g of ethanol) affected consciousness. One hundred and two participants enjoyed red wine either alone, in pairs, or in groups of up to six. The findings revealed that red wine consumption heightened feelings of pleasure and arousal, decreased awareness of time, and enhanced present-moment focus. Participants reported increased imagination and described their surroundings as more captivating, while also experiencing a profound sense of spiritual connection, peace, and unity with their environment. Notably, these altered states of consciousness were consistent across various social contexts and genders, with older participants deriving greater pleasure and younger individuals expressing heightened fascination with their surroundings. Such effects suggest that savoring wine in thoughtfully curated social settings might evoke consciousness experiences akin to mystical encounters [50].

Another revelatory study tracking 5,505 participants aged 55 to 80 over seven years examined the correlation between alcohol consumption and depression risk. The results indicated that moderate alcohol intake (5 to 15 g per day) was associated with a lower likelihood of depression, with wine drinkers (2 to 7 drinks per week) showing a particularly strong protective effect. Conversely, excessive drinking was linked to an increased risk of depression. These findings imply that moderate consumption of wine may help reduce depressive symptoms, while heavy alcohol intake appears to have the opposite effect [51].

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