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# Sulfites in wine effect on cardiovascular diseases

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**Abstract**
The leading causes of death are still cardiovascular diseases worldwide. Central to the cardiovascular system are reductions in the *in vivo* production and bioavailability of nitric oxide. Food ingredients have received widespread attention in preventing cardiovascular diseases. Epidemiological studies showed that moderate and regular wine consumption, especially red wine consumption, was beneficial for a comparatively lower incidence of coronary heart disease in France. Sulfite at high concentrations in wine has been found to regulate nitric oxide bioavailability in the nitrate–nitrite–nitric oxide pathway. The ability of sulfite to convert nitrite into nitric oxide might have some beneficial effects on cardiovascular diseases. Because sulfite is a harmful substance in wine according to public perception, many studies need to be performed in the future.

**Keywords:** sulfite, nitric oxide, cardiovascular diseases, nitrite, wine, bioavailability

## Introduction

Cardiovascular disease (CVD) is the main cause of the mortality in the world now [1, 2]. CVD is a broad wide scope of diseases, including myocardial diseases and vascular system diseases that affect the heart, brain and other important organs. Studies have revealed the important role of nitric oxide (NO) in maintaining the cardiovascular system [3]. NO homeostasis disorder plays a crucial role in acute ischemic events and is closely related to the development of chronic cardiovascular diseases. In cardiovascular diseases, the decline in NO bioavailability is a key event [4, 5]. Therefore, preventing the reduction of nitric oxide bioavailability may help reduce the incidence of CVD and maintain the function of multiple organ systems.

Food ingredients have received widespread attention in preventing chronic CVD. Based on epidemiological studies, The incidence of coronary heart disease in France is relatively low, despite the high content of saturated fat in its traditional diet. It has been reported that drinking a moderate amount of red wine every day can help achieve this effect [6]. Interventional studies showed that after the ingestion of wine, the function of acute and chronic vascular were improved by measuring flow-mediated dilation [7]. The mechanism of wine's impact on health is extremely complex. However, the regulation bioavailability of NO is a key characteristic of dietary intake of food. It is important to identify the specific ingredients of food that may have nutritional effects, which will help improve dietary guidelines and design the optimal preventive nutrition programme for specific diseases. The role of sulfite in enhanced nitrite-dependent nitric oxide production for cardiovascular diseases was invoked in this paper.

## Source of sulfite in wine

It is said that wine is the ancient and most popular alcoholic drink in the world. According to archaeological discoveries, Mesopotamia began its first large-scale wine production around 5400 BC. The winemaking process includes preparation of must, control of alcohol fermentation, and aging process of wine in barrels. Afterward, Wine is bottled and then store or distribute through retail stores. In order to prevent oxidative stability of wine and avoid microbial spoilage of wine, sulfite will be added regularly during the whole brewing process and before bottling [8].

Sulfur dioxide (also known as "sulfite" in winemaking) with antioxidant and antiseptic properties has been widely used as a preservative application in the food industry, especially in enology since the nineteenth century [9] Sulfur dioxide in winemaking can prevent oxidation, inhibit the growth of spoilage microorganisms, promote the growth of *Saccharomyces cerevisiae* [10]. Sulfur dioxide can also improve the Infusions of phenolic substances from the peel and seeds during the maceration process and make wine color more stable [11]. There are several forms of sulfur dioxide, such as gas, aqueous solution or salt (such as sodium pyro sulfite or potassium pyrosulfate) [12]. Winemakers may use sulfur dioxide during grape pressing, storage, fermentation, or before bottling [9].

Although it was proposed to explain the antibacterial effect of sulfite with various mechanisms, it is most likely that degradation of disulfide bonds in proteins leads to loss of microbial function. Bisulfides can bind to nucleic acids and lipids, resulting in damage to microbial membranes [13, 14]. For its antioxidant effect, sulfite is preferably oxidized prior to other compounds of must or wine; therefore, The quality and sensory characteristics of wine have been improved [12]. In addition, sulfite can reacts with oxidation byproducts to protect the quality of wine. Non enzymatic oxidation reaction and oxidase (such as polyphenol oxidases) are the important reasons for the oxidative browning of must or wine, while sulfite can inhibit the activity of nonenzymatic oxidation reactions and oxidases [9, 14].

However, even without the addition of sulfite, there was still a certain amount of sulfite in wine due to the amino acid metabolism by yeast [14]. The concentration of natural sulfites in wine is closely related to yeast strain and fermentation conditions [15]. To date, the maximum allowable amount of sulfite in wine varies in different regions of the world; for example, the maximum allowable amount for total sulfite were 350 mg/L in the United States and Japan, 250 mg/L(containing sugars<35 g/L) and 300 mg/L (containing sugars≥35 g/L) in Australia, 150 mg/L

(red wines, containing sugars≤5 g/L) and 200 mg/L (white and rosé wines, containing sugars ≤5 g/L) in the European Union. According to the World - International Grape and Wine Organization OIV, the upper limit of total sulfite in various wines was 150 mg/L (red wine containing reducing substances ≤ 4 g/L); 200 mg/L (white and rosé wines containing reducing substances ≤4 g/L); 300 mg/L (red, rosé and white wines containing reducing substances >4 g/L); and 400 mg/L (some sweet white wines) [16].

**Production of NO in cardiovascular diseases**

It seems that no less than two systems can affect the production/homeostasis of NO. The L-arginine-NO pathway was the first discovered pathway in mammals [17]. In this pathway, NO is formed through the oxidation of L-arginine and molecular oxygen acts as electron acceptor. This pathway is a complicated and complex pathway that requires several cofactors. If any cofactor becomes a limiting factor, the NO produced by NOS will shut down, and NOS will produce superoxide in many cases. The nitrate-nitrite-NO pathway was the alternate route as a complementary system of NO production. The alternative pathway uses nitrate and nitrite as substrates in the gradual reduction process. Oral symbiotic bacteria were crucial to the initial stage of the nitrate-nitrite-NO pathway because their task is to use enzymes to reduce nitrate to nitrite [18, 19]. Nitrite can be reduced to NO by various nitrite reductases under certain conditions, which include carbonic anhydrase (Cu) [20], xanthine oxidoreductase [21-23], aldehyde oxidase [24], sulfite oxidase (Mo) [25], deoxyhemoglobin [26-28], deoxymyoglobin [29, 30], neuroglobin [31, 32], cytochrome C [33], NOS (Fe) [34], and by acidic disproportionation [35]. The relative contribution of each of these pathways may vary depending on prevailing conditions [36, 37].

The successive production of NO is crucial for the integrity of the cardiovascular system and the reduction of NO bioavailability is the key to the development of many cardiovascular diseases [38]. In cardiovascular diseases, the ability of endothelial NOS to generate NO by catalyzing L-arginine is weakened, and alternative sources of NO from dietary intake of food (i.e., salivary nitrate-nitrite-NO pathway) can compensate for the fall in NO production catalyzed by NOS [39, 40]. Therefore, simply supplementing L-arginine is not the most effective strategy for increasing NO production in cardiovascular disease patients. The nitrate-nitrite-NO pathway has potential as a maintenance system for NO bioavailability in cardiovascular diseases.

**Potential negative health effects of sulfite in wine**

Sulfites are a common food additive and a ubiquitous ingredients in wine. All wines contain sulfite as a natural by-product produced by yeasts during wine Fermentation. But the majority of sulfites are added to wine in the form of sulfite salts (such as sodium sulfite or sodium metabisulphite) before bottling. However, In spite of all the advantages of the sulfite, excessive sulfite impart an undesirable taste and may pose serious health risks related to allergic reactions in some consumers. Most sulfite-sensitive individuals may experience a variety of symptoms, including dermatitis, urticaria, angioedema, bdominal pain, diarrhea, bronchoconstriction, and anaphylaxis [41, 42]. Nevertheless, reactions manifesting in migraine and headache account for the majority of cases of sulfite sensitivity [43]. It is estimated that approximately 1% of the population has some clinical sensitivity to sulfite, with increasing risk in asthmatic people [44, 45].

**Potential health benefits of sulfite in wine**

Nitrite *in vivo* in circulation and tissues usually comes from intake of diet and/or *in vivo* production. Exogenous nitrite is obtained through the intake of vegetables, meat products, and other foods, mainly through the transformation of dietary nitrate by symbiotic bacteria in the oral microbiota [46]. It can be known from previous literature that nitrates can be extracted from plasma by the salivary glands, however, the reason for this process has not been explained yet. This process results in a 10-20 times higher nitrate level in saliva compared with plasma [47]. The nitrate reductase of symbiotic facultative anaerobe in the oral cavity can convert about 20% of nitrate into nitrite [19, 47]. Nitrite is converted into NO in the acidic environment of the stomach after swallowing [48]. The acidification process of nitrite is very complicated, and the concentration of NO produced by acidified nitrite is related to many factors, such as pH, nitrite concentration, reducing agents, and oxygen content [35]. Umeo *et al*. demonstrated that sulfite can enhance the production of NO in acidified saliva containing nitrite and acidic buffer solution, and as the concentration of sulfite increases, the concentration of NO increases from 0 to 0.1mM. [49]. When sulfite was added to the simulated wine containing nitrite (data not shown), the production of NO was detected. These findings suggest that sulfite may directly convert nitrite into NO under acidic conditions, although in light of the findings above, the precise mechanisms of sulfite in NO production has not been resolved so far. The ability of sulfite to effectively convert nitrite into NO may be the reason for some beneficial effects on some cardiovascular disease（Fig. 1).

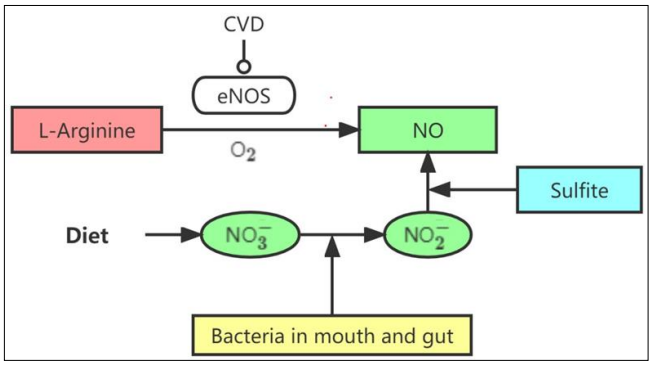


**Fig 1:** The hypothetical mechanisms of sulfite on NO production. The ability of eNOS to catalyze L-arginine to form NO is reduced in cardiovascular diseases. Nitrate and nitrite can be sequentially reduced to produce bioactive NO through microbial and sulfite reductive pathways. Sulfite may produce sufficient NO in cardiovascular disease by enhancing the nitrate-nitrite-NO pathway. (NOS nitric oxide synthase NO nitric oxide, $NO_3^-$ nitrate, $O_2$ Oxygen, CVD cardiovascular disease, $NO_2^-$ nitrite)

**Conclusion**

The nutritional function of food can play a crucial and cost-effective role in reducing the risk of disease. To date, no direct intervention study has been conducted to evaluate the beneficial effects of sulfite in wine to cardiovascular diseases. Prior to this discovery, the public perception remained that sulfite is a harmful substance in wine. Now,

most research focused on its toxicity characteristics, and little is known about the potential health benefits of sulfite in wine. A few studies have shown beneficial effects on the modulation of NO bioavailability. Studies that determine whether the beneficial effects of sulfites will exceed the harmful effects have not been carried out to date. If this is proven to be true in human studies, wine containing appropriate amounts of sulfite with nitrate may become a functional food for preventing cardiovascular disease.

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**References**

1. Mathers CD, A Lopez, C Stein, *et al*. "Deaths and Disease Burden by Cause: Global Burden of Disease Estimates for 2001 by World Bank Country Groups." In Disease Control Priorities Project Working Paper 18. Bethesda, MD, 2001.
2. WHO (World Health Organization). The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002b.
3. Palmer RMJ, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of end otheliumderived relaxing factor. Nature,1987:327(6122):524-6.
4. Seals DR, Jablonski KL, Donato AJ. Aging and vascular endothelial function in humans. Clin Sci,2011:120(9):357–75.
5. Cau SB, Carneiro FS, Tostes RC. Differential modulation of nitric oxide synthases in aging: therapeutic opportunities. Front Physiol,2012:3:218.
6. Renaud S, R Gueguen. The French paradox and wine drinking. Novartis Found. Symp. 216:208-217. discussion,1998:217-222:152-208.
7. Agewall S, Wright S, Doughty RN, *et al*. Does a glass of red wine improve endothelial function? Eur Heart J,2000:21(1):74–8.
8. Grainger K. Wine Faults and Flaws. Wine Qual, 2009, 67–77.
9. Giacosa S, Río Segade S, Cagnasso E, *et al*. Chapter 21-SO2 in Wines: Rational use and possible alternatives. In Red Wine Technology; Morata, A., Ed.; Academic Press: Cambridge, MA, USA, 2019, 309–321. [Cross Ref]
10. Morgan SC, Tantikachornkiat M, Scholl CM, *et al*. The effffect of sulfur dioxide addition at crush on the fungal and bacterial communities and the sensory attributes of Pinot gris wines. Int. J. Food Microbiol,2019:290:1–14.
11. Guerrero RF, Cantos Villar E. Demonstrating the efficiency of sulphur dioxide replacements in wine: A parameter review. Trends Food Sci. Technol,2015:42:27–43.
12. Zoecklein BW, Fugelsang KC, Gump BH, *et al*. Sulfur Dioxide. In Production Wine Analysis; Springer: Berlin/Heidelberg, Germany, 1990, 185–206. [CrossRef]
13. Jackson RS. Wine Science: Principles and Applications (Food Science and Technology), 4th ed.; Academic Press; Elsevier Inc.: New York, NY, USA, 2014.
14. Waterhouse AL, Sacks GL, Jeffffery DW. Understanding wine Chemistry; John Wiley & Sons: Hoboken, NJ, USA, 2016. [CrossRef]
15. Eschenbruch R. Sulfifite and sulfifide formation during winemaking—A review. Am. J. Enol. Viticult,1974:25:157–161.
16. Emmanouil Kontaxakis, Emmanouil Trantas, Filippos Ververidis. Resveratrol: A Fair Race Towards Replacing Sulfifites in Wines. Molecules,2020:25:2378. http://dx.doi.org/10.3390/molecules25102378.
17. Stuehr DJ. Mammalian nitric oxide synthases. Biochim Biophys Acta,1999:1411:217–30.
18. Duncan C, Dougall H, Johnston P, *et al*. Chemical generation of nitric oxide in the mouth from the enterosalivary circulation of dietary nitrate. Nat Med,1995:1:546–51. [CrossRef]
19. Doel JJ, Benjamin N, Hector MP, *et al*. Evaluation of bacterial nitrate reduction in the human oral cavity. Eur J Oral Sci,2005:113:14–9.
20. Aamand R, Dalsgaard T, Jensen FB, *et al*. Generation of nitric oxide from nitrite by carbonic anhydrase: a possible link between metabolic activity and vasodilation. Am J Physiol Heart Circ Physiol,2009:297:H2068–74.
21. Li H, Samouilov A, Liu X, Zweier JL. Characterization of the effects of oxygen on xanthine oxidase-mediated nitric oxide formation. J Biol Chem,2004:279:16939–46.
22. Webb A, Bond R, McLean P, *et al*. Reduction of nitrite to nitric oxide during ischemia protects against myocardial ischemia-reperfusion damage. Proc Natl Acad Sci USA,2004:101:13683–8.
23. Webb AJ, Milsom AB, Rathod KS, *et al*. Mechanisms underlying erythrocyte and endothelial nitrite reduction to nitric oxide in hypoxia: role for xanthine

oxidoreductase and endothelial nitric oxide synthase. Circ Res,2008:103:957–64. [CrossRef]
24. Li H, Cui H, Kundu TK, *et al*. Nitric oxide production from nitrite occurs primarily in tissues not in the blood: critical role of xanthine oxidase and aldehyde oxidase. J Biol Chem,2008:283:17855–63.
25. Wang J, Krizowski S, Fischer Schrader K, *et al*. Sulfite oxidase catalyzes single-electron transfer at molybdenum domain to reduce nitrite to nitric oxide. Antioxid Redox Signal,2015:23:283–94.
26. Cosby K, Partovi KS, Crawford JH, *et al*. Nitrite reduction to nitric oxide by deoxyhemoglobin vasodilates the human circulation. Nat Med,2003:9:1498–505.
27. Crawford JH, Isbell TS, Huang Z, *et al*. Hypoxia, red blood cells, and nitrite regulate NO-dependent hypoxic vasodilation. Blood,2006:107:566–74.
28. Nagababu E, Ramasamy S, Abernethy DR, *et al*. Active nitric oxide produced in the red cell under hypoxic conditions by deoxyhemoglobin-mediated nitrite reduction. J Biol Chem,2003:278:46349–56.
29. Rassaf T, Flögel U, Drexhage C, *et al*. Nitrite reductase function of deoxymyoglobin: oxygen sensor and regulator of cardiac energetics and function. Circ Res,2007:100:749–54.
30. Shiva S, Huang Z, Grubina R, *et al*. Deoxymyoglobin is a nitrite reductase that generates nitric oxide and regulates mitochondrial respiration. Circ Res,2007:100:654–61.
31. Petersen MG, Dewilde S, Fago A. Reactions of ferrous neuroglobin and cytoglobin with nitrite under anaerobic conditions. J Inorg Biochem,2008:102:1777–82.
32. Tiso M, Tejero J, Basu S, *et al*. Human neuroglobin functions as a redox-regulated nitrite reductase. J Biol Chem,2011:286:18277–89.
33. Castello P, David PS, McClure T, *et al*. Mitochondrial cytochrome oxidase produces nitric oxide under hypoxic conditions: implications for oxygen sensing and hypoxic signaling in eukaryotes. Cell Metab,2006:3:277–87.
34. Gautier C, van Faassen E, Mikula I, *et al*. Endothelial nitric oxide synthase reduces nitrite anions to NO under anoxia. Biochem Biophys Res Commun,2006:341:816–21.
35. Weitzberg E, Lundberg JO. Nonenzymatic nitric oxide production in humans. Nitric Oxide,1998:2(1):1–7. [CrossRef]
36. Gladwin MT, Schechter AN, Kim Shapiro DB, *et al*. The emerging biology of the nitrite anion. Nat Chem Biol,2005:1:308–14.
37. Van Faassen EE, Bahrami S, Feelisch M, *et al*. Nitrite as regulator of hypoxic signaling in mammalian physiology. Med Res Rev,2009:29:683–741.
38. Vita JA, Keaney Jr JF. Endothelial function: a barometer for cardiovascular risk? Circulation,2002:106(6):640–2.
39. Lundberg JO. Cardiovascular prevention by dietary nitrate and nitrite. Am J Physiol Heart Circ Physiol,2009:296(5):H1221–3.
40. Lundberg JO, Weitzberg E. Nitrite reduction to nitric oxide in the vasculature. Am J Physiol Heart Circ Physiol,2008:295(2):H477–8.
41. Vally H, Misso NLA, Madan V. Clinical effects of sulphite additives. Clin Exp Allergy,2009:39(11):1643‑1651.
42. Timbo B, Koehler KM, Wolyniak C, Klontz KC. Sulphites−a food and drug administration review of recalls and reported adverse events. J Food Prot,2004:67(8):1806‑1811.
43. Costanigro M, Appleby C, Menke SD. The wine headache: Consumer perceptions of sulfites and willingness to pay for non-sulfited wines. Food Quality and Preference,2014:31:81‑89. DOI:10.1016/j.foodqual.2013.08.002.
44. Vally H, Misso NLA, Madan V. Clinical effects of sulphite additives. Clin. Exp. Allergy,2009:39:1643‑1651.
45. Lisanti MT, Blaiotta G, Nioi C, Moio L. Alternative methods to SO2 for microbiological stabilization of wine. Compr. Rev. Food Sci. F,2019:18:455‑479.
46. Lundberg JO, Weitzberg E, Cole JA, *et al*. Nitrate, bacteria and human health. Nat Rev Microbiol,2004:2(7):593–602.
47. Spiegelhalder B, Eisenbrand G, Preussman R. Influence of dietary nitrate on nitrite content of human saliva: possible relevance to *in vivo* formation of N-nitroso compounds. Food Cosmet Toxicol,1976:14:545–8. [CrossRef]
48. Benjamin N, O'Driscoll F, Dougall H, *et al*. Stomach NO synthesis. Nature,1994:368(6471)：502.
49. Umeo Takahama, Sachiko Hirota. Effects of the Food Additive Sulfite on Nitrite-Dependent Nitric Oxide Production under Conditions Simulating the Mixture of Saliva and Gastric Juice. Agric. Food Chem,2012:60(4):1102–1112.