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Review Article

# Wine consumption and intestinal redox homeostasis

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ABSTRACT

Regular consumption of moderate doses of wine is an integral part of the Mediterranean diet, which has long been considered to provide remarkable health benefits. Wine's beneficial effect has been attributed principally to its non-alcoholic portion, which has antioxidant properties, and contains a wide variety of phenolics, generally called polyphenols. Wine phenolics may prevent or delay the progression of intestinal diseases characterized by oxidative stress and inflammation, especially because they reach higher concentrations in the gut than in other tissues. They act as both free radical scavengers and modulators of specific inflammation-related genes involved in cellular redox signaling. In addition, the importance of wine polyphenols has recently been stressed for their ability to act as prebiotics and antimicrobial agents.

Wine components have been proposed as an alternative natural approach to prevent or treat inflammatory bowel diseases. The difficulty remains to distinguish whether these positive properties are due only to polyphenols in wine or also to the alcohol intake, since many studies have reported ethanol to possess various beneficial effects. Our knowledge of the use of wine components in managing human intestinal inflammatory diseases is still quite limited, and further clinical studies may afford more solid evidence of their beneficial effects.



**Contents**



*Abbreviations:* AKT, serine/threonine protein kinase (v-akt murine thimoma viral oncogene homolog1); apoB48, apolipoprotein B48; CD, Crohns disease; COX-2, cyclooxygenase-2; Cys, cysteine; DSS, dextran sodium sulfate; ERK, extracellular signal-regulated kinase; GRP, grape reaction product; GSH, reduced glutathione; IBD, inflammatory bowel disease; IKB, inhibitor of NF-κB; IL, interleukin; iNOS, inducible nitric oxide synthase; IFN, interferon; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate reduced; NF-κB, nuclear factor-κB; Nrf2, nuclear factor erythroid-2-related factor 2; PGE-2, prostaglandin E-2; ROS, reactive oxygen species; SIRT-1, silent mating type information regulation-1; TNF-α, tumor necrosis factor alpha; UC, Ulcerative Colitis

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## Introduction

A large number of studies, both in experimental models and in humans, have investigated the antioxidant properties of wine. The majority of studies on wine's effects have been performed on the cardiovascular system; its moderate consumption is generally considered to protect against coronary heart disease, and to be associated with a lower incidence of oxidative stress-related degenerative diseases [1]. However, during absorption wine components accumulate in the intestinal mucosa, where they reach higher concentrations than in other tissues, and can exert their activities.

The gastrointestinal tract is the first barrier against environmental agents, and is responsible for immune tolerance of microbiota [2]; it is prone to oxidative damage due to its exposure to the luminal oxidants present in foods. For instance, discrete quantities of reactive oxygen species (ROS) are essential for the recognition of nutrients, commensal and pathogenic bacteria, as well as for killing and processing pathogens during inflammatory immune response. However, increased free radical production and impaired antioxidant defenses have been related to the progression of intestinal chronic inflammation, which characterize a group of human diseases known as Inflammatory Bowel Diseases (IBD) [3]. Maintenance of the correct gastro-intestinal redox balance, which depends on dietary compounds, is thus an important aspect for human health.

The beneficial effect of wine has been mainly attributed to its non-alcoholic portion having antioxidant properties, which contains a large variety of phenolic compounds; these are mostly present in red wine [4]. Likewise implicated are antioxidants, such as ascorbic acid and sulfur dioxide, normally added during white-wine processing [5].

This review will discuss experimental and clinical data suggesting a link between wine consumption and intestinal function. In particular, it will focus on the relevant potential protective mechanisms that wine components may exercise on the cell signal network, specifically induced during tissue damage characterized by oxidative and inflammatory reactions.

## Maintenance of redox intestinal homeostasis

The intestinal tract is continually attacked by luminal microbes and by oxidized compounds from the diet, exposing it to recurrent oxidative changes. Intestinal epithelial cells act as a selective permeable barrier, which allows the absorption of nutrients, electrolytes and water by transcellular and paracellular pathways, also affording their intracellular compartmentalization and trafficking towards the body. These cells are able to regulate the traffic of antigens towards gut-associated lymphoid tissues, in order to discriminate between innocuous and pathogenic antigens, acting as a crossroad between tolerance and the immune response.

Evidence for the need of a proper dietary intake of antioxidants to maintain low intracellular levels of oxidative species is manifold. ROS and their oxidized products may be considered as part of a network signaling system controlled by antioxidant defenses. For instance, moderate quantities of ROS can act as biological signal molecules, which are involved in different phases of the inflammatory immune response and of autophagic processes activated by luminal agents in intestinal cells. These events imply the production of hydrogen peroxide ($H_2O_2$) and superoxide anion ($O_2^{-\bullet}$) or nitric oxide (NO) at specific intracellular sites, i.e. mitochondria, membrane nicotinamide adenine dinucleotide phosphate reduced (NADPH) oxidase, endothelial inducible NO synthase (iNOS) and myeloperoxidase in inflammatory cells [6]. $H_2O_2$ regulate redox sensitive transduction pathways, such as phosphatidylinositol 3-kinase/AKT, mitogen-activated protein kinase/extracellular signal regulated kinase kinase / extracellular signal-regulated kinase (ERK) and c-jun N-terminal kinase, and also regulate activation of the oxidative stress-responsive nuclear transcription factor-κB (NF-κB), which is involved in inflammatory reactions [7,8]. However, although cell inflammation and oxidative reactions are considered to be a primary host defense, excessive inflammatory reactions, with overproduction of $O2^{-\bullet}$, $H_2O_2$, NO and HOCl by activated leukocytes, can overwhelm the tissue's antioxidant defenses and may contribute to functional impairment of the enteric mucosa, leading to an aberrant response to luminal agents. These events have been extensively considered in the pathogenesis of IBD and have been associated to chronic abnormal inflammatory and immune responses [3].

An antioxidant intestinal environment reflects the intestinal mucosa's response aimed at preventing oxidative damage, and is maintained by a complex dynamic recycling system in which different molecules undergo well-established oxido-reductions. The chief molecules involved are antioxidant enzymes, i.e. superoxide dismutase, catalase and glutathione peroxidases, as well as non-enzymatic molecules some of which originate from the diet, such as ascorbic acid, tocopherols and amino-thiols compounds [9]. To a great extent, ascorbate, reduced glutathione (GSH), cysteine (Cys) and sulfur dioxide are produced under conditions used in winemaking (see section below).

## Principal non-alcoholic components of wine

There is a wide variation in wine compounds, the composition being affected by several factors including the grape varieties used, winemaking technology, and conditions under which the wine is aged and stored. The most abundant non-alcoholic components are phenolic compounds, which are generally called polyphenols, and that may roughly be divided as flavonoid and non-flavonoid compounds. Wine flavonoids can in turn be subdivided into flavan-3-ols, anthocyanins and flavonols. Catechin and epicatechin are the most representative flavan-3-ols in monomeric form; proanthocyanidins are oligomers, while condensed tannins are polymers. Non-flavonoid wine components are benzoic and hydroxycinnamic acids (caffeic, ferulic and *p*-coumaric acids) with their tartaric esters (caftaric, fertaric and coutaric acids), and stilbenes [10,11].

Although *Vitis vinifera* is the dominant grape used in wine production, there are significant varietal differences within this species [12]; the phenolic composition of wine also depends on processing in the winery [13]. Red wine is a whole-berry extract made by fermenting the juice in the presence of grape skin and seeds (which contain most of the phenols), while white wine is a juice product. Thus the total amount of phenols found in a typical glass of red wine is in the order of 100–200 mg, versus 25–50 mg in a glass of white wine [10].

In red wine, tannins contribute to the mouth feel of wines, but they also form pigmented polymers in association with anthocyanins, to provide the stable pigments that give red wine its long-term color stability. In white wine, the most important phenolic compounds are hydroxycinnamic acids and, in minor quantities, flavan-3-ol monomers [10].

Phenolic concentration and composition change significantly during vinification when considerable amounts of phenolics are degraded or oxidized [14]. Aging or fermenting in oak barrels enables oxygenation to occur, and various different compounds with organoleptic properties are released from the wood. Oak-treated wines contain volatile phenols including vanillin, furanic derivatives, lactones, terpenes and hydrolysable tannins (mainly