

Moderate alcohol consumption and the immune system: A review

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Increasing evidence suggests that light to moderate amounts of polyphenol-rich alcoholic beverages like wine or beer could have health benefits. Scientists have long debated the effects of alcohol on immune function, showing on the one hand, that high doses of alcohol consumption can directly suppress a wide range of immune responses, and that alcohol abuse is associated with an increased incidence of a number of infectious diseases. On the other hand, moderate alcohol consumption seems to have a beneficial impact on the immune system compared to alcohol abuse or abstinence. Therefore, the link between alcohol consumption, immune response, as well as infectious and inflammatory processes remains not completely understood. With this in mind, it is important to realise that other factors, unrelated or indirectly related to immune function, like drinking patterns, beverage type, amount of alcohol, or gender differences, will affect the influence that alcohol consumption may have on the immune system. This review summarises published data describing the effects that light to moderate amounts of polyphenol-rich beverages like wine or beer seem to have on immunity in healthy adults.

Immunity: Alcohol: Polyphenol-rich beverages

Alcohol consumption and immunity

Scientific interest in investigating the beneficial health effects of moderate alcohol consumption started in the late 1950s with the *Seven Countries Study*¹. Since then, numerous epidemiological studies have corroborated the inverse relationship between moderate alcohol intake and cardiovascular risk morbidity and mortality. Regarding the immune system, researchers have long discussed how alcoholic beverages can affect host defence. Alcohol can directly suppress various immune responses, and clinical studies have found alcohol abuse to be associated with an increased incidence of a number of infectious diseases^{2,3}. Although the acute and chronic use of alcohol is deleterious for health and generally viewed as being immunosuppressive, it is not clear that documented alcohol-elicited changes in immune function are of clinical significance⁴. There are several studies supporting an increased incidence of infections among alcoholics^{3,5}, but these relations are often attributed to concomitant complications of alcoholism, including nutritional deficiencies, gastrointestinal and hepatic conditions and socioeconomic status⁶.

On the other hand, moderate alcohol consumption (up to three to four drinks per day) has been associated with either no risk⁷ or a decreased risk for upper respiratory infections⁸. Since moderate alcohol consumption has been suggested to have a beneficial impact on the immune system compared to alcohol abuse or abstinence^{8–12}, the link between alcohol consumption, immune response, as well as infectious and inflammatory processes remains controversial and not yet completely understood. In reviewing the literature, it is important to realise that other factors, unrelated or indirectly related to

immune function, such as drinking pattern, amount of alcohol, beverage type or gender differences, are directly implicated in the relationship between alcohol consumption and the immune system^{10–13} (Fig. 1). This review summarises published evidence of how moderate alcohol consumption can play a role in the regulation of the immune response in healthy adults, and the determinants of this modulation (Table 1).

Amount of alcohol

There are several mechanisms by which alcohol can affect immunity. Alcohol seems to impair the ability of white blood cells to migrate to sites of injury and infection, to induce functional abnormalities of T and B lymphocytes, natural killer cells and monocytes/macrophages, and to alter cytokine production^{14–16}. However, despite the fact that both cell-mediated and humoral immune responses have been shown to be depleted in high-dose consumers of alcohol^{17,18}, studies in humans and experimental animals suggest that low-doses of ethanol may enhance the immune response^{9,11,12}. In humans, a moderate intake of alcohol in individuals exposed to rhinoviruses was associated with a decreased risk of developing the common cold, suggesting that moderate consumption of alcohol may enhance the immune response, resulting in a more effective host defence⁸. This enhancing effect might depend on the type of beverage (whether it is fermented or distilled), as well as on the amount and duration of ethanol intake.

With regard to cell-mediated immunity, a reduction in CD3+, CD4+, and CD8+ cell numbers has been found after chronic alcohol administration in male rats¹⁹. In contrast, in humans an increase in absolute values of the CD3+

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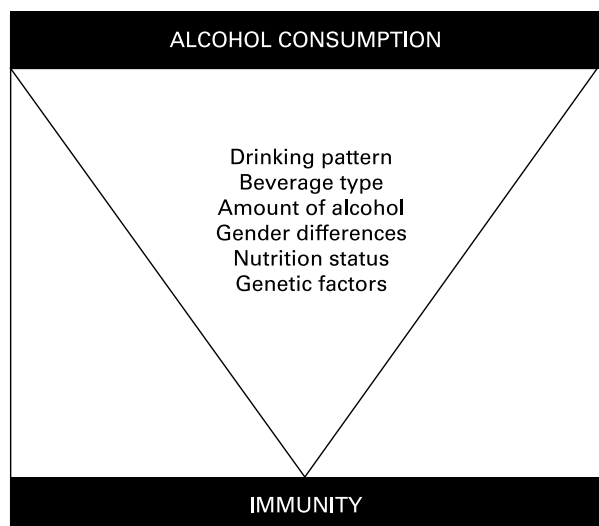


Fig. 1. Individual factors in adults that can moderate the effect of alcohol consumption on immunity.

lymphocytes has been recently found after 30 days of moderate beer consumption¹¹. Although the first study was made in animals, and the second in humans, the results suggest that the effect of alcohol intake on T lymphocyte subsets may depend on the amount consumed.

Cytokines are signalling proteins produced in response to infection or cell damage. The presence of damaged cells triggers the body's defence responses, including the release of cytokines, resulting in a vicious cycle of inflammation, cell death and scarring. Alcoholic pathology is well known to be associated with a disruption in cytokine balance and functions^{15,20,21}. Increased serum tumour necrosis factor (TNF)- α and interleukin (IL)-6 concentrations together with decreased IL-10, interferon (IFN)- γ and IL-2 levels have frequently been found in alcoholic patients with liver cirrhosis^{22,23}. After an intervention of 30 days of moderate beer consumption in humans, an increased production of IL-2, IL-4, IL-10 and IFN- γ was found¹¹. Similarly, an *in vitro* study has suggested that some of beneficial health effects of moderate beer intake may relate to its ability to interfere with pro-inflammatory cytokine cascades²⁴. Moreover, Mandrekar and co-workers have suggested that moderate alcohol consumption (2 ml vodka/kg body weight) has dual anti-inflammatory effects that involve augmentation of IL-10 and attenuation of monocyte inflammatory responses²⁵.

These results could support a role, via an anti-inflammatory mechanism, for moderate alcohol intake in cardiovascular disease (CVD) prevention. This outcome underscores the importance of taking into account the amount of alcohol consumption when evaluating the immune response. Therefore, further studies focused on drinking pattern are necessary to elucidate the effect of moderate alcohol consumption on the immune response.

Beverage type

It is important to highlight other components like polyphenols, antioxidants and vitamins present in beer or wine^{26,27}, when

studying the health effects of these beverages. Ethanol may be detrimental to immune cells due to the generation of free radicals during clearance; however, alcoholic beverages containing antioxidants should be protective against immune cell damage^{27,28}. One of the main topics that needs further research, therefore, is the clarification of how different types of alcoholic and non-alcoholic beverages influence specific biological markers, in order to differentiate which effects are due to the alcohol *per se* and which could be related to other components. In animal models, the consumption of ethanol only led to lower levels of white blood cells; however, the same amount of alcohol consumed as red wine resulted in no suppression of the immune response. This could be due to the action of certain compounds in red wine that could be contributing to prevent suppression of the immune system caused by alcohol²⁷. Similarly, wine intake, especially red wine, has been identified as having a protective effect against the common cold²⁹. Nevertheless, this remains controversial. Daily moderate consumption of alcohol (500 ml of a 12% ethanol dilution), and 500 ml of red wine, red grape juice, and dealcoholised red wine for 2 weeks at doses which inversely correlate with CVD risk did not show any effects on human immune cell functions³⁰. However, the design of this study could be questioned since the duration may have been insufficient to affect the immune system; probably it would take up to six weeks to see changes and differences in the immune system.

In the MONICA study, an epidemiological study, moderate consumption of either wine or beer appeared to be associated with lower levels of systemic inflammatory markers in three different European areas (Germany, Scotland, and France). Although the authors have suggested that ethanol itself might be largely responsible for the potential anti-inflammatory effects of these beverages³¹, this remains controversial due to the high content of polyphenols and antioxidant vitamins in these types of fermented alcoholic beverages. After moderate red wine consumption, as compared with gin, a more pronounced decrease in TNF- α -induced adhesion of monocytes to endothelial cells has been observed³². Moreover, Estruch and co-workers³³ found an additional anti-inflammatory effect by decreasing C-reactive protein (CRP), as well as monocyte and endothelial adhesion molecules, after 28 days of red wine intake compared to gin with the same amount of ethanol (30 g per day).

In fermented alcoholic beverages, apart from alcohol and polyphenols in red wine (quercetin, rutin, catechin, epicatechin and resveratrol), other relevant components (for example, in beer) that could also influence the immune system are total carbohydrate and soluble fiber content, minerals, trace elements and vitamins such as phosphorous, silicon, magnesium, potassium, niacin, riboflavin, pirodixin, folates and vitamin B12^{26,34–36}.

Gender differences

Generally, women seem to be more susceptible to auto-immune or inflammatory diseases, although they have a lower risk of infections than men, especially during the pre-menopausal years. This can be attributed to women's high levels of oestrogens that help to stimulate immunity and fight disease^{37–40}. One mechanism by which oestrogens

Table 1. Summary of presented studies reporting effects on immunity with moderate alcohol consumption

Reference	Study methods	Effect on immunity
Cohen <i>et al.</i> , 1993 ⁸	Design: Prospective study for 3 years. Subjects: 154 men and 263 English women. Amount*: 0.1 to 2 alcoholic drinks/day.	Moderate drinkers were more resistant than abstainers to common cold virus for non-smokers.
Fenech <i>et al.</i> , 1997 ²⁸	Design: Intervention for 24 h. Subjects: 4 healthy men. Amount*: 300 ml of red or white wine.	Moderate wine consumption protects against hydrogen peroxide-induced DNA damage.
Takkouche <i>et al.</i> , 2002 ²⁹	Design: Epidemiologic cross-sectional study. Subjects: 4.272 faculty staff of five Spanish universities. Amount*: 0.0 to 160.4 g/week of alcohol.	Wine consumption, especially red wine, decrease the incidence of common cold.
Badía <i>et al.</i> , 2004 ³²	Design: Crossover trial for 28 days. Subjects: 8 healthy men. Amount*: 30 g ethanol/day as red wine or gin.	TNF- α -induced adhesion of monocytes to endothelial cells was almost abolished after red wine consumption and was partially reduced after gin consumption.
Estruch <i>et al.</i> , 2004 ³³	Design: prospective randomized crossover trial for 28 days. Subjects: 40 healthy workers of Hospital Clinic, Barcelona, Spain. Amount*: 30 g ethanol / day as either red wine or gin.	Both wine and gin showed anti-inflammatory effects by reducing plasma fibrinogen and IL-1 α levels.
Watzl <i>et al.</i> , 2004 ³⁰	Design: randomized single-blind trial for 2 weeks with four intervention periods. Subjects: 24 healthy German males. Amount*: 500 ml of red wine or 500 ml of a 12% ethanol dilution.	Neither red wine nor diluted alcohol intake had any effect on the immune system.
Winkler <i>et al.</i> , 2006 ²⁴	Design: <i>In vitro</i> study. Isolated human peripheral blood mononuclear cells stimulated with mitogen phytohaemagglutinin. Methods: Neopterin production and tryptophan degradation were measured.	Beer interferes with immunopathogenetic pathways which involve Th-1 type cytokine IFN- γ .
Mandrekar <i>et al.</i> , 2006 ²⁵	Design: 18 h intervention period. Subjects: 19 men and women, aged 21 – 60 years from University of Massachusetts Medical Center, USA. Amount: 2 ml vodka/kg body weight.	Moderate alcohol intake in humans attenuates monocyte inflammatory responses: inhibition of nuclear regulatory factor kappa B and induction of interleukin 10.
Romeo <i>et al.</i> , 2007 ¹²	Design: 30 days intervention period. Subjects: 57 Spanish healthy adults. Amount*: 330 mL of beer for women and 660 mL for men, respectively.	Absolute values of leukocytes, neutrophils, lymphocytes and basophils increased in women as well as basophils in men. Oxidative burst capacity also increased after beer consumption.
Romeo <i>et al.</i> , 2007 ¹¹	Design: 30 days intervention period. Subjects: 57 Spanish healthy adults. Amount*: 330 mL of beer for women and 660 mL for men, respectively.	IgG, IgM, and IgA concentrations, as well as IL-2, IL-4, IL-10, and IFN- γ cytokine production increased while IFN- γ /IL-10 ratio decreased after beer consumption.

*Amount of alcohol or beverage considered as a moderate consumption of alcohol.

could modulate the immune reaction is by regulating cytokine expression³⁹ and reducing pro-inflammatory cytokines⁴⁰. Several studies have directly examined gender differences in the effects of alcohol on inflammatory and immune responses reporting that females exhibit greater sensitivity to alcohol than males^{11,41–43}. Combined differences in pharmacokinetics may increase the vulnerability of women to the effects of ethanol. The mechanisms that may underlie these differences could be gender differences in the physiological processing and metabolic clearance of alcohol and differential sensitivity of the nervous system to alcohol. Some researchers have suggested that differences are mainly due to a lower alcohol-dehydrogenase activity in women, rather than to differences in gastric emptying or in the hepatic oxidation of ethanol⁴⁴. Furthermore, there is also evidence implicating the direct involvement of hormones in the gender differences observed regarding alcohol consumption. Heavy drinking has been suggested to depress oestrogen levels, nullifying oestrogen's beneficial effects on the immune system, and weakening a woman's ability to fight infections⁴⁵ and Colantoni and co workers⁴³ also suggested the role for plasma testosterone levels as liver protector from ethanol-induced oxidative. After one month of moderate beer consumption, women have been found to have increased numbers of leukocytes, neutrophils lymphocyte and CD3+ cells as compared to men¹¹. There is clearly a need for a better understanding of the biological mechanisms underlying gender differences in ethanol consumption.

Conclusions and perspectives

There is enough evidence to suggest that there are some compounds in polyphenolic-rich alcoholic beverages such as wine or beer that prevent suppression of the immune system or could trigger a protective effect. In other words, healthy adults who regularly consume a low to moderate amount of beer or red wine could be less prone to infections, and an anti-inflammatory effect could be one explanatory factor of the protective effects of moderate consumption on CVD. Yet some issues remained unresolved and require further research. The effects on the immune system may be due not only to the small amount of alcohol but also to the antioxidants and other components in these types of beverages. Intervention studies might help to elucidate the mechanisms by which moderate alcohol consumption exerts an immunomodulatory effect. However, since interventional endpoint studies in humans are not feasible because of ethical concerns, prospective observational studies are also required to assess the long-term dose-response relationship. Finally, we would like to stress the fact that although the moderate consumption of beer or wine seem to exert some benefits on the immune response in healthy adults, given the serious health risks associated with exceeding two drinks per day⁴⁶, increased alcohol consumption cannot be recommended. In addition, it is important to highlight that the messages related to the benefits of moderate consumption of alcohol have always been addressed to adult populations. Children, adolescents, pregnant women and elderly people are recommended not to drink any beverage containing alcohol.

Conflict of interest statement

AM has research funding from Cerveza y Salud Information Centre, the Spanish arm of European Brewers Association, and is a member of the Cerveza y Salud Scientific Committee. JR has had student support and research grants from Cerveza y Salud Information Centre. JW, EN, LED and SG have no conflicts of interest to declare. The review was co-written by all authors.

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