REVIEW ARTICLE

Impact of moderate wine consumption on immune-mediated diseases

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ABSTRACT

This review critically assesses scientific literature in order to determine whether alcoholic beverages can positively or negatively affect the incidence and severity of immune-mediated disorders, including autoimmune diseases. Few scientific studies explore the association between alcoholic beverages and the immune system, in contrast to the extensive literature dedicated to the cardiovascular system. Because wine is the most investigated product in this review, it does not take into account studies that evaluate the role of alcohol itself without specifying the beverages included (e.g., wine, spirits and beer).

The analysis of the data regarding the diseases reviewed here (allergies, celiac disease, the common cold and COVID-19, chronic inflammation bowel diseases, type 1 diabetes, dermatitis herpetiformis, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus and thyroid disorders) revealed that, in principle (although with differences between the various pathologies), moderate consumption of wine does not negatively affect the risk of development or the progression of immune-mediated diseases. In some cases, the effect is mainly attributable to the alcohol itself, in others the wine is responsible for a more favourable trend compared to other alcoholic beverages.

This review was limited by the scarcity of available papers, so that new prospective studies on the association between wine consumption and immune-mediated diseases should also be specifically designed to draw more solid conclusions.

KEYWORDS: Autoimmune disease, immune-mediated diseases, grapes, wine

INTRODUCTION

Human and animal survival relies on the adequate functioning of the immune system, which constantly monitors the situation in the body, identifying and providing protection from infections, other offending agents (such allergens and non-self molecules), or atypical biological structures (such as cancer cells). A well balanced diet ensures the optimisation of all cellular functions, including those related to the immune system, which draws energy and nutrients from the ingested food. In addition to the micro- and macronutrients required by the human body, certain molecules have a specific role in the development and functioning of the immune system: of these, substances capable of reducing chronic inflammation are particularly important.

When the immune system does not function properly, it can consider harmless molecules/tissues to be foreign, giving rise to immune-mediated diseases which can be grouped as follows: autoimmune diseases, when the body triggers an immune response against itself (such as celiac disease, type 1 diabetes, psoriasis, etc.); immunodeficiency disorders, when the body is unable to activate an immune response against external agents (pathologies not considered in this review); and allergic reactions, when the body develops an unsuitable and excessive immune response to molecules - contained in drugs, pollen and food - which are safe for the general population.

Numerous epidemiological studies that have been carried out since the second half of the last century have shown that there is an inverse relationship between the moderate consumption of alcohol (mainly wine) and the morbidity/ mortality associated with some chronic-degenerative pathologies. The most significant results have been observed in the reduction of cardiovascular risk (Teissedre *et al.*, 2018), but relatively few published studies have evaluated the influence of moderate wine consumption on the onset and control of immune-mediated diseases (Watzl *et al.*, 2004; Romeo *et al.*, 2007). There has been much discussion on this subject, with conflicting results: studies on humans focus mostly on alcohol abuse, and in these conditions alcohol is commonly considered to be harmful to health and generally immunosuppressive (Zhang *et al.*, 2008; Molina *et al.*, 2010; Szabo & Saha, 2015); however, immunosuppression can also occur in response to other concomitant factors, such as the nutritional deficiencies often observed in people who abuse alcohol (Barve *et al.*, 2017).

These kinds of studies are also often biased, because alcohol itself is evaluated without specifying the specific beverage studied (e.g., wine versus spirits) and conditions of consumption (e.g., fasting versus intake during a meal).

The aim of this paper is to assess whether moderate wine consumption can positively or negatively modulate the incidence and evolution of immune-mediated disorders, including autoimmune diseases. To this end, a scientific literature review on the subject was conducted. The studies in which the beverages under examination are not specified (wine, spirits and beer, etc.) have not been considered.

MATERIALS AND METHODS

The most important scientific databases of references and abstracts on life sciences (PubMed, MEDLINE, Embase and CAB-Abstract) were systematically searched (from database inception to December 2023) using the terms "grape", "wine" and "*Vitis vinifera*", in combination with "immune-mediated and autoimmune diseases" (also with the terms allergy, celiac disease, Chron's disease, cold and COVID-19, dermatitis herpetiformis, inflammatory bowel disease-IBD, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, thyroid disorders, hypo- and hyperthyroidism and ulcerative colitis), and by filtering the results for "human studies" and "controlled trials". Case reports on allergic reactions were considered when the association with wine was well documented. Reviews and papers that referred to alcohol without specifying the alcoholic beverage were excluded. Moreover, studies performed in vitro, on laboratory animals and on purified molecules were retained only when considered useful for improving the discussion or for suggesting mechanisms responsible for observed effects on humans. The papers were thus selected according to their compliance with the chosen inclusion criteria.

RESULTS AND DISCUSSION

The immune-mediated pathologies considered in this review are listed in alphabetical order and not by clinical importance; the papers that met the chosen inclusion criteria are summarised in Table 1.

1. Allergy

An allergy is a reaction of the body (i.e., the production of antibodies by the immune system) to certain molecules which are harmless to most people. The offending molecules (found, for example, in food, drug and pollens) are known as allergens/antigens. The most common class of antibodies involved in allergic reactions is IgE, although there are also forms of allergy (especially delayed ones) that involve cell-mediated or mixed mechanisms. Allergic reactions can manifest themselves in different tissues and organs: lower airways, nasal mucosa, skin, eyes, cardiovascular and gastrointestinal systems. The symptoms are caused by the body's release of chemical mediators (such as histamine) following the formation of antigen-antibody complexes. The severity of an allergy varies from person to person and can range from mild discomfort (tingling of the tongue or lips) to anaphylactic shock, which can be fatal (Sicherer and Sampson, 2018).

The IgE-mediated allergy to wine is not very common and it can involve various compounds: grape proteins, of which the main allergen is Lipid Transfer Protein (LTP); proteins derived from egg, milk, vegetables or fish that are used as additives or processing aids; mould (*Botrytis cinerea*) and yeasts (such as *Saccharomyces cerevisiae*) (Wüthrich, 2018).

TABLE 1. Summary of the papers selected according to the inclusion criteria. (Part 1/4)

Disease	Study details	Number of subjects	Grape or beverages studied	Objectives of the study	Main outcomes	Ref
Allergy	Case report	One 19-year-old man	Wine, microbrewery beer, champagne.	To confirm the role of alcoholic beverages on allergic reactions shown by the patient (constriction of the throat, wheezing, nasal blockage and urticaria). Clinical symptoms were triggered by wine, champagne and beer, but not by spirits.	The patient showed an IgE-mediated sensitisation to mould. The yeasts used in the beverages were responsible for the allergic reactions.	Bansal et al. (2017)
	Case report	One 33-year-old woman	Beer, red and white wines.	To identify the causes of clinical reactions (ocular pruritus, eyelid angioedema, globus sensation, dysphonia, diarrhea, urticaria and dizziness) to beer, and red and white wines, given other alcoholic beverages were tolerated.	The allergic reactions were associated with Saccharomyces cerevisiae, used in the fermentation of wines and beer.	German-Sanchez et al. (2022)
	Case report	One 34-year-old woman with severe anaphylactic reactions to wine, fresh white or blue grapes, and raisins.	Grape, raisins and wine.	To identify the main allergens of grape.	The patient was reactive to Lipid Transfer Protein (LTP) without association with pollinosis.	Schäd et al. (2005)
	Case report	One: the same patient as in the previous study (anaphylaxis to LTP)	Grape, raisins and wine.	To increase tolerance to grape and derivatives by increasing the doses of grapes (first dose 20 mg).	Within three days the patient tolerated a daily dose of 20 g of grape (i.e., approximately 3 grapes).	Schäd et al. 2010)
Cold and COVID-19	Epidemiological study: Prospective cohort study	4,272 people from 5 Spanish universities M: 67 %; F: 33 % Age: 21-69 years old	Beer, white and red wine and spirits.	To study the correlation between the intake of alcoholic beverages and incidence of the common cold; questionnaire was filled every 10 weeks for 1 year	Strong inverse relationship was observed between wine intake and cold incidence. No correlation was found for beer and spirits.	Takkouche et al. (2002)
	Epidemiological study: Prospective cohort study	16,559 people from the UK who tested positive for COVID-19 M: 47.1 %; F: 52.9 % Age: 66.3 ± 8.6 years old 457,399 people from the UK who tested negative for COVID-19 M: 44.7 %; F: 55.3 % Age: 69.3 ± 8.1 years old	Beer, white and red wines, champagne and spirits.	To evaluate if alcoholic beverage type and quantity could modulate incidence of and mortality due to COVID-19.	The moderate consumption of wine (both red and white) and champagne had a negative correlation with the risk of disease. No positive effect was observed for beer and spirits.	Dai et al. (2022)

TABLE 1. Summary of the papers selected according to the inclusion criteria. (Part 2/4)

Disease	Study details	Number of subjects	Grape or beverages studied	Objectives of the study	Main outcomes	Ref
	Epidemiological study: Prospective cross-sectional study	1,857 DM1 patients M: 51.9 %; F: 48.1 % Age: 15-60 years old	Beer, wine and spirits.	To investigate the cross-sectional association between moderate alcohol consumption and risk of complications.	Beer consumption had a significant U-shaped relationship with macroalbuminuria only. Moderate wine consumption showed a U-shaped trend for proliferative retinopathy, macroalbuminuria and neuropathy (latter parameter not statistically significant).	Beulens *et al.* (2008)
	Epidemiological study: Cross-sectional multicentre study (Finnish Diabetic Nephropathy Study)	3,608 DM1 patients M: 52.6 %; F: 47.4 % Age: 28.9-46.8 years old	Beer, wine and spirits.	To assess the association between alcoholic beverage consumed and DM1 complications (nephropathy and retinopathy).	There was an increased risk of nephropathy and retinopathy in abstainers compared to light consumers. Compared with wine drinkers, DM1 patients who drank spirits had a higher risk of developing nephropathy (odds ratio 2.80). This effect was significant in the men but not in the women.	Harjutsalo *et al.* (2014)
Diabetes mellitus type 1 (DM1)	*Clinical trial:* Randomised, placebo-controlled, double blind study	10 DM1 patients 7 males, 3 females Age: 43.9 ± 9.0 years old	White wine, alcohol-free wine.	To study the metabolic effect of ingestion of wine with a standard 600-calorie meal in a period of 90 min (80-100 g of alcohol for men and 48-60 g for women). Patients abstained from alcohol for three days before the test.	No effect of alcoholic wine on blood levels of glucose, triglycerides, free fatty acids, glycerol, cortisol and growth hormone. The postprandial ketosis increased when alcoholic wine was taken.	Kerr *et al.* (2009)
	Clinical trial: Randomised, placebo-controlled study	10 DM1 males Age: 34 ± 3 years old	40 mL vodka (aperitif) + 400 mL red wine (with meal) + 40 mL cognac (with coffee). Control: mineral water	To verify the effect of moderate alcohol consumption (~ 1 g alcohol/kg bw) on blood glucose and insulin levels.	No changes in glycemia and insulinemia.	Koivisto *et al.* (1993)
	Clinical trial: Cross-over intervention study	6 DM1 patients 5 males, one female Age: 38 ± 5 years old	Elementary mixed meal without and with 300 mL red wine (3-month interval between the two).	To investigate the influence of moderate wine consumption on different metabolic parameters (postprandial plasma amino acid and protein kinetics).	Although it was not the main objective of the study, the consumption of red wine was not found to affect the postprandial glycemia.	Tessari *et al.* (2002)
	Clinical trial: Placebo-controlled study	6 DM1 males Age: 19-51 years old	Dry white wine.	To investigate the effects of consumption of dry white wine (0.75 g/kg bw) versus mineral water on glycemia.	Compared to mineral water, the consumption of the dry white wine at 09.00 resulted in lower fasting and post-prandial glycemia when measured the following morning.	Turner *et al.* (2001)

TABLE 1. Summary of the papers selected according to the inclusion criteria. (Part 3/4)

Disease	Study details	Number of subjects	Grape or beverages studied	Objectives of the study	Main outcomes	Ref
Multiple Sclerosis (MS)	*Epidemiological study:* Comprehensive longitudinal study	973 patients M: 26 %; F: 74 % Age: 47 ± 11 years old	Red wine.	To evaluate the role of alcohol and red wine consumption on MS progression.	Higher intake of red wine was associated with a lower cross-sectional level of neurologic disability but increased the level of T2 hyperintense lesion volume.	Diaz-Cruz *et al.* (2017)
Psoriasis	*Epidemiological study:* Cross-sectional study	6,497 patients with confirmed diagnosis of psoriasis Higher number of females (undefined)	Beer, wine and liquor.	To determine the influence of alcoholic beverages consumption on Psoriasis Disability Index (PDI) and Psoriasis Life Stress Inventory (PLSI).	The number of beers/days had a weak positive correlation with the PDI, while wine showed a significant weak negative correlation with both PDI and PLSI.	Davidsson *et al.* (2005)
	Epidemiological study: Prospective cohort study	116,671 women (nurses) with confirmed diagnosis of psoriasis Age: 27-44 years old Period: 1991-2005	Beer, light beer, red wine, white wine and liquor.	To evaluate the association between different types of alcoholic beverages and the risk of developing psoriasis.	There was a positive association between beer and risk of psoriasis (Relative Risk = 1.76). No significant increase of risk was observed for light beer, wine and liquor.	Qureshi *et al.* (2010)
Rheumatoid arthritis (RA)	*Epidemiological study:* Prospective cohort study	34,141 women from the Swedish Mammography Cohort Age: 54-89 years old Duration: 6 years	Beer, wine and liquor.	To analyse the association between alcohol intake and incidence of RA in women. Alcohol consumption data were collected with two food frequency questionnaires. Participants with newly diagnosed RA were identified using National Registers.	Moderate consumption of alcohol (> 45 g alcohol/week) was associated with a 52 % reduced risk of RA compared to abstainers. The decrease in risk was similar for all three types of alcoholic drinks.	Di Giuseppe *et al.* (2012)
	Epidemiological study: Prospective cohort study	98,995 women Duration: 21 years	Spirits or aperitifs and wine.	To analyse the association between the most consumed drinks (coffee, tea, alcohol and soft drinks) and the risk of RA in women.	In ever-smokers, moderate liquor intake (1-3 glasses/week compared to non-consumers) was associated with a lower risk of RA; moderate wine consumption (4-10 glasses/week compared to < 1 glass/week) showed a decrease in seropositive RA; no effects with other alcoholic beverages.	Ascione *et al.* (2023)

TABLE 1. Summary of the papers selected according to the inclusion criteria. (Part 4/4)

Disease	Study details	Number of subjects	Grape or beverages studied	Objectives of the study	Main outcomes	Ref
Systemic Lupus Erythematosus (SLE)	*Epidemiological study:* Prospective cohort study	90,728 women from the Nurses' Health Study I Age:30-55 years and 113,327 women from Nurses' Health Study II Age: 25-42 years old	Wine, beer and liquor.	To investigate the association between alcohol consumption and SLE.	There was an inverse association between moderate alcohol consumption and SLE risk. Women who drank ≥ 2 servings/week of wine showed a significant decrease in SLE risk.	Barbhaiya *et al.* (2017)
	Epidemiological study: Cross-sectional study	About 59,000 women (about 25 %) from the two Nurses' Health Studies described by Barbhaiya et al., 2017. Age: 25-55 years old	Wine, beer and liquor.	To evaluate a possible association between alcohol consumption and concentration of SLE-associated circulating chemokines/cytokines	The lower circulating stem cell factor may have been responsible for the lower SLE risk in women who consumed > 5 g/day of alcohol vs non-drinkers. Type of drink was not differentiated.	Hahn *et al.* (2020)
Thyroid disorders	*Epidemiological study:* Prospective cohort study	140 subjects with new diagnosis of hypothyroidism vs 560 controls. In both groups: M: 16 %; F: 84 % Age: 45-62 years old	Beer, wine and spirits.	To analyse the association between alcohol intake and incidence of hypothyroidism in conditional mulivariate regression model using a questionnaire.	Subjects had a lower alcohol consumption during the last year than the controls (3 vs 5 units per week). Of the beverages, wine and beer were consumed the most in both groups. No differences were found between beer and wine drinkers, sex and region of residence.	Carlé *et al.* (2012)
	Epidemiological study: Prospective cohort study	272 subjects with Graves' hyper-thyroidism vs 1088 controls. In both groups: M: 15 %; F: 85 % Age: 31-55 years old	Beer and wine.	To analyse the association between alcohol intake and incidence of the autoimmune Graves' hyperthyroidism in a mulivariate regression model using a questionnaire.	Alcohol consumption was associated with a dose-dependent reduction of the incidence of Graves' disease. No difference was observed between beer and wine.	Carlé *et al.* (2013)
	Epidemiological study: Cross-sectional study	4,649 randomly selected subjects. Age: Males: 60-65 years old Females: 18-65 years old	Beer and wine.	To evaluate the association between alcohol intake (questionnaire) and prevalence of thyroid enlargement and nodularity (ultrasonography).	There was an association between increasing levels of alcohol intake and lower prevalence of thyroid enlargement and solitary nodules. No difference between beer and wine drinkers.	Knudsen *et al.* (2001)

M = males; F = females

In this review, allergies associated with wine additives (lysozyme) or processing aids (protein from egg, milk, and fish gelatine/isinglass) have not been considered, since till now they are not scientifically documented in any papers. The papers regarding allergies listed in Table 1 are mostly case reports and confirm what is already known in the literature, namely the role of LTP (Schäd *et al.*, 2005; Schäd *et al.*, 2010) and yeast proteins (Bansal *et al.*, 2017) in the onset of the few documented cases of allergic reactions.

2. Celiac disease

Celiac disease is a chronic autoimmune disease associated with gluten, a protein complex present in many cereals, such as wheat, barley and rye. Until diagnosis and gluten-free diet, people suffering from celiac disease will develop an inflammation in the small intestine, flattening the intestinal villi, and consequently reducing the ability to absorb nutrients (malabsorption) (Iversen and Sollid, 2023).

At present, the only effective therapy consists in completely eliminating toxic cereals from the diet in order to in most cases avoid the possible consequences of ingesting gluten (iron deficiency anemia, rickets/osteoporosis and intestinal lymphoma).

No studies meeting the inclusion criteria of this paper were found in the literature on the role of wine in the positive or negative modulation of celiac disease. Studies on the subject tend to focus on informing consumers suffering from celiac disease of the alcoholic beverages they can take without risk: wine, cider and spirits (vodka, gin, whiskey, brandy and rum, etc.) are commonly considered safe when consumed in moderate quantities (National Celiac Association, 2020); while wine is in this list, it should be noted that certain wines used to be clarified using wheat proteins, which was permitted until recently as a processing aid in oenological practices, albeit very rarely used (Marchal *et al.*, 2002).

3. Chronic inflammatory bowel diseases

Several chronic diseases that affect the intestine involve the immune system, the most common being Chron's disease and ulcerative colitis.

Crohn's disease (CD) was first described in a case series presented at the annual meeting of the American Medical Association in 1932 (Crohn *et al.*, 1984). Although CD affects the entire intestine, the distal ileum is the most affected; the pathology is characterised by periods of exacerbation and periods of remission. Pathogenesis results from interactions between environmental factors, the immune system, predisposing genetic factors and changes in the host microbiome, leading to significant intestinal mucosal damage (Petagna *et al.*, 2020).

Ulcerative colitis is a chronic inflammatory bowel disease that affects the lining of the large intestine; initially located in the rectum, it can extend to the colon. The pathogenesis of ulcerative colitis has only limited identification; it is believed to be a multifactorial disease, which includes a certain genetic predisposition, an alteration of the epithelial barrier of the colon, and an anomalous immunological reaction to antigens and environmental factors that are still poorly defined.

In the scientific literature there are numerous studies that take into consideration the consumption of alcohol (and in particular wine) in people suffering from inflammatory bowel diseases (IBD; for an overview of the topic see Swanson *et al.*, 2011; Ramos and Kane, 2021). Generally speaking, patients with IBD report a worsening of symptoms following alcohol consumption, but wine is better tolerated than other alcoholic drinks. The specific effects of wine, however, go beyond the effect on the immune system and mainly involve other metabolic pathways (such as anti-inflammatory properties capable of contributing to the control of the disease). It should be highlighted that negative consequences of wine consumption in IBD patients have also been described (decreased fecal calprotectin levels and increased intestinal permeability) and these aspects require appropriate in-depth analysis. Given the importance and extent of these diseases, the authors of this review decided to dedicate a future publication to inflammatory bowel pathologies, in which all the factors involved will be considered.

4. Common cold and COVID-19

Bacterial and viral diseases are very common within the general population, especially during the winter months. While it is not involved in the genesis of these diseases, the immune system is essential as it responds to the causal external agent, thus allowing recovery. Given the recent COVID-19 pandemic, and therefore the interest in diseases transmitted by viruses and bacteria, it was decided to also include the few studies that link wine consumption to the incidence or evolution of these illnesses.

Takkouche *et al.* (2002) carried out a two-year study to verify whether the consumption of alcohol, and/or specific alcoholic beverages, was able to modulate the incidence of the common cold. The study included 4,272 employees from 5 Spanish universities, who filled in a questionnaire upon enrolment and then every 10 weeks for one year. The results indicate that the incidence of the common cold was not related to total alcohol, beer or spirits intake. However, the cold incidence rate (RR) for drinkers of > 14 glasses of wine (both white and red) per week compared to abstainers was 0.56 (95 % confidence interval, 0.38 - 0.82). A less significant reduction was also observed with 1-7 glasses/week (RR 0.77) and 8-14 glasses/week (RR 0.71). While this association was found in both white wine and red wine, it was more significant in the latter: after adjustment for alcohol content, drinking more than 14 glasses/week was associated with an RR of 0.39 for red wine and 0.80 for white wine. These results could be at least partially associated with the different contents of flavonoids in the wine, which, according to Tanaka *et al.* (2019), is approximately 88 mg in red versus 3.5 mg in white wine.

Numerous studies have attempted to identify which factors positively affect the incidence and severity of COVID-19. In their study, Dai *et al.* (2022), considered the consumption of different type of alcoholic beverages.

They enrolled 473,957 subjects from the UK, of which 16,559 had tested positive for COVID-19 at least once. The subjects belonging to both groups (testing positive or negative for COVID-19) were comparable in terms of age (66.3 ± 8.6 versus 69.3 ± 8.1) and gender distribution (47.1 % males and 52.9 % females). The information on type of alcoholic beverage consumed and relative quantity that was acquired via a questionnaire revealed a decreased relative risk of COVID-19 in subjects who had consumed red wine (by 16 % for > 5 glasses/week versus abstainers), white wine and champagne (by 8 % for > 5 glasses/week). This inverse and protective association was not observed for beer and spirits, for which the relative risks tended to be higher. The differential effect observed between the various types of alcoholic beverages may be due to their content in biologically active molecules: red wine, which showed the greatest effectiveness in this study, is the richest in polyphenols, in contrast to spirits which contain few polyphenols and high amounts of alcohol. Meanwhile, although beer contains polyphenols, it did not show a protective effect; the authors thus hypothesised that the positive effect of wine (including champagne) was linked to specific molecules, such as stilbenes (including resveratrol) and proanthocyanidins. The suggested association should be further verified, as it is known that white wine and champagne have a very low stilbene content (Jeandet *et al.*, 2006; Suprun *et al.*, 2021).

Despite the uncertainties (the age range does not cover the entire population, the consumption of alcoholic beverages refers to the period before the pandemic, etc.), this study indicates the favourable role of moderate wine consumption in the protection from COVID-19.

5. Dermatitis herpetiformis

Dermatitis herpetiformis (DE), also known as DH or Duhring's disease, is a chronic condition that manifests itself as intense itching and lesions of the skin. While it is more common in young adults, it can also appear in children and older subjects (Reunale *et al.*, 2021).

DE is caused by an immune system reaction to gluten and is sometimes associated with celiac disease (15-25 % of patients), but there are sometimes no other signs of this pathology. The name, herpetiformis, refers to the cluster formation of the lesions, which is also typical of *Herpes simplex* infections (but which do not have the same aetiology). Patients may develop other autoimmune disorders (such as hypothyroidism, pernicious anaemia, and type 1 diabetes) and small-bowel lymphoma. The lesions are due to IgA deposits in the dermal papillary tips, which attract neutrophils. The disease can be cured by applying a pharmacological therapy (until stabilisation of the disease) alongside a gluten-free diet. As previously described for celiac disease, grape derivatives are permitted in the DE diet, and thus wines and fortified wines (sherry and port), avoiding wines clarified using wheat proteins.

6. Diabetes Mellitus (Type 1)

Diabetes mellitus (DM) is a disease characterised by the presence of hyperglycemia, which can be caused by insufficient insulin production or its inadequate action. There are two types of diabetes: type 1 (DM1), with no insulin secretion, and type 2 (DM2), resulting from reduced insulin sensitivity and/or secretion by the pancreas (appearing in adulthood). DM1 affects about 3-5 % of people with diabetes and usually appears in childhood or adolescence and leads to an absolute insulin deficit. In DM1, circulating antibodies directed against cells producing insulin are detected. It is for this reason that this form of diabetes is classified as one of the so-called "autoimmune" diseases (Antar *et al.*, 2023). The damage that the immune system induces against the cells that produce insulin is thought to be linked to hereditary and/or environmental factors, such as diet, lifestyle and contact with specific viruses (Zorena *et al.*, 2022). Of the pathologies mediated by the immune system, diabetes is the most frequent among the young population. Despite this, regarding the role of alcoholic beverages in the control of metabolic parameters, there are far less published studies on DM1 than on DM2.

To study the effect of acute ingestion of wine on metabolic parameters, ten DM1 patients (7 males and 3 women) were asked to drink, with a standard 600-calorie meal, either wine containing alcohol (80-100 g/day of alcohol for men and 48-60 g/day for women) or an equivalent volume of alcohol-free wine over a period of 90 min (Kerr *et al.*, 2009): the resulting blood levels of glucose, triglycerides, free fatty acids, glycerol, cortisol and growth hormones were not found to significantly differ. Meanwhile, postprandial lactate levels increased when alcoholic wine was drunk (P = 0.014). Postprandial beta-hydroxybutyrate levels decreased when alcohol-free wine was consumed, and significantly increased when wine containing alcohol was consumed (P < 0.001). The authors concluded that patients with DM1 may be at risk of ketosis when consuming alcoholic beverages. In another study (Tessari *et al.*, 2002), no effect on postprandial glycemia was observed in 6 DM1 patients (5 males and 1 female) who received an elementary mixed meal without and with 300 mL red wine (with a 3-month interval between the two). Meanwhile, moderate wine intake with a meal showed higher fibrinogen, glucagon concentration and first-pass splanchnic uptake of leucine and phenylalanine, as well as lower dietary phenylalanine oxidation, a selective decrease in plasma amino acid concentrations, and no impairment in endogenous proteolysis and albumin synthesis.

A study by Koivisto *et al.* (1993) considered the effect of alcohol consumption on two metabolic parameters: blood glucose and insulin levels. Before, during and after a 700-kcal meal, the subjects (10 DM1 male patients) received a quantity of alcohol corresponding to about 1 g/kg body weight, which was administered as follows: 40 mL of vodka as an aperitif, 400 mL of red wine with the meal, and 40 mL of cognac with coffee. The same experimental design was then applied replacing the alcohol with mineral water. No significant differences were observed in the studied blood parameters of the two experimental sessions.

Turner *et al.* (2001) reached different conclusions when they studied the effect of the evening consumption of alcohol in

the form of dry white wine on the glycemia measured the following day. Six men with DM1 were recruited and asked to drink either dry white wine or an equivalent volume of mineral water within 90 min. Patients received a meal at 7 pm and wine (0.75 g ethanol/kg body weight) or mineral water two hours later. The results indicated that, in DM1 patients, the moderate alcohol consumption in the evening after a meal can cause hypoglycemia, both before and after breakfast the following day. Compared to the session in which the patients drank mineral water, alcohol did not induce changes in insulin levels; according to the authors, hypoglycemia may therefore be due to the reduced nocturnal blood levels of the growth hormone.

The EURODIAB Prospective Complications Study (Beulens *et al.*, 2008) evaluated the role of the moderate intake of different alcoholic beverages in microvascular complications in 1,857 (964 males) patients suffering from DM1. In particular, the following complications were monitored: retinopathy, neuropathy and nephropathy. A significant U-shaped association was observed between alcohol consumption and the risk of different microvascular complications, both in males and females. When beverages were considered separately, the following results were obtained: i) beer consumption showed a significant U-shaped relationship ($p = 0.027$) for macroalbuminuria only (odds ratio 0.33, 0.13-0.81), and ii) wine consumption always showed a U-shaped trend for proliferative retinopathy, macroalbuminuria and neuropathy, but no significant difference was found for the latter parameter. For the moderate wine drinkers (30-70 g/week of alcohol), the odds ratios were 0.85 (0.52-1.37) for proliferative retinopathy, 0.57 (0.38-0.85) for neuropathy and 0.48 (0.25-0.93) for macroalbuminuria. Spirits tended to be associated with an increased risk of the studied complications occurring.

The study by Harjutsalo and the FinnDiane Study Group (2014) had similar objectives and obtained similar results; in fact, also in this study, an increased risk of nephropathy and retinopathy was observed in DM1 abstainer patients when compared to light wine consumers. Moreover, with wine consumers as the reference group, a higher risk of nephropathy was observed in men who drank spirits (odds ratio of 2.80; 95 % CI 1.15-6.81). No difference was found between wine drinkers and beer drinkers (odds ratio of 0.83; 95 % CI 0.37–1.82), or mixed drinkers (odds ratio of 1.33; 95 % CI % 0.60–2.92). In women, no difference in the risk of nephropathy was found between the different types of drinks. When consumers of spirits were compared to wine and beer drinkers, the relationship between alcohol consumption and retinopathy showed results similar to those for nephropathy (odds ratio of 2.32; 95 % CI 1.35-4.00). No difference between the sexes was observed for retinopathy.

The positive effects shown by the papers discussed above can only be partially justified by the presence of resveratrol in the wine due to its very low concentration. In fact, as shown in the study by Movahed *et al.* (2020), such positive effects are achievable with a supplementation of resveratrol at a dose of 500 mg twice/day for 60 days: the oxidative stress markers

of DM1 significantly improved, with decreasing fasting glycemia and hemoglobin A1c levels.

7. Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system (McGinley *et al.*, 2021). The inflammation triggered by the immune system can damage the myelin cells, the oligodentrocytes that are specifically responsible for their production, and the nerve fibres themselves. This process is called demyelination and results in areas of myelin loss or damage (plaques). Plaques can occur anywhere in the central nervous system, but are more frequent in the optic nerves, cerebellum and spinal cord; they can evolve from an initial inflammatory status to a chronic phase, in which they show sclerotic characteristics (Frohman *et al.*, 2006).

The search carried out in the databases regarding MS and applying the established inclusion criteria resulted in only one paper, but which was of interest (Diaz-Cruz *et al.*, 2017): the authors evaluated the influence of wine (and alcohol) consumption on the progression of MS in a group of 923 patients (74 % of which were females) with a mean MS duration of 14 ± 9 years. Data on alcohol and red wine consumption over the course of the previous years was obtained by a self-administered questionnaire and was calculated as servings/week. The study showed that, compared to non-drinkers, the MS patients who reported a higher intake of alcohol (> 4 drinks/week) or red wine (> 3 glasses/week) had a lower cross-sectional level of neurological disability (odds ratios 0.41 $p = 0.0001$ and 0.49 $p = 0.0005$ respectively) and lower MS Severity Score (mean difference -1.753; $p = 0.0002$ and -0.705 $p = 0.0007$ respectively). However, compared to the abstainers, the patients who consumed 1-3 glasses/week of red wine had an increased T2 hyperintense lesion volume (T2LV). Atrophied brain T2 lesion volume is an important MRI (Magnetic Resonance Imaging) marker of MS progression: its increase is a sign of clinical worsening. The biochemical mechanisms underlying the conflicting clinical findings reported above are currently being researched.

8. Psoriasis

Psoriasis is an inflammatory disease that in most cases is associated with well-circumscribed, erythematous papules and plaques covered with silvery scales. The aetiology of psoriasis is unknown, but the immune system may be implicated, with T cells having a central role, which can be responsible for the hyperproliferation of keratinocytes. Although the symptoms are usually minimal, mild to severe itching can occur with possible important aesthetic consequences (having also severe psychologic implications); some people may develop a severe form of the disease affecting the joints (psoriatic arthritis) (Armstrong and Read, 2020). Several scientific papers have been published on the alcohol consumption of people with or at risk of psoriasis, but very few distinguish between the various types of drinks; therefore, only the two papers described below met the selection criteria.

In a prospective study of 116,671 nurses (Qureshi *et al.*, 2010) the correlation between the consumption of different alcoholic beverages and the risk of developing psoriasis was evaluated. The results indicated that women who consumed beer had a 1.76 times higher risk of developing the disease than women who did not drink alcohol. No risk increase was recorded for the nurses who consumed wine (both white and red), alcohol-free beer, and liquors.

A study by Davidsson *et al.* (2005) on 6,497 patients with psoriasis revealed a slightly negative correlation between wine consumption and psoriasis severity parameters (Psoriasis Disability Index and Psoriasis Life Stress Inventory). The authors suggested different possible reasons to explain these protective effects: i) the wine drinkers had more suitable skin care, ii) the general characteristics and/or habits (e.g., social status, education and diet) in people who drink wine may differ to those who do not, and iii) some wine compounds can have positive effects, such as tannic acid, which inhibits protein kinase C (PKC) and thus has an anti-psoriasis effect (Arnold *et al.*, 1993). Due to the limited number of available papers, it is difficult to draw conclusions on the positive or negative impact of wine consumption on the symptoms of people suffering from psoriasis.

9. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disease that affects the joints, resulting in pain, swelling and deformation; it can also involve other organs and systems, such as the heart, lungs, eyes, skin and vessels (Smolen *et al.*, 2016). Rheumatoid arthritis affects about 1 % of the general adult population with greater frequency in women between 40 and 50 years of age. Rheumatoid arthritis is a multifactorial disease, but it is believed that certain environmental factors can cause the immune system to function improperly (molecular mimicry) or to modify some antigens that it should otherwise regard as its own (self-reactivity). RA is classified as seropositive or seronegative, referring to whether the patient shows positive or negative for the blood rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), two proteins frequently found in people suffering from this pathology. Seropositive patients (RF-positive) may manifest different and more aggressive symptoms than seronegative patients (RF-negative) (Romão and Fonseca, 2021; Scott *et al.*, 2003).

As a result of their 6 year-study, Di Giuseppe *et al.* (2012) showed that moderate alcohol consumption (about 45 g alcohol/week) by women was associated with a 52 % decrease in RA risk (relative risk 0.48, 0.24-0.98), regardless of type of alcoholic beverage consumed (beer, wine or spirits). The biological effect thus seemed to be mediated by the alcohol itself, but the authors highlight that there are uncertainties regarding the risk of RA associated with the intake of higher quantities of alcohol.

Ascione *et al.* (2023) evaluated the possible modulation of RA risk as a result of alcoholic beverage consumption in a prospective study of 98,995 women. The results showed that among ever-smokers: i) moderate spirits intake (1-3 glasses/week) reduced risk of having RA compared to non-consumers of spirits (odds ratio 0.63, 95 % CI, 0.43-0.91), and ii) moderate wine consumers, had a lower risk of being RA seropositive.

The observed protective effects of all the alcoholic beverages considered in the two studies described above contrast with those reported in a randomised study by Khojah *et al.* (2018) on the effectiveness of resveratrol, which is found only in wine. The enrolled 100 RA patients were divided into two groups: one treated with the usual drug therapy and the other receiving the same therapy along with a supplement of 1 g/day of resveratrol. In the three-month study, the group which took resveratrol supplement showed an appreciable improvement based on certain biochemical parameters and disease severity scores. This inconsistency with the results of Di Giuseppe *et al.* (2012) and Ascione *et al.* (2023) may be due to the fact that the intake of resveratrol present in wine is not comparable to supplemented resveratrol (Di Lorenzo *et al.*, 2021).

10. Systemic Lupus Erythematosus or SLE

Affecting 0.2 % of the global population, Systemic Lupus Erythematosus (SLE) is a chronic autoimmune multisystem disease with mild to severe or even life-threatening symptoms. In most patients, signs of the disease comprise purplish marks on the sides of the nose and under the eyes, but other skin areas and organs can also be affected: kidneys (affected in 60 % of cases, with changes in their function), joints, the hematopoietic system, central nervous system, cardiovascular system and lungs (Zucchi *et al.*, 2023). The immunological alterations typical of SLE (detectable via laboratory tests) are mainly the production of autoantibodies against different cells; over 100 autoantibodies have been associated with this pathology (Dema and Charles, 2016).

In a prospective cohort study (Barbhaiya *et al.*, 2017), the authors investigated the possible association between alcohol consumption and SLE risk among the 204,055 women involved in the Nurses' Health Study Cohorts. All the women filled out an initial questionnaire, which was updated every two years, regarding alcohol (wine, beer, or liquor) consumption, lifestyle, health practices and disease diagnoses. Diagnoses of SLE were based on classification criteria and confirmed via a medical record review. Women who consumed > 2 servings/week of wine showed a significant decrease in SLE risk ($p < 0.033$) compared to non-wine drinkers, with an average hazard ratio of 0.65 (0.45-0.96), corresponding to a 35 % lower frequency. A similar but weaker trend was found for beer, while no protective association was demonstrated for hard liquor consumption. When excluding the data from the few heavy drinkers (> 30 g/day), the statistical significance is higher, suggesting the results follow a U-shape curve.

In the attempt to scientifically explain the "protective" effect of alcohol against the risk of SLE, Hahn *et al.* (2020) evaluated some plasma parameters, such as cytokines and chemokines, notoriously associated with this pathology. Approximately 25 % of the women who took part in the two previously cited Nurses' Health Studies were enrolled.

The Stem Cell Factor (SCF), which is a hematopoietic cytokine, has a critical role in SLE pathogenesis. Among the measured biochemical parameters, SCF showed a reduction in its circulating levels in women characterised by moderate alcohol consumption; this effect may reduce systemic inflammation and justify the suggested inverse relationship between alcohol consumption and SLE risk. A limitation of this study is that it did not evaluate the influence of a single alcoholic beverage (beer, wine, or spirit) on the protective effect on SLE.

11. Thyroid disorders

Hyperthyroidism is a condition of hyperactivity of the thyroid, which causes an increase in the levels of circulating thyroid hormones and a consequent acceleration of the vital functions of the organism. Graves' disease is an autoimmune disease and is among the most common causes of hyperthyroidism (Smith and Hegedüs, 2016; Kahaly, 2020). In this disorder, the immune system produces antibodies that stimulate the thyroid gland to produce and secrete an excess of thyroid hormones. This situation results in hyperthyroidism with an enlarged thyroid.

Carlé et al. (2013) studied the influence of alcohol (beer and wine) intake on the incidence of Graves' autoimmune disease. Two groups were studied: 272 patients with new thyroid dysfunction cases versus 1,088 control participants (thyroid disease-free subjects). The participants provided detailed information on current and previous alcohol intake and other possible interfering factors, such as smoking habit, age, gender and region of residence. The results showed that during the last year the subjects with hyperthyroidism had a lower alcohol intake than the controls. The multivariate odds ratio ranged between 0.56 (0.39-0.79) for an intake of 3-10 units/week to 0.22 for > 21 units/week. One unit corresponded to approximately 15.0 g of alcohol. No difference was observed between beer and wine, and no significant influence by the considered interfering factors (sex, region of residence) was found. The authors concluded that there was a significant association between moderate alcohol consumption (> 6 g/day) and the reduction of the incidence of Graves' disease. The protective effect may be due to the alcohol itself or to active molecules contained in both beverages (antioxidant compounds). It was observed that subjects who consumed wine had a better lifestyle and a healthier diet than those who drank beer; however, this was not found to improve protection from this thyroid disorder.

Hypothyroidism is a pathology associated with the insufficient production and/or action of thyroid hormones at the tissue level. Among the various forms of hypothyroidism, there is one involving autoimmune genesis, the Hashimoto's disease (Geetha et al., 2023). Hashimoto's disease is characterised by the presence of anti-thyroid peroxidase antibodies, which define the autoimmune form; it is probably the most common form of hypothyroidism and is often accompanied by other autoimmune diseases, such as celiac disease, lupus, type 1 diabetes and rheumatoid arthritis.

The data obtained by Carlé et al. (2012) between 1997 and 2001 in a population-based, case-control study showed that taking alcohol in doses of up to 3 units/day can provide protection from the incidence of overt autoimmune hypothyroidism. When comparing the reference group with a recent (previous year) intake of 1–10 units of alcohol per week the odds ratios (95 % confidence interval) were: 1.98 (1.21–3.33) for 0 units/week; 0.41 (0.20–0.83) for 11–20 units/week; and 0.90 (0.41–2.00) for > 21 units/week. One unit corresponded approximately to 15.0 g of alcohol. This effect was independent of the type of beverage drunk (beer or wine), sex or geographical region of provenance. The authors suggested that the protective effect may be due to either the alcohol itself or to other substances (including those that have antioxidant properties) present in both beverages.

Goitre consists of enlargement of the thyroid gland and can be classified as either endemic (i.e., when it affects more than 10 % of the population of a given geographical area) or sporadic. In endemic goitre, the increase in the size of the thyroid gland is the consequence of iodine deficiency, which induces lower thyroid hormone synthesis. Other causes of goitre are the two autoimmune thyroid diseases described previously (Hashimoto's thyroiditis and Grave's disease) (Cleveland Clinic, 2022).

A cross-sectional population study by Knudsen et al. (2001) aimed to verify the association between alcohol consumption (as beer or wine) and the occurrence of pathological forms of the thyroid gland (goitre and solitary nodules). To this end, a group of 4,649 randomly selected subjects of both sexes underwent ultrasonography to detect any thyroid enlargement and multiple/solitary nodules and filled in a questionnaire in order to calculate their alcohol intake. A much lower prevalence of thyroid diseases was associated with participants whose alcohol consumption was classified as moderate (i.e., 8-28 drinks/week for women and 8-42 for men) or high (i.e., > 28/42 drinks/week) than that of abstainers and low consumers (< 7 drinks/week). The odds ratios relative to the control subjects (abstainers) were 0.74 (0.57-0.96) for moderate and 0.44 (0.22-0.88) for high alcohol consumers. The effects were independent of the type of beverage consumed (beer or wine). These results suggest that the alcohol itself has a possible protective effect on thyroid diseases.

CONCLUSIONS

Although there is a general consensus that alcohol consumption is detrimental to the immune system, the scientific studies discussed in this review led to substantially different conclusions. Disregarding the problem associated with fining agents based on wheat, egg and milk proteins, it can be concluded that allergic or celiac subjects (including people suffering from dermatitis herpetiformis) can consume wine in moderation (normally considered 1 glass/day for women and 2 glasses/day for men). Exceptions are some rare cases of immune-mediated reactivity to grape (LTP) or

yeast proteins, for which the consumption of wine should be evaluated on a case-by-case basis.

Despite the small number of published works, the available data indicates that moderate wine consumption plays a protective role in the onset of some viral infections, such as the common cold and COVID-19. Corroborative data were obtained in studies on champagne, white and red wines, with a tendency for the latter to be the most effective.

In general, the information in this review indicates that DM1 patients can consume wine in moderation. Moderate intake of wine with meals would not interfere with the main metabolic parameters (glucose, triglycerides, free fatty acids, glycerol and cortisol), but it would be necessary to keep some observed effects under control (e.g., ketosis, hypoglycemia in the morning of the day after consumption). It is worth noting that Kerr *et al.* (2009) showed an increase in ketosis when the alcohol intake was "liberal"; i.e., well above the doses associated with moderate consumption.

Moderate wine consumption was not found to have any negative effects on the risk of diabetes complications (retinopathy, neuropathy and macroalbuminuria), while the consumption of spirits by men and abstainers was associated with an increased risk (Harjutsalo *et al.*, 2014).

The study by Movahed *et al.* (2020) may partially support the positive role of wine as they demonstrated that supplementation with 1000 mg/day of resveratrol produced a significant effect on fasting blood glucose and glycated haemoglobin (also called HbA1c) in patients with DM1. Similarly, the study by Khojah *et al.* (2018) of patients with rheumatoid arthritis showed that resveratrol intake at the dose of 1 g/day improved significantly both biochemical parameters and disease severity scores. It should be emphasised, however, that the amount of resveratrol that can be taken with moderate wine consumption (i.e., 2.8 mg/L of red and 1 mg/L of white wines) is much lower than that given in supplementation studies.

Conflicting data was found in the only selected work associating wine consumption with multiple sclerosis (Diaz-Cruz *et al.*, 2017). Moderate wine consumption was not associated with an increased risk of psoriasis or Lupus erythematous; conversely, it would seem to improve some psoriasis-associated parameters.

Moderate alcohol consumption has been reported to have a protective effect on thyroid disease (both hypo- and hyperthyroidism); however, this effect was not dependent on type of alcoholic beverage and should therefore be associated with the alcohol itself.

LIMITATIONS

The general conclusions that can be drawn from this review are that the moderate use of wine does not seem to increase the risk of immune-mediated diseases or negatively modify their progression. However, it is important to note that the number of papers meeting the selected inclusion criteria was extremely low, and even limited to a single study for certain pathologies (multiple sclerosis). There are a number of possible reasons for this lack of data: 1) It is difficult to programme structured studies which involve the long-term monitoring (sometimes lasting for years) of large populations when aiming to associate wine consumption with immune-mediated pathologies. These experimental approaches can be affected by numerous confounding factors (type of diet, smoking, physical activity and social bias), rendering it sometimes impossible to determine a direct association. 2) The data are mostly based on surveys conducted on groups of people who do not always accurately describe their daily habits (reporting bias). 3) The doses of reported ingested wine may not be accurate due to a recall bias (being reported via a questionnaire) and a prevarication bias (the consumption of alcohol is a sensitive topic). 4) In addition to having all the limitations listed in the first point, prospective studies are approved with difficulty by ethical committees when the use of alcoholic beverages is proposed. 5) Studies that indicate a null effect on a given pathology are not always sent for publication (and thus do not become widespread), since the authors know that such papers are rarely accepted by scientific journals, as they are considered non-innovative (publication bias).

In light of the limitations of such studies, further research on humans needs to be promoted. The International Organisation of Vine and Wine (OIV), to which most of the authors of this paper contribute, has as one of its missions the collection, evaluation, discussion and dissemination of available scientific data on the consumption of grapes and derivatives and associated effects on health and diseases, without disregarding the importance of promoting research in the area. The authors hope that this review will provide useful information for planning new experimental studies that can confirm or not what is known today.

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