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Review article

Wine, alcohol and pills: What future for the French paradox?

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ABSTRACT

The present review discusses the acquisitions obtained to date on the subject of wine consumption, health and cardiovascular protection. We distinguished the cardiovascular effects related to the consumption of wine and other alcoholic beverages focusing on non-alcoholic wine fraction: polyphenols and especially resveratrol. In the second part of the review we have addressed the issue of resveratrol bioavailability and the importance of wine matrix and phytocomplex highlighting the biological effects that can be obtained with nutraceuticals and resveratrol pills compared to the daily consumption of a glass of red wine.

Contents

1. Introduction

The French paradox may be defined as the protection from cardiovascular disease in the broadest sense afforded by moderate consumption of alcoholic beverages, especially wine. The phenomenon was reported for the first time by Prof. Serge Renaud in The Lancet [1]. Since then a large body of evidence has been provided. In particular, moderate alcohol consumption reduces the cardiovascular risk associated with arterial hypertension both in women [2] and in men [3] and has been included among the health lifestyle factors for the primary prevention of coronary heart disease [4] and heart failure [5]. It has proved to be able to lower the risk of lower-extremity arterial disease [6], to improve the long-term prognosis after an acute myocardial infarction [7,8] and to reduce cardiovascular [9], coronary heart disease and all-cause mortality [10,11,12]. Alcohol consumption reduces the risk of myocardial infarction and coronary heart disease events not only in Caucasians, but also in Chinese men [13]. The effect of components of a healthy lifestyle, such as regular exercise, is additive, the risk of fatal ischemic heart disease and all-cause mortality being the lowest among moderate drinkers who are physically active [14]. These

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protective effects may be mediated by the effects of alcohol consumption on biological markers associated with the risk of coronary heart disease: alcohol consumption is associated with higher levels of high density lipoprotein cholesterol and of adiponectin, and with lower levels of fibrinogen [15]. However, other authors argue that the lower cardiovascular morbidity and mortality rates recorded in moderate drinkers are due to the fact that moderate drinking is a marker of higher social level and a more favorable clinical and biological profile rather than to alcohol consumption per se [16]. Another alternative explanation is the systematic error of including frail and ill elderly subjects, who have stopped alcohol consumption because of ill health, in the group of non-drinkers, as this would artificially increase the risk of cardiovascular events and mortality among non-drinkers as compared to moderate drinkers [17]. Moreover, other authors have found a direct relationship between alcohol consumption and carotid intima-media thickness in Finnish young adults, and between alcohol consumption and coronary calcification in young American adults, especially in Black men; these findings suggest that alcohol may have pro-atherogenic effects instead of protective effects [18,19]. Actually, the very first studies suggested that the consumption of wine, rather than the consumption of alcoholic beverages in general, affords protection against cardiovascular disease [20].

2. Review

2.1. Wine or alcohol

Studies distinguishing between the consumption of spirits and beer/wine have found that only spirits increase mortality, not wine [21] and very recent studies have provided further evidence that moderate wine consumption, not alcohol consumption is associated with cardiovascular protection: the GISSI Prevention Trial [22] has shown that moderate wine intake is associated with a lower incidence of cardiovascular events and lower total mortality in patients with established heart disease as compared to non-drinkers and the Tromse Study [23] has shown that wine consumption may be associated with reduced risk of venous thromboembolism, whereas spirit intake is associated with an increase in such risk as compared to non-drinkers. However, objections have been raised also against wine consumption. Researchers have attempted to distinguish the effects of alcohol from those of other components of wine, by setting up parallel group studies and comparing whole wine to ethanol and grape extracts. They failed to record any protective effects of grape extracts on blood lipids and hemostatic factors in healthy volunteers [24] and on the formation of atherosclerotic plaques in apolipoprotein E-deficient mice [25]. Wine purchases have been found to be associated with the purchase of healthier food [i.e. more fruit and vegetables and less meat, fatty cheese and milk] and with a generally more healthy lifestyle than drinkers of beer and/or spirits [26,27,28]. The association of wine intake with lower cardiovascular morbidity and mortality as compared to non-wine drinkers has therefore been ascribed to differences in lifestyle and socio-economic factors between wine consumers and non-consumers.

The inconsistency in findings and the conflicts in interpretation are more or less irreconcilable and the contributions by most epidemiological studies do not help, as they do not distinguish between alcohol and wine consumption.

2.2. Non alcoholic wine fraction: resveratrol and polyphenols

In view of the difficulty in interpreting the current body of evidence, a different approach to the issue is required. Guidelines for the interpretation of causal relationships within the context of observational epidemiological studies can be very helpful. This is the case of Hill's criteria, which are particularly important in the assessment of biological plausibility i.e. the search for an explanation among well-known pathophysiological processes supported by scientific evidence [29].

In the case of wine, this means finding particular components of the beverage that distinguish it from pure ethanol or other alcoholic beverages.

Wine is a complex matrix that contains many compounds of biological interest besides ethanol, which accounts at most for 15% of the beverage. Polyphenols are among the most interesting constituents, as they are all biologically active and could play a role in the protection afforded by wine [30]. However, these compounds occur also in other matrices: for instance, catechin is found in green tea, in fruit, in vegetables and in chocolate [31,32], quercetin in apples and onions [33,34], kaempferol in cabbage [35], hesperidin in lemons [36] and so on. Thus, they are not an exclusive prerogative of wine, with one exception: resveratrol, a polyphenol that belongs to the stilbene family and occurs in therapeutically relevant quantities only in red wine [30]. No other food that usually presents in Western diet contains this compound in important quantities [37], not even white wine as only a hydro-alcoholic mixture can extract this polyphenol from grape skin and ensure its transference into wine; this occurs during red wine, but not during white wine processing, in which contact with must is much shorter and does not allow the extraction to occur. This is the reason why most white wines contain only very small amounts of resveratrol [38]. This stilbene occurs also in peanuts and in cranberries, but its importance is negligible because the polyphenol cannot be properly absorbed from these matrices [39,40]. Other than red wine, an important source of resveratrol in nature is the root of *Polygonum cuspidatum* Siebold & Zucc. [41], a Chinese medicinal plant, traditionally used for treating several minor diseases in China, Korea and Japan and listed in the Pharmacopoeia of the People's Republic of China used [42]. Unfortunately, *P. cuspidatum* Siebold & Zucc. contains the low bioavailable resveratrol-glucoside, pyceid or polydatin, about three times more than resveratrol aglycone [43] and the clinical effect of resveratrol derived from this source is to date questionable with only two references available on medical databases. The same is true for grapes, which contain fairly large quantities of resveratrol, which cannot be absorbed from the gut [44].

Red wine is not always the same and one should talk about red wines in plural: their content in resveratrol may differ considerably [from 0.09 mg/l to more than 7 mg/l] according to the geographical area of production, the kind of vine and the enological methods adopted for their production [45,46]. This explains the considerable variability in experimental and clinical studies with red wine, when it cannot be checked analytically beforehand. For instance, one knows that a group of subjects has drunk red wine, but the actual quantity of resveratrol that they have ingested is unknown. This applies, above all, to epidemiological studies [47,48,49] (Fig. 1).

2.3. Resveratrol bioavailability: wine matrix

Another issue related to resveratrol complicates the interpretation of its role in the cardiovascular protection afforded by wine even further, namely to establish whether it is absorbed from the gut and, if so, to what extent. This is essential as activity depends on bioavailability.

One aspect that is in favor of the active role of resveratrol in the cardioprotection afforded by wine is the fact that it is absorbed only when it is ingested in wine [50]. Pharmacokinetic studies in the 1990s [51,52], which have been confirmed by more recent ones [53], have shown that when wine is ingested resveratrol is absorbed up to a

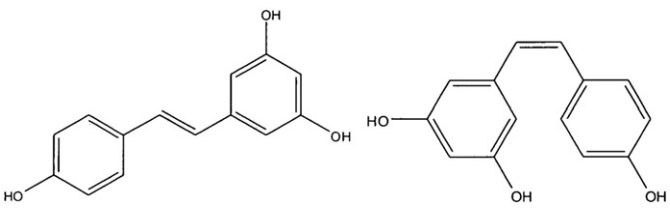

Fig. 1. Chemical structure of *trans* (left) and *cis*-resveratrol (right).