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Alcohol and aging: From epidemiology to mechanism

Stuart S. Adamson [a], Lear E. Brace [a], Brian K. Kennedy [a,b,*]

[a] Buck Institute for Research on Aging, Novato, CA 94945, USA
[b] Departments of Biochemistry and Physiology, Yong Loo Lin School of Medicine, National University Singapore, Singapore

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Abstract

Alcohol is one of the most widely encountered drugs in the world and is credited with a wealth of health interactions. Light to moderate regular consumption (14–28 g daily) can promote heart health, protect against Type II diabetes, and likely extend overall lifespan. However, higher consumption rates lead to the detrimental effects more widely associated with ethanol consumption, including decreased motor control, cardiotoxicity, insulin resistance, and liver disease. Despite high consumption rates in the elderly population, there has been little focus on alcohol's multifaceted effects in the context of aging. Ethanol interacts with numerous genetic targets that are already associated with aging (such as mitigation of the mechanistic target of rapamycin and activation of FOXO3A), and its dose-dependent lifespan extension depends on still poorly understood connections to these pathways. This review focuses on ethanol's relationship to aging and lifespan in multiple animal models, and it demonstrates how understanding the complicated role of this ubiquitous chemical could be vital in order to apply our knowledge of mechanisms mediating the aging process to the human population.

Keywords: Alcohol; Ethanol; Lifespan; Healthspan; Aging; Hormesis

1. Introduction

The effect of ethanol on mammals has been extensively researched and cataloged, revealing quite controversial and intriguing results. Although alcoholic beverages are a complex mixture of chemicals, ethanol is the primary active ingredient and is credited with both positive and negative health effects [1]. Understanding these health interactions is critical given ethanol's widespread global consumption. A 2015 survey reported 86% of individuals over 18 years-old have consumed alcohol at some point, 70% in the last year, and 56% in the last month [2]. This could be a critical factor impacting human healthspan (the time a human being remains healthy before decline). Heavy chronic consumption has a devastating impact on brain pathophysiology, motor function, and memory [3–5], yet one daily global standard drink (14 g of ethanol) could have lasting protective benefits for human health [1,6].

Ethanol consumption can be beneficial or deleterious depending on the dose consumed. Over-consumption is the leading cause of premature death among individuals 15–49 years of age [7]. Abuse is cardiotoxic [1], accounts for over 40% of all liver disease deaths [8], and increases the risk of cancers of the mouth, esophagus, pharynx, larynx, liver, and breast [9]. However, regular mild or moderate doses of ethanol are cardioprotective [10] and reduce the risk of Type II Diabetes [11,12]. Controlled doses have also been shown to extend overall lifespan in *Caenorhabditis elegans* and rodent models [13,14], and are associated with reduced mortality in humans [15]. This dose-dependent response is termed hormesis: a phenomenon where low-dose stimulation has the opposite response as high-dose, and it is quite common in toxicology studies. Fig. 1 compares the physiologic hormesis of ethanol consumption, demonstrating how a low dose can improve body function and health, but excess consumption can drive maladaptive responses.

* Corresponding author. Buck Institute for Research on Aging, Novato, CA 94945, USA
E-mail address: bkennedy@nus.edu.sg (B.K. Kennedy).

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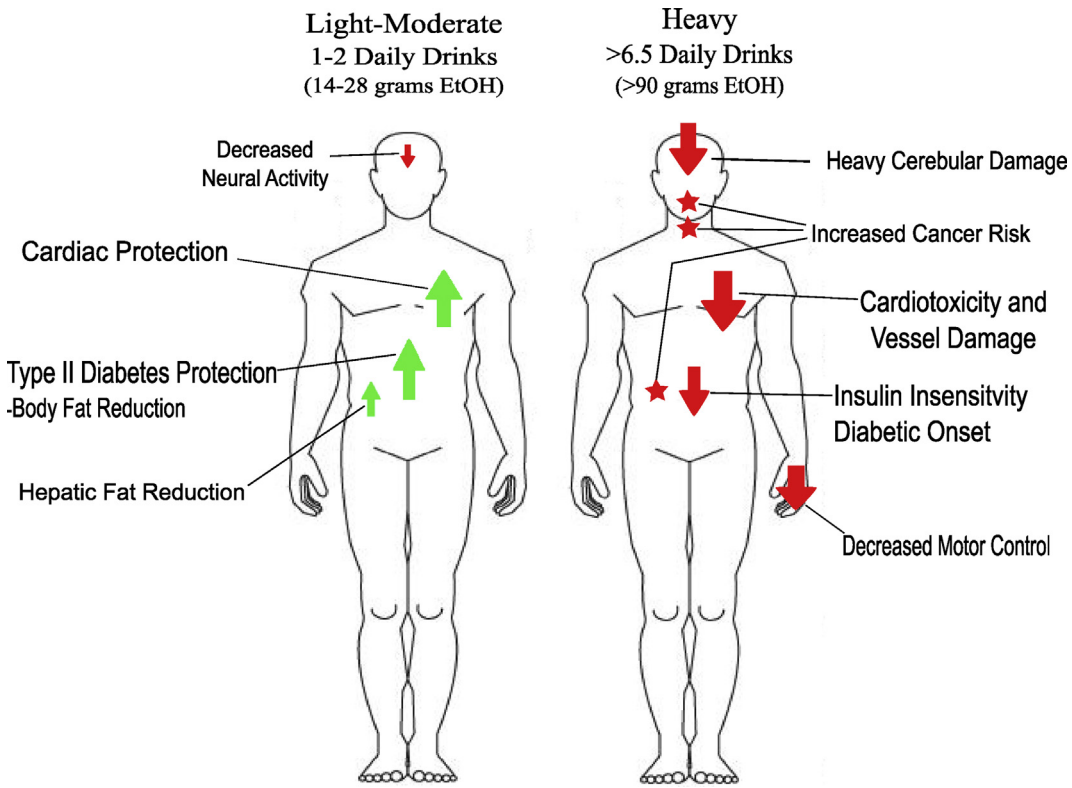

Fig. 1. Hormetic response of ethanol consumption: the dose makes the poison. Protective benefits at moderate intake are largely reveresed by overconsumption.

As the global population ages it has become increasingly more important to understand the health effects of ethanol on the aging body. While the elderly appear to be more sensitive to the effects of alcohol [16,17], the risk-to-benefit ratio is more favorable to those over 50 than those under 50 [1]. Unfortunately, alcohol abuse is considered an underreported problem among the elderly, and one-third of alcoholics developed their drinking problems in their 40's and 50's [18]. In the context of aging, discovering the most advantageous dose and delivery of ethanol could be the difference between an improved healthspan and an accelerated decline.

The presentation of ethanol in different alcoholic beverages (beer, wine, spirits, etc.) could also influence the efficacy of ethanol's healthspan effects. It is important to consider that many alcoholic drinks, especially beer, are calorie-laden, and a high caloric intake is widely known to amplify the health decline associated with aging phenotypes [19,20]. Red wine is often considered the best mode of ethanol delivery because of its relatively low-calorie content and presence of polyphenols, such as resveratrol, that have been reported to independently enhance healthspan [10]. Since ethanol is still considered the primary component impacting human health [1] and because most animal studies employ ethanol directly, we have chosen to focus this review on ethanol specifically, but the other components that constitute alcoholic beverages should not be ignored.

Here we survey the relationship between light to moderate alcohol consumption and aging. We will address the dose-dependent alterations on lifespan and discuss ethanol's age-based plasticity. Our focus is to compare and contrast the effects of ethanol between humans and animal models, where limited studies on its potential benefits have been performed. Finally, we will conclude by highlighting inconsistencies in the field and propose efforts to improve our overall understanding of the mechanistic connections between ethanol and human aging.

2. Ethanol's aging-related links and mechanisms

A recent meta-analysis linked light ethanol consumption to a dose-dependent increase in lifespan [15]. This association is understood to be J-shaped, with an immediate protection at low doses followed by an increasing risk of mortality at higher doses [10,21]. Fig. 2, from O'Keefe et al., 2014 [1], demonstrates the maximal survival benefit to be between 0.5 and 1 drink (7–14 g) daily for women and between 1 and 2 drinks (14–28 g) for men [1]. Furthermore, the inverse relationship to mortality (hormetic zone) persists until a doubling of the above doses, after which increasing consumption becomes harmful [15]. This hormetic response is conserved in studies on mice [14], though it is not yet possible to track an optimal dose. However, these findings point to the efficacy of using a rodent model to address mechanisms by which moderate ethanol consumption reduces long-term mortality.

The effect ethanol has on lifespan is further intriguing considering the increasing evidence that the mammalian body's sensitivity to it varies with age [17]. This phenomenon has been explored in mouse and rat models, revealing that ethanol causes more dramatic changes to intoxication levels and motor control

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