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Trends in the Medicinal Use of Alcohol

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Abstract: The negative effects of alcohol on the human body are well known and often a subject of debate in medicine. Alcohol has been used for anesthesia and pain relief for several thousand years. The direct injection of ethanol into tumors causes cell dehydration and thrombosis of small blood vessels, leading to ischemia, necrosis, and eventual destruction of the tumor. Some studies suggest that moderate daily ethanol consumption may reduce the risk of coronary heart disease and stroke. The use of ethanol and wine in medicine has always been controversial. Research on alcohol and wine has revealed diverse and sometimes contradictory effects. However, wine, with its chemically complex and diverse composition, has many beneficial properties, including antioxidant, antimicrobial, and antitumor effects. The chemistry of wine and the beneficial physiological effects of its compounds, particularly derivatives of cinnamic acid, are noteworthy.
This paper presents research from various scientists on the medical use of wine, analyzing data that help assess its potential positive impact on human health.

Key words: ethanol, wine, resveratrol, antioxidation, flavonoids.

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Introduction

Any beverage containing more than 1.2% alcohol by volume is classified as an alcoholic beverage.

Ethanol, also known as ethyl alcohol or wine alcohol, along with water, is the main component of most alcoholic beverages. Ethanol concentration varies from 40-95% (vodka, rum, gin, whiskey, tequila) to 4-24% (wine, liqueur, beer). Some very sweet liqueurs may have a higher sugar content than ethanol [Li R et al., 2018].

Ethanol in beverages is produced by yeast fermentation of carbohydrates. It can also be synthesized from ethylene obtained through petroleum hydrocarbon cracking. However, the alcoholic beverage industry generally agrees not to use synthetic ethanol from ethylene due to impurities. To determine whether synthetic ethanol was used to enhance alcohol content, control analyses measure the ^{14}C isotope content of ethanol.

Scientific research confirms that wine and other alcoholic beverages contain both volatile and non-volatile aromatic compounds. In addition to ethanol, vodka's chemical composition includes acetaldehyde, methanol, and propanol, and some varieties may also contain glycerol and even coumarin, despite distillation removing most extraneous substances [Abel et al., 1978]. Rum is rich in esters, notably ethyl propionate, phenethyl alcohol, lactones, vanillin, and others [Cochrane et al., 2020].

Volatile compounds in alcoholic beverages include aliphatic hydrocarbons, carbonyl compounds, alcohols, monocarboxylic acids and their esters, nitrogen- and sulfur-containing compounds, carbohydrates, terpenes, heterocyclic, and aromatic compounds. Non-volatile substances in alcoholic beverages include residual sugars, di- and tricarboxylic acids, tannins, polyphenols, and inorganic salts.

Scientists note that volatile compounds in alcoholic beverages primarily originate from three sources: raw materials, fermentation, and wooden barrels used for aging. During aging, an unpleasant odor may develop, likely due to volatile sulfur compounds. Many compounds are released from the barrel walls, including monosaccharides (pentoses, quercitol), carboxylic acids, and lactones (5-butyl-4-methyl-dihydro-2(3H)-furanone). The presence of aromatic compounds indicates lignin degradation (oxidation) in oak barrels. Some flavored alcoholic beverages may contain synthetic substances and ingredients, including essential oils or their mixtures, artificial additives, and colorants to enhance taste [Rietjens SJ et al., 2014].

Ethanol

Ethanol (chemical formula: C_2H_5OH) is a simple, monohydric alcohol. Anhydrous ethanol is a transparent, colorless, volatile liquid with a boiling point of 78.5°C, a melting point of -114.1°C, and a density of 789 kg/m³. It is widely used in scientific research laboratories and industry as a solvent for resins, fats, and oils, as well as in various pharmaceutical and cosmetic productions.

Several scientists have noted that ethanol has anesthetic and analgesic properties with a history spanning thousands of years. There is little evidence on how frequently surgeons used it for these purposes before the discovery of inhalation anesthetics. However, ethanol can induce general anesthesia [Park E.-J et al., 2014]. Researchers have studied the effects of ethanol injection into the spinal cord in rats aged 2-7 days and 6-7 days. In neonates, ethanol reduced the amplitude of the monosynaptic reflex. At anesthetic concentrations, both in neonates and adults, ethanol reversibly suppressed post-synaptic population excitatory potentials. The effects of ethanol on the spinal cord resemble those of inhalation general anesthetics [Wong SM et al., 1997]. Studies have also documented the successful use of ethanol

injections for trigeminal neuralgia as a non-invasive analgesic, especially in patients where medication alone could not control the neuralgia [Sharr MM et al., 1977]. Research has shown that an absolute majority of patients experienced pain relief [Fan P et al., 2009].

Ethanol injections, which cause dehydration and necrosis of tumor cells, accompanied by thrombosis of small blood vessels, lead to tumor ischemia and destruction. In a study comparing two groups of patients with metastatic liver cancer, one group received ethanol injections in addition to chemotherapy, while the other did not. The results showed an almost 15% difference in survival rates in favor of the ethanol-treated group. Although the study was small-scale, a 2020 study by Swierz and co-authors noted that "this issue is quite intriguing and requires further research" [Swierz MJ et al., 2020]. Research on ethanol injection for spinal cord tumors indicates that intratumoral ethanol injection is minimally invasive and requires further clinical investigation. The study also noted that it is effective in treating peripheral metastases, can be used repeatedly, and does not preclude other treatments such as open surgery [Clemmesen et al., 1941].

It is noteworthy that over the past two decades, increasing epidemiological studies have confirmed a link between alcohol consumption and a lower risk of coronary heart disease (CHD), a leading cause of death in many developed countries. In the United States, studies have determined that after nearly 15 years of observation, the incidence of CHD was lower in men who consumed ethanol. The frequency also decreased in women, but only among those who consumed alcohol in low to moderate amounts. In individuals with normal blood pressure, the risk of ischemic stroke may be reduced by alcohol's distinct properties, as well as by decreased vascular damage and thrombosis caused by lipid deposits. In a health study of male physicians, those who consumed more than one drink per week had a lower risk of stroke than those who consumed less than one drink per week. Scientists concluded that men who consumed ethanol daily in controlled amounts had a 26% lower risk of peripheral vascular disease. The relationship between alcohol consumption and arterial hypertension is also intriguing. Some studies have shown that low alcohol consumption does not affect blood pressure or causes only a slight decrease, while others indicate an increase in blood pressure with higher alcohol intake. Thus, this issue remains an area for further research.

Ethanol's therapeutic properties are also evidenced by the fact that it is a treatment option for ethylene glycol and methanol intoxication, alongside fomepizole. The toxicity of these alcohols arises from their metabolites [Rietjens SJ et al., 2014]. Ethanol acts as a substrate for alcohol dehydrogenase and competes with the aforementioned toxic alcohols, thereby reducing their metabolism.

Wine

Wine is chemically complex and contains numerous active compounds. It is produced from grapes through fermentation. Notably, the world's oldest wine has been discovered in Georgia. Archaeological excavations in two Neolithic-era villages in Georgia, south of Tbilisi—Gadachrili Gora and Shulaveris Gora—have uncovered wine vessels. Chemical analysis of eight such vessels confirmed the presence of wine residues, with the oldest dating back to 5980 BCE [David Keys et al., 2003].

Wine is a hydroalcoholic solution containing various chemical components, including aldehydes, ethers, ketones, lipids, minerals, organic acids, phenols, soluble proteins, sugars, and vitamins. In addition to ethanol, glycerol, and 2,3-butanediol, it contains carbonyl compounds, 90% of which is acetaldehyde (50-100 mg/L). Interestingly, the aldehyde content in red and white wines is similar. The low aldehyde concentration can be attributed to sulfur dioxide, which reacts with aldehydes to form α-hydroxysulfonic acids, reducing the amount of free aldehydes. Additionally, aldehydes may be chemically bound to ethanol in the form of acetals.

Wine also contains small amounts of other aliphatic aldehydes and ketones, such as 3-hydroxy-2-butanone, 3-hydroxy-2-pentanone, 2-methylbutanal, 3-methylbutanal, and 2-heptanone. As for acetals, the primary aromatic component is 1,1-diethoxyethane, along with other compounds like 2,4-dimethyl-

1,3-dioxane and 2,4,5-trimethyl-1,3-dioxolane. Among volatile acids, acetic acid is the most abundant. However, it is known that yeast produces only small amounts of acetic acid during anaerobic fermentation. Scientists believe that any significant increase in acid content is caused by bacterial spoilage. Acetic acid bacteria can oxidize ethanol to acetaldehyde, which then further oxidizes to acetic acid. Additionally, among non-volatile acids, tartaric, malic, citric, and succinic acids are typically the most abundant.

Both white and red wines contain ethyl esters of short-chain acids as well as acetate esters of fusel alcohols. The longest-chain ethyl esters belong to decanoic and dodecanoic acids. Moreover, wines contain many esters derived from grapes, such as methyl anthranilate, which is considered a key aromatic compound. Several esters of di- and tricarboxylic acids have been identified in wines from different grape varieties, including 2,3-butanediol monoacetate, methylethyl succinate, diethyl malonate, diethyl malate, and ethyl esters of 2-hydroxyglutaric acid and its γ-lactone. The presence of mono- and diethyl esters of tartaric acid has been confirmed in multiple studies.

Bacterial decarboxylation of amino acids primarily produces amines, though yeast enzymatic reactions may also contribute in smaller amounts. Some amides found in wine may form from amines during fermentation. Diamines are more prevalent in red wine than in white wine. Additionally, certain pyrroles, thiazoles, and piperazines, along with acetamides, have been detected. Beyond chemical compounds, wine contains numerous terpenes, hydrocarbons, terpenic aldehydes and ketones, terpenic alcohols, their ethers, and their oxidation products.

Red wines contain small amounts of phenols such as M-cresol, guaiacol, 4-ethylphenol, 4-vinylphenol, 4-ethylguaiacol, 4-vinylguaiacol, eugenol, and 2,6-dimethoxyphenol.

Red wine is a rich source of digestive probiotics, including Bifidobacteria, Bacteroides, Prevotella, and Enterococci. It supports digestive system function by activating enzymes necessary for fat and protein digestion and stimulating the production of certain vitamins [Queipo-Ortuño MI et al., 2012; Nash V et al., 2018].

By reviewing and analyzing scientific research, we are once again convinced of how complex and interesting the chemical compounds found in wine are and how each of these compounds can contribute to maintaining and improving human health. Here, I will focus on several chemical compounds based on their characteristics.

Wine contains anthocyanic acid derivatives, anthocyanins, flavonols, and tannins. The anthocyanins and tannins derived from grapes are the primary pigments in wine. The main flavonols include quercetin-3-glucoside, quercetin-3-glucuronide, and myricetin-3-glucoside, while kaempferol-3-glucoside, kaempferol-3-galactoside, and isorhamnetin-3-glucoside are present in smaller amounts. Additionally, caffeoyl tartaric acid and coumaroyl tartaric acid contribute to the pigmentation of grapes and wine, giving red wine its distinctive color.

Anthocyanins are water-soluble compounds with a 4'-hydroxyflavylium structure. The stability of wine color increases with the methylation, glycosylation, and acylation levels of anthocyanins. Individual anthocyanins differ in the number of hydroxyl and methoxy groups in their molecular structure, as well as in the type and number of sugars attached glycosidically. Additionally, aliphatic and aromatic acids can be linked to the aglycone skeleton. In acylated anthocyanins, cinnamic acid, and particularly p-coumaric acid, are esterified with the hydroxyl group at the sixth position of the glucose molecule, which is glycosidically linked to the aglycone. Grapes and wine typically contain five major anthocyanins—delphinidin, petunidin, malvidin, cyanidin, and peonidin—along with their 3-monoglucosides and 3,5-diglucosides.

Scientific studies using cell cultures, animal models, and human clinical trials demonstrate that anthocyanidins and anthocyanins possess antioxidant and antimicrobial properties, improve neurological health, and protect against various non-communicable diseases. These studies confirm the health benefits

of anthocyanidins and anthocyanins, which are primarily due to their strong antioxidant properties. Anthocyanin chalcones and quinonoid bases, with a conjugated double bond system and keto groups, are effective antioxidants that neutralize free radicals. Additionally, the glycosylated B-ring structure of anthocyanins contributes to their high antioxidant activity, where ortho-hydroxylation and methoxylation significantly enhance this effect.

Certain groups of flavonoids are characterized by their phytoconstituents, which exhibit anti-inflammatory, antimutagenic, anticancer, and antimicrobial properties. Chemically, flavonoids represent a major class of polyphenolic compounds that are closely linked to the organoleptic and health-promoting properties of red wine. Despite the lack of sufficient epidemiological and in vivo evidence on this topic, factors such as human age, metabolism, alcohol consumption, the complex chemical composition of wine, and the wide spectrum of in vivo biological effects suggest that scientists have been cautious when drawing conclusions from studies linking wine consumption to specific health benefits. Nevertheless, several studies highlight the protective properties of phenolic compounds in wine against diseases such as cardiovascular conditions, certain cancers, obesity, neurodegenerative disorders, diabetes, allergies, and osteoporosis. The absorption and metabolism of flavonoids in wine play a significant role in their effects on human health. However, there remains a substantial gap between our understanding of the bioavailability of wine flavonoids and their health-promoting effects.

The water-soluble polyphenols present in wine are known as tannins, which are found in many plant-based foods. The tannins in wine, also known as astringent compounds, are primarily present in red wine, although some white wines (those aged in wooden barrels or fermented on grape skins) also contain them. Scientists suggest that tea polyphenols and tannins, in general, exhibit anticancer properties. Additionally, it has been shown that many tannin molecules reduce various mutagenic activities, likely due to their antioxidant properties. Tannins and related compounds are known to inhibit the formation of superoxide radicals. The antimicrobial activity of tannins has also been confirmed, as they inhibit the growth of numerous fungi, yeasts, bacteria, and viruses.

Tannins also exhibit various physiological effects, such as accelerating blood clotting, lowering blood pressure, reducing serum lipid levels, and modulating immune responses. The dose and type of tannins play a crucial role in these effects [Chung KT et al., 1998]. Astringent compounds strongly bind to proline-rich salivary proteins, drying the palate and disrupting the non-keratinized mucosa of the oral cavity, which may impair taste receptor function. Scientists note that the 10-15% ethanol content in wine enhances this effect. The high cholesterol content in the keratinized mucosa helps protect against potential disruptions in the oral cavity. Researchers also point out that polyphenols strongly bind to lipid droplets in fatty foods, which should be taken into account [Dufourc EJ et al., 2021].

One of the most important compounds in the stilbenoid group of polyphenols is resveratrol (3,5,4′-trihydroxy-trans-stilbene). Based on its chemical structure, resveratrol consists of two phenolic rings connected by an ethylene bridge. This natural polyphenol is found not only in grapes but also in more than 70 plant species, particularly in grape skin and seeds. It is often referred to as a phytoalexin, acting against pathogens, including bacteria and fungi. As a natural dietary ingredient, numerous studies have demonstrated that resveratrol has very high antioxidant potential.

Resveratrol also exhibits anti-cancer activity and is considered a potential agent for the prevention and treatment of several types of cancer, as confirmed by multiple in vitro and in vivo studies. Based on these research findings, scientists suggest that resveratrol can suppress all stages of carcinogenesis (e.g., initiation, promotion, and progression). Moreover, other bioactive effects have been identified, including anti-inflammatory, cardioprotective, vasorelaxant, phytoestrogenic, and neuroprotective properties. Nevertheless, the use of resveratrol remains a major challenge for the pharmaceutical industry due to its poor solubility and bioavailability.

Another important aspect is that resveratrol (E-5-(4-hydroxystyryl)benzene-1,3-diol) not only has two phenolic rings but also exists in two isomeric forms: cis- and trans-resveratrol. The trans form is

dominant in terms of its natural occurrence and is associated with various biological activities. Under ultraviolet radiation, the trans form can isomerize into the cis form. The low bioavailability of resveratrol makes its therapeutic application difficult. Therefore, modifying the structure of resveratrol has attracted significant attention from researchers, leading to the synthesis of numerous resveratrol derivatives, including methoxylated, hydroxylated, and halogenated forms [Park E.-J et al., 2014].

Resveratrol exists in food products in glycosylated forms, known as piceid. Enzymes present in the human digestive tract can oxidize polyphenols (and subsequently inactivate them), but glycosylation prevents enzymatic oxidation of resveratrol, thereby preserving its biological effects, stability, and enhancing its bioavailability. Additionally, it has been determined that intestinal cells can only absorb the aglycone form of resveratrol, requiring glycosidase for absorption. Thus, the relative proportion of aglycone and glycosylated resveratrol in food and beverages can influence its absorption rate [Fan P et al., 2009].

In vitro studies have shown that glycosylated analogs exhibit stronger bioactivity. For example, both resveratrol and piceid have similar antioxidant properties, but while piceid is more challenging for cells to absorb, it appears to be more effective than resveratrol due to its reaction with radicals. The same applies to the effectiveness of resveratrol glycoside against the hepatitis B virus [Park S., et al., 2017]. Additionally, hydroxylated piceatannol has been found to possess pronounced anti-inflammatory, immunomodulatory, antiproliferative, antileishmanial, antileukemic, and protein-tyrosine kinase inhibitory effects.

An interesting compound is pterostilbene, a naturally occurring methoxylated analog of resveratrol. This compound exhibits greater lipophilicity than resveratrol, which enhances its bioavailability and results in stronger bioactivity, including anti-cancer, anti-lipidemic, anti-diabetic, and cardioprotective effects.

Among the many positive physiological effects of resveratrol, its ability to act as a potent antioxidant stands out. Furthermore, the antioxidant activity of resveratrol depends on the structure of its molecular core and the arrangement of functional groups. The number of hydroxyl groups plays a crucial role in antioxidant activity through various mechanisms, such as free radical scavenging and chelation of metal ions. Studies have shown that the determinant of antioxidant activity is not only the hydroxyl group at the 4' position but also the 3- and 5-OH groups [Stivala L.A., et al., 2001].In simulated aqueous environments, quantum chemistry and computational kinetics methods have been used to study the antioxidant effects of hydroxyl (•OH) and hydroperoxyl (•OOH) radicals. These studies have shown that trans-resveratrol can act as an efficient scavenger of •OOH and potentially •OOR radicals [Iuga C., et al., 2012].

Resveratrol can also be used in pharmaceutical products to reduce or prevent lipid oxidation, thereby inhibiting the formation of toxic substances due to oxidation. It contributes to extending the shelf life of pharmaceutical products and preserving the quality of food products.

The antioxidant properties of resveratrol have been successfully utilized to protect cells from oxidative stress caused by hydrogen peroxide. Pre-treatment with resveratrol helps cells survive and defend against ultraviolet radiation-induced cell death. The cellular-level protection achieved with resveratrol is partially attributed to its ability to act both as a direct antioxidant and as an inducer and modulator of the cellular antioxidant system, thereby balancing the cellular redox status [Konyalioglu S., et al., 2013].

As previously mentioned, numerous scientific studies have confirmed the strong antioxidant properties of resveratrol. However, it is also crucial to consider research findings indicating that its beneficial effects are hindered by low bioavailability. Scientists have attempted to improve resveratrol's lipophilicity through esterification processes. Approximately 12 different esterified acyl chlorides have been synthesized, including butyryl chloride, capryloyl chloride, capryl chloride, eicosapentaenoyl chloride, lauroyl chloride, myristoyl chloride, and others. Experimental studies have demonstrated that these synthesized compounds effectively inhibit the oxidation of low-density lipoproteins (LDL) induced by

copper ions and can suppress DNA damage caused by hydroxyl radicals [Daniel A., et al., 1987].

The bacteriostatic and antifungal effects of resveratrol have also been studied. It exhibits significant bacteriostatic activity, particularly against Gram-positive bacteria [Paulo L., et al., 2010]. Resveratrol induces DNA fragmentation in Escherichia coli and effectively inhibits the growth of Candida albicans [Weber K., et al., 2011]. Dimethoxy resveratrol derivatives also exhibit antifungal activity against C. albicans and 11 other Candida species [Houille B., et al., 2014].

Several studies have indicated that stilbenoids, including resveratrol, possess anti-inflammatory activity. Their targets include cyclooxygenase (COX), 5-lipoxygenase (5-LOX), and protein kinase B [Dvorakova M., et al., 2017]. Resveratrol inhibits COX-1 and COX-2 activity and suppresses the activation of transcription factors. Research has demonstrated that resveratrol reduces the secretion of inflammatory mediators [Zhou Z.X., et al., 2018]. Additionally, resveratrol inhibits microglial activation, which leads to the suppression of pro-inflammatory factors, reactive oxygen species production, and inflammatory signaling pathways that cause neuroinflammation [Zhang F., et al., 2010]. In vitro studies indicate that resveratrol regulates inflammatory processes by reducing NF-κB activation and preventing mitochondrial dysfunction at moderate and high concentrations. These results were confirmed in vivo, where resveratrol suppressed TNF-α production and NF-κB activation, reduced neutrophil infiltration in the intestinal mucosa, and inhibited intestinal tumor formation by modulating anti-inflammatory miRNA. Furthermore, resveratrol significantly suppresses the TLR-4/MyD88/NF-κB signaling pathway during lysophosphatidylcholine-induced inflammation, which may be beneficial in the treatment of atherosclerosis.

Conclusion

From the studies discussed above, it can be concluded that the difference between a drug and a poison is the dosage. A certain amount of ethanol intake reduces the risk of various diseases, and its injections may be used in the treatment of tumors, neuralgia, and intoxications, which remain relevant applications even in modern medicine.

Additionally, numerous beneficial properties of wine constituents have been reviewed, emphasizing the potential for incorporating wine into modern medicine as a therapeutic agent. The impact of winemaking technology on its composition has also been highlighted. It can be confidently stated that traditional Georgian Qvevri wine stands out for its beneficial properties. The concentration of anthocyanins, tannins, flavonols, and resveratrol in wine is highly dependent on the winemaking process, as these compounds are primarily accumulated in grape skin, seeds, and stems. Scientific research results suggest that Georgian Qvevri wine—produced by fermenting the skins, seeds, and stems together—contains a richer chemical fraction of bioactive compounds compared to industrially filtered wines.

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