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Red wine and Resveratrol, their effect on human health

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Abstract

Based on several in vitro and in vivo studies, it appears that a certain amount of daily consumption of wine can prevent to some degree various chronic diseases. This is mainly due to the presence and number of important antioxidants in red wine. Wine polyphenols, especially resveratrol, anthocyanins and catechins, are the most effective antioxidants in wine. Resveratrol is thought to help prevent cardiovascular disease by neutralizing free radicals but also protecting the nervous system and other organs. The term "French Paradox" is used to describe the relatively low incidence of cardiovascular disease in the French population despite the high consumption of fats. However, in the case of heavy wine consumption, ethanol limits the benefits of the action of polyphenols in wine. From the literature review it appears that the combined- synergistic effect of wine phenols is superior to their individual action. Resveratrol requires red wine polyphenols for optimal antioxidant activity. Research has shown some positive effects, but several more studies are needed to draw safe conclusions as not many clinical trials have been performed in humans. Advances in technology have enabled new techniques to recover the valuable ingredients of red wine from by-products of vinification for their use in pharmacy and cosmetology. Consumers are now looking for

natural products to enhance their health and beauty. The uses of wine ingredients give new perspectives for their utilization in the pharmaceutical industry and cosmetology.

Keywords: Red Wine, Resveratrol, Polyphenols, French paradox, Free radicals, Antioxidants, Alzheimer ’s disease

Introduction

Viticulture and winemaking are ancient knowledge and their history is lost in the depths of the centuries. Wine is not only one of mankind's oldest beverages, but also one of the first recorded medicines. Throughout its history, wine was deified on the one hand, but accompanied by negative properties on the other, medicine and poison at the same time. It has been used in Medicine for thousands of years, while the destructive effects of its excessive consumption became apparent very early on. Through the bibliographic search it appears that clinical studies are limited by their observational nature as well as by the difficulties to isolate the benefits of wine from other cooperative factors. Despite the doubts, there is reasonable consensus on the beneficial effects of moderate wine consumption on cardiovascular disease, diabetes, osteoporosis, perhaps neurological disease, and longevity. Observations are less enthusiastic about cancer. Further research and more clinical studies as well as collaboration of many different scientific fields are certainly needed. Considering these limitations, one can claim with relative safety that moderate consumption of wine seems beneficial while giving added value to the product as it could be a field of business and commercial activity.

Wine has contributed manifold to the creation of human culture, serving nutritional, medical and religious needs. Wine is an important element of Western Civilization as we know it today. It was a medicine, an "opportunity" for social interaction; it was used and is used in religious ceremonies, religions and sects. It gained importance and place in the kitchen and in the cellars, but also as an economic good.

The knowledge of winemaking spread from the Middle East and Mediterranean Europe around the world. The research on the history of its spread is based on the archaeobotanical remains of the vine, which are mainly the gigarta. Only finding gigarts does not prove the possibility of wine production, but sure signs of wine making are the stems. Any findings are confirmed by radiocarbon-14 dating, climate and environmental reconstruction, along with archaeobotanical evidence, including grape pollen, starch and residue found on ceramics. Organic compounds are identified by a combination of chemical techniques, including spectrometry (FT-IR, GC-MS and LC-MS-MS). Table 1 summarizes the chronology of the history of wine from antiquity to modern times.

Table 1 The History of wine from antiquity to modern times (19th century)

PERIOD	AREA	EVENT/FINDING	SOURCE
6.000 BC.	Georgia / Tbilisi	Vases were found, the most ancient findings of wine production to date	McGovern, et al.,2017
5.400 BC.	Iran, Zakros Mountains	Traces of tartaric acid and signs of vinification were detected in ceramics	McGovern, et al.,2006
4.300-4.200 BC.	Greece, Dikili Tas	Remains were found in a vessel which are considered to be evidence of fermentation. The oldest indication of vinification in Europe so far	Valamoti, 2007 ,
4100 BC.	Armenia, Areni-1 excavation	Earliest winery found with fermentation vats, press and utensils and traces of malvidin in fragments of outdoor linen and pottery	Barnard et al., 2011
3150 BC	Aigypt, Abydos	The tomb of Scorpion King I contained 700 wine vessels believed to have been imported from the eastern Mediterranean.	McGovern, et al,.2009
3000 BC	Greece, Toumba of Sitagro	Charred gills from wild vines were found, and in other layers gills that now have characteristics of Vitis Vinifera.	Valamoti, 2009 Renfrew, 2003
3000-2000 BC.	Greece, Aegean and Crete	Systematic Winemaking in Aegean settlements, with the most famous in the Proto-Minoan II settlement of Myrtos (2900-2200 BC), clay vats, cup with gigarta, pithos-prochoi with traces of grapes.	Pagomenou, 2002
2600-2400 BC	Iraq - Mesopotamia ancient city of Ur West of the city of Nasiriyah,	Systematic Winemaking in Aegean settlements, with the most famous in the Proto-Minoan II settlement of Myrtos (2900-2200 BC), clay vats, cup with gigarta, pithos-prochoi with traces of grapes.	Plotkin, 2021
1700 BC	Israel, Nahariya	Tel Kabri excavation, wine cellar with wine storage vessels found (1), In the book of Genesis, Noah plants a vineyard after the Great Flood recedes and becomes the first man to produce wine (2).	Koh, A., Yasur-Landau, A. and Cline, E., 2014 (1), Plotkin, 2021 (2)
1330 BC	Egypt, Western Thebes,	36 red and white wine amphorae were found in Tutankhamun's tomb - 26 of them with the first wine labels stating year of production, vineyard location and winemaker eg: 'Year four. Very good quality wine from the House of	McGovern, 2009

	Valley of the Kings	Aton of the West River. Head Winemaker Kai.”	
1200-539 BC	Middle East -	The Phoenicians flourished from about 1200 to 540 BC. Two Phoenician shipwrecks were found off the coast of the Middle East, loaded with loads of wine, these are the oldest shipwrecks with wine, they date back to 750 BC. .	Ballard R.D. et al., 2002
700 -146 BC	Ancient Greece and colonies	Wine becomes a symbol for commerce, religion, the arts and is commemorated by Homer, classical writers and philosophers. As the Greek city-states colonized areas, they brought vines from the Black Sea to Spain. Evidence of the importance of wine production in social, religious (god Dionysus), artistic and economic life is given by mosaics and vases with representations and a multitude of ancient coins that have been found in many archaeological excavations.	Kakrdis, 1986, Kourakoy-Dragona, 2006, Poulaki-Pantermali, 2014 , Bekatorou A.., 2020
146 BC. – 380 AC.	Roman Empire	Wine is a central part of their culture. The Romans brought the cultivation of grapes to the valleys of the Rhine and Moselle, the Danube and the rivers of France. The Romans invented oak barrels. In 121 BC first mention of the term "vintage" for the wine of the Roman golden age - "Opimian vintage".	Phillips, R., 2002, Robinson, J., 2006, Plotkin, M., 2021
380–1492 AC	Roman Empire and Byzantium	The Roman Empire adopts Christianity and wine plays an important role in the formality of its worship. Its importance for the liturgy prompts the Catholic Church to produce it. Monks in Italy and France work as viticulturists and winemaking technology is perfected. This led to the development of the concept of "terroir". The first naming system in the world was created in Portugal. The art of winemaking also flourished in Byzantium until its conquest.	Anagnostakis, 2006 Plotkin, 2021
16th century	Europe	Several technological innovations are promoted (use of glass bottle and cork) and sparkling wine production begins	Crawford, 2020
15th – 19th century	America, Oceania	The art of winemaking travels around the world with explorers and settlers.	Plotkin, 2021

Newer times – 19th - 21st century

In 1805 the Franciscan friars create the first winery in California, wine production gradually develops in the USA, and today it is the 4th largest wine producing country in the world after France, Italy and Spain. The industrial revolution and the rapid development of technology and science gave additional possibilities to viticulture. Even though from ancient times until today the way of wine production does not differ in its main points, the lack of scientific knowledge and techniques gave a product that was quite different in quality and organoleptic characteristics from today. In the past to enhance the taste, they sweetened the wines by adding honey and diluted them with salt water or even added ash or resin, and added herbs to enhance their aromas (Plotkin, 2021).

Innovations during the 19th century simplified many winemaking tasks, such as pressing, crushing, filtering and transferring wine, allowing the production of some very different types of wine, particularly fresh and fruity flavors, through aromatic preservation and minimizing the effect of oxygen. The global wine market size was valued at US$417.85 billion in 2020 (winetitles.com).

In the early 1950s several researchers – including Émile Peynaud in France who is considered the father of modern oenology and Brad Webb in California et al. isolated the first culture of malolactic bacteria. Interest in winemaking revived in the 1950s after World War II, and in 1976, Californian white and red wine were judged the best in a blind tasting (Paris Competition) by French experts. The Competition of Paris (Jugement de Paris), made the winemakers of the New World to realized that they could make first quality wines. This interest led to productive competition and efforts to improve the quality of all wines worldwide. The results are beneficial for the wines of the New World, France and the rest of the Old World.

The use of wine as medicine from ancient times to the present day

Ancient Mesopotamia (5000- 1400 BC)

Armenian traders from southern Georgia spread the knowledge of winemaking to the southern regions of the Euphrates River to the cities of Uruk, Ur, and later Babylon and Kisk (in

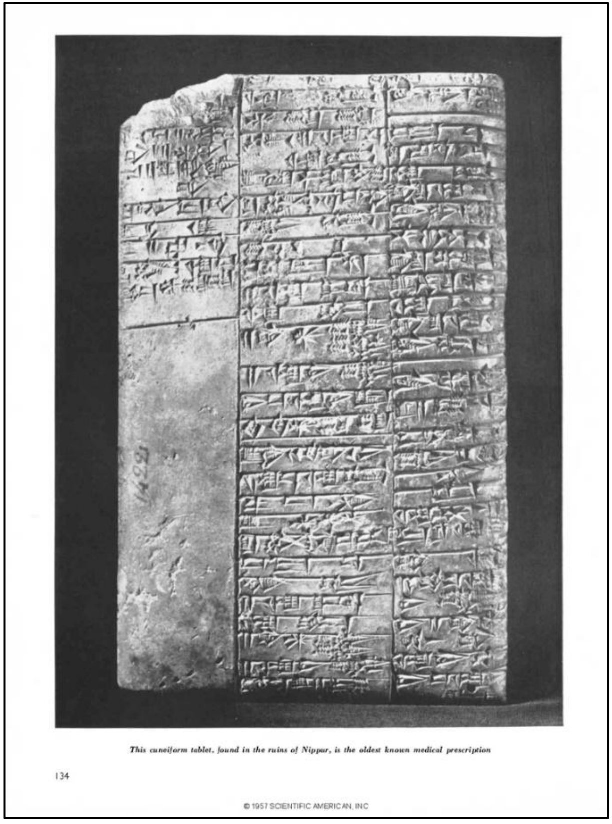


Figure 1 The oldest medicinal recipe, Mesopotamia, www.jstor.org/stable/24941891 .

present-day Iraq), where the Sumerian civilization flourished from 5,000 BC. The first evidence for the use of wine as a medicinal ingredient dates back to the Sumerian era in Mesopotamia, when the Sumerian Pharmacopoeia was created, which is also considered the oldest pharmacopoeia in the world. Nikolova et al. (2018) refer to Bourke who argues that "..Tabatu is the first medicinal drink mentioned in the Babylonian Pharmacopoeia, which is prepared from small amounts of fermented fruit juice or wine mixed with water" (Bourke in Nikolova et al. 2018 p. 15).

Ancient Egypt (3000 - 332 BC) Wine is an integral part of ancient Egyptian medicine, Egyptian papyri dating back to 2,000 B.C. record its use. The medicinal drinks used were mainly derived from cereals, from grapes, but also from palm juice and used as solvents for various medicinal ingredients - herbal, animal or mineral (Nikolova, 2015). According to Plotkin, the fact that various Egyptian papyri were written centuries apart, but contain identical recipes, indicates that they were effective and therefore survived through time (Plotkin, 2021).

Ancient China (3800 BC - 220 AD) In ancient China, alcoholic beverages, including wine, were also used to dissolve other ingredients believed to have a healing effect. As Norrie (2005) mentions, Franz Hübotter (1957) in his book on Sino-Tibetan Pharmacology and Prescription includes 87 recipes, 19 of which are prepared with wine. Hübotter also points out that wines used for therapeutic purposes are produced from cultivated grapes from the European V. Vinifera and not from wild grapes (Hübotter as cited in Nikolova, 2015). **Ancient India (1500–800 BC)** During the Vedic period of ancient India (1500–800 BC), wine was recognized for its healing powers. In the sacred Hindu text, the Vedas, wine (Soma) was worshiped as the liquid god for its medicinal properties. An Indian medical text of the sixth century BC. described wine as "the refresher of mind and body, an antidote to insomnia, sadness and fatigue". Ancient Sanskrit writings are also among the first to record the use of wine as a surgical anesthetic. When Alexander the Great invaded India in 327 BC, historians believe he returned to Europe with advanced medical knowledge borrowed from Hindu surgeons and physicians, thus influencing Greek medicine (Crawford, 2020). **Israel – Palestine (1220 BC - 70 AD)** During Biblical times, wine was used primarily as a sedative and antiseptic. This is documented in the Holy Book of the Jewish Talmud (536 BC - 427 AD), the Old Testament (c. 400 BC) and the New Testament. As Plotkin (2021) writes in the Talmud, it is mentioned that wine is beneficial for health in general, for the treatment of problems of the heart, eyes and intestines and possibly as a cure for impotence. Psalm 104 is the most well-known and is used to characterize the properties of wine: "..and wine that gladdens the heart of man.." (Psalm 104:15 Old Testament) (Plotkin, 2021). **Ancient Greece (900 - 146 BC)** The ancient Greeks saw wine as an integral part of their daily diet, as they believed it stimulated the appetite and was a source of valuable nutrients for health. The first detailed accounts of ancient Greek medicine are reported by Homer. Descriptions of the beneficial properties of wine can be found in the Iliad and the Odyssey. There are references to almost 150 wounds in both epics and in details that suggest considerable knowledge of medical practice. Achilles and Odysseus talk about wine, the Greek warriors returning home in the Odyssey bring wine, water and wheat with them, the Trojans also drink wine, as do the Cyclops. According to Kourakou-Dragona (2006) "the fact that nowhere does Homer mention the drinking of plain water has led to the assumption that the wine was mixed with water, so that they could drink water without fear of dysentery, due to the antiseptics and medicinal properties of wine". (Kourakou-Dragona, 2006). Hippocrates (450 – 370 BC), born several hundred years after Homer, is considered the father of Medicine. He considered wine an important therapeutic ingredient and prescribes its use as a sedative and antiseptic. He also recommended wine as a preventive medicine and considered its regular consumption as the key to good health. He used wine as a diuretic, antipyretic, to treat many different ailments, such as anxiety, eye pain, soft ulcers and head injuries and included wine in the diet of almost all diseases, especially during the convalescent period.. According to Lucia as Norrie (2005) states, "[Hippocrates] did not make excessive claims about wine, but incorporated it into the regimen for almost all acute and chronic diseases, and especially during the convalescent period." (Norrie, 2005). As Crawford (2020) reports, after Hippocrates, a number of prominent Greek physicians wrote about the medicinal uses of wine. How well-known were Theophrastus from Eresus (372–287 BC), Mnisitheos (320–290 BC) and Athenaeus (170–230 BC), who even wrote that: "In the medicine [wine] is more beneficial, it can be mixed with liquid medicines and brings help to the wounded." The wines from the Greek island of Thassos, produced from dried grapes, were especially awarded for their aesthetic and medicinal properties. This wine was supposed to have the ability to induce abortions, cure insomnia and, when mixed with vinegar, cure eye diseases. The Pramnios wine of Ikaria was known for its therapeutic effect and is also mentioned by Galeno. (Crawford, 2020). Theophrastus (371–287 BC) was a student of Aristotle. He is considered "the father of botany" because he wrote the first comprehensive treatise on plants covering their structure, growth and reproduction. His work, also known by its Latin translation as 'Historia Plantarum', influenced botany and medicine for more than 20 centuries. It records the use of aromatic wines and their effect on the sense of taste. Theophrastus made a contribution to the art of viticulture: he wrote about the effects of environmental conditions on the taste and aroma of wine (the first reference to what is now in a way called terroir) and about planting conditions, as well as grafting and pruning methods (Poulaki-Padermali, 2014). Mnesitheos (320-290 BC) was a famous physician who practiced in Athens, a follower of Hippocrates, and wrote a treatise entitled "Diet and Drink", he declared about wine: "In medicine it is more beneficial, it can mixed with liquid medicines and brings help to the wounded .. While dark wine is more favorable to physical growth, white wine is thinner and more diuretic. yellow wine is dry and better for digesting food." In essence, he observed that red wines contained more nutrients (Plotkin, 2021). **Roman era** Dioscorides the Pedanius (1st century AD), a Greco-Roman physician with his 5-volume work "On the Matter of Medicine", or "De materia medica" won, together with Hippocrates and Galen, a supreme place in the History of Medicine . The work has been a prototype for pharmacopoeia, botany and medicine for more than 1,500 years. Dioscorides recommended the use of wine for a wide range of ailments, including heart disease, digestive disorders, and respiratory problems. Like Hippocrates, he determined which wine should be taken for each disease, separating the effects of old, new, dry and sweet wines. Dioscorides recommended therapeutic uses for other parts of the vine, such as leaves, flowers, stems and tendrils (Plotkin, 2021). Asclepiades (124–40 BC), wrote the essay On the Dosage of Wine, in which he described the medicinal virtues of various Greek and Roman wines.

Another Roman physician, Aurelius Cornelius Celsus (25 BC–50 AD), wrote about the healing virtues of wine, and prescribed wines from various regions of Italy and Greece for a range of clinical indications. Pliny the Elder (23/4–79 AD), a famous statesman and physician of Rome, devoted a section to wine in his encyclopedia of plants and medicine, Naturalis Historia. (Norrie, 2005). Galen (129–199 AD) was the second greatest Greek physician of Antiquity after Hippocrates and made many references to his work on wine. As a gladiator physician, he treated various types of wounds with wine to prevent infection. His complex medicinal preparations (known as "Galenics"), often containing wine, dominated European medicine until the late Middle Ages. Later, when Galen became imperial physician to the emperor Marcus Aurelius, his duties extended to the selection of suitable wines for the emperor. He recommended drier and lighter wines instead of the thick, sweet concoctions that were popular (Crawford, 2020). He created a catalog of wines from different regions, describing their specific chemical characters and physiological effects (Jouanna, J.,2012).

Christendom and Islam As the Christian world began to grow, wine retained an important role, particularly as a symbol. According to physician and wine historian Philip Norrie, St. Luke was originally a Greek physician and therefore would have known of wine's efficacy as an antiseptic from the teachings of Hippocrates, and possibly Pliny and Dioscorides. (Norrie, 2005)

With the rise of Islam and its spread in Persia, the prohibition of alcohol led to many changes in Muslim-conquered areas and brought challenges to Persian and Arab physicians. The Koran forbids alcohol and therefore presented the Arab doctors with a dilemma. Muslim healers such as Rhazes (Abū Bakr Muhammad ibn Zakariyyā al-Rāzī; 854–925) and Avicenna (Ibn Sina; 980–1037) used wine mainly for external purposes, such as wound dressings. The first distillation of wine is believed to have been done by the Muslims, a process that greatly increases the alcohol content and made possible the production of highly alcoholic drinks. (Plotkin, 2021).

Middle Ages and later times The practice of medicine in medieval times was mainly by monks who used medicines based mainly on herbs and secondarily on animal products and mixed with wine. The first medical schools opened in the 9th century, the most important being the Schola Medica Salernitana in Salerno in southern Italy. Women also studied at the Salerno school, in fact the most famous of the doctors who graduated from the school, the famous Trotula or Mother Trot of Salerno (11th century AD) who was involved in obstetrics, wrote: "warm wine in which has boiled butter' to be used to treat uterine prolapse after childbirth' (Norrie, 2005). After Salerno, other medical schools were founded such as in Naples, Palermo, Montpellier and Bologna. As Crawford (2020) mentions, the important physician Arnaldus de Villanova (1240–1311 AD), who taught at the University of Montpellier in the south of France, was the author of the first book, the “Liber de vinis” that talked about the medicinal properties of wine. Perhaps the most important of all Arnaldus wrote was that through his teaching he promoted wine as an antiseptic (Crawford, 2020). One of the famous doctors, Henri de Mondeville, a French surgeon of the 14th century, advocated the use of "good wine" in the treatment of diseases and especially in the regeneration of the blood. The surgeon Hieronymus Brunschwig (1450–1533) treated gunshot wounds with a mixture of strong wine, brandy, and herbs (aqua vite composita). The Italian physician Baldassare Pisanelli (16th century) recommended wine to the diet of the elderly as a “supplementary source of warmth to overcome the coldness that accompanies old age” (Crawford, 2020). The Swiss medical teacher Theophrastus Bombastus Von Hohenheim known as Paracelsus (1493–1541) stated: “Whether wine is food, medicine or poison is a matter of dosage” (Crawford, 2021).

Patients were given alcoholic drinks and for another reason the water was usually contaminated with typhoid or cholera, and the milk ran the risk of containing tuberculosis. The only safe drinks were spirits, and most therapeutic of all wine began to be prescribed and used by hospitals as a medicine and was mentioned in all the Pharmacology publications of the Universities of Europe (Norrie, 2005).

It is characteristic that one of the biggest expenses of hospitals was for wine as it appears in the records of Leicester Hospital, England, in 1773. The famous microbiologist Louis Pasteur (1822-1895) described wine as "the healthiest of all drinks". And as late as 1892, Professor Alois Pick of the Vienna Institute of Hygiene recommended adding wine to water to sterilize the water during the Hamburg cholera epidemic. Dr Francis Anstie, a London physician, advised in 1877 that fortified wines were excellent when used as a "dietary aid in the debilitation of old age" and recommended light wines of lower alcohol content for use on a daily basis with lunch and dinner. to protect against disease in healthy individuals. The famous doctor Dr. Jean Martin Charcot, in his “Traité de Médecine,” his 10-volume encyclopedia of current European medicine, published between 1899 and 1905, recommended wine-based treatments for a range of ailments (Norrie, 2005). Also according to Kourakou-Dragona (2006): "in the 19th century the wine of the Bordeaux region was considered a common medicine for women who had just given birth..."

Dr Robert Druitt publicized the health benefits of French wine in a series of articles published in British medical journals in the 1860s (Crawford, 2021).

Towards the end of the 19th century and the beginning of the 20th, alcoholism was recognized as a medical disease and the harmful side effects of excessive alcohol consumption began to be recognized. The temperance movement was particularly influential in the US and UK, resulting in prohibition in the US from 920 to 1933. Echoing the teachings of their predecessors, many physicians continued to support wine by advocating appropriate prescription based on its type of wine and the disease being treated (Crawford, 2021 & Norrie, 2005).

Modern Era The "French Paradox" was the reason why wine began to arouse the interest of researchers at the end of the 20th century, namely the observation that mortality from coronary heart disease is lower in France than would be expected from the high rate of smoking and high intake of saturated fat in the country. The "French Paradox" would be the cause for a number of epidemiological studies and researches and will be analyzed in more detail in the 4th chapter of this thesis. The television appearance of Serge Renaud, FrenchEthanol consumption and its effects epidemiologist in 1991 on CBS sparked a wave of wine sales in the United States, increasing red wine sales by 40% (https://renaudsociety.org/).

Introduction

The effects of excessive alcohol consumption on health depend on:

1. the average volume

2. the frequency of consumption

3. the consumption pattern, i.e. the way it is consumed with food or not (Jackson, 2020)

According to international recommendations, the recommended amount of alcohol is 1 drink per day for women and 2 for men (National Alcohol Action Plan 2019 – 2023, 2021). Voskoboinik et al (2016) define light drinking as <7 Standard Drinks (STD) per week, moderate as 7-21 STD/week, and heavy drinking as >21 STD/week. This translates to <1 STD/day for low consumption, 1-3 STD/day for moderate consumption and >3 STD/day for heavy consumption, where 1 standard drink is defined as 12 g of pure ethanol (Voskoboinik et al., 2016). Women should consume less than men because they are generally smaller and have a relatively higher fat-to-muscle ratio than men, and they have half the amount of alcohol dehydrogenase (ADH - an enzyme that metabolizes ethanol) as men (Harvard Health , 2013 and Gordis, 1999). The main contributor to the increase in alcohol-attributable deaths is not chronic disease as a result of lifelong alcohol use, but fatal injury, which is largely due to heavy episodic drinking among young people. (World Health Organization, 2018). Table 2 below summarizes the main consequences of excessive alcohol consumption.

Table 2 Diseases and risks from alcohol abuse Adapted from WHO (2011) and from Jernigan, al. (2000)
Neuropsychiatric Disorders: The most common is alcohol use disorder (AUD = alcohol use disorder) which can range from mild to very severe (Alcoholism). Epileptic seizure is another disease affected by alcohol, in addition to withdrawal-induced seizures Many other neuropsychiatric disorders are associated with alcohol, but whether or to what extent they are caused by alcohol consumption is unclear (Samokhvalov et al., 2010).
Gastrointestinal Diseases: cirrhosis of the liver and pancreatitis (both acute and chronic) can be caused by alcohol consumption. Higher levels of alcohol consumption exponentially increase the likelihood of developing these diseases.
Cancer: Heavy alcohol consumption is considered a carcinogenic habit and has been associated with the following types of cancer (Baan et al, 2007): cancers of the colon, breast, larynx, liver, esophagus, oral cavity and pharynx. The higher the alcohol consumption, the greater the risk of cancer. Even drinking two drinks a day causes an increased risk of certain cancers, such as breast cancer in women (Hamajima et al., 2002).
Intentional injuries: alcohol consumption, particularly heavy drinking, has been linked to suicide and violence against others.
Unintentional injuries: almost all categories of unintentional injury are affected by alcohol consumption. The effect is strongly related to the level of alcohol concentration in the blood and the effects on psychomotor abilities (reduction of reflexes and spatial perception). Higher levels of alcohol consumption create an exponential increase in risk. Unintentional injuries include traffic accidents, falls, drowning. poisoning and other unintentional injuries. Injuries are the biggest statistical risk from excessive alcohol consumption.
Cardiovascular disease: the relationship between alcohol consumption and cardiovascular disease is complex. Light to moderate alcohol consumption may have beneficial effects on morbidity and mortality against ischemic heart disease and ischemic stroke. However, the beneficial cardio-protective effect of drinking disappears when heavy alcohol consumption occurs. Heavy alcohol consumption has deleterious effects on hypertension, cardiac arrhythmias, and hemorrhagic stroke, regardless of drinking pattern (Rehm et al., 2010).
Fetal alcohol syndrome and complications of preterm birth: alcohol consumption by the expectant mother can cause conditions that are detrimental to the health and development of newborns
Diabetes mellitus: there is a link between diabetes and alcohol. Light to moderate alcohol consumption can be beneficial, while heavy alcohol consumption is harmful (Rehm, J., 2011).

Absorption and metabolism of alcohol

Alcohol is absorbed in the human body from the stomach at a rate of 20-25%, and the small intestine at a rate of 75-80%, while it is basically metabolized in the liver and other tissues of the body, such as in the mucosa of the gastrointestinal system, the lungs, the kidneys, brain, etc. In total, 90-95% of the alcohol consumed is metabolized in the body, while 2-10% is eliminated through the lungs, kidneys or even bile. Most of the ethanol in the body is broken down in the liver by the enzyme alcohol dehydrogenase (ADH) which converts ethanol into the toxic compound acetaldehyde (CH3CHO), a highly toxic and carcinogenic compound. However, acetaldehyde is generally short-lived and is rapidly converted to the less toxic acetate (CH3COO-) by another enzyme, aldehyde dehydrogenase (ALDH). Acetate is then broken down into carbon dioxide and water, mostly in tissues outside the liver.

10% of ethanol is metabolized in the liver by the P450 2E1 enzyme, which is more activated in people with long-term alcohol use, with a small portion metabolized by the enzyme catalase (MyDr.com.au, 2016).

Moderate wine consumption and good health

Nutritional value The calorific value of ethanol (7.1 kcal/g) is almost twice that of carbohydrates (4.1 kcal/g). Thus, it was a valuable caloric source. It is estimated that alcohol can provide approximately 6% of the energy in the average diet (Alcohol and Nutrition, 2022). Wine contains small amounts of several vitamins, especially several B vitamins, such as B1 (thiamine), B2 (riboflavin) and B12 (cobalamin) and vitamin E. However, wine is essentially devoid of vitamins A, C, D and K. In addition , ethanol may interfere with vitamin uptake. Wine contains various minerals in readily available forms, especially potassium and iron. As in the case of chlorine, wines produced near the sea have a higher sodium content (Ribéreau-Gayon et al., 2006).

This low sodium content of wine may allow wine to be consumed by those on a low sodium diet, taking diuretics, for example those with high blood pressure or who have had a heart attack. While the high ratio of potassium to sodium in wine (20:1) makes it one of the most effective sources of potassium. Potassium is the dominant cation in wine and its concentrations are between 0.5 and 2 g/l, with an average of 1 g/l. Wines from noble rot have the highest potassium content. Red wine contains more potassium than white wine due to the ability of phenols to inhibit the precipitation of potassium bitartrate (Ribéreau-Gayon et al., 2006).

However, excessive alcohol consumption can disrupt the beneficial effect of wine components and especially the intake of calcium, magnesium, selenium and zinc and increase the excretion of zinc through the kidneys (Jackson, R., 2020). Also, although wine, and especially red, contains soluble fiber (0.94-1.37 g/L in red and 0.19-0.39 g/L in white), the amount it contains is not enough to contribute significantly to the daily recommended fiber content essential in the human diet (Díaz-Rubio, M. and Saura-Calixto, F., 2006). Besides the metals found in higher concentration (K, Ca, Mg), metals such as Fe, Cu, Zn, Mn, V and Cr are necessary or useful in a number of physiological processes in wine yeasts, but also for human health. However, high concentrations of metals in wines can endanger the health of the consumer, Hg, Pb and Cd are considered undoubtedly toxic, with some potential for toxicity for Cu, Ni, Cr, V, Zn, Ag and Al at high concentrations (Marais and Blackhurst, 2009 in M. Blesić et al 2017).

Epidemiological studies – alcohol consumption and health In studies, such as Thun et al. (1997) but also by Doll et al., (2005) shows that daily moderate alcohol consumption is associated with a reduction in mortality from all causes, and this effect is more evident when daily wine consumption is made, as published in their study by Grønbæk et al. (2000) in Denmark. In another study by Truelsen, T. et al. (1998) in the famous "Copenhagen study" conducted among a population of 13,329 eligible men and women, aged 45 to 84 years and for 16 years of follow-up, observed differences in the effects of beer, wine and spirits on the risk of stroke. The different polyphenolic compounds contained in wine in combination with each other and with ethanol are responsible for the protective effect on stroke risk.

According to Grønbæk et al., (2000) in their study examining the relationship between the intake of various types of alcohol and death from all causes, coronary heart disease and cancer, which involved 13,064 men and 11,459 women aged 20 to 98 years, concluded that "Wine intake may have a beneficial effect on the all-cause mortality index that is additional to that of alcohol. This effect can be attributed to the reduction in deaths from both coronary heart disease and cancer." Notably, those who drank heavily but did not drink wine were at greater risk than those who included wine in their alcohol intake. Wine drinkers also had significantly lower mortality from both coronary heart disease and cancer than non-wine drinkers.

Renaud et al. (2004) in their study of 35,000 middle-aged men in France concluded that only moderate wine intake was associated with a protective effect on all-cause mortality. The reason was that in addition to the positive effect of wine consumption against cardiovascular diseases, a very moderate intake of wine also protects against cancer and other causes, as

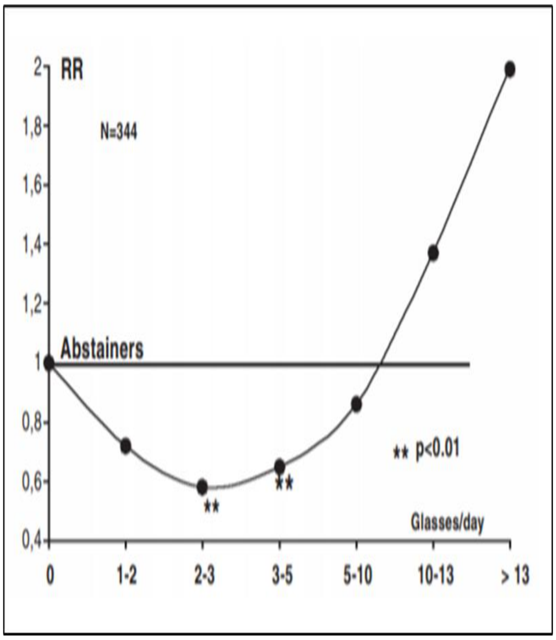


Figure 2. Deaths from all causes in relation to wine consumption – J-shaped curve Grønbæk et al., (2000)

confirmed by Grønbæk et al. (2000) in Denmark. In 2019 a study by Chiva-Blanch, G. and Badimon, L. also shows that the relationship between alcohol consumption and health burden appears with two aspects, i.e. it is protective when consumed in low and moderate amounts and harmful in high amounts, even and when consumed occasionally (Chiva-Blanch, G. and Badimon, L., 2019).

The research of Jani, B. et al. (2021) on the association between alcohol consumption patterns (drink type, frequency and consumption with food) and the risk of adverse health outcomes concluded that: Consumption of red wine with food and the spread of alcohol intake over a 3-4 days were associated with a lower risk of mortality and vascular events among regular drinkers. (Jani, B. et al., 2021) The results of the studies are now expressed with the famous J-shaped curve mentioned above in the text.

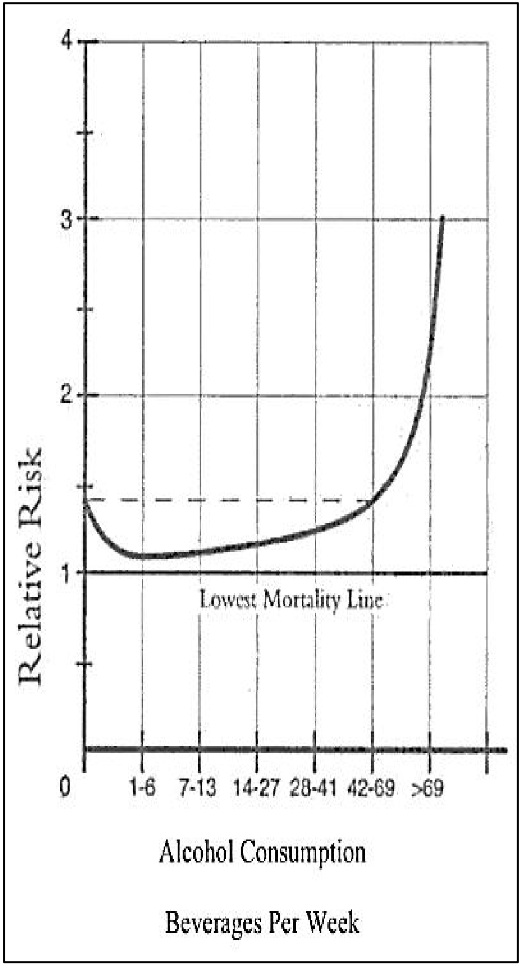


Figure 3. Alcohol and all-cause mortality. The horizontal line is the mortality of abstainers, with the X-axis depicting wine glasses/week. It is obvious that the increased mortality also applies to abstinence, but it increases greatly with excessive consumption. Source: Renaud, S. et al. (2004)

Figure 3 is from the study by Renaud et al. (2004), and represents the curve in question (surge curve). Roerecke and Rehm (2010) conclude: "For drinkers who have one to two drinks per day without episodic heavy drinking, there is substantial and consistent evidence from epidemiologic and short-term experimental studies for a beneficial association against the risk of ischemic heart disease (IHD)) compared to those who abstain completely for life'. In a recent study published by Ma H, all (2021) investigating the frequency and amount of alcohol consumption along with food consumption in relation to mortality based on a very large sample of 316,627 data drinkers (excludes those who do not drink at all) and with a median 8-year follow-up, reinforces the view that eating food with alcohol is the best combination for health. The authors classified the participants into categories according to the habit (Drinking Habit Scores, DHS), so people who reported drinking frequency three or more days/week and consumed alcohol with meals were in the "most favorable" category (Ma et al., 2021).

Why red wine? Red is known to be ten times higher in polyphenols than white, and this difference results, as mentioned in a previous chapter, from the different vinification method. This is also the reason why white wine has a much smaller share of published articles in the literature. There are few studies that directly compare the effects of the two types of wine. Convincing evidence for a proper comparison between them is therefore insufficient.

Bertelli (2006) argues that the relatively unknown compounds detected in white wines, such as tyrosol, caffeic acid and shikimic acids, could explain the biological basis of the cardioprotective effect of white wine as well. Through the bibliographic study, some points are raised that need further research in relation to wine:

(1) the need for analytical characterization of red wine components, as the content of important components, such as resveratrol, is significantly affected by local factors, such as climate and local oenological practices•

(2) the bioavailability of red wine components, which appears to be sufficient, as a wide range of biological effects have been documented even at their low concentrations, which can be induced even with moderate chronic wine consumption•

(3) how important is the color of the wine, as well as the consumption of white wine has been reported to offer a beneficial effect, for example on the respiratory system, thanks to its content of antioxidants: caffeic acid, tyrosol and hydroxytyrosol, but it has not studied enough.

(4) the World Health Organization's recommendation to "investigate the potential protective effects of ingredients other than alcohol in alcoholic beverages."

Antimicrobial and Antioxidant properties of wine

Anti-inflammatory and anti-aging substances have the ability to sometimes delay and reverse the body's damage due to aging or disease, improving the body's long-term health.

Molecular aspects of aging Telomere shortening is one of the hallmarks of molecular aging. Known as the biological clock, telomeres are nucleotide repeat regions (TTAGGG) located at the end of chromosomes. Telomere shortening will cause other health complications, including cardiovascular and neurological diseases (Puspitasari Y., Schwarz L. and Camici G., 2021). The shortening of telomeres is inhibited by an enzyme called telomerase. Telomerase joins telomeric DNA at the ends of telomeres, increasing their length and counteracting shrinkage caused by cellular replication (Gavia-García, G. et al., 2021).

Reactive oxygen species, oxidative stress and antioxidants The theory of free radicals (reactive oxygen species - ROS) was proposed in 1956 by Dr. D. Harman. According to this theory, ROS are produced during metabolic processes, released from mitochondria, and accumulate with age, thereby causing oxidative damage to cellular lipids, proteins, and DNA. Free radicals are necessary for a number of metabolic processes (e.g. signaling pathways, lipid metabolism, cellular respiration, phagocytosis, fighting infections and enhancing the antibacterial and antifungal functions of the immune system, etc.) (Harman, 1956).

The term "oxidative stress" is used to describe the state of oxidative damage that occurs when the critical balance between free radical production and antioxidant defenses is disrupted. It is a disturbance between the production of oxygen free radicals and the ability of cells to inactivate them when they are in excess, with the help of antioxidants. Oxidative stress is considered a key factor in the development of many diseases and manifests itself faster due to poor nutrition, smoking and in general the modern lifestyle, posing a health risk. It is associated with damage to a wide range of molecules, such as lipids, proteins and nucleic acids and prevents cell regeneration.

But what are antioxidants? According to Aziz et all (2019) there are several ways of categorizing antioxidants:

1. On the basis of what they are produced, they are distinguished between those produced endogenously by cells (e.g. albumin, bilirubin, uric acid) and those that are ingested with food (e.g. carotenoids, vitamins, polyphenols and others).

2. Based on their activity, they can be classified as enzymatic and non-enzymatic antioxidants. For example vitamin C, vitamin E, plant polyphenols, carotenoids and glutathione are non-enzymatic antioxidants, and they work by interrupting the chain reactions of free radicals.

3. Based on solubility, antioxidants can be classified as water soluble or fat soluble antioxidants e.g. ascorbic acid - vitamin C is water soluble while tocopherol - vitamin E is fat soluble.

4. According to size, antioxidants can be categorized as small or large molecule antioxidants. The main small antioxidant molecules are vitamin C, vitamin E, carotenoids and glutathione (GSH). Large molecule antioxidants include enzymes (SOD, CAT and GPx) and proteins (albumin) that absorb free radicals and prevent them from attacking other proteins.

5. Based on their origin they are categorized as natural or synthetic (Aziz et al., 2019).

Many of the natural antioxidants of particular interest are phenols and polyphenols as well as carotenoids and vitamins. The action of these antioxidants and their mechanism of action is dictated by the structural characteristics of the molecules involved, the system in which they exist as well as the current conditions (Healthia, 2021). Their presence in food and beverages reduces the risk of cardiovascular disease, certain cancers and diabetes (Teissedre et al., 2018 and Klatsky, 2009).

Antimicrobial action of wine Alcohol is not particularly antimicrobial in the concentrations found in wine (alcohol's disinfectant capacity is for concentrations above 70%). Thus, the antibiotic activity of wine is probably more related to the phenols and acids it contains and the higher the alcohol content, the greater its antibiotic activity (Friedman, M., Henika, P. and Levin, C. , 2015 and Vaz et al., 2012). The pH of wine ranges from 2.8 to 4.0, with the low pH preventing the growth of microorganisms and enhancing the antiseptic action of the sulfur compounds in the wine (Ribereau-Gayon et al., 2000). The low pH and the presence of various organic acids seem to accentuate the antimicrobial activity of both wine phenolics and ethanol. (Vaz et al., 2012).

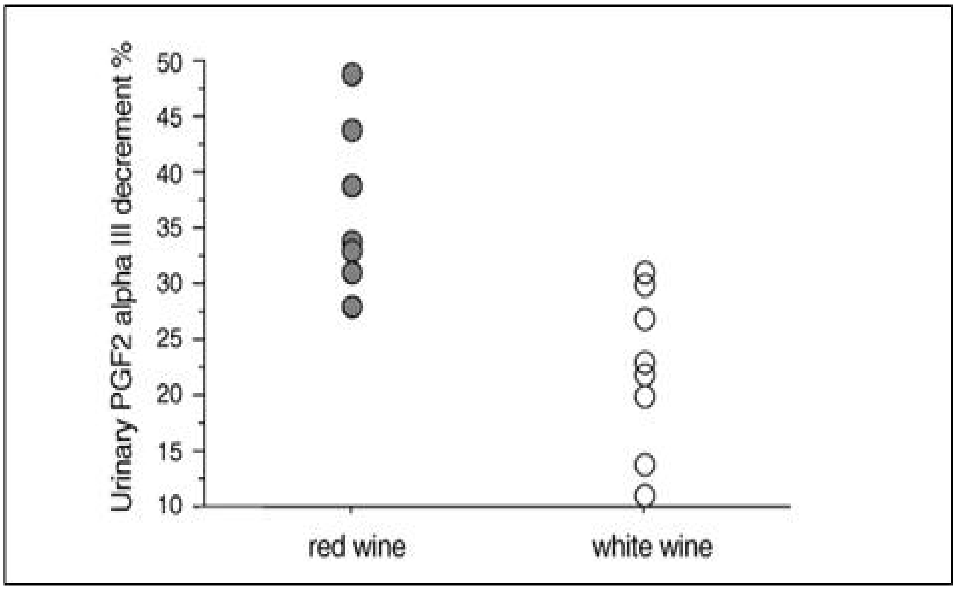
Anthocyanins, which are mildly toxic to viruses, protozoa and bacteria, become even more toxic to them after fermentation. Some phenolic compounds in wine are bacteriostatic and fungicidal (Rodríguez Vaquero, M., Alberto, M. and Manca de Nadra, M., 2007)).

According to Lee et al., (2006) as cited in Jackson, R. (2020) polyphenols can also inhibit enteric pathogens such as Clostridium difficile, C. Perfringens and other bacterioids. Jackson, R. (2020) in his literature review also states that although wine is more effective than other weak antimicrobial agents such as bismuth salicylate, it is slow to act according to the study by Weisse et al. (1995), and its full action can occur after several hours as reported by Møretrø and Daeschel, (2004) and Dolara et al. (2005)(Jackson, R., 2020).

Red wine can suppress the formation of biofilms by pathogens in the oral cavity (Munoz-Gonzalez et al., 2014). The effect of wine consumption against the latter two groups of viruses is reflected in the reduced incidence of the common cold in moderate drinkers (Cohen et al., 1993), especially in red wine drinkers (Takkouche et al., 2002).

Antioxidant activity of red wine

In a survey by Qureshi et al. (2014) in a group of women aged 50 to 69 years, regarding food and beverage consumption habits, and their contribution to antioxidant intake, women with higher antioxidant intake (significant factors were coffee, tea, red wine, blueberries , walnuts,



oranges, cinnamon and broccoli) were at lower risk for cardiovascular disease, heart arrhythmia, hypertension and diabetes. In the same study it was observed that women with regular moderate consumption of red wine were found to have the lowest risk (Qureshi et al, 2014). The antioxidant potential of wine is determined by its ability to react with free radicals or interfere with their production (Tsang et al, 2005). In a study by Pignatelli et al (2006), the antioxidant activity of red and white wine was investigated in healthy volunteers by measuring the content of prostaglandin-F2-III (PGF2α-III), an indicator of isoprostate production, in urine after 15 days of consumption. 300 ml/day of red or white wine of the same alcoholic strength (12.5%, v/v). The concentrations of polyphenols and ethanol in the blood plasma were also measured. A greater decrease in PGF2α-III was seen in those given red wine compared to those who consumed white, which was attributed to red wine's higher polyphenol content. The researchers report: “The percent decrease in PGF2α-III was significantly higher in subjects who consumed red wine compared to those who consumed white. Analysis of plasma polyphenols showed the presence of three polyphenols, resveratrol, caffeic acid and catechin. We were unable to find any detectable amount of quercetin or other polyphenols in the blood” findings are illustrated in Figure 4.

Figure 4. Reduction rates of PGFa-III production in healthy volunteers after consumption of red and white wine.

Wine and the heart: is wine more cardioprotective than ethanol? Studies over twenty years have shown that daily alcohol consumption significantly reduces the incidence of other cardiovascular diseases, such as hypertension (Hines et al. 2001), heart attack, stroke, and peripheral artery disease (Berger et al., 1999) Alcohol consumption is also associated with a reduction in the likelihood of intermittent claudication, which is a common marker of peripheral artery disease (Mukamal et al., 2006). The clearest benefit of moderate alcohol consumption, especially of wine, is associated with a reduction in the mortality rate of almost

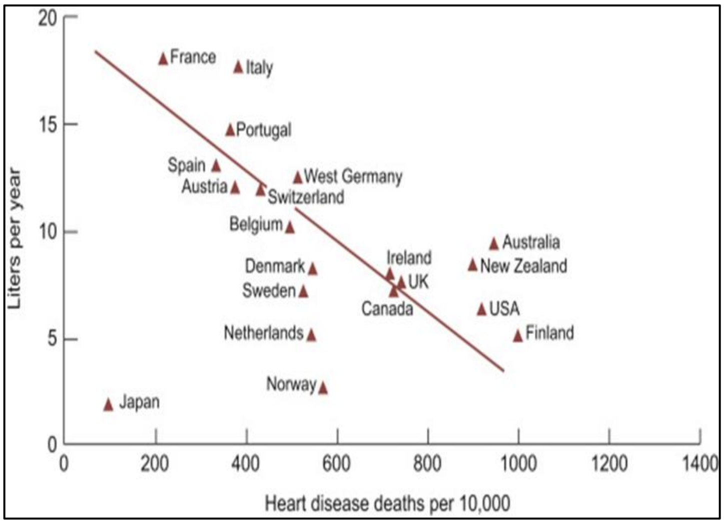


Figure 5. Relationship of per capita alcohol consumption to heart disease mortality rates, men aged 55-64 in 20 countries source: Jackson (2020)

30% - 35% due to cardiovascular diseases Low consumption of red wine has been shown to reduce the blood pressure of hypertensive patients (Cavallini, G. et al ., 2015). result as reported in their study by Haseeb, Alexander and Baranchuk. In his article, Jackson (2020) presents a diagram from research by La Porte, Cresanta, and Kuller, on the relationship between alcohol consumption and death from atherosclerotic heart disease (Jackson, 2020).

Atherosclerosis Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis. Although associated with several independent factors, most lesions are associated with the lipid-oxidized subset of cholesterol complexes (LDLs). However, the complete definition of the cellular and molecular interactions involved has been hindered by the etiological complexity of the disease. (Lusis, 2000).

Wine polyphenols contribute to the prevention of atherosclerotic plaque because they have the ability to regulate the production of NO in the vascular endothelium. Maintenance of endothelial health is considered a prerequisite against atherosclerosis. The researchers concluded that red wine significantly enhanced the expression of endothelial NO synthesis and therefore the release of NO from endothelial cells. In a study by Anselm et al. (2007) observed that platelet NO production increased after daily intake of red grape juice (7 mL/kg body weight) in healthy humans for 14 days. (Anselm E, et al., 2007).

Another study highlighted the positive effect of wine against blood pressure, concluding that moderate wine consumption, if associated with a healthy dietary pattern, such as the Mediterranean, could help hypertensive patients improve their blood pressure and quality of life , reducing cardiovascular morbidity and mortality rates (Carollo et al, 2007).

In a clinical trial by Hansen et al. (2005) found that moderate consumption of red wine for 4 weeks was associated with desirable changes in HDL and other factors compared to drinking water with or without red grape extract. This study contrasts with others that have highlighted the synergistic action of polyphenols with wine alcohol and have been highlighted above. One such survey by Al-Awwadi et al. (2004) showed that red wine polyphenolic extract, with or without ethanol, reduced blood pressure in insulin-resistant rats, an effect associated with a reduction in ROS production. Another mechanism for the antihypertensive effect of wine polyphenols is the downregulation of renal Na+ channel expression, which causes decreased sodium reabsorption and thus affects blood pressure (Awwadi et al., 2004). Figure 6-2 shows the antiatherogenic effects of wine polyphenols. Drinking red wine inhibits:

1. the oxidation of LDL

2. the formation of macrophage-foam cells and

3. atherosclerotic lesions of the aorta (Aviram, M. and Fuhrman, B., 2002).

There are various opinions regarding the effect of moderate wine consumption on platelet aggregation in humans. In healthy volunteers who consumed 300 mL of wine daily for two weeks, Pignatelli et al. (2002) found lower collagen-induced platelet aggregation in red but not white wine drinkers (Pignatelli et al., 2002). However, other studies have found no differences between drinking red or white wine and platelet aggregation (Kikura, et al.. 2004). According to Artero et al (2015) polyphenols in wine have been shown to regulate platelet aggregation and animal studies support this view (Artero et al, 2015). Quercetin in particular has been shown to inhibit platelet activation through the activation of their antagonistic mechanisms through opposing prostaglandins. (Gresele, P. et al. , 2011)

Red wine consumption reduced total cholesterol and LDL in patients after myocardial infarction as shown by a study by Rifler et al. (2011). The results show a positive effect of low wine consumption on blood parameters (reduction of total cholesterol and LDL, increase of erythrocyte membrane fluidity and its antioxidant status). They demonstrate that moderate consumption of red wine even for a short period of time when accompanied by a diet inspired by the Mediterranean diet, improves the lipid and antioxidant profile of the blood in patients with previous coronary ischemic events. (Rifler et al, 2012).

In a recent study by Domínguez-López et al. (2021) in postmenopausal women who are at higher risk of developing cardiovascular disease due to, among other things, changes in their lipid profile and body fat. A strong correlation was observed between wine consumption and urinary tartaric acid. Total cholesterol and LDL were inversely related to the amount of urinary tartaric acid. Wine intake has beneficial effects on the cardiovascular health of postmenopausal women, as the tartaric acid biomarker decreases (Domínguez-López et al., 2021). A recent 2021 study by Fragopoulou, E., et al., provided evidence for the possible inclusion of light to moderate wine consumption in the diet of patients with heart disease (Fragopoulou, et al., 2021).

Also in a new research by Salazar, H. et al. (2022) dietary flavonoids, stilbenes, the main sources of which are red wine and extra virgin olive oil, are associated with a lower prevalence of atherosclerosis in middle-aged adults (Salazar, H. et al., 2022).

Diabetes Mellitus, Metabolic syndrome and obesity As Jackson (2020) reports, wine consumption has been shown to reduce insulin resistance in type 2 diabetes, which is attributed to the action of wine polyphenols that neutralize oxygen free radicals. Type 2 diabetes occurs when the body's cells do not respond properly to the presence of insulin. When the β-cells of the pancreas, from which insulin is produced, begin to malfunction and fail, then the glucose level rises above the normal limit and type 2 diabetes occurs. Metabolic syndrome is a cluster of medical conditions, including obesity and insulin resistance, that increase the risk of developing type 2 diabetes and cardiovascular disease (Pfizer 2022), which has become a global epidemic. The incidence of metabolic syndrome is also lower in wine drinkers and may be due to the effect of alcohol on metabolism, the effect on endothelial NO synthesis, hypoglycemic and hypolipidemic effects of phenolics such as resveratrol, but also the antidiabetic properties of Vanadium which found in wine. (Rosell et al., 2003 and Su et al., 2006 and Leighton et al., 2006 and Brichard and Henquin, 1999, as cited in Jackson, 2020). The contribution of wine consumption to the daily dietary intake of vanadium of the French population was estimated at 11 μg/day per person. (Teissèdret et al., 1998)

Lida et al. (2012) as reported by Jackson (2020) conclude that only the predominant anthocyanin malvidin has a significant hypoglycemic effect, while finding that moderate consumption of dry wine did not have adverse effects on glucose control in type 1 diabetes mellitus. Although wine contains residual sugars, the most common, fructose, are poorly transported throughout the gastrointestinal tract. Most of the sugars are quickly removed from the blood by the liver, where they are metabolized to glycerol and often stored as fat. They do not stimulate the release of pancreatic insulin. Red wine also appears to slow the progression of kidney damage, which in several cases is associated with diabetes (Zhu et al., 2017).

The same conclusions were reached in a study by Tresserra-Rimbau, A. et al. (2015) with 5801 elderly participants at high cardiovascular risk which showed that moderate red wine consumption is associated with a lower prevalence of metabolic syndrome in an elderly Mediterranean population at high cardiovascular risk (Tresserra-Rimbau, A. et al., 2015).

Le Roy et al. (2020) report an association between red wine polyphenols and gut microbiota diversity, with a weak association with white wine and no association with beer, cider, spirits, or all alcoholic beverage. The authors find a unique interaction between red wine polyphenols and gut microbiota regulation. It is noted that even the consumption of red wine every fifteen days was enough to observe some effect (Le Roy et al., 2020). A new 2022 study, presented at the American Heart Association's Epidemiology, Prevention, Lifestyle & Cardiometabolic Health Conference, analyzed data from nearly 312,400 adults who did not have type 2 diabetes, cardiovascular disease or cancer when they started the study. The researchers found that drinking alcohol with meals – particularly wine – was associated with a 14% reduced risk of type 2 diabetes compared to drinking alcohol without food. Study author Dr Hao Ma, MD, a biostatistician at the Tulane University Obesity Research Center in New Orleans, says: "the results suggest that if someone is consuming alcohol with a meal, wine may be a better choice" (Hao Ma et al, 2022).

Neurodegenerative diseases and red wine There are many studies showing that moderate consumption of red wine also provides protection against neurodegenerative diseases. This property is due to the presence of phenolic compounds that have an antioxidant effect, as oxidative stress is involved in many forms of cellular and molecular damage.

A potential method of delaying and/or preventing the onset of AD is to act on modifiable (non-genetic) risk factors, including diet. Excessive wine consumption is associated with brain damage, increases the risk of dementia with direct neurotoxic effects. However, light to moderate wine consumption appears to reduce the risk of dementia and cognitive decline and is age-dependent. Through a literature search it is concluded that wine consumption can serve as a protective factor for cognitive decline and has related the healthy properties of wine to its polyphenolic content and antioxidant properties. Conversely, excessive wine consumption is associated with factors that in turn promote the onset of dementia, such as hypertension and diabetes. Thus, the protection, attenuation or intensification of AD and other similar diseases may be based on the amount and frequency of wine consumption, individual characteristics and individual lifestyle (Reale et al. 2020).

One of the first major studies that highlighted the beneficial effect of moderate alcohol consumption against neurodegeneration was the "Nurses' Health Study", which began in 1976 in the USA. Lead researchers were from the Channing Laboratory at Brigham and Women's Hospital, Harvard Medical School and the Harvard T.H. Chan School of Public Health and involved 121,700 registered nurses, ages 30 to 55, who completed a mailed questionnaire about their lifestyle and health. Between 1995 and 2001, and every two years, they followed their health and assessed cognitive function in 12,480 participants, ages 70 to 81, with follow-up assessments in 11,102 of them two years later. In this study, with the evaluation of Stampfer et al. (2005), observed that women who drank 1.0 to 14.9 g of alcohol per day had a 20% lower risk of cognitive impairment compared to non-drinkers over two years. These results were found for all types of alcoholic beverages, supporting the view that alcohol is responsible for this effect (Stampfer, et al. 2005).

As stated in their publication by Moreno-Arribas et al. (2020) the first research (wine only) done and the first results suggesting a protective effect of moderate red wine consumption in NA was published in the late 90s by Orgogozo, et al. (1997) with data from a cohort of elderly participants in the Bordeaux region (Orgogozo, et al. , 1997 and Moreno-Arribas et al., 2020).

In another study in the Netherlands by Nooyens, et al. (2014), however, also found that only red wine consumption, and not any other type of alcoholic beverage, was inversely associated with the development of cognitive decline in a middle-aged population. In this study, 2613 men and women of the Doetinchem area, aged 43-70 years (1995-2002), were examined for cognitive function (global cognitive function and the memory, speed and flexibility domains) and assessed twice, over a period of 5 years old. It was observed that, in women, total alcohol consumption was inversely associated with decline in overall cognitive function over a 5-year period, while no association was observed in men. No other type of alcoholic beverage was associated with a favorable effect on cognitive decline. In conclusion, only (moderate) red wine consumption was consistently associated with less severe cognitive decline. Therefore, as the researchers report, it is very likely that the non-alcoholic substances in red wine are responsible for any effects on maintaining cognitive function (Nooyens, 2014).

Later, other studies reported similar results and confirmed that the favorable effect is observed mainly from red wine. Unlike other alcoholic beverages, such as spirits, for which increased risks have been reported, the protective associations reported for wine may be explained by components other than ethanol. Wine is considered a dietary source of phytochemicals and, in particular, red wine is rich in a wide variety of polyphenolic compounds with potential neuroprotective actions. Flavonoids not only activate key respiratory enzymes in mitochondria (Schmitt-Schillig et al., 2005), but also reduce and the production of active oxygen species, stimulating the production of appropriate enzymes that act against inflammation (Martin, 2011). The research of Martín, S. et al. (2011) this time in vitro, in human astrocytes, investigated the neuroprotective effect of Merlot red wine and its isolated polyphenols and evaluated their action in human astroglial cells (oxidative stress was induced with the Fenton reaction). The result was that pre-incubation with Merlot red wine for 24 hours caused a significant increase in cell viability. The most abundant polyphenols found in Merlot red wine were the flavonoids catechin (37.8 mg/l), epicatechin (52.3 mg/l), quercetin (5.89 mg/l) and procyanidins (15.2 mg/l). l), the hydroxybenzoic acid gallic acid (16.7 mg/l), and the phenolic alcohol tyrosol (31.4 mg/l). The potential protective role of these polyphenols when isolated was then evaluated in treated Fenton reaction U373 MG cells. Polyphenols reduced the generation of reactive oxygen species and increased the activity and protein expression of various antioxidant enzymes. Of the polyphenols, quercetin and procyanidins showed the highest neuroprotective effect. According to the researchers, the study showed that Merlot red wine can exert a beneficial effect in the prevention or treatment of neurodegenerative diseases related to oxidative stress, such as Alzheimer's disease or Parkinson's disease. They consider that the results support that wine has antioxidant properties, attributed mainly to the polyphenols present in high amounts, and provide hope for the treatment and prevention of neurodegenerative diseases related to oxidative stress (Martín, 2011). In an article by Moreno-Arribas et al. (2020) review the research of recent years on the relationship of diet and wine in particular, and the human microbiome in relation to the onset of AD. The authors report that various microorganisms - bacteria are involved in the pathogenesis of the disease.

Neuroprotective effects of wine polyphenols. In general, the molecular mechanisms of the neuroprotective actions of red wine can be classified as: (i) Anti-inflammatory activities and antioxidant capacity, including free radical and metal scavenging (ii) Modulation of cell signaling pathways, and (iii) They antagonize the formation of toxic amyloid aggregates through direct binding to specific proteins (Caruana, M., Cauchi, R. and Vassallo, N., 2016) According to Wang, J. et al. (2014) the mode of action of wine polyphenols exhibits a remarkable ability to simultaneously and synergistically regulate multiple molecular targets, suggesting a greater potential for therapeutic efficacy in the complex pathogenesis of AD and NP, Through the last decades of research it has become increasingly accepted the notion that compounds contained in red wine exert neuroprotective and neurorescue effects not only through antioxidant actions but also through a combined ability to antagonize amyloid accumulation, suppress neuroinflammation, modulate signaling pathways, and reduce mitochondrial dysfunction. (Wang et al., 2014). However, as scholars Caruana, M., Cauchi, R. and Vassallo, N., (2016) point out, findings from in vitro studies must be properly extrapolated to the in vivo situation, as many of the existing in vitro data have used abnormal concentrations of polyphenols with the parent molecule (aglycone) instead of the in vivo metabolites produced during digestion and/or metabolic processing. At the same time, to effectively translate experimental knowledge into clinical therapeutic benefit, it is necessary to better study metabolism, absorption profiles, and factors influencing bioavailability (Mancuso et al., 2012).

Pulmonary function and wine consumption Several studies have investigated the association between alcohol intake and lung function. A study by Stanton Siu et al (2010) found that light to moderate drinkers had a better pulmonary function index than abstainers (Stanton Siu, 2010). Benefits of moderate alcohol consumption include anti-inflammatory effects (Pratt and Vollmer, 1984), improved mucosal clearance, and immediate bronchodilation. Alcohol itself is a moderate bronchodilator and probably relaxes bronchial smooth muscle. The way, duration and concentration of alcohol intake are variables that alter this property. Alcohol has been accused of triggering asthma attacks but at the same time it is also considered a therapeutic agent/reliever of its symptoms (Sisson, 2007). Sulfites in wine are generally considered to be irritating to sensitive people (which is why they must be listed on the wine label for allergy sufferers), although the role of sulfites and/or wine in causing asthma may have overestimated as its other compounds may adversely affect asthmatic subjects (Vally and Thomson, 2001).

White wine supremacy An interesting study by Scheunemann et al. (2002) highlighted the positive antioxidant effect of wine, and in fact with slightly more benefits from white than red wine, over other alcoholic beverages in the positive effect on pulmonary function indicators. The research by Siedlinski, M. et al reached the same conclusions about the favorable effect of white wine on lung function. (2011) who also studied the beneficial effect of resveratrol as a supplement on respiratory function. The researchers showed the positive assocn association of white wine consumption and higher FEV1 levels in the general population, which is more pronounced in smokers. Because of this observation they conclude that "white wine may be effective in detoxifying molecules derived from cigarette smoke that increase the oxidative or inflammatory load in the lungs and, hence, the positive associations of white wine intake with lung function are more readily apparent in smokers compared to people who have never smoked." Consequently, white wine consumption is associated with a lower risk of moderate airway obstruction. And resveratrol intake is associated with higher FVC in the general population, which they say needs further study (Siedlinski, M. et al., 2011). Vasquez et al. (2018) in a study that analyzed data from 1333 adults over a period of 20 years and examined their lung function concluded that "..light to moderate alcohol consumption was associated with a significantly reduced rate of decline in FVC during adulthood..." (Vasquez et al. , 2018). In a very recent study, Wang, D. et al. (2022) examined the relationship between mixed alcohol consumption and lung function in an adult population of 16,268 participants from three cities in China. Ethanol content (by weight) varied between beverages and was assumed to be 4% for beer, 10% for red wine, 18% for Chinese rice wine, and 45% for high spirits. Alcohol consumption was calculated by average alcohol intake per day (g/day). Drinkers were divided into moderate drinkers or heavy drinkers according to China's Dietary Guidelines, which recommend that alcohol consumption should not exceed 25 g/day for men and 15 g/day for women. Furthermore, when alcohol consumption on any drinking day exceeded 60 grams, they were also considered to be in the heavy drinker category (Wang, D. et al., 2022). The results of their study are presented in Table 3 below.

Table 3 Correlation of average daily amount of alcohol consumption and type of drink with lung function in the total population (n =16268) https://pubmed.ncbi.nlm.nih.gov/35080021/

Variable	*n*	FEV_1/FVC estimated changes (95% CI)	FEV_1 estimated changes (95% CI)	FVC estimated changes (95% CI)
Drinking				
No	12,860	ref	ref	ref
Moderate	2147	0.51 (−0.09, 1.11)	**70.03 (46.72, 93.35)**	**74.92 (47.47, 102.38)**
Heavy	1261	0.39 (−0.39, 1.17)	8.23 (−22.10, 38.55)	−5.64 (−41.35, 30.07)
Drinking type				
No	12,860	ref	ref	ref
Liquor	1495	0.02 (−0.75, 0.71)	26.22 (−2.25, 54.69)	28.30 (−5.23, 61.83)
Beer	153	0.27 (−1.73, 2.27)	15.37 (−62.26, 93.01)	5.79 (−85.64, 97.23)
Red wine	319	0.94 (−0.43, 2.32)	**105.31 (51.89, 158.73)**	**98.91 (35.99, 161.82)**
Rice wine	242	1.68 (−0.09, 3.26)	7.77 (−53.66, 69.21)	−32.22 (−104.57, 40.14)
Mixed	1199	0.61 (−0.16, 1.38)	**70.63 (40.65, 100.61)**	**76.96 (41.66, 112.27)**

NOTE: Adjusted for sex, age, BMI, smoking status, pack-years, passive smoking status, physical activity, occupational hazard exposure, self-reported CVD, and hypertension. Values in bold have a $P < 0.05$.

Findings showed a significant association between moderate alcohol intake and increased FEV1 and FVC among red wine and spirits drinkers. An improvement in prices was also observed in the mixed type of consumption. The researchers conclude that "moderate alcohol intake may be a protective factor for lung function, especially when red wine is consumed" (Wang, D. et al., 2022). Researchers from the University of Illinois, Chicago (2003) report in their article that "red wine destroys the bacteria that cause lung infections, and heart disease". The bacterium Chlamydia pneumoniae is an intracellular gram-negative pathogen responsible for 5-30% of acute respiratory tract infections worldwide. However, while the infection starts in the respiratory tract, the bacterium spreads systemically into the bloodstream and can lead to the development of a chronic infection. The bacteria can spread from the lungs into the bloodstream, possibly leading to a build-up of plaque in the arteries and thereby contributing to heart disease. In this in vitro study, the researchers report, Pinot Noir extracts and resveratrol destroyed the bacteria, and they believe that drinking wine may help prevent not only lung infections, but also heart disease by eliminating C. pneumoniae from blood circulation (Schriever, C., Pendland, S. and Mahady, G., 2003).

Research for other conditions Red wine and cancer As mentioned in chapter 4, alcohol intake increases the risk of developing cancer. In an article by Chen, S. et al. (2019) reported that 3.6% of human cancers worldwide originate from chronic alcohol consumption, including oral, liver, breast and other organ cancers. They examined the role of red wine in human cancer cell growth, colony formation and RNA Pol III gene transcription. They concluded that consumption of red wine, especially aged wine, dramatically reduced the growth rates of human cancer cells and colony formation, while diluted ethanol at the same concentration enhanced cell growth. Red wines also induce cancer cell death and inhibit Pol III gene transcription. These results suggest that red wine may contain some bioactive components with the potential to suppress cancer growth. Thus, identifying bioactive components in red wine and enhancing their yield ratio during production processes could improve its quality, and benefit red wine drinkers (Chen, S. et al., 2019). One of the study's authors Glenn D. Braunstein, MD, said that: "the results do not mean that white wine increases the risk of breast cancer, but that the grapes used in these varieties may not have the same protective items in red".

Vision Fraser-Bell et al. (2006) after their research on the effect of wine consumption on vision, in a survey of 5875 participants, when they examined, among other factors, the effect of alcohol and red wine consumption on macular degeneration, the main cause of blindness in adults over 65 years old. A similar relationship has been found for cataract development. In both cases, the wine's antioxidants are considered the active protective factor. The same researchers observed that heavy alcohol consumption (>5 drinks per session) was significantly associated with greater risk. Beer consumption was associated with a higher risk of developing advanced degeneration, while wine consumption appeared to be protective for retinal health (Fraser-Bell et al., 2006).

Osteoporosis Many risk factors, including dietary influences and hormonal supplementation, can affect its progression and severity. Of these factors, moderate alcohol consumption has been found to favor good bone health (Ilich et al., 2002). Research by Tucker et al. (2009) showed evidence consistent with higher benefits from wine than other alcoholic beverages due to the effect of its phenolics (Tucker et al., 2009). Other studies are needed with clinical trials that measure bone changes so that they can be used to create formulations to prevent and treat osteoporosis.

Resveratrol

Although plants containing resveratrol have been used effectively in traditional medicine for more than 2000 years, resveratrol was first isolated in 1939 by Michio Takaoka from the root of the medicinal plant Veratrum album (White hellebore) (Takaoka, 1939 as cited by Pezzuto, 2019).

As reported by Dourtoglou, et al (1999), Langcake and Price detected resveratrol in 1976 in grapes and in 1992, Siemann and Creasy discovered its presence in red wine In the same research by Siemann and Creasy (1992) they suggested that there a link between red wine's resveratrol and the potential health benefits of drinking it. In their research they report that wine has been shown to reduce lipid levels in human serum. Resveratrol concentration was measured in selected wines using HPLC and spectrophotometry. (Langcake & Price, 1976, Siemann & Creasy, 1992, as cited in Dourtoglou, et al., 1999).

Resveratrol exhibits a wide range of beneficial properties and this may be due to its molecular structure, which gives it the ability to bind to many biomolecules. Among these properties it is worth highlighting its action as an anti-cancer agent, anti-platelet aggregation agent and antioxidant, as well as its anti-aging, anti-inflammatory, anti-allergic effect. These beneficial biological properties have been studied both in vitro and in vivo. The issue of resveratrol bioavailability is of the utmost importance and is determined by its rapid elimination from the body and the fact that its absorption is extremely efficient. Elucidation of aspects such as stability and pharmacokinetics of resveratrol is fundamental to understanding and applying its therapeutic properties (Gambini et all, 2015). Geographical origin, variety, cultivation methods and winemaking processes all appeared to affect the concentration of resveratrol in wines. Analysis of the wines indicated that resveratrol may be the active ingredient in the wines that caused the reduction in serum lipids. This is proven by a simple search for the term "resveratrol" with limit: clinical trials (clinical trials) in PubMed gives for the years 2002 to 2021, one hundred and ten results for separate researches on the effect of resveratrol in clinical trials (Figure 6)

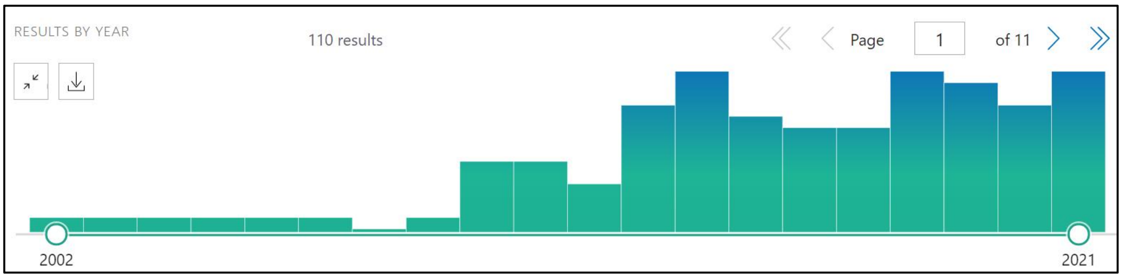


Figure 6. PubMed: A total of 110 trials were reported. resveratrol; limit: clinical trials - Search Results - PubMed (2021).

Resveratrol properties Resveratrol, a phytoalexin, is a non-flavonoid polyphenolic compound, belongs to the class of stilbenes, and is found in the skin of red grapes, in other fruits, such as various types of berries and fruits (e.g. peanuts) and is considered to have beneficial effects on man. It is a fat-soluble compound that appears in both trans-(E) and cis-(Z) isomers, contains two phenolic rings and three hydroxyls

Some plants produce resveratrol and other stilbenoids in response to stress, injury, fungal infection, or ultraviolet (UV) radiation. Stilbenoids are hydroxylated derivatives of stilbene and have a C6-C2-C6 structure. They belong to the family of phenylpropanoids, which is a group of organic compounds synthesized in plants from the amino acids phenylalanine and tyrosine (Salehi et al., 2018).

Of the two stereoisomers of resveratrol, the trans isomer is the more stable and more abundant in nature, and both coexist in varying proportions in wine and other foods. The trans-form undergoes photoisomerization and transforms to the cis- form when exposed to UV radiation as shown in Figure 7 (Dong, et al, 2016).

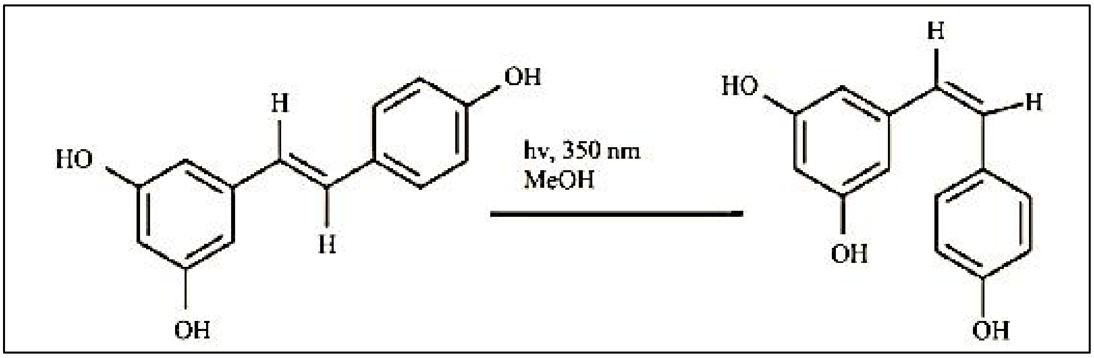


Figure 7. Photoisomerization of trans-resveratrol due to UV radiation. (Dong et al, 2016)

Main sources of resveratrol Resveratrol can be found in a wide variety of natural foods, including peanuts, grapes, various types of berries, cocoa, dark chocolate, and red wine (Higdon, 2014). The highest levels of resveratrol are found in Fallopia Japonica (524 μg/g), which has been used in traditional Asian medicine for inflammatory treatments. In the vine it is the main stilbene and it is found in the skin of its grapes and from there it is also detected in their products, such as grape juice, wine and even vinegar. The dominant form in grapes and grape juice is trans-resveratrol and mainly its β-glucoside, trans-resveratrol-3-O-β-glucoside or trans-piceid. The amount of resveratrol in grape skins (and to a much lesser extent in grape skins and flesh) varies with grape variety, geographic origin, and exposure to fungal infection or severe drought (Frémont, 2000).

The longer the wort remains with the pips and worts, the greater the extraction of phenolic components, among which is resveratrol. White and rosé wines contain less resveratrol than red wines because the skins, unlike red wines, are removed early in the production process. Due to variations between wine types, vintages and regions, it is very difficult to make accurate estimates of resveratrol content in the thousands of wines from wineries worldwide (Siemann and Creasy, 1992).

According to a review article by Stervbo, U., Vang, O., & Bonnesen, C. (2007) who reviewed dozens of studies on resveratrol content in different grape varieties and regions, there is a wide variation in resveratrol levels. between different varieties and regions. This discrepancy can be explained by the fact that resveratrol is produced by the grape in response to exogenous stress factors and depends on local climate fluctuations. For example, a dry year is less favorable to fungi than a wetter year, so less resveratrol will be synthesized from the grape. Another factor in the variation of resveratrol content in red wines is the vinification technique, as double maceration is associated with high levels of resveratrol. Red wine contains trans-Resveratrol on average: 1.9 ± 1.7 mg/l, ranging from undetectable levels to 14.3 mg/l. No region can be said to produce wines with a significantly higher level of trans-resveratrol than the other regions. The levels of cis-Resveratrol follow the same trend as trans-Resveratrol. In the same research it is reported that the average level of its glycoside (trans-piceid) in a red wine can be up to 29.2 mg/l, i.e. three times higher than that of trans-resveratrol (Stervbo, et all., 2007).

In a more detailed search of the "Phenol-Explorer" database by Neveu et all, (2010) for the National Research Institute of France, data from a number of studies were collected to measure resveratrol from various sources. For red wine, 36 studies were studied including two Greek studies (Kallithraka et al., 2001 and Dourtoglou et al., 1999) In this case the average concentration of resveratrol for red wine is 2.7mg/l (0.27 mg/100ml) – and not significantly different from the Stervbo, et al., (2007) study mentioned earlier. The database was posted on the website: http://phenol-explorer.eu/contents/polyphenol/592.

Bioavailability, metabolism and pharmacokinetics of resveratrol When taken orally, resveratrol is well absorbed by humans, but its bioavailability is relatively low because it is rapidly metabolized and eliminated. Resveratrol is absorbed in the human body by the intestinal villi of the small intestine and exhibits lipophilic characteristics, which lead to high absorption (Gambini et al., 2015). The absorption of resveratrol from living tissues is due to the breakdown processes, which occur in the lumen of the intestine and in the liver. After absorption, it is very rapidly metabolized in hepatocytes with a half-life between 8 and 14 minutes (Fabjanowicz, 2018). Studies of the pharmacokinetics of trans-resveratrol in humans found only trace amounts of resveratrol in plasma following oral single doses of trans-resveratrol of 5 to 25 mg (Walle, 2011). Figure 8 summarizes its metabolism in the liver.

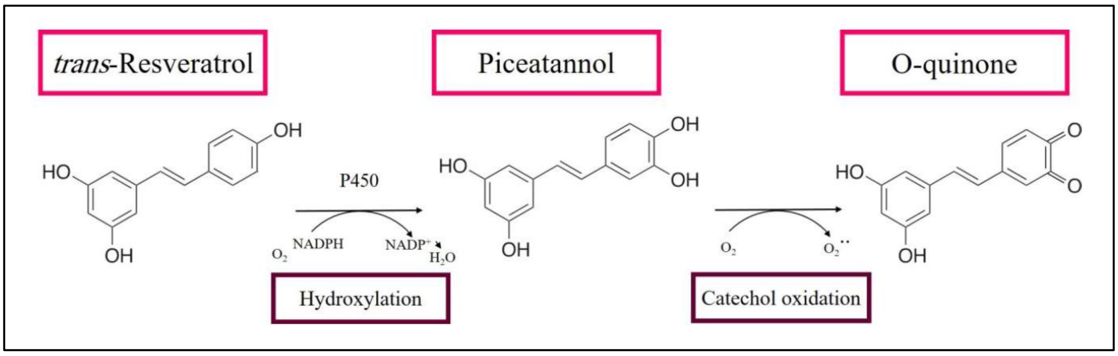


Figure 8. Metabolism of trans-resveratrol in the liver source: Shaito, A. et al. (2020)

In vitro tests showed that resveratrol in hepatocytes is almost completely metabolized under the influence of cytochrome P450 and converted into the form of piceaethanol and tetrahydroxystilbene. The polyphenol piceatannol, a metabolic derivative of resveratrol, was found to inhibit the growth of adipose tissue cells (Vitaglione et al., 2005). In a study by Vitaglione, et all (2005) the bioavailability of trans-resveratrol after moderate consumption of red wine in 25 healthy people was investigated with three different scenarios. Wine consumption was associated with different dietary approaches: without food, with a standardized meal, and with a low- and high-fat meal. The result was that the bioavailability of trans-resveratrol was shown to be independent of the meal or its lipid content. The findings in human serum of trans-resveratrol glucuronides, rather than the free form of the compound, with high inter-individual variability, raises some doubts on the health effects of dietary resveratrol consumption and suggests that the benefits associated with red wine consumption could possibly be due to the overall antioxidant pool present in red wine. (Vitaglione, et al, 2005). In a study by Vaz-da-Silva et al.(2008) in 24 healthy adults with trans-resveratrol supplementation given at a dose of 400mg, its absorption was found to be delayed, but not reduced, by the presence of food in the stomach. The rate of absorption of trans-resveratrol after a single oral dose of 400 mg was significantly delayed by the presence of food. However, the extent of absorption, as inferred from the plasma concentration/time curve, was not similarly affected (Vaz-da-Silva et all , 2008). A third study by la Porte et all found that the bioavailability of resveratrol was reduced in the case of a high-fat diet, but not with co-administration of quercetin or alcohol. From a pharmacokinetic point of view, the results show that despite rapid absorption resveratrol undergoes rapid intestinal and hepatic metabolism and is considered a relatively non-toxic and well-tolerated agent. Doses up to 450 mg/day are reported to be safe for a 60 kg person. Among its few adverse effects are nephrotoxicity and gastrointestinal disturbances (mainly diarrhea) (la Porte et all, 2010).

What does resveratrol do? Its protective effect is thought to occur through sirtuins also known as "longevity genes". This activation of sirtuins is one way resveratrol can delay aging and the onset of age-related diseases.

It also activates the "Autophagy" of cells (Glick, Barth and Macleod, 2010). It is known that reduced calorie intake activates autophagy through the activation of Sirtuin 1 or SIRT 1 protein (Yu, W. et al., 2018). Resveratrol is able to induce autophagy independently of SIRT1 by reducing the activity of the target of rapamycin (mTOR). Thus, this ability of resveratrol to induce autophagy through two different methods means that it may be useful through slowing aging and certain diseases (Morselli et al., 2010).

The potential benefits of consuming resveratrol

Resveratrol and cardiovascular disease According to Gligorijević et al. (2021) resveratrol interacts with approximately 20 molecular targets and affects the function of many molecules associated with cardiovascular disease. In clinical trials with animals, its beneficial effect on cardiovascular health has been demonstrated: resveratrol stimulates endothelial production of nitric oxide, reduces oxidative stress, inhibits vascular inflammation and prevents platelet aggregation, also reduces blood pressure and heart rate hypertrophy in hypertensive animals and slows the progression of atherosclerosis. A number of direct and indirect target molecules mediating the aforementioned cardiovascular effects of resveratrol have been identified (Gligorajevic et al., 2021). A study by Kwon, J. et al.(2012) found that esveratrol has a positive effect on factors that cause cardiovascular problems by protecting against metabolic syndrome and regulating insulin.

A 2012 study by Tomé-Carneiro, J., (2012) involving 75 participants taking statins to prevent cardiovascular disease showed improvement when combined with daily intake of resveratrol-enriched grape extract. After six months, the participants experienced a reduction in several cardiovascular risk factors. LDL cholesterol decreased by 4.5%, oxidized LDL, and apolipoprotein B decreased by 9.8% (Tomé-Carneiro, 2012, Magyar, K. et al., 2012). In the follow-up study, participants received double the initial dose for another six months. Two biomarkers, tumor necrosis factor-α (TNFa) and interleukin-6 (IL-6), decreased while levels of the anti-inflammatory interleukin-10 increased. This fact is positive because chronic inflammation contributes to disease. (Tomé-Carneiro et al., 2012). A recent study by Menezes-Rodrigues, F. et al. (2021) showed that preventive treatment with resveratrol and grape products significantly reduced the incidence of severe ischemic events as well as mortality in an animal model. The researchers suggest further research to better understand mechanisms such as oxidative stress control, intracellular Ca2+ homeostasis and mitochondrial dysfunction and to reduce the knowledge gap between preclinical studies and human trials of resveratrol (Menezes-Rodrigues, F . et al., 2021)

Resveratrol and diabetes Epidemiological data show that the number of people with diabetes is expected to increase dramatically to 592 million by 2035 (Zhang, T. et al. , 2021). In a randomized, placebo-controlled clinical trial by Movahed et al.(2013), 66 participants with type 2 diabetes received either resveratrol 500 mg twice daily or placebo (capsule without medication) for 45 days. At the end of the study, the resveratrol treatment group had significant reductions in blood sugar levels and hemoglobin A1c (a lower value indicates better diabetes control). Positive changes in cholesterol levels and blood pressure were also observed in the same patients (Movahed et al., 2013). Zhu et al. (2017) in a meta-analysis of nine clinical trials involving 283 patients with type 2 diabetes found that in all nine trials resveratrol supplementation improved: 1. Fasting glucose values 2. Systolic and diastolic blood pressure 3. Changes in hemoglobin A1c, LDL and HDL were negligible

Resveratrol and cancer In post-surgical colon cancer patients treated with resveratrol, tumor cell proliferation appears to be reduced (Patel, et al., 2010), while chemoprotective effects have also been found for breast cancer (Zhu, W ., et al., 2012). A study by Agarwal, B., & Baur, J. A. (2011) states that Trans-resveratrol is more active than cis-resveratrol and is believed to have more positive effects against inflammation and cancer cell proliferation (Agarwal, B. , & Baur, J.A. , 2011)

Since 2001, an International Patent has been recognized by the World Intellectual Property Organization for the use of resveratrol as an ingredient in sunscreens as studies have shown that it is a very effective UV filter for use in sunscreens, especially in combination with other antioxidants (Freitas et al. 2015).

A recent study by Bhattacharya, S. and Sherje, A. (2020) highlighted the possibility of using Emulgel with a sunscreen composition with resveratrol/green tea extract to act as a good photoprotective formulation with satisfactory antioxidant activity.

Resveratrol appears to be a promising agent, relevant for both chemoprevention and cancer therapy. As an adjuvant treatment, in particular, resveratrol showed synergistic effects with the chemotherapeutics 5-FLU and CIS, thereby increasing the sensitization of cancer cells. It exhibits abilities to reduce the negative effects of conventional therapies on non-target cells and tissues, reducing risks and enhancing the effectiveness of treatments. (Varoni et al., 2016)

In the article by Patra, et al. (2021) which is a bibliographic study of many earlier researches states that from them it follows that "resveratrol has a strong chemopreventive efficacy due to its antioxidant action. It shows apoptotic, autophagic, anti-angiogenic, anti-inflammatory and anti-metastatic potential in several types of cancer (breast, lung, myeloma, cervical, leukemia, colon, ovarian and stomach). Initiation of apoptosis and autophagy associated with cell death in in vitro and in vivo models treated with resveratrol is cell and tumor type dependent” (Patra et al. 2021).

Resveratrol and metabolic syndrome Some studies have shown that it has a beneficial effect on glucose metabolism and temporarily increases insulin sensitivity in diabetics (Baile, 2011, Fischer-Posovszky, 2010 and Kwon, J. et al., 2012). In obese subjects, it confers a protective and antioxidant effect (De Groote et al., 2012 and Wong, et al. 2011) and reduces resting metabolic rate through a mechanism that mimics caloric restriction (Wong, et al., 2011). Research by Timmer, S. (2011) also demonstrated that 30 days of resveratrol supplementation in obese humans induces metabolic changes that mimic those resulting from calorie restriction (Timmer, 2011). Poulsen, et al. (2013) in a another study of obese men found similar results, but with no significant changes in body mass index or body fat percentage (Poulsen, 2013). Bhatt, (2012), found that administration of resveratrol improved the glycemic index in patients with diabetes, reduced systolic blood pressure but did not reduce body weight (Bhatt, 2012). Other studies differ, Tabrizi et al., (2020) in a systematic review and meta-analysis of randomized controlled trials conducted on the effect of resveratrol intake on weight loss concluded that resveratrol affects body weight, BMI, circumference waist circumference and fat mass and significantly increased muscle tissue but did not affect leptin and adiponectin levels (Tabrizi et al., 2020).

Resveratrol and longevity In research by Pacholec, M., et al. (2010) and Beher, D., et al. (2009) does not appear to directly affect SIRT1 but rather AMPK and NAD+, and this is thought to be the main cause of its effect on lifespan.

Resveratrol and neurodegenerative diseases

Resveratrol appears to slow the build-up in the brain of beta amyloid, a protein that plays a key role in Alzheimer's disease. In the study by Miziak et al. (2021) mentions the potential therapeutic use of resveratrol as a promising, safe and well-tolerated treatment option for Alzheimer's disease patients.

Osteoporosis In a study by Wong et al. (2020) in which resveratrol was given to postmenopausal women for 24 months in a randomized, placebo-controlled trial (75 mg twice daily) found that a low dose of resveratrol improved bone status in the participating women (Wong et al., 2020).

Resveratrol and covid-19 According to Gligorijević, N. et al. (2021) because resveratrol can alleviate numerous factors associated with cardiovascular disease, it has the potential as a functional adjunct to reduce the severity of COVID-19 disease in patients with a poor prognosis due to cardiovascular complications. Resveratrol was shown to moderate the main pathways involved in the pathogenesis of SARS-CoV-2. Regular intake of a resveratrol-rich diet or resveratrol-based supplements may contribute to a healthier cardiovascular system, prevention and control of cardiovascular disease, including cardiovascular disease complications associated with COVID-19. (Gligorijević, N. et al., 2021)

Antimicrobial activity of resveratrol According to Friedman (2013) resveratrol is reported to inhibit the growth of microbial species such as Staphylococcus aureus, Enterococcus faecalis - also known as Group D Streptococcus or Enterococcus - and Pseudomonas aeruginosa as well as several fungi that cause skin infections, and the formation of biofilms of E. coli and P. aeruginosa, as well as of the bacterium Vibrio cholerae. In a study by Mallo, N., Lamas, J. and Leiro, J. (2013) it acts against the protozoan Trichomonas vaginalis (T. Vaginalis), the cause of the sexually transmitted disease of trichomoniasis.

Dermatology and cosmetic use of resveratrol

In an article by Ratz-Łyko, Anna & Arct, Jacek. (2018) states that its popularity in cosmetology and dermatology is mainly linked to its proven ability to penetrate the skin barrier and its anti-aging effect. Formulations with resveratrol have been shown to stimulate the proliferation of fibroblasts and help increase the concentration of collagen III. Resveratrol has an affinity for estrogen protein receptors, helping to stimulate the production of type I and II collagen there. In addition, it has antioxidant properties, so it can protect cells from oxidative damage associated with the effects of free radicals and UV radiation in the skin, reducing the expression of AP-1 and NF-kB factors and slowing the process of photoaging of the skin. In addition, the authors suggest the use of resveratrol as a new therapeutic ingredient in the treatment of acne vulgaris (Ratz-Łyko, Anna & Arct, Jacek., 2018).

Conclusions – perspectives Salehi, B. et al. (2018) in their review article entitled "Resveratrol: A Double-Edged Sword in Health Benefits", published in 2018 summarized the latest scientific data arising from a number of studies on the effect of resveratrol on the human body. In the same research it is reported that at nanomolar dose concentrations, resveratrol acts as a powerful antioxidant, while at micromolar (μM) dose, it interacts as an agonist or antagonist showing cell proliferation/cytoprotective responses or cytostatic/apoptotic effects, respectively. Regarding side effects: taking resveratrol does not cause side effects and only people with certain rare medical conditions, such as non-alcoholic fatty liver disease (NAFLD), may experience side effects (Salehi, 2018).

In addition to its cardioprotective activity, resveratrol also exerts antitumor, antiviral, neuroprotective, anti-inflammatory and antioxidant properties and affects the regulation of many processes, including but not limited to anti-inflammatory, neuroprotective or antiapoptotic effects. An interesting research by Mortreux, M. et al. (2019) concluded that the use of resveratrol has also been shown to preserve bone and muscle mass and suggest its use for long-term space missions such as trips to Mars (Mortreux, M. et al., 2019).

The above properties prompted the scientific community to look for new natural sources and methods of its synthetic preparation. One method that has been developed is to increase its production from the grape by applying chemical agents given that it is a phytoalexin that is produced when the plant receives stimuli. The most common chemical induction methods of their synthetic production routes are based on spraying the grapes with three substances: Sodium Silicate, Aluminum Trichloride, Alliete (clay preparation). The grapes are then picked a day later and separated by HPLC after extraction and measurement of their stilbene content.

In addition to the above method, exposure to solar radiation was also used. It has been established that the sun affects the synthesis of phenolic derivatives in grapes. Although one would expect sun exposure to have a beneficial effect on the production of resveratrol and stilbenes, excessive exposure to sunlight reduces the plant's ability to biosynthesize stilbenoids (Creasy G.L., 2002).

Conclusion

According to the literature research, the moderate consumption of wine - and especially red wine - has a beneficial effect on human health, as long as there are no other factors that prohibit alcohol, such as underlying diseases, pregnancy and young age.

The polyphenols of wine and especially resveratrol have attracted the attention of many researchers and many studies have been published about its effect on the human body. However, most studies are either epidemiological or animal or laboratory research. More human clinical trials are needed to better understand the mechanistic effects of wine components on the human body. The fact that each individual substance alone requires a large amount to work – for example the resveratrol supplements that are administered have a multiple concentration of that present in natural form in wine, reinforces the view that for a better effect on health resveratrol and the rest compounds contained in wine require the synergy of each other to act beneficially. Therefore, the combined effect of red wine polyphenols is superior to that of its individual compounds and it is this effect that gives the benefits to human health. The substances contained in the wine and their joint action, make them complement each other, and produce the desired effect, such as protection from cardiovascular diseases, neurodegenerative diseases and other ailments, giving well-being and a better quality of life while reducing mortality. This is because it contains compounds with antioxidant, anti-inflammatory and lipid-enhancing effects. However, the various studies have shown that the reality is very complex and several issues, in particular the daily intake, bioavailability or in-vivo antioxidant activity, have not yet been resolved and require further research.

Technological development makes it possible to improve the quality of wines, use the by-products of winemaking and develop tools and techniques for their recovery to have a greater added value. The consumer public today is more mature than ever in trying new products for their health and personal care. New products have already been developed by the pharmaceutical industry and cosmetology that follow this trend. The use of wine as well as the recycling of wine by-products is an opportunity to provide valuable materials to pharmaceutical, cosmetic, nutritional products and food industries, contributing to reduced costs and environmental impacts associated with the disposal of these by-products in production areas.

However, although some applications of these agro-industrial by-products have been found to date, their utilization needs additional commitment regarding the development of new extraction, isolation, purification and recovery processes to obtain higher amounts of healthy bioactive phytochemicals. Efforts should also focus on the isolation and structural elucidation of novel grape phenolic compounds, using chromatographic and spectroscopic tools. In this sense, appropriate procedures on the target product and time-saving technologies that will allow a better integration of the obtained results for the sectoral industries, will provide successful achievements for phytochemical recovery and innovative products, which could contribute to reduce the environmental pressure in the wine-growing regions from wine-making by-products and to promote the application of individual bioactive substances for food fortification, and the production of medicines and cosmetics for the benefit of the wine-producing sector.

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