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REVIEW

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Insights into grape-derived health benefits: a comprehensive overview

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Abstract

Grapes, renowned for their diverse phytochemical composition, have long been recognized for their health-promoting properties. This narrative review aims to synthesize the current research on grapes, with a particular emphasis on their role in disease prevention and health enhancement through bioactive compounds.

A comprehensive review of peer-reviewed studies, including *in vitro*, *in vivo*, and clinical investigations, was conducted to elucidate the relationship between grape consumption and health outcomes. The review highlights the positive association of grape intake with a decreased risk of chronic diseases such as cardiovascular disease, type 2 diabetes, and certain cancers. Notable bioactive components like resveratrol are emphasized for their neuroprotective and antioxidative capabilities. Additionally, the review explores emerging research on the impact of grapes on gut microbiota and its implications for metabolic health and immune function.

This updated review underscores the importance of future research to fully leverage and understand the therapeutic potential of grape-derived compounds, aiming to refine dietary guidelines and functional food formulations. Further translational studies are expected to clarify the specific bioactive interactions and their impacts on health.

Keywords Antioxidants, Chronic disease prevention, Grapes, Health promotion, Polyphenols

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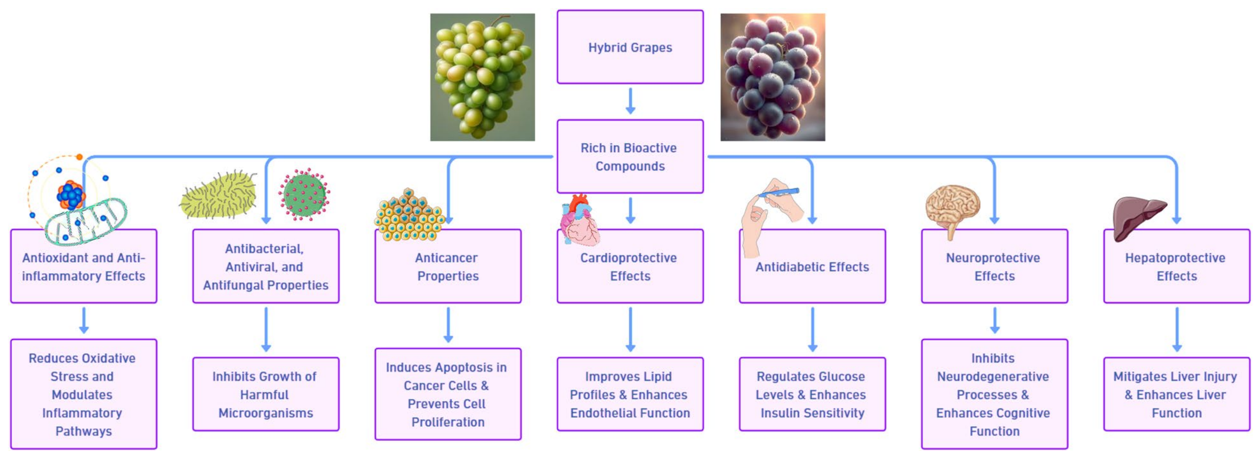
Graphical Abstract



Introduction

Grapes (Vitis spp.), cultivated across various climatic zones worldwide, present a rich diversity in species and hybrids (Gutierrez et al., 2021). From the classic European *Vitis vinifera* to American varieties like *Vitis labrusca* and innovative hybrids, each brings unique qualities and adapts differently to environmental conditions, significantly enriching the global viticulture landscape (Gutierrez et al., 2021). The introduction of *Vitis vinifera* initiated the era of European-influenced grape cultivation in Brazil. This development notably advanced in the mid-19th century when Italian immigrants introduced the Isabel grape (*Vitis labrusca*), marking a pivotal shift towards American grape varieties that were better adapted to the climatic conditions of Brazil (Camargo et al., 2010; Wijekoon et al., 2022). This initial adaptation laid the groundwork for technological advancements in pest and disease management, and by the 20th century, the resurgence of fine grapes for wine and fresh consumption catalyzed the tropical viticulture era, particularly in Brazil's northeastern semiarid region (Rogiers et al., 2022). Breeding efforts have since developed American cultivars with enhanced qualities, while the challenges of cultivating European varieties such as *Vitis vinifera* have remained due to their specific climatic and productivity requirements (Camargo et al., 2010). The mid-1990s export limitations due to a focus on seeded table grape cultivars prompted a need for seedless varieties, which, despite initial setbacks in bud fertility and disease susceptibility, led to the development of more robust cultivars capable of biannual cropping and stable yields. Nevertheless, issues such as environmental adaptability, disease resistance, and the high cost of licensing underline the ongoing need for Brazil to achieve technological autonomy in grape cultivation (Ribeiro, 2016; Table et al., 2020; Zecca et al., 2020). In recent years, grape industry has been buzzing with innovation.; growers have introduced over 20 new types of grapes, many without seeds, which are becoming popular in the market. However, these new grapes aren't without their issues; they sometimes struggle to cope with Brazil's hot, dry climate and are prone to diseases. Also, the fees for growing these grapes, along with limits on where and how much can be grown, are causing headaches for local farmers; that's why there's a growing push for Brazil to create its own grape varieties that are perfectly suited to its climate and free from these constraints. (Camargo et al., 2010; de Freitas Laiber Pascoal et al., 2022; M. C. Ribeiro, 2016; Table et al., 2020). The diversity of grape varieties is as rich as their potential health benefits, encompassing a range of colors and flavors. White grape varieties such as Array 15®, Sugar Crisp®, Sweet Globe®, Cotton Candy®—developed by International Fruit Genetics (IFG)—and Autumn Crisp® by Sun World, offer a sweet and refreshing taste. Red grapes, not to be outdone, include the luscious Sweet Celebration® and Candy Snaps® from IFG, the robust Timko® with the She gene, and the vibrant Scarlotta Seedless® from Sun World. Black grapes such as the elongated Sweet Sapphire®, the distinctive Sable®, and the striking Midnight Beauty®, also from Sun World, provide a depth of flavor and richness that is as visually appealing as it is nutritious; they can be cited as examples, since more than 70 cultivars developed by these companies are available to licensed producers (Camargo et al., 2010; da Silva et al., 2019). The grape is the third most exported fruit in Brazil, after mango and melon, with the

São Francisco Vale accounting for 99% of total Brazilian grape exports since the year 2002, with volumes reaching 45,000 tons in 2019. Besides being economically important, its cultivation contributes to society in the generation of jobs, generating up to five direct jobs per hectare (Landau, 2020). In such a large production, there is not to be alarmed the existence of waste, which represents 40%, resulting from the non-following of the quality parameters determined by the exporters causing the discarding of the non-suitable ones. They take as determinants of the standard, characteristics such as coloration, caliber (mm), acidity, size of the bunch, quantity of bunches inside the bowl, weight of the bowl, presence of physical contaminants and rotten berries, organization of the bowls in the box (Rotili et al., 2022). Being a great challenge for the industry, the transformation of this waste into value-added by-products, destining them to reprocessing, so that they do not generate negative impacts. According to recent studies , the waste generated from wine and juice production in 2013, almost 3.8 tons of grape pomace, caused environmental, social and economic problems (Caponio et al,. 2023). This destination of by-products is, a major challenge for the wine industry Sugars (glucose and fructose), organic acids (malic, tartaric, citric, lactic, acetic, and succinic acids), amino acids (arginine, proline, alanine, ammonium, g-amino butyric acid, cystathionine, and glutamic acid), peptides, proteins, vitamins (thiamine, riboflavin, pyridoxine, α-tocopherol, choline, folate, niacin, and ascorbic acid), carotenoids (lutein, β-carotene, neochrome, neoxanthin, violaxanthin, luteoxanthin, flavaxanthin, and zeaxanthin), flavor components (β-ionone, β- damascene, furaneol, and 2-phenylethanol), and phenolic compounds (iso flavonoids, anthocyanins, flavanols, flavanols (quercetin), proanthocyanins, hydroxycinnamic and hydroxybenzoic acids, stilbenes, lineoids, coumarins, anthocyanins, catechin, and epicatechin) are the chemical composition of grapes (Tabeshpour et al., 2018).

Grapes can have different profiles of phenolic compounds, which in wines, can be altered by their processing or type (Gomez et al., 2020; Nassiri-Asl & Hosseinzadeh, 2016; Tabeshpour et al., 2018; Zhu et al., 2021). Thus, some wines may be genetically richer in polyphenols than others. Therefore, quantitative and qualitative analysis on the distribution of polyphenols in seeds and skins among grape varieties should be conducted separately about their health benefits. The polyphenolic content in grapes, and consequently in wines, is inherently linked to the genetic makeup of the grape varieties (Lu et al., 2023). To elucidate the extent to which genetic differences influence the health benefits of grapes, focused quantitative and qualitative analyses on the polyphenols present in the seeds and skins are essential (Güler, 2023); such detailed studies will shed light on the potential health-promoting properties unique to each variety (Lee et al., 2023).

Grape-based products have gained popularity due to their health benefits and rich nutritional profile, including polyphenols, vitamins, and minerals (Alasalvar et al., 2021; Sabra et al., 2021). These attributes, alongside grapes' role in reducing oxidative stress and chronic disease risk, align with modern preferences for natural and functional foods (Zhou et al., 2022). The versatility of grapes, enjoyed as fresh fruit, juice, and in fermented forms, along with their cultural significance, further boosts their appeal. Particularly, compounds like resveratrol have attracted attention for their cardiovascular, antimicrobial, and antioxidative properties, contributing to the growing demand for grape-derived products (Chang et al., 2019; Sharma et al., 2022b). As consumers become more health-conscious, the demand for food products with added health benefits has risen, positioning grapes as a valuable commodity in the functional food market (Ferrer-Gallego & Silva, 2022; Onuh et al., 2023).Recognizing the shift towards health-centric food choices, the industry has been keen on developing grape-based products that align with the dietary needs and the preventive health approaches sought by consumers (Ferrer-Gallego & Silva, 2022; Gómez-Gaete et al., 2024). In recent years, the burgeoning interest in the role of diet in maintaining health and preventing disease has cast a spotlight on the nutritional and therapeutic potential of grapes (Luo et al., 2021). The rationale for this scrutiny is twofold: firstly, grapes are a widely consumed fruit with a rich history of use in traditional medicine; secondly, they are a repository of a multitude of bioactive compounds, with emerging evidence pointing to their potential in modulating disease pathways.

This study presents a comprehensive examination of the relationship between grape-derived compounds and health, with a specific focus on how genetic diversity among grape varieties influences their phenolic profiles and subsequent health advantages. The investigation into polyphenols in grape seeds and skins reveals distinctive health-promoting attributes linked to the genetic constitution of various grape cultivars, an aspect scarcely addressed in the prevailing literature. This research aims to deepen the understanding of the precise contributions of grape bioactives to disease prevention and health enhancement, potentially leading to refined dietary recommendations and the advancement of functional food applications. Given the changing dietary habits and the increasing prevalence of lifestyle-related diseases, this study's significance lies in its comprehensive assessment of current grape research. It synthesizes the latest findings from *in vitro, in vivo,* and clinical studies to thoroughly evaluate the health potential of grape-derived compounds. By highlighting the preventive roles of these compounds against diseases, the study emphasizes the dietary importance and therapeutic promise of grapes, thereby steering future nutritional strategies and health-related innovations.

Review methodology

The primary objective of this narrative review was to highlight advancements pertaining to grape utilization in human health, focusing on their compositional attributes and prospective health advantages. A meticulous search was conducted across several databases, including PubMed/Medline, Web of Science, Wiley, and Cielo. This search utilized specific Medical Subject Headings (MeSH) terms such as "Antioxidants/analysis," "Flavonoids/analysis," "Health Promotion," "Humans," "Phenols/analysis," "Phytochemicals/analysis," "Plant Extracts/chemistry," and "Vitis/chemistry," ensuring each reference to plant species conformed to the accepted nomenclature as per the Plants of the World Online (POWO, 2024). The literature search focused on articles published from the year 2018 up to August 08, 2022. The selection criteria mandated that the articles be full-length, accessible in English, Spanish, or Portuguese, and available either freely or via subscription. The exclusion criteria encompassed abstracts in any form, conference proceedings, symposia contributions, annals, undergraduate thesis works, and articles in languages other than the specified three. Eligible studies, particularly those scrutinizing the composition of hybrid grapes, were cataloged in a spreadsheet to facilitate organized analysis and synthesis of the data. The most representative data were summarized in figures and tables, with all botanical names verified against the POWO database to ensure accuracy (POWO, 2024).

Grapes bioactives: a brief overview

Classification of bioactive compounds in grapes

Grapes are endowed with an array of bioactive compounds, intricately linked to their health-promoting properties. These compounds can be systematically classified into:

- Phenolic Acids: Comprising hydroxybenzoic and hydroxycinnamic acids, these compounds are foundational to the antioxidant capacity of grapes (Zhou et al., 2022).
- Flavonoids: This diverse group includes flavonols (such as quercetin and kaempferol), flavan-3-ols (catechins and proanthocyanidins), anthocyanins, and flavanones, renowned for their extensive health benefits including antioxidant, anti-inflammatory, and cardioprotective effects (Zhuang et al., 2023).
- Stilbenes: Resveratrol is the most notable stilbene in grapes, recognised for its neuroprotective and antioxidative properties (Farhan & Rizvi, 2023).
- Lignans: Present in smaller quantities, lignans contribute to the overall antioxidant profile of grapes (Buljeta et al., 2023; Rahaman et al., 2023).

Extraction techniques for grape bioactive compounds

The extraction of bioactive compounds from grapes is a pivotal step in utilizing these phytochemicals for health benefits; the methods employed can significantly affect the yield, purity, and efficacy of these compounds; therefore, a detailed examination of the extraction techniques is essential for maximizing the therapeutic potential of grape-derived bioactives (Gil-Martín et al., 2022). Conventional extraction methods have relied on solvent extraction techniques, using a variety of solvents such as ethanol, methanol, water, or a combination thereof. These methods, while effective, often require large volumes of solvents and extended extraction times; moreover, they may not always be selective for certain bioactive compounds and could lead to the co-extraction of undesirable substances (Gil-Martín et al., 2022). In response to the limitations of conventional techniques, recent advancements have led to the development of novel extraction methods that are more efficient, selective, and environmentally friendly.

- Supercritical Fluid Extraction (SFE), typically employs supercritical carbon dioxide. SFE is renowned for its efficiency in extracting high-purity compounds without the use of toxic solvents, thus providing a 'greener' alternative (Chaves et al., 2020).
- Ultrasonic-assisted extraction (UAE), which utilizes ultrasonic waves to disrupt the plant cell walls, facilitating the release of bioactive compounds; this method is not only faster but also energy-efficient and has been found to increase the extraction yield (Shen et al., 2023).
- Enzyme-assisted extraction (EAE) is a technique that uses specific enzymes to break down complex plant matrices, allowing for the targeted release of bioactive compounds. EAE is particularly useful for obtaining high-value compounds that are bound within the plant cell walls (Streimikyte et al., 2022).
- Pulsed Electric Field (PEF) extraction is a non-thermal method that applies short bursts of high voltage to the grape tissue (Athanasiadis et al., 2023). PEF creates pores in the cell membranes, which enhances the mass transfer of bioactive compounds from the cells to the extraction solvent (Athanasiadis et al., 2023).

Each of these methods has its own set of advantages and optimal conditions for different classes of bioactive compounds. The choice of extraction method will ultimately depend on the specific compound of interest, the desired purity, and the intended application.As research progresses, the optimization of these extraction methods continues, paving the way for more efficient and sustainable practices in the utilization of grapes as a source of health-promoting bioactives. The practical applications of these innovative extraction techniques are well-documented in the scientific literature. For instance, v studies demonstrated the efficacy of Supercritical Fluid Extraction (SFE) by obtaining proanthocyanidins from grape seeds, which are known for their antioxidant properties. They reported that SFE, using supercritical CO2, yielded extracts with high purity and antioxidant activity (de Souza et al., 2020). Ultrasonic-assisted extraction (UAE) was effectively utilized by other researchers to extract resveratrol from grape leaves; their findings indicated that UAE significantly improved the extraction efficiency of resveratrol compared to traditional methods, and also reduced the extraction time from hours to minutes (Sun et al., 2018). In a study focused on enzyme-assisted extraction (EAE), illustrated that by using cellulase and pectinase enzymes, they could enhance the yield of phenolic compounds from grape pomace, a by-product of the wine industry. The enzymatic treatment facilitated the release of bound phenolic compounds, which are often underutilized in grape waste materials (Meini et al., 2019). Lastly, the use of Pulsed Electric Field (PEF) extraction has been used in recent studies to extract anthocyanins from grape residues; their research found that PEF treatment led to a significant increase in the extraction yield of anthocyanins, which are valuable for their use as natural colorants and for their antioxidant benefits (Bocker & Silva, 2022; Donsì et al., 2010). These examples underscore the potential of advanced extraction methods to not only improve the efficiency and sustainability of bioactive compound extraction from grapes but also to contribute to the valorization of grape by-products in the food and pharmaceutical industries.

Table 1 summarizes the various advanced extraction techniques utilized for isolating bioactive compounds from grapes, highlighting their unique advantages.

Grape bioactives: polyphenols and beyond

Grapes contain a plethora of phenolic compounds, which are central to the fruit's antioxidant, anti-inflammatory, and cardioprotective effects (Sabra et al., 2021; Shahidi & Yeo, 2018). These phenolics exist in various forms, including free phenolics, esterified phenolics, insoluble-bound phenolics, and non-extractable polyphenols (NEPPs), each with unique properties affecting their bioavailability and biological activity (Zhang et al., 2020). Free phenolics, readily available in the fruit matrix, are known for their immediate bioactivity (Panzella et al., 2020). These compounds, including flavonoids and phenolic acids, exhibit potent antioxidant properties. Their direct interaction with cellular targets provides immediate health benefits, such as reducing oxidative stress and modulating inflammatory pathways (Panzella et al., 2020). Esterified phenolics, formed by the linkage of phenolic acids to sugars or alcohols, exhibit enhanced stability and solubility (Shahidi & Hossain, 2023). This form contributes to the gradual release of phenolics in the gut, potentially offering sustained antioxidant activity. The esterification process affects the absorption and metabolic fate of these compounds, thus influencing their bioactivity (Shahidi & Hossain, 2023). Insoluble-bound phenolics, tethered to cell wall components, are released during digestion or food processing (Shahidi & Yeo, 2016). These compounds, often overlooked in conventional extraction methods, contribute to long-term health benefits, particularly in gut health and chronic disease prevention and the microbial fermentation of these bound phenolics in the colon produces metabolites with systemic health benefits (Shahidi & Yeo, 2016). NEPPs, a significant fraction of dietary polyphenols, are

Table 1 Overview of advanced extraction techniques for bioactive compounds from grapes

Extraction Technique	Description	Advantages	References
Supercritical Fluid Extraction (SFE)	Utilizes supercritical CO2 (Carbon Dioxide) to extract compounds	High purity; no toxic solvents; environmentally friendly	(Chaves et al., 2020)
Ultrasonic-assisted Extraction (UAE)	Employs ultrasonic waves to disrupt cell walls and release compounds	Fast; energy-efficient; increases yield	(Shen et al., 2023)
Enzyme-assisted Extraction (EAE)	Uses enzymes to break down plant matrices for targeted compound release	Useful for high-value, bound compounds; enhances yield	(Streimikyte et al., 2022)
Pulsed Electric Field (PEF) Extraction	Applies high voltage bursts to create cell membrane pores	Non-thermal; enhances mass transfer of compounds	(Athanasiadis et al., 2023) (Bocker & Silva, 2022; Donsì et al., 2010)

not absorbed in the upper gastrointestinal tract but are metabolized by the gut microbiota (González-Sarrías et al., 2017). This process yields a range of metabolites with potential health-promoting properties, highlighting the important role of the gut microbiome in unlocking the health benefits of grape phenolics (González-Sarrías et al., 2017).

Grape by-products from Brazilian vineyards, such as skins, seeds, and stems, are valuable sources of phenolic compounds with diverse bioactivities. These phenolics are categorized based on their chemical properties and bioavailability into free, esterified, and insoluble-bound forms, each offering unique contributions to health and potential applications in nutraceuticals and functional foods (Peng & Shahidi, 2023).

Free phenolics are readily available and bioactive upon consumption, contributing immediate antioxidant and anti-inflammatory effects (Shahidi & Ambigaipalan, 2015). Found predominantly in the skins and seeds of Brazilian grapes, these compounds, including flavonoids like quercetin and phenolic acids such as gallic acid, play critical roles in mitigating oxidative stress and modulating inflammatory responses (de Camargo et al., 2019). Their immediate bioactivity makes them prime candidates for acute therapeutic applications, particularly in antioxidant-rich supplements aimed at rapid response mechanisms in the body (Rathod et al., 2023).

Esterified phenolics, formed through the linkage of phenolic acids to sugars or other organic compounds, exhibit enhanced stability and solubility, making them suitable for applications that require controlled release (Kumar & Goel, 2019). In the digestive tract, these compounds are slowly hydrolyzed, releasing antioxidants gradually and providing prolonged protective effects against oxidative damage (de Camargo et al., 2014, 2016). This property is particularly beneficial for developing functional foods designed to deliver sustained health benefits throughout the gastrointestinal system, supporting long-term wellness and chronic disease management (Plamada & Vodnar, 2021).

Insoluble-bound phenolics are integrated into the cellular structures of grape by-products and are not readily extractable; these compounds are released primarily during digestive processes or specific food processing techniques like fermentation, which are common in Brazilian grape by-product management (Shahidi & Yeo, 2016). The slow release and subsequent microbial fermentation in the colon transform these phenolics into metabolites that contribute to gut health and the prevention of chronic conditions and the inclusion of these phenolics in dietary fibers can enhance the functional value of grape-based dietary supplements, targeting gut health and systemic inflammation (Rathod et al., 2023; Wang et al., 2022).

The diverse forms of phenolic compounds in Brazilian grape by-products hold significant potential for enhancing health through various mechanisms (Rathod et al., 2023). Free phenolics are ideal for immediate effects, esterified phenolics for sustained release, and insoluble-bound phenolics for long-term benefits, particularly impacting gut health and chronic disease mitigation (de Camargo et al., 2022). The strategic extraction and formulation of these phenolics can lead to innovative health products tailored to specific health outcomes, leveraging the rich biodiversity of Brazilian grape varieties (Shahidi & Hossain, 2023).

The grape can be used for table consumption, such as juices, oils, jellies and, mainly, in the form of wine, which has been closely associated with food, particularly in Mediterranean countries, and for many years, moderate and regular wine consumption was associated with health benefits (Daldoul et al., 2020; Kowalczyk et al., 2022; Olivati et al., 2019). In the last two decades, several epidemiological and clinical studies around the world have pointed out that moderate drinking produces positive effects on antioxidant capacity (Barbalho et al., 2020; Muñoz-Bernal et al., 2021; Yu et al., 2019) lipid profile, and the coagulation system, which may be associated with decreased incidence of cardiovascular disease, overall mortality, and other chronic diseases (Rasines-perea & Teissedre, 2017; Zhu et al., 2021). Most studies focus their attention on red wine components (mainly polyphenols and especially resveratrol) with the aim of explaining the observed relationship between wine consumption and cardiovascular disease incidence (Sabra et al., 2021; Zhu et al., 2021). Although the chemical components of grapes and wine may vary, similar beneficial effects have been observed in red wine varieties related to their higher polyphenol content (Rasines-perea & Teissedre, 2017) (de Andrade Bulos et al., 2023). Polyphenols form a group of bioactive compounds, they have in their chemical structure multiple units of phenol and external elements that link these rings together. Thus, distinctions are made between phenolic receptors, stilbenes (resveratrol), chlorogenic acid, coumarins, lignin and flavonoids. Flavonoids are the most abundant polyphenols in our diets; they can be divided into several classes according to their common structure composed of 2 aromatic rings joined by 3 carbon atoms that form an oxygenated heterocycle. It can be divided into subclasses depending on the type of heterocycle involved: flavones, flavanols, isoflavones, flavanones, anthocyanidins, catechins and proanthocyanins (Hou et al., 2019; Muñoz-Bernal et al., 2021; Nassiri-Asl & Hosseinzadeh, 2016; Sabra et al., 2021). Dietary intake of polyphenols is highly variable, and it is difficult to achieve an accurate estimate of dietary intake of polyphenols due to poor characterization of polyphenols in foods and the large variability in polyphenol content within foods (Rasines-perea & Teissedre, 2017). Several factors can affect the content of polyphenols in daily foods, such as environmental conditions, storage, and food processing. For example, sun exposure, rainfall, different crop types, and degree of ripeness can affect polyphenol concentrations and proportions in different ways (Jideani et al., 2021). Generally, phenolic acid concentrations decrease during ripening, while anthocyanin concentrations increase (Swallah et al., 2020; Xu et al., 2011; Zhu et al., 2021). In addition to polyphenol compounds, grape seed oil also contains healthy fatty acids, particularly unsaturated fatty acids such as linoleic and oleic acids that increase the nutritional value of grape oil when used in food or dietary supplements (Jing et al., 2014; Orsavova et al., 2015; Tabeshpour et al., 2018). Studies have shown that grape seed oil displays anti-inflammatory, antioxidant, cardioprotective, and anticancer properties, which may be due to the occurrence of linoleic acid, tocopherol, carotenoids, phytosterol, in addition to some polyphenolics compounds such as proanthocyanins, resveratrol, and quercetin (Dave et al., 2023; Vislocky & Fernandez, 2010).

The different chemical groups of polyphenols identified in different parts of fruits were summarized in Fig. 1; the figure organizes grape polyphenols into main classes including phenolic acids, lignans, stilbenoids, and various flavonoid subclasses, highlighting compounds like hydroxybenzoic and hydroxycinnamic acids.

Bioavailability, absorption, metabolism, and excretion of bioactive compounds from grapes

Polyphenols are the most numerous and widely distributed group of bioactive inclusions (Abbas et al., 2017) and present different sets of pharmacological activities attributed to their particular characteristics and structural complexity, which interfere with the limit and speed of absorption in the intestines (Liu et al., 2019) (Sharma et al., 2022a). In the human body, grape-derived polyphenols undergo a series of transformations during absorption, metabolism, and excretion (Aloo et al., 2023). Key polyphenols such as resveratrol, quercetin, catechins, and anthocyanins are metabolized through phase II biotransformation processes, leading to the formation of

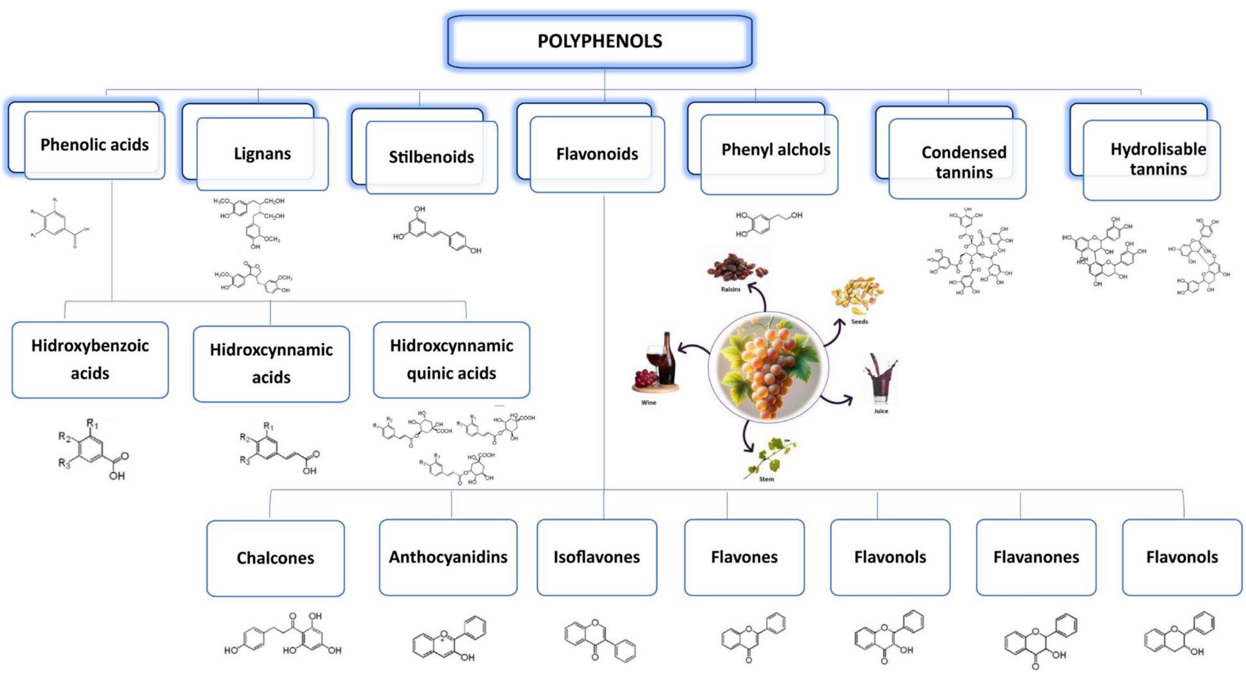


Fig. 1 Chemical groups of polyphenols identified in different fruit parts (L. Zhang et al., 2021). The figure illustrates the various classes of polyphenolic compounds found in grapes, categorized into phenolic acids, lignans, stilbenoids, flavonoids, phenyl alcohols, condensed tannins, and hydrolysable tannins. Each class is further subdivided to detail the specific types of compounds, such as hydroxybenzoic acids, hydroxycinnamic acids, and hydroxycinnamic quinic acids under phenolic acids, as well as chalcones, anthocyanidins, isoflavones, flavones, flavonols, flavanones, and flavonols within the flavonoids. The figure illustrates the various classes of polyphenolic compounds found in grapes, categorized into phenolic acids, lignans, stilbenoids, flavonoids, phenyl alcohols, condensed tannins, and hydrolysable tannins. Each class is further subdivided to detail the specific types of compounds, such as hydroxybenzoic acids, hydroxycinnamic acids, and hydroxycinnamic quinic acids under phenolic acids, as well as chalcones, anthocyanidins, isoflavones, flavones, flavonols, flavanones, and flavonols within the flavonoids

methylated, sulfated, and glucuronidated derivatives (Di Lorenzo et al., 2021). For instance, resveratrol can be metabolized to resveratrol-3-O-glucuronide and resveratrol-3-sulfate in the liver and intestine, illustrating the body's capacity to modify these compounds for enhanced solubility and excretion (Poór et al., 2022). Similarly, quercetin is transformed into quercetin-3-O-glucuronide, among other metabolites, facilitating its clearance from the body (Mirza et al., 2023). These metabolic alterations are important for understanding the bioavailability and biological activity of polyphenols post-ingestion (Bešlo et al., 2023). The predicted structures of these metabolites, based on common metabolic pathways, suggest variations in their hydroxyl, methoxy, and glycosidic groups, which are critical for their interaction with biological targets and subsequent health effects.

Phenolic compounds in grapes are predominantly found in bound and non-extractable forms, tightly associated with cellular structures or complexed within the fibrous matrix. These forms are significant due to their delayed bioavailability and distinct metabolic pathways compared to free phenolics (Kohut et al., 2023). Bound phenolics, often linked to carbohydrates and proteins, are integral to the plant's structural framework. In grapes, these phenolics are primarily located in the skins and seeds and are released during the fermentation process or via enzymatic activities during digestion (Zhang et al., 2020). Their release pattern influences not only the flavor profile of grape-based products but also the bioavailability of health-promoting metabolites (Zhang et al., 2020). Non-extractable polyphenols (NEPPs) constitute a considerable portion of dietary phenolics and are characterized by their resilience to conventional extraction techniques (Ding et al., 2020). NEPPs are significant due to their extensive metabolism by gut microbiota, which converts them into a range of metabolites with potential health benefits. These metabolites have been associated with reduced risks of chronic diseases such as cardiovascular disease, diabetes, and certain cancers due to their anti-inflammatory and antioxidant properties (Martínez-Meza et al., 2023). The quantification of bound and non-extractable phenolics requires specialized analytical techniques that can disrupt complex matrices. Approaches such as enzymatic treatments followed by high-performance liquid chromatography (HPLC) or mass spectrometry (MS) (Oliva et al., 2021) are employed to identify and quantify these compounds. Recent advancements have also explored the use of solid-phase extraction (SPE) (Allen et al., 2013) and ultra-performance liquid chromatography (UPLC) for more efficient and accurate profiling (Lukić et al., 2019). The health implications of bound and non-extractable phenolics are important, primarily due to their transformation into bioactive compounds within the gut and these transformations contribute significantly to the antioxidative and anti-inflammatory activities observed in pharmacological studies (Kohut et al., 2023).

Flavones, isoflavones, flavanols and anthocyanins are frequently glycosylated (H. Zhang et al., 2014) in the gastrointestinal mucosa and colonic microflora. Anthocyanins are absorbed without de-glycosylation in the stomach, via specific transporters, such as sodium-dependent glucose co-transporter 1 and facilitative glucose transporters 1, while in the small intestine, they are mainly absorbed as aglycones. High polymeric anthocyanins are easily degraded into low-polymeric forms or smaller phenolic acids by colonic microbiota, which improves their absorption (Panchal & Brown, 2023). In this way, we understand that polyphenols pass through the small intestine without being absorbed; going through extensive metabolism and complex reactions, catalyzed by the intestinal microbiota, being biologically transformed into their relatively more bioavailable metabolites (Iannone et al., 2017). Derived metabolites circulate in plasma and can penetrate tissues (Del Rio et al., 2013; Manach et al., 2004). According to Williamson et al. (2017) the maximum dosage of polyphenols in postprandial blood are generally less than 1uM, however for intestinal catabolic the maximum concentrations can reach 100 times more than the original compound. The elimination of polyphenols and their derivatives is carried out mainly via urinary and biliary excretion. Studies report that the half-life of these compounds in plasma varies from 2 to 3 h for anthocyanins and flavanols, 4 to 8 h for isoflavones and can reach 28 h for quercetin. They were demonstrating that the regular and frequent consumption of foods with these chemical compounds elevated these metabolites in the plasma (Percival & West, 2013). Anthocyanins for having modulatory effects on several signaling pathways involved in the cell cycle are seen in scientific circles as promising anticancer and antimutagenics therapies. On the other hand, due to the rapid oxidation of phenolic hydroxyl groups in quinones, anthocyanins are particularly unstable hydrophilic compounds. They also suffer the influence of external factors such as pH or temperature that can negatively affect their biological activities, which to be overcome, along with their pharmacokinetic limitations, designing new drug release systems is of utmost importance to exert their potential health-promoting effects. Fruits and plants rich in anthocyanins indicated anticancer properties when targeting multiple cross-linked signaling pathways in cancer metabolism, including oxidative stress, inflammation, angiogenesis, and apoptosis (Fakhri et al., 2020).

Health benefits and therapeutic potential of hybrid grapes

Antioxidant and anti-inflammatory

Oxidative stress arises from an excess of reactive oxygen species (ROS) over our ability to neutralize them, leading to cell damage and chronic diseases. (Rasines-perea & Teissedre, 2017; Zhu et al., 2021) (Scheau et al., 2021, Shahidi, 2000). *V. vinifera* L. grapes enhance cellular antioxidant defenses, particularly through polyphenolic compounds that influence inflammatory responses and cyclooxygenase-2 activity (Fig. 2). Studies highlight the potential of grape extracts in reducing oxidative stress, suggesting their use in functional foods and nutraceuticals (Li et al., 2014; Stevens & Revel, 2018) (Shahidi & Wanasundara, 1992). The oxidative activity of *V. vinifera L.* grapes has a direct relationship between total phenolic compounds and flavonoids (Yu et al., 2019). Polyphenols may affect vascular inflammation and injury not only as antioxidants but also as modulators of inflammatory redox signaling pathways (Li et al., 2014; Tabeshpour et al., 2018). One of the important anti-inflammatory mechanisms is the inhibition of eicosanoid-generating enzymes, including phospholipase A2 and cyclooxygenase. Polyphenols act by modulating cyclooxygenase-2 activity and gene expression in different cell types (Fraternale et al., 2011; Rocha et al., 2012; Tabeshpour et al., 2018). Nitric oxide (NO) is an essential component in the maintenance of vascular health, and is a key intravascular antithrombotic factor, but causes inflammatory response if converted to peroxin trite in the presence of free radicals (Orsavova et al., 2015). Ribeiro et al. utilized various *in vitro* methodologies to measure the antioxidant capabilities of grape pomace, revealing a significant capacity determined by DPPH, ABTS, FRAP methods, and the β-carotene/linoleic acid auto-oxidation assay (V. M. Ribeiro et al., 2018). Further biological assays conducted by Bortolini et al. showed that grape extracts decreased the production of reactive oxygen species in mitochondria isolated from rat livers and could help restore oxidative balance in arthritis models, indicating their value in functional foods or nutraceuticals (Bortolini et al., 2022). This was supported by findings from V. M. Ribeiro et al. (2018) and Di Renzo et al. (2014), who observed

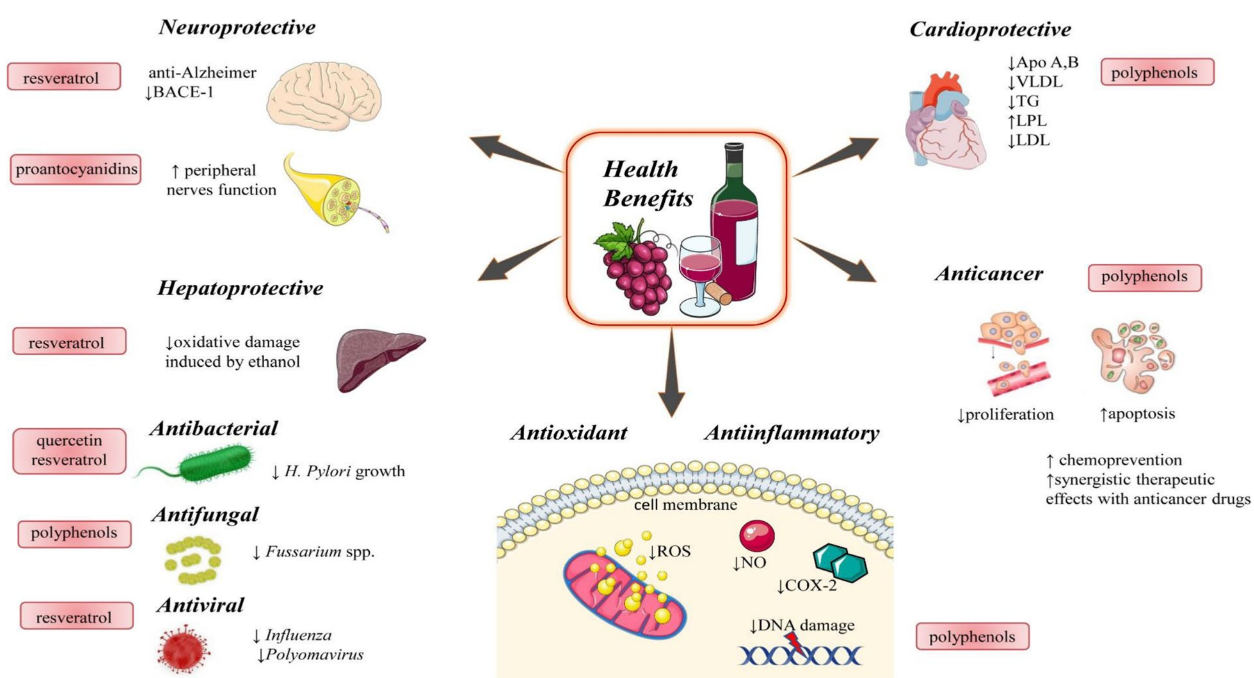


Fig. 2 Summarized scheme with mechanisms of the main pharmacological properties of bioactive compounds from grapes. It delineates the multifaceted health benefits associated with bioactive compounds in grapes. These compounds, including resveratrol, quercetin, and polyphenols, are depicted as having neuroprotective properties, such as anti-Alzheimer's effects and enhancement of peripheral nerve function. Hepatoprotective effects are indicated by resveratrol's ability to mitigate ethanol-induced oxidative damage. Antibacterial and antifungal activities are shown by the inhibition of *H. pylori* growth and suppression of Fusarium spp. Antiviral activities against Influenza and Polyomavirus are also noted. The cardioprotective role is associated with improved lipid profiles, while anticancer activities are highlighted by the inhibition of cell proliferation and induction of apoptosis, with implications for chemoprevention and enhanced efficacy of anticancer drugs. The antioxidant effects are demonstrated through the reduction of reactive oxygen species and DNA damage, and the anti-inflammatory action is shown by the suppression of nitric oxide and COX-2 enzyme activity, which contributes to the overall anti-inflammatory response. Abbreviations and symbols: ↑increase, decrease, BACE-1 (beta-site APP-cleaving enzyme 1), Nitric oxide (NO), cyclooxygenase- 2 (COX-2), Apolipoprotein (apo) A, B, very low-density lipoprotein (VLDL), triglycerides (TG) levels, lipoprotein (LPL)

no changes in superoxide dismutase activity with grape product consumption (Di Renzo et al., 2014) (Bocker & Silva, 2022). The anti-inflammatory effects were highlighted by Nishiumi et al. (2012), who found grape-derived products suppressed the inflammatory marker NF-κB and reduced COX-2 and iNOS protein expression, which are linked to inflammatory processes. hus, both suppressive actions demonstrate the anti-inflammatory activity of grape metabolites (Bocsan et al., 2022; Cruz-Machado, 2010; Gao & Zhang, 2021).

Antibacterial, antiviral and antifungal effects

Quercetin and resveratrol, both active polyphenols in grape muscadine skin extracts, have inhibitory effects against *H. pylori* with minimum bactericidal concentrations of 256 μg/mL and 128 μg/mL, respectively. Polyphenols in grape seed extract have antibacterial effects at a concentration of 3 mg/mL against methicillin-resistant *Staphylococcus aureus*, which may be by disrupting the cell wall or cell membrane (Nassiri-Asl & Hosseinzadeh, 2016), and also reduced ergosterol biosynthesis correlated with inhibition of folate pathways (Simonetti et al., 2020). There are relationships between antiviral activities of resveratrol and grapes (Blesso, 2019; Dave et al., 2023; Systems & Leporatti, 2022). Another research studied the effect of resveratrol against polyomavirus, which later in 2011 also showed anti-influenza activity (Dembitsky et al., 2011). The ethanolic extract of *V. vinifera L*. exhibits antifungal activities against *Fusarium,* demonstrating that high amounts of polyphenols in this plant play an important role in the observed antifungal effects (Gratl et al., 2021; Kelly et al., 2018). Building upon the evidence of grapes' health-promoting properties, a study employing monkey cell cultures *in vitro* provides compelling insights into the potential antiviral activity of grape juice. Researchers observed a significant decrease in viral infectivity, which became undetectable within minutes when exposed to concentrations ranging from 25–2,000 mg/mL of proanthocyanidins extracted from grape juice (Vislocky & Fernandez, 2010). These findings suggest a notable antiviral effect of proanthocyanidins, a group of bioactive compounds abundantly found in grape juice, thereby extending the fruit's benefits beyond its established antioxidant and cardioprotective roles.

Anticancer effects

Cancer remains one of the leading causes of mortality globally, prompting ongoing research into preventive dietary strategies (GBD, 2022). In the realm of dietary interventions for cancer prevention and treatment, the Mediterranean Diet emerges as a paradigm of nutritional excellence, renowned for its positive health outcomes; this diet, characterized by a high intake of vegetables, fruits, whole grains, legumes, and nuts, complemented by moderate consumption of fish and poultry, and a reduced intake of red and processed meats, encapsulates the dietary traditions of the Mediterranean region (Montagnese et al., 2020). A cornerstone of this diet is the inclusion of fruits, notably grapes, and the moderate consumption of red wine, which have been associated with a decreased risk of certain cancers, including breast cancer (Montagnese et al., 2020). The Mediterranean Diet's protective effect against cancer can be attributed to its rich assortment of bioactive compounds, particularly polyphenols found abundantly in grapes and red wine. Resveratrol, a polyphenolic compound in grape skins and red wine, has garnered attention for its anti-inflammatory, antioxidant, antimicrobial and anti-tumorigenic properties (Kursvietiene et al., 2023; Sharifi-Rad et al., 2022). Epidemiological and clinical studies have elucidated the diet's role in modulating the risk and progression of cancer, emphasizing its potential in improving patient prognosis, especially in breast cancer (Porciello et al., 2020; Vitale et al., 2023). The integration of grapes and grape-derived products within the Mediterranean Diet underscores the synergy between dietary patterns and specific food components in cancer prevention (Dayi & Oniz, 2022). The consumption of grapes and red wine, within the recommended limits, contributes to the diet's antioxidative and anti-inflammatory profile, enhancing its cancer-preventive potential (Minzer et al., 2020). This dietary approach aligns with the holistic perspective of cancer prevention, emphasizing the importance of dietary quality and diversity in mitigating disease risk. In this quest, the anticancer effects of grape compounds, particularly polyphenols, have gained attention for their potential to inhibit the initiation, progression, and metastasis of various cancers (Sharma et al., 2022a) (Fig. 2). Grape seeds are rich in proanthocyanidins, which have been shown to induce cancer cell apoptosis, reduce inflammation, and prevent the proliferation of cancer cells (Wang et al., 2020). These compounds have shown promise in preventing skin, breast, and colon cancer in pre-clinical models (Wang et al., 2019). They have also been studied for their potential to mitigate the side effects of chemotherapy. Found in dark-colored grapes, anthocyanins can interfere with the signaling pathways that cancer cells use to grow, communicate, and spread (Posadino et al., 2023). Their potential anticancer effects have been observed against several cancer types, including leukemia, and liver and lung cancers (Câmara et al., 2022). Flavonoids such as Quercetin, Myricetin can modulate several signaling pathways in cancer cells, affecting cell cycle arrest, apoptosis, and inflammation and their anticancer properties have been observed in different types of cancers of the breast, colon, and liver, among others (Sehitoglu et al., 2014). Resveratrol, a stilbenoid found primarily in grape skins, has been extensively studied for its anticancer effects. It's believed to act by modulating pathways related to cell division and apoptosis, inflammation, and angiogenesis. Studies have demonstrated the potential of resveratrol to inhibit the growth of multiple cancer types, including breast, prostate, lung, and colorectal cancers. Additionally, it has shown synergy when combined with traditional chemotherapeutic agents. In a recent study, grape seed extract showed anticancer effects and induced apoptosis in colon cancer cell lines. Demonstrated that grape seed extract not only enhanced the anticancer effect of 5-fluorouracil in a dose-dependent manner *in vitro*, but also reduced 5-fluorouracil-induced mucositis in mice after chemotherapy, and its protective effect was more obvious in the proximal jejunum than in the distal small intestine (Cheah et al., 2014). The anticancer effects of resveratrol metabolites, including resveratrol-3-O-sulfate, resveratrol-3-O-glucuronide and resveratrol-4-O-glucuronide on colon cancer cells have been established. At a concentration of 30 μM, they inhibited the proliferation of metastatic colon cancer cells and caused strong cell accumulation in the S phase of the cell cycle. At concentrations of 10 or 20 μM, they showed synergistic chemotherapeutic effects with SN38 and oxaliplatin in metastatic colon cancer cells (SW620) (Nassiri-Asl & Hosseinzadeh, 2016; Soares et al., 2015). Other studies reported the positive effects of bioactive grape compounds, mainly resveratrol exhibiting several physiological activities, especially anticancer and anti-inflammatory activities analyzed *in vitro* and in experimental animal and human models. The anticancer activity of this compound is mainly due to the induction of apoptosis by various pathways, as well as the alteration of gene expression, leading to a decrease in tumor initiation, promotion and progression. Other effects of anti-inflammatory activity are through modulation of enzymes and pathways that produce inflammation mediators and also induction of programmed cell death in activated immune cells (Aires et al., 2021; Ghate et al., 2014). A study comparing the effects of a polyphenol-rich grape pomace extract on redox status using *in vitro* and *in vivo* models demonstrated that the extract has potent antioxidant and chemo-preventive properties *in vitro*, as it scavenges free radicals (DPPH• or ABTS•+) and prevents DNA damage induced by ROO• and OH• radicals. It is established that ROO•. are the main initiating factors of the cascade reactions of lipid peroxidation, causing the extract, in low concentrations, to be considered as a chemo preventive agent with ROO• and lipid peroxidation cause mutations in DNA. It also confirms that the extract has *in vitro* preventive properties against the effects of UV radiation, since UV radiation is one of the main producers of OH•. These findings confirm the potent antioxidant and chemo preventive properties *in vitro* of other grape extracts of the Vitis vinifera species (Veskoukis et al., 2012).

Cardioprotective effect

Recent research highlights the cardioprotective potential of hybrid grapes, notably through their polyphenolic composition, including resveratrol and proanthocyanidins, which are instrumental in preventing LDL oxidation and enhancing endothelial function (Fan et al., 2022; Otręba et al., 2021) (Fig. 2). Resveratrol, in particular, is credited with anti-inflammatory actions and improving lipid profiles (Fan et al., 2022; Otręba et al., 2021). Furthermore, grape seed extracts containing proanthocyanidins have been evidenced to lower blood pressure and improve arterial health (Huang, 2023). Anthocyanins contribute to cardiovascular protection by decreasing arterial stiffness and improving cholesterol metrics (Câmara et al., 2022). Additionally, the flavonoid quercetin is noted for its vascular benefits and lipid metabolism modulation (Kozłowska & Szostak-Węgierek, 2022). The inhibition of platelet aggregation by polyphenols is also a recognized cardioprotective mechanism, along with their influence on Apolipoprotein A and B, and the modulation of lipoprotein metabolism (Sabra et al., 2021). Lastly, polyflavan-3-ols in V. vinifera L. have been verified to inhibit platelet aggregation and LDL oxidation (Gomez et al., 2020). In a clinical study, it has been investigated the effect of grape juice consumption in 20 individuals diagnosed with coronary heart disease for 14 days and observed that there was a significant reduction in CD40L protein, which is associated with increased production of free radicals, expression of adhesion molecules and expression of pro-inflammatory cytokines (Albers et al., 2004). Observed in another *in vivo* study, in humans, showed antihypertensive effects and increased the levels of antioxidant agents (Vaisman & Niv, 2015). In the study by Maggi-Capeyron et al. (2001) phenolic acids (gallic, caffeic, p-coumaric, synaptic and ferulic) present in wine showed, *in vitro*, the ability to negatively modulate AP-1, which is an inflammatory marker. Noratto et al. (2011) treated vascular endothelial cells with inflammation induced by LPS (bacterial lipopolysaccharides) with grape extracts (20 mg gallic acid equivalent/L) and showed that there was an inhibition of the translation of interleukins 6 and 8, mediated by the inhibition of the activity of NF-kB (Maggi-Capeyron et al., 2001; Noratto et al., 2011). In the study conducted with grape extract powder (GPE), which is an organic solvent extract of whole freeze-dried table grapes, researchers demonstrated that the treatment caused growth inhibition and reduced the ability of colony formation and migration of DU-145 and PC-3 M prostate cancer cells. Less aggressive DU-145 cells showed greater sensitivity to the antiproliferative and anti-colony effects of GPE than to PC-3 M cells (Kumar et al., 2018). *Vitis* vinifera extract (50 μg mL − 1, 4-h incubation) significantly reduced the increase of oxaliplatin-dependent superoxide anion and lipid peroxidation in rat astrocytes, not interfering with oxaliplatin mortality in HT-29 cancer cells. Vitis vinifera reduced oxidative damage by maintaining the anti-cancer activity of oxaliplatin (Micheli et al., 2018).

Antidiabetic effects of grape compounds

With diabetes on the rise, the search for natural antidiabetic agents has brought grape polyphenols, abundant in wine and juice by-products, into focus due to their demonstrated ability to regulate glucose and enhance insulin sensitivity (2023, Arifah et al., 2022). The escalating prevalence of diabetes has intensified the search for effective natural antidiabetic compounds (Arifah et al., 2022). Notably, grape polyphenols, particularly those found in wine and juice by-products such as grape pomace (comprising grape seeds and skins), have garnered attention for their potential to modulate blood glucose and improve insulin sensitivity. The antidiabetic efficacy of these compounds is partly attributed to their interaction with various proteins and enzymes linked to glucose metabolism (Li et al., 2014; Rasines-Perea & Teissedre, 2017) (Fig. 2). *In vitro* studies focusing on grape-derived polyphenols such as resveratrol, quercetin, rutin, caffeic acid, and gallic acid have elucidated their beneficial impact on ectonucleotides activities, adenosine deaminase, and platelet aggregation in diabetic models. It has been observed that resveratrol treatment at doses of 10 and 20 mg/kg effectively mitigated lipid peroxidation in the liver and kidneys of diabetic rats, suggesting a protective effect against diabetes-induced oxidative stress (Systems & Leporatti, 2022). Furthermore, research exploring the administration of grape seed extract (GSE), rich in procyanidins B1 and C1, during mesenchymal stem cell (MSC) transplantation in a streptozotocin-induced type I diabetes model revealed remarkable benefits. This combined GSE/MSC treatment significantly regulated glucose homeostasis and insulin secretion, alongside improvements in inflammatory markers and oxidative stress parameters. This synergy suggests that GSE, when administered with MSCs, can aid in the regeneration of beta cells in type I diabetes, offering a promising therapeutic avenue (Farid et al., 2022). Additionally, *in vitro* experiments utilizing intestinal cell models have demonstrated that quercetin, a component of grape pomace, effectively reduces blood glucose levels. These findings corroborate the antidiabetic potential of the polyphenolic content in grape components, emphasizing the role of grape seeds and skins in diabetes management (Hegedüs et al., 2022). Studies show that different proteins and enzymes are involved in these antidiabetic activities (Li et al., 2014; Rasines-perea & Teissedre, 2017). carried out *in vitro* tests with the polyphenol's resveratrol, quercetin, rutin, caffeic acid and gallic acid on the activity of ectonucleotides, adenosine deaminase and platelet aggregation in control and diabetic rats. The results obtained demonstrated an increase in the levels of lipid peroxidation in the liver and kidney of diabetic rats and the treatment with resveratrol (10 and 20 mg/kg) prevented this increase (Systems & Leporatti, 2022). A study conducted to evaluate the role of grape seed extract (GSE) administration during MSC transplantation in streptozotocin-induced type I diabetes (STZ), and also to test some of the components of GSE [procyanidins (P)-B1 and P-C1] in conjunction with MSCs, *in vivo*, with the intention of determining whether one of them was more effective in alleviating the measured attributes of diabetes than the entire GSE, showed that GSE/MSC therapy in type I-induced diabetic rats dramatically controlled the homeostasis of glucose and insulin secretion; Along with, improvement in levels of inflammatory markers and oxidative stress, demonstrating that co-treatment with GSE and MSCs *in vivo* regenerates beta cells in type I-induced diabetic rats (Farid et al., 2022). *In vitro* studies, using intestinal cell models, demonstrate that quercetin reduces blood glucose levels, proving the effect of the polyphenol content of grape pomace (grape seeds and skins) on diabetes (Hegedüs et al., 2022).

Neuroprotective efects

Oligomers of resveratrol, including (+) -vitisinol, (+)-ε-viniferin, (+)-ampelopsin A, (+)-vitisin A and (-)-viticin B, that were isolated from a stembark extract of *V. vinifera*, have inhibitory effects on BACE-1 (beta-site APP-cleaving enzyme 1) *in vitro*. BACE-1 inhibition is an important target for the treatment of Alzheimer's diseases as β-secretase in neurons is essential to produce beta-amyloid (Nassiri-Asl & Hosseinzadeh, 2016). Studies with resveratrol demonstrate positive results for treatment of mice with Alzheimer's related to age, disease, better cognition impairment, and increasing the life span of the animals (Nassiri-Asl & Hosseinzadeh, 2016; Systems & Leporatti, 2022; Yu et al., 2019). Administration of grape seed proanthocyanins (500 mg/kg) could improve abnormal peripheral nerve functions and impaired nervous tissues in the spinal cord of rats with type 2 diabetes mellitus. In addition, this dose showed no inhibitory effect on Ca^{2+} overload in sciatic nerves (Li et al., 2014; Rasines-perea & Teissedre, 2017). Singh et al. found that resveratrol promotes neuroprotection by enhancing cellular antioxidant defenses and triggering neuroprotective pathways. This compound's multifaceted action, observed *in vitro* in human cells and *in vivo* in rodents, offers protection against ischemic damage in the heart and brain, primarily due to its antioxidant, anti-inflammatory, and anti-apoptotic effects, along with other pathways (Singh et al., 2013; Xia et al., 2019).

Hepatoprotective effects

Studies have demonstrated that resveratrol mitigates hepatic injury resulting from toxic insults and oxidative stress; its protective role involves enhancing the expression of antioxidant enzymes, reducing inflammatory cytokines, and curbing fibrosis through the suppression of hepatic stellate cell activation (Alshehri & Alorfi, 2023). Animal models with induced liver injury have shown that resveratrol treatment can reduce markers of liver damage such as ALT and AST, pointing towards its potential hepatoprotective effect (Alshehri & Alorfi, 2023). Proanthocyanidins have demonstrated the ability to scavenge free radicals and reduce oxidative stress in the liver; they also modulate liver enzyme levels and improve overall liver function. *In vivo* experimental models with drug-induced liver injuries, grape seed extracts rich in proanthocyanidins have been shown to reduce liver damage and fibrosis (Amer et al., 2022). Anthocyanins exert their hepatoprotective effects primarily through their antioxidant capacities (Câmara et al., 2022). They mitigate oxidative stress in hepatocytes, thereby preventing liver damage. Studies on rodents have suggested that anthocyanin supplementation can alleviate liver injury by decreasing oxidative stress markers and improving liver enzyme profiles (Sangsefidi et al., 2021). Polyphenols have demonstrated abilities to reduce inflammation in the liver and improve its regenerative capacity (Rudrapal et al., 2022). Dietary supplementation with grape-derived polyphenols in animal models has resulted in decreased levels of pro-inflammatory markers and improvement in the histological appearance of the liver (Rana et al., 2022). Through a diet, in rats, that included 15% grape seed powder, their tissues were protected, including the liver, against oxidative stress induced by 20% ethanol (Dembitsky et al., 2011). In this study, it was suggested that the intake of functional foods helps prevent chronic degenerative liver diseases. Study with groups of hamsters fed a hyper lipidic diet and flour with grape compost for 28 days showed that the diet did not interfere with the reverse transport of cholesterol and significantly improved the antioxidant status, exhibiting high activities of SOD and Cat enzymes even after administration of a hyperlipidemic diet, avoiding oxidative stress and the consequent inflammation and steatosis of the hepatic tissue, which was verified by normal levels of AST and ALT proteins in the groups (Ishimoto & Vicente, 2020). Even the excessive consumption of dietary fat, the results show that the treatment with grape juice protected the liver of the animals, maintaining the percentage of viable cells, apoptotic cells and non-apoptotic cells without alteration (V. M. Ribeiro et al., 2018). As outlined in Table 2, the bioavailability and therapeutic potential of bioactive components in grapes such as polyphenols, anthocyanins, resveratrol, proanthocyanidins, and quercetin, demonstrate a range of health benefits including antioxidant, anti-inflammatory, and anticancer effects (Table 3).

Human clinical studies

Many human intervention studies have been reported with grape-derived beverages, such as red wine and whole red grape juice, featuring a complex array of polyphenols, including anthocyanins and resveratrol. In a review of human intervention studies carried out between 2010 and 2023, the main results analyzed were the antioxidant effect, acting to prevent oxidative reactions and ROS formation, and also its anti-proliferative and anti-inflammatory properties, benefiting various cellular processes (Nguyen, 2023; Springer & Moco, 2019; Tomé-Carneiro et al., 2012). Another study analyzed the relationship between the consumption of grapes and non-alcoholic grape products (raisins and whole juice) with two different age groups from 2 to 19 years old ($n=9622$) and adults aged 20 or more years ($n=12{,}251$), the surprising results that the consumption of grape derivatives is associated with a healthier eating pattern, with lower fat intake and added sugar, in both groups (Ergün, 2021; Percival & West, 2013). A recent study analyzed 13 articles, 12 studies controlled *in vivo* and 1 controlled *in vivo* and *in vitro* and the results satisfied positive results with the use of Grape Seed Extract as a pre-treatment to prevent or delay Parkinson's disease and post-treatment to relieve or reduce the symptoms of Parkinson's disease. Demonstrating significantly reduced damage caused by oxidative stress and improved antioxidant status in all subjects (Nguyen, 2023).

Synergistic effects of combinatory treatment of grapes' bioactive compounds and conventional drugs

The combination of natural compounds and conventional drugs is becoming an intriguing approach in therapeutic strategies. Grapes, a rich source of bioactive compounds, have been researched for their potential synergistic interactions with various drugs, enhancing therapeutic outcomes or attenuating side effects.

Resveratrol and statins

Both resveratrol and statins have cholesterol-lowering effects. Resveratrol enhances endothelial nitric oxide production, promoting vasodilation, while statins inhibit.

Table 2 Bioavailability, metabolism, and therapeutic potential of grape bioactive components

Bioactive compounds	Bioavailability and metabolism	Health benefits	References
Polyphenols (Flavones, Isoflavones, Flavanols, Anthocyanins)	absorbed without deglycosylation in the stomach metabolized by intestinal and colonic microbiota into bioavailable forms postprandial plasma levels < 1 µm; intestinal concentrations up to 100-fold higher half-lives: 2–28 h	Antioxidant, Anti-inflammatory, anticancer, Cardioprotective effects	Abbas et al., 2017; Liu et al., 2019; Panchal & Brown, 2023; Williamson et al., 2017; Manach et al., 2004; Percival & West, 2013
Anthocyanins	direct absorption in stomach via specific transporters degraded into low-polymeric forms for improved absorption by colonic microbiota	Antiviral, Anticancer, Cardioprotective, Hepatoprotective properties	H. Zhang et al., 2014; Panchal & Brown, 2023; Fakhri et al., 2020
Resveratrol	exhibits inhibitory effects against *H. Pylori* synergizes with chemotherapeutic agents	Antibacterial, Antifungal, Antiviral, Anticancer, Cardioprotective, Neuroprotective, Hepatoprotective	Nassiri-Asl & Hosseinzadeh, 2016
Proanthocyanidins	rapidly metabolized with significant bioavailability	Anticancer, Cardioprotective, Antidiabetic, Neuroprotective, Hepatoprotective effects	Vislocky & Fernandez, 2010; Cheah et al., 2014; Farid et al., 2022
Quercetin	absorbed in the small intestine as aglycones, with extensive metabolism circulating plasma derivatives	Antioxidant, Anti-inflammatory, Antibacterial, Anticancer, Aardioprotective, Antidiabetic, Neuroprotective effects	Simonetti et al., 2020; Sehitoglu et al., 2014; Hegedüs et al., 2022

Table 3 Summary of grape-derived bioactive compounds and their effects on health

Biological Property	Tested Bioactive Compound(s)	Model	Dose	Method	Effect	Reference
Antioxidant Anti-inflammatory	Flavonoids, Polyphenols	Clinical study	750 ml red wine daily with McDonald´s and Mediterranean Meal	Randomized crossover trial	↑ Antioxidant potential confirmed against chronic non-communicable diseases linked to inflammation	Renzo et al., 2014
	Total Phenolics, Flavonoids	*In vitro* (HepG2 cells)	150 mg/mL grape extract	Cell treatment	↑ Antioxidant and radical scavenging; ↓ cell proliferation (25–82%)	Li et al., 2014
	Resveratrol	*In vivo* (animal)	Varied fat content diets with grape juice/red wine/coat solution	Plasma ORAC DPPH methods	↑ CAT activity up to 273% with high polyphenol content drinks compared to control	Ribeiro, 2018
Antibacterial Antiviral Antifungal	Resveratrol	*In vivo* (animal)	Ethanolic grape skin and flesh extract 2.5 g/kg, p.o, for 12 weeks	Daily oral dose	↓Oxidative stress ↑ Immune function ↓Angiogenesis	Nassiri-Asl & Hosseinzadeh, 2016
Neuroprotective	Quercetin	*In vivo* (animal)	Öküzgözü grape juice 2 mL/kg, for 28 days (quercetin equivalent of 5.2 ± 0.19 µg/mL)	Cell treatment	↑ Antioxidant capacity, ↑LDL oxidation protection ↑ neuroprotective effects	(Pirinççioğlu et al., 2012)
	Resveratrol	*In vitro* (animal cells)	1, 3, or 30 µM	Cell treatment	↑ Neuroprotection	Singh et al., 2013
		Clinical study	100 mg/kg body weight daily	Daily oral dose	↓Cytokines ↓Chemokines	
Antibacterial	Quercetin, Resveratrol	*In vivo* (Human cells)	3 mg/mL in grape seed extract	Treatment cells	↑ Antibacterial effects against methicillin-resistant *Staphylococcus aureus*	Nassiri-Asl & Hosseinzadeh, 2016
Antifungal	Gallic Acid, Quercitrin	*In vivo* (Human)	Not reported	Daily oral dose	↓Ergosterol biosynthesis ↓Folate pathways	Simonetti et al., 2020
Hepatoprotective Cardioprotective	Phenolic Compounds	*In vivo* (animal) *In vitro*	Control, Hyperlipidemic, 20% wine/juice pomace flour supplemented diets	Daily oral dose Cell treatment	↑Antioxidant status ↓ Oxidative stress ↓Inflammation ↓liver steatosis ↑ Cardioprotection	Ishimoto & Vicente, 2020
Cardioprotective	Phenolic Acids, Flavonoids, Anthocyanins, Stilbenes, Lipids	*In vivo* And Clinical study	250–375 mg/kg/day (animal); 200 or 400 mg or placebo (human)	Daily oral dose, Randomized study	↓ Elevated blood pressure ↑Endothelial function ↓Oxidative stress	Sabra et al., 2021; Vaisman & Niv, 2015
Antidiabetic	Polyphenols	*In vitro* (Human cells)	0.26 or 10 mg/mL	Cell treatment	↓α-amylase ↓α-glucosidase	Ćorković et al., 2022
Anticancer	Resveratrol	*In vivo* (animal)	5, 15, 45 mg/kg resveratrol and 200 mg/kg NAC	Daily injection dose	↓Oxidative injury	Bohara et al., 2022

CAT Catalase, *CG* Control Group, *DH* Diet High in fat, *GJ* Grape Juice, *H* Hyperlipidemic, *HD* High Density, *NAC* N-Acetyl-L-Cysteine, *ORAC* Oxygen Radical Absorbance Capacity

3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), a key enzyme in cholesterol synthesis (Soner & Sahin, 2014). Studies have shown that the combination of resveratrol and statins results in a more pronounced reduction in low-density lipoprotein (LDL) cholesterol and improvement in endothelial function than either agent alone (Soner & Sahin, 2014).

Proanthocyanidins and antihypertensive drugs

Proanthocyanidins are known to enhance endothelial function and reduce blood pressure, while conventional antihypertensives act via various mechanisms, like angiotensin-converting enzyme (ACE) inhibition or calcium channel blockade (Odai et al., 2019). Some studies indicate that grape seed extracts, rich in proanthocyanidins, can potentiate the blood pressure-lowering effect of certain antihypertensive medications (Odai et al., 2019).

Anthocyanins and diabetes medications

Anthocyanins have been shown to improve insulin sensitivity and reduce blood glucose levels. When combined with conventional diabetes drugs like metformin, which reduces hepatic glucose production, a potential synergistic glucose-lowering effect is suggested (Solverson, 2020). Preliminary clinical studies have demonstrated improved glycemic control in patients consuming anthocyanin-rich foods alongside standard diabetes treatments (Burton-Freeman et al., 2019).

Polyphenols and non-steroidal anti-inflammatory drugs (NSAIDs)

Grape-derived polyphenols exhibit anti-inflammatory properties by inhibiting pro-inflammatory cytokines. When combined with nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit cyclooxygenase (COX) enzymes, there is potential for enhanced anti-inflammatory action with reduced side effects (González-Ponce et al., 2018). In animal models, the combination of grape polyphenols and NSAIDs resulted in more pronounced anti-inflammatory effects with reduced gastrointestinal toxicity typically seen with NSAIDs (González-Ponce et al., 2018).

Flavonoids and chemotherapeutic agents

Grape-derived flavonoids, like quercetin, have been observed to induce apoptosis in cancer cells. In combination with chemotherapeutic drugs, there might be an enhanced anti-cancer effect and possibly reduced resistance to chemotherapy (Zhai et al., 2021). *In vitro* pharmacological studies with cancer cell lines have shown that the combined treatment of grape flavonoids and certain chemotherapeutic drugs can result in an enhanced reduction in cell viability (Liskova et al., 2021; Zhai et al., 2021).

The results of a study demonstrated in freeze-dried red grape juice, in doses up to 0.01 μg, cardioprotective effects against doxorubicin-induced toxicity in heart-derived H9c2 myocytes. In contrast, at doses of 0.01 μg to 0.05 μg, it increased oxidative stress in heart cells, probably due to pro-oxidant effects of juice, as indicated primarily by the increase of reactive nitrogen and antioxidant species enzymatic levels (Nassiri-Asl & Hosseinzadeh, 2016). In contrast, Boccalandro et al. (2011) suggested that melatonin is an antioxidant present in grapes, after finding an inverse relationship between melatonin and malondialdehyde (MDA) levels in the fruit of *V. vinifera* cv. Malbec (Boccalandro et al., 2011). Polyphenols in abundance, present in grape pomace extract, have shown dual effects both *in vitro* and *in vivo*. *In vitro*, the extract eliminated free radicals and inhibited peroxyl-induced DNA damage and Hydroxyl radicals, but *in vivo*, induced oxidative stress by increasing the carbonyl groups of the protein in erythrocytes and cardiac cells, increasing plasma Thiobarbituric acidic reactive substances, and decreased concentration of glutathione in the liver (Veskoukis et al., 2012). Liang et al. (2014) conducted a study with 24 grape cultivars V. vinifera, where they found a direct relationship between total phenolic compounds and flavonoids and antioxidant activity (Liang et al., 2014). The literature reports on the comparative effect of sitagliptin with and without resveratrol on clear cell kidney cancer, demonstrating that renal function was significantly improved by sitagliptin and/or resveratrol, while significantly increasing tissue antioxidant defenses when administered simultaneously, reinforcing the hypothesis that the combination of sitagliptin and resveratrol may be an appropriate treatment method to improve clear cell kidney cancer (Almatroodi et al., 2022). While the synergistic effects of combining grape bioactive compounds with conventional drugs can offer enhanced therapeutic benefits, it is also fundamental to consider potential negative interactions; the complex interplay between the polyphenolic content of grapes and certain medications may lead to altered drug metabolism or efficacy. For instance, grape-derived compounds like resveratrol may interact with cytochrome P450 enzymes, potentially affecting the pharmacokinetics of drugs metabolized by these pathways (Foti, 2023). Furthermore, the high antioxidant properties of grape compounds, while beneficial in many contexts, could theoretically reduce the effectiveness of certain chemotherapeutic agents that rely on oxidative mechanisms to exert their cytotoxic effects (Vélez et al., 2023). Therefore, while exploring the beneficial synergies, it is necessary to conduct comprehensive studies to fully understand and mitigate any adverse outcomes stemming from the concomitant use of grape bioactives and conventional medications.

Toxicology and safety data

Most of the evidence on disease prevention using bioactive compounds from grapes comes from *in vitro* or animal experiments, which generally use very high doses compared to what humans consume through diet. There is no consensus regarding the recommended effective dose of all bioactive compounds found in grapes to achieve the various beneficial health effects. According to experimental studies, doses of 2.5 or 5.0 mg/kg of resveratrol recorded the expression of enzymes involved in cell survival signaling pathways, while higher doses of 25 and 50 mg/kg, potentiated signs of cell death. Other authors claim that doses of 5 g/day of resveratrol help prevent diseases such as cancer, metabolic syndrome, Alzheimer's disease, among others (Genovese et al., 2008; Li et al., 2014). Khadem-Ansari et al (2011), Ben Youssef et al (2021) relate the effects of grape vitamins, mostly, to the phenolic compounds that are part of its composition. However, the occurrence of these compounds in a relevant concentration in the grape and its derivatives does not guarantee the effective action in the organism, being important to evaluate aspects such as isomerism, conjugation with other descendent in the product or in the organism, in addition to the transformation during processing, among others, that may influence the bio accessibility, bioavailability and bioactivity of phenolic compounds (Ben Youssef et al., 2021; Khadem-Ansari et al., 2011; Li et al., 2014; Rocha et al., 2012). Studies have shown that resveratrol at doses of 0.5 and 1 g was completely safe and what gastrointestinal adverse effects appeared with doses of 2.5 and 5 g. Maximal plasma levels (CMax) and areas under the curve (AUC) of the metabolites were greater than those of resveratrol. Resveratrol has chemo preventive effects by decrease circulating levels of insulin-like growth factor1 and insulin-like growth factor-3 binding protein (Nassiri-Asl & Hosseinzadeh, 2016).

Therapeutic perspectives, limitations and clinical pitfalls

As evidenced in several studies, the bioactive compounds in grapes have anti-inflammatory, antimicrobial, anticancer properties, help with glycemic and cholesterol control, among other effects. The articles assume that a sufficient dose for an effect is needed with each consumption and that, unlike minerals and vitamins, the active component is not temporarily stored or retained in the body. The active component is not temporarily stored or retained in the body. On the other hand, for components such as grape flavonoids, which are not stored in the body, the magnitude of the effect is dose dependent. A truly important question in this area would be what value is needed for the smallest biologically significant effect that would be effective and observable over an adequate period, also considering (Blesso, 2019; Gratl et al., 2021; Olędzki et al., 2022; Olivati et al., 2019; Sabra et al., 2021). The sub-compounds that accumulate and become apparent over weeks, months or even years. Therefore, one proposition is that balanced daily intake of food sources is recommended to achieve desirable levels of these compounds under normal physiological conditions (Springer & Moco, 2019). Grapes, both as whole fruits and as sources of bioactive compounds, have been linked to an array of health benefits, from cardiovascular protection to anti-cancer properties. Yet, while the scientific literature provides promising insights, there are limitations and clinical gaps that warrant consideration. Much of the evidence on grapes' health benefits stems from *in vitro* studies. The behavior of bioactive compounds in cell cultures does not necessarily translate directly to complex physiological systems in living organisms. The therapeutic potential of grape-derived compounds can be limited by their bioavailability. While these compounds may exhibit strong therapeutic effects in studies, the fraction that becomes available for use by the body's cells after consumption can be minimal. The optimal dose of grape-derived compounds for therapeutic purposes remains unclear. Variability in study dosages makes it challenging to determine a universally recommended intake. Grapes come in various species, each with a distinct profile of bioactive compounds. This heterogeneity can lead to inconsistencies in research findings, depending on the grape species or variety used. Many studies on grapes' health benefits are of short duration and long-term effects, particularly concerning chronic disease outcomes, are less documented. While numerous animal and *in vitro* studies have showcased the benefits of grapes, large-scale randomized controlled trials in humans are fewer; these are critical for establishing causality and real-world effectiveness. The interactions between grape-derived compounds and conventional medications remain under-researched. This gap is important as many populations of interest (e.g., the elderly) are often on multiple medications. The biological effects of grapes and their compounds may vary based on genetics, age, gender, and health status, tailored research to understand these differential effects is sparse. Much of the current research focuses predominantly on certain compounds like resveratrol, potentially overshadowing other beneficial compounds in grapes. The potential health benefits of grapes and their derived compounds are undoubtedly promising. However, the existing limitations and clinical gaps underscore the need for continued, rigorous research. Addressing these clinical pitfalls will provide a more comprehensive understanding, paving the way for more definitive recommendations and applications in clinical settings.

Conclusion and future perspectives

The current review explores the multifaceted health benefits attributed to grape-derived bioactives, particularly emphasizing their role in combating chronic diseases such as cardiovascular disorders, diabetes, and cancer. By synthesizing data from a spectrum of *in vitro*, *in vivo*, and clinical studies, it affirms the substantial impact that these bioactive compounds, notably polyphenols, can have on disease prevention and health optimization. The review aligns with the study's aims by detailing the pharmacological potential of grapes, underscored by their diverse array of antioxidants that contribute significantly to anti-inflammatory, antimicrobial, anticancer activities, and regulatory effects on glycemic and cholesterol levels. Despite the compelling evidence, the review identifies a critical gap in human-based clinical trials and bioavailability studies, underscoring the need for further research to validate these preliminary findings and translate them into concrete dietary recommendations. Moreover, the review calls for an expanded investigation into the chemical compositions of various grape varieties, especially those less explored, to uncover additional health benefits and enhance our understanding of grapes' contributions to dietary health and disease prevention. Moving forward, the focus should be on: i) conducting comprehensive clinical trials to establish the efficacy of grape-derived bioactives in human health and determine optimal consumption guidelines; ii) investigating the bioavailability and metabolic pathways of these compounds in humans to understand their actual impact on health. Exploring the synergistic effects of grape bioactives with conventional drugs to enhance therapeutic outcomes and minimize adverse interactions; iii) diversifying research to include a broader range of grape varieties and delve into less-studied bioactives to uncover new health-promoting potentials; iv) examining the long-term effects of grape consumption on chronic disease prevention and management. In embracing these future research directions, the potential of grapes in health maintenance and therapeutic interventions can be fully harnessed, bridging the gap from bench to bedside.

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All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. That is revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and, confirming to be accountable for all aspects of the work.

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