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REVIEW

# The α-Amylase and α-Glucosidase Inhibition Capacity of Grape Pomace: A Review

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## Abstract

The concept of functional foods is gaining more importance due to its role in maintaining a healthy status and preventing some metabolic diseases. The control of diabetes, in particular type-2 (T2DM), could be considered a big challenge since it involves other factors such as eating habits. From the pharmacological point of view, inhibiting digestive enzymes, such as α-amylase and α-glucosidase, is one of the mechanisms mainly used by synthetic drugs to control this disease; however, several side effects are described. For that reason, using bioactive compounds may appear as an alternative without presenting the complications synthetic drugs available on the market have. The winemaking industry generates tons of waste annually, and grape pomace (GP) is the most important. GP is recognized for its nutritional value and as a source of bioactive compounds that are helpful for human health. This review highlights the importance of GP as a possible source of α-amylase and α-glucosidase inhibitors. Also, it is emphasized the components involved in this bioactivity and the possible interactions among them. Especially, some phenolic compounds and fiber of GP are the main ones responsible for interfering with the human digestive enzymes. Preliminary studies in vitro confirmed this bioactivity; however, further information is required to allow the specific use of GP as a functional ingredient inside the market of products recommended for people with diabetes.

**Keywords** Grape pomace · α-Amylase and α-glucosidase inhibition · Functional ingredients · Phenolic compounds · Fiber · Antidiabetic activity

## Introduction

Functional foods contain biologically active compounds, which are responsible for providing health benefits beyond their nutritional capacities (Alongi & Anese, 2021), in particular antioxidant, anti-inflammatory, and antidiabetic activities assessed at in vitro level (Banwo et al., 2021). These capacities turn into health claims after their recognition and authorization, according to the region regulations. For example, according to the European law, it is included inside the Reg. (EU) n. 353/2008 (Alongi & Anese, 2021).

Diabetes is one of the health challenges of the twenty-first century and the number of adults affected by diabetes is more than tripled over the past 20 years. The 10th edition 2021 of the International Diabetes Federation (*IDF*) shows that 537 million adults are currently living with this disease (International Diabetes Federation, 2021). IDF estimates that there will be 643 million adults with diabetes by 2030 and 783 million by 2045. The inhibition of some digestive enzymes, such as α-amylase and α-glucosidase, is one of the options to control this disease by synthetic drugs. However, gastrointestinal discomfort and lactic acidosis are some adverse effects reported (Venkatakrishnan et al., 2019). Currently, there is evidence about the in vitro ability of several fruits, vegetables, and mushrooms to inhibit the activity of these human digestive enzymes (Lin et al., 2022; Papoutsis et al., 2021; Vadivel et al., 2012).

In this regard, Mediterranean diet could be a good option since it is based on local products, mainly of vegetal origin, scarcely processed, and stored for a short time (Sáez-Almendros et al., 2013). However, this food chain generates big amounts of by-products, being necessary to find environmental friendly strategies to revalorize them (Berry, 2019). In this frame,

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several food industry by-products have been demonstrated to present α-amylase and α-glucosidase inhibition activities, fostering their valorization and the circular economy issue (Fernandes et al., 2020b; Khan et al., 2016; Mahindrakar & Rathod, 2021; Mwakalukwa et al., 2020). For example, the wine industry, which is related to the Mediterranean diet (Ditano-Vázquez et al., 2019), generates more than 9 million tons of grape pomace (GP) per year (Ferri et al., 2017), representing an environmental challenge. An amount of 20–25 kg of GP is estimated to be obtained from 100 kg of grapes and big amounts of this by-product are produced, mainly seasonally (Lavelli, 2021; Muñoz-Bernal et al., 2021).

GP has been recognized to prevent insulin resistance and inflammation (Martínez-Maqueda et al., 2018; Rodriguez Lanzi et al., 2016). In addition, different compounds present in GP such as phenols and fiber were attributed to present antihyperglycemic effects, mainly through the inhibition of the enzymes α-amylase and α-glucosidase (de Paulo Farias et al., 2021; Saikia & Mahanta, 2016). Therefore, the aim of this review was to highlight the potential of GP in inhibiting α-amylase and α-glucosidase enzymes, serving as a possible tool in the diabetes control.

## Methodology

Existing studies related to the GP ability to inhibit α-amylase and α-glucosidase enzymes were gathered to discuss the results currently available. The literature research was carried out in the Scopus database through the period 2002–2022, using initially the keyword "grape pomace." The search revealed active research on this topic with 1642 articles, out of which 1451, 67, 57, and 49 were research articles, reviews, conference papers, and book chapters, respectively. Most of them (1379) were published from 2012 to 2022, 2021 being the year with the highest number of publications (231).

Then, the research was restricted to scientific papers focused on the inhibition of α-amylase and α-glucosidase by GP, using the keywords "grape pomace + alpha amylase" and "grape pomace + alpha glucosidase." The number of documents available was reduced to 15 and 20 for the first and second keyword, respectively. This topic has been studied from 2010 onwards, especially in 2020 and 2021. The articles were categorized into the following scientific areas: agriculture and biological sciences (55%), biochemistry (30%), and chemistry (15%). Spain and Chile played the major role in researching this topic. The list of the publications was screened based on the title, authors, and year, and studies not related to the agricultural, biological, and chemistry fields were excluded. After identifying and screening, 10 research articles were selected to discuss the use of GP to inhibit the activity of α-amylase and α-glucosidase.

## Diabetes

Diabetes mellitus (DM) is a chronic non-communicable disease (WHO, 2021) that occurs when the endocrine pancreas is not able to secrete suitable amount of insulin, or when the body does not respond to the insulin it produces. The disease is mainly classified into many types; however, the most common are type 1 (T1) and type 2 (T2) DM. The first one is mainly the consequence of an autoimmune T-cell-mediated reaction against the insulin-producing β-cells of the pancreas. As a result, the body produces very little or no insulin. The second one is the most common type of diabetes, in which hyperglycemia is mainly due to insulin resistance and reduction of insulin production (Gharravi et al., 2018; Mahindrakar & Rathod, 2021; Tan et al., 2019). The insulin resistance is described to be the result of intracellular lipid-induced inhibition of insulin-stimulated insulin-receptor substrate (IRS)-1 tyrosine phosphorylation that determines a reduced IRS-1-associated phosphatidyl inositol 3 kinase activity (Petersen & Shulman, 2006).

A reduced life expectancy is found in both DM types, even if it is shorter in the T1DM compared to T2DM, as a consequence of a higher incidence of cardiovascular diseases and acute metabolic disorders in the former (Wise, 2016). In all forms of diabetes, an early stage diagnosis and management are important to prevent or slow down the potential complications such as diabetic nephropathy, retinopathy, cardiovascular diseases, and diabetic foot ulcer (Khalil, 2017). The potential risk factors, especially for the T2DM, include obesity and unhealthy diets, mainly due to the excessive increase of carbohydrates and fat intake, as well as physical inactivity (Tan & Chang, 2017). Currently, the westernized diet increases the prevalence of specific forms of malnutrition (overweight, obesity, metabolic syndrome, among others), which is exacerbated by the present COVID-19 pandemic (FAO, 2020). Moreover, diabetes is an important risk factor for COVID-19 complications (McGurnaghan et al., 2021; Nassar et al., 2021). Under this point of view, the increasing prevalence of T2DM worldwide is a consequence of a complex interplay of socioeconomic, demographic, environmental, and genetic factors (Tan et al., 2019).

In order to control T2DM, it is encouraged to correct the lifestyle, to reduce the body mass index, and the use of oral antidiabetic drugs. For example, the most used in T2DM management are insulin secretagogues, drugs that reduce insulin resistance, and carbohydrate digestive enzyme inhibitors (AGIs) (Campbell, 2007; Fernandes et al., 2020b). The enzymes α-amylase and α-glucosidase are the main ones inhibited. Both are hydrolases, the activity of α-amylase being to catalyze the starch hydrolysis and it needs the presence of calcium as a metal co-factor. This enzyme is produced in the salivary glands and pancreas, and then it is secreted into the mouth and the small intestine, respectively (Papoutsis et al., 2021). The di- and oligosaccharides obtained after the α-amylase activity undergo further hydrolysis to glucose, carried out by α-glucosidases, located in the brush border of the small intestine (Li et al., 2022).

These enzymes are recognized as targets for modulating the postprandial hyperglycemia (Yang & Kong, 2016), maintaining the overall body glucose levels (Gummidi et al., 2021), and they are present in several plant species due to their bioactive compounds (de Sales et al., 2012).

Acarbose is an AGI, specifically a pseudo-tetrasaccharide that has a nitrogen between the first and second glucose molecules, possessing a particular high affinity for the α-glucosidase enzyme (Tuyen et al., 2021). Both enzymes are inhibited in a competitive way, reducing their affinity to the oligosaccharides from dietary starch as well as decreasing the monosaccharide formation rate (Rosak & Mertes, 2012).

Nevertheless, the carbohydrate digestive enzyme inhibitors are not free from side effects, such as flatulence and diarrhea, abdominal pain, and a reduced nutrient absorption (Wang et al., 2020). In particular, acarbose often generates side effects as a consequence of its non-specific inhibition of α-amylase. This results in an excessive accumulation of undigested carbohydrates in the large intestine (Cardullo et al., 2021).

Taking into account this consideration, the search for more specific and better tolerated α-glucosidase and α-amylase inhibitors with limited effects is an important issue. Therefore, the use of phytochemicals is encouraged, as a consequence of their effectiveness, availability, and low toxicity (de Paulo Farias et al., 2021; Kadouh et al., 2016; Lv et al., 2019). So far, some plant extracts have been reported to counteract T2DM by inhibiting digestive enzymes even stronger than the commercial drugs (Tan & Chang, 2017) or acting synergistically with them (Boath et al., 2012). Natural extracts, especially the ones rich in proanthocyanidins, have shown the ability to inhibit the intestinal α-amylase and α-glucosidase, potentially constituting an alternative to the synthetic AGIs (Yilmazer-Musa et al., 2012).

## Grape Pomace

The wine production represents a huge part of the agriculture and beverage industries. Therefore, it generates a high amount of waste, GP being the most important one (Ilyas et al., 2021). In this regard, 1 kg of GP is produced from each 6 L of wine (García-Lomillo & González-SanJosé, 2017). Among the current applications of this by-product, its uses as fertilizers (especially grape stems), heat producers, and cattle feed are the most highlighted (Antonić et al., 2020; Maragkoudakis et al., 2013; Ribeiro et al., 2015). In addition, GP can be used to produce some value-added components such as edible acids (citric, tartaric, and malic acids) and dietary fiber, as well as ethanol (Ilyas et al., 2021). Moreover, GP is the starting point for preparing alcoholic spirits like Italian grappa (Cisneros-Yupanqui et al., 2021).

After the winemaking process, part of the bioactive compounds in grapes is transferred to the wine; however, a high concentration remains in the residues (Fontana et al., 2013; Gonçalves et al., 2017; José Jara-Palacios et al., 2014; Messina et al., 2019; Ribeiro et al., 2015). Therefore, the recognition of GP as a source of health-promoting components has highly encouraged its use as a food ingredient within the industry (Carmona-Jiménez et al., 2018; Pérez-Jiménez et al., 2009; Rodríguez-Morgado et al., 2015). Among the components found in GP, phenolic compounds and dietary fibers are the most reported in the literature, whose proportion after the winemaking process is up to 85 and 70%, respectively (Rocchetti et al., 2021).

## Grape Pomace Health-promoting Components

Phenolic compounds are found in most plants and more than 10,000 structures have been detected so far (Alqahtani et al., 2013). Their great potentials as powerful bioactive compounds, health-promoting, and disease-preventing have increased the interest in these secondary metabolites in recent years (Ebrahimi & Lante, 2021; Tan & Chang, 2017). The content of phenolic compounds and their composition rely on the growth region, climate, and grape variety, among other factors related to the winemaking process (Muñoz-Bernal et al., 2021). The phenolic compounds in grape berries are distributed in the pulp, seeds, and skin, these two last ones being the main sources (Gonçalves et al., 2017), especially of procyanidins (Álvarez et al., 2012). Part of these bioactive compounds remain in the GP after the winemaking, along with important quantities of catechins, epicatechins, and flavan-3-ols, mainly due to the hydrogen bonds and their hydrophobicity (Barba et al., 2015; Cisneros-Yupanqui et al., 2020a; Muñoz-Bernal et al., 2021). In addition, the phenolic compounds present in GP have shown a good stability, especially as a powder, during the storage (Cisneros-Yupanqui et al., 2020b), showing its potential to be considered as a food ingredient. So far, the phenolic compounds present in GP have had different applications, as summarized in Table 1. In all the cases, the concentration of phenolic compounds and antioxidant activity has increased after the fortification with GP, regardless the food matrix (Fernández-Fernández et al., 2022; Lavelli et al., 2016; Rainero et al., 2021) and the type of GP employed. In some cases, the addition of GP was useful to delay the lipid oxidation (Cisneros-Yupanqui et al., 2020a; García-Lomillo et al., 2017) not only the one derived from the winemaking process, but also the GP from the juice industry, when applying it in frozen salmon burgers at 2% (Cilli et al., 2019). Moreover, the addition of GP has increased the characteristics of a fortified wheat bread and pasta, presenting a better volume, firmness, taste intensity, and color (Šporin et al., 2018; Tolve et al., 2020). However, the firmness and consistency of a GP-fortified yogurt

**Table 1** Phenolic compounds from grape pomace used in the fortification of different food products

| Winery by-product | Food matrix | Grape by-product concentration | Results | References |
|---|---|---|---|---|
| Red (Valpolicella) grape pomace (GP) from winemaking | Corn oil | 1, 2, 3% of GP powder | -Epicatechins were the most predominant phenolic compounds found in GP<br>-Corn oil + 1% GP delayed the corn oil oxidation by 10% | Cisneros-Yupanqui et al. (2020a) |
| GP, seeds, and skin from winemaking | Home-made yogurt | 5 mg/mL of winery by-products | -GP, seeds and skin fortified yogurts obtained higher TPC and antioxidant activity than the control<br>-The total lactose and fat percentage were lower in yogurts supplemented with GP, seeds, and skin<br>-The firmness and consistency of the yogurt did not change significantly when adding GP, seeds, and skin along 21 days of storage | Iriondo-DeHond et al. (2020) |
| Unfermented white GP with a further selection of skins | -Tomato puree<br>-Flat bread | 3% and 10% of grape skin for tomato and bread, respectively | -Almost all the white grape skin phenolics were found in the enriched foods<br>-Proanthocyanidin solubility was lower in bread than in tomato puree | Lavelli et al. (2016) |
| Red (Merlon) and white (Zelen) GP from winemaking | -Wheat bread | 6%, 10% and 15% of GP | -The TPC was improved mostly in the bread fortified with 15% of GP flour, Merlot having the highest concentration<br>-The TPC and the antioxidant activity were highly correlated with the GP flour addition<br>-GP flour addition has an influence on the bread volume, firmness, taste intensity, and crumb and crust color | Šporin et al. (2018) |
| GP, seeds and skin from red winemaking | -Frozen beef patties | 2% of GP, seeds, and skin | -The frozen beef patties fortified with grape skins were the most effective in inhibiting TBARS, due to the TPC | García-Lomillo et al. (2017) |
| Red (Corvina) GP with a further selection of skins | -Durum wheat semolina | 5 and 10% of GP, replacing semolina | -The TPC and antioxidant activity of the fortified pasta was enhanced<br>-The fortified pasta obtained a higher fiber content, from 5.6 to 8.2% than the control (3%) | Tolve et al. (2020) |
| Red (Cabernet) GP with a further selection of skins | -Breadsticks | 5 and 10% of GP, replacing the common wheat flour | -The TPC and antioxidant activity of the fortified breadsticks were enhanced, 10% addition obtaining significantly the highest values | Rainero et al. (2021) |

did not change considerably when comparing to the control (Iriondo-DeHond et al., 2020).

On the other hand, fiber, especially the dietary one, has been studied to promote diverse beneficial effects such as improving the gastrointestinal function, reducing the low-density lipoprotein (LDL) cholesterol, and moderating the response of the postprandial insulin response (Mildner-Szkudlarz et al., 2013). In addition, fiber helps in reducing the risk of cardiovascular diseases and it is defined as an edible carbohydrate analogous, digestion and absorption resistant through small intestinal tract with a fermentation (partial or complete), in the large intestine (Solari-Godiño et al., 2017). Dietary fiber can be classified as soluble and insoluble, the former including β-glucans, hemicellulose, pectin, and oligosaccharides (Dong et al., 2022). The soluble dietary fiber is recognized for lowering glucose levels and controlling obesity in patients with T2DM (Xie et al., 2021), while insoluble fiber prevents constipation and hemorrhoids by going fast through the gastrointestinal tract, providing bulk to the feces (Ain et al., 2019).

GP has been reported to be a rich source of fiber (from 44.2 to 62.6%), which allows its use into bakery and dairy products (Fernández-Fernández et al., 2019, 2022; Oladiran & Emmambux, 2018; Rainero et al., 2021). Furthermore, grape by-products contain mainly cellulose, hemicelluloses, glycans, and pectin (Fontana et al., 2013; Mildner-Szkudlarz et al., 2013; Oladiran & Emmambux, 2018), and the insoluble dietary fraction, such as lignin, has been the most reported one in this type of residue, presenting good water and oil holding capacity as well as antioxidant activity (Mildner-Szkudlarz et al., 2013; Saikia & Mahanta, 2016). The term antioxidant dietary fiber has been introduced to define a products that present both natural antioxidants and the beneficial effects of dietary fiber (Sánchez-Alonso et al., 2007). For example, it could present antioxidant properties and inhibit lipid and protein oxidation (Garcia-Lomillo et al., 2016; Lavelli, 2021; Marchiani et al., 2016; Sáyago-Ayerdi et al., 2009). The association and health effect of dietary fiber and phenolic compounds are appreciated at the large intestine level (Solari-Godiño et al., 2017). Moreover, the ability of phenolic compounds to modify the gut microbiota, improving and inhibiting the growth of beneficial and pathogenic bacteria, respectively, was reported (Gowd et al., 2019).

## Grape Pomace as α-Amylase and α-Glucosidase Inhibitors

Phenolic compounds have been recognized for presenting several bioactivities, including the antidiabetic one, which is mostly related to their capacity of decreasing the postprandial glycemic levels, especially through the inhibition of human digestive enzymes (Alqahtani et al., 2013; Martinez-Gonzalez et al., 2017; Tan & Chang, 2017), with a consequent reduced dietary starch digestion and absorption (Hogan et al., 2011). The inhibition of these enzymes by diverse type of phenolic compounds has been well studied in the literature (Oladiran & Emmambux, 2018; Rocha et al., 2020; Shobana et al., 2009). Phenols are the most involved in these bioactivities (Kato-Schwartz et al., 2020) by binding to either the sites or the substrate of the digestive enzymes, making them inactive (Oladiran & Emmambux, 2018). Some characteristics of phenolic compounds such as the molecular weight, number, and position of substitution are suitable for their digestive enzyme inhibitory activity (Fernandes et al., 2020b). In addition, flavonoids have been recognized to interfere with the α-amylase activity by forming covalent bonds with starch during cooking and in the stomach, decreasing its availability as a substrate for the enzyme (Takahama & Hirota, 2018). Procyanidins of grape seeds are responsible for presenting health-promoting effects such as antioxidant and antihyperglycemic by inhibiting α-amylase and α-glucosidase enzymes (Fernandes et al., 2020a; Takahama & Hirota, 2018; Yilmazer-Musa et al., 2012). These compounds are polymers of flavan-3-ols, which are formed exclusively by catechin and/or epicatechin units (Álvarez et al., 2012). Procyanidins have more potential interaction sites than the monomeric phenolic compounds, so they could crosslink easily with different molecules, such as enzymes (Lavelli et al., 2016). On the other hand, proanthocyanidins have been shown to inhibit these key enzymes, due to their high polymerization degree and numerous hydroxyl groups (Huamán-Castilla et al., 2021). In particular, the high degree of polymerization of these molecules present in ripe fruits showed more potent inhibition of α-amylase and α-glucosidase than the less-polymerized ones, which are typically present in unripe fruits (Zhang et al., 2020).

In addition, proanthocyanidins and anthocyanins have been demonstrated to exert a major role in inhibiting α-amylase and α-glucosidase, respectively (Lavelli et al., 2015), in comparison to acarbose (Yilmazer-Musa et al., 2012). Regarding catechins, it was suggested that galloylated catechins and catechol-type catechins present a higher α-amylase inhibitory activity than non-galloylated and pyrogallol-type ones (Takahama & Hirota, 2018; Yilmazer-Musa et al., 2012). Moreover, galloyl groups from catechins were related to inhibiting the α-amylase activity by binding other sites than the active one as well as presenting good affinity to human α-amylase (Miao et al., 2014). Catechins were also found to suppress and enhance the amylopectin and amylose digestion, respectively, by forming starch-catechins complexes without modifying the α-amylase activity (Liu et al., 2011). In addition, resveratrol could delay the activity of both enzymes (Fernandes et al., 2020a). However, phenolic compounds enhance or decrease the α-amylase activity when low and high concentrations are used, respectively (Yang

**Table 2** Grape pomace as α-glucosidase and α-amylase inhibitor

| References | Winery by-product | Stabilization protocol | Extraction method | Enzyme inhibition activity | Methods of study | Results |
|---|---|---|---|---|---|---|
| Fernandes et al., (2020a) | Red (Syrah-Seibel), white (Muscat), and mixed grape pomaces from winemaking | Seeds and skin were milled and sieved (10-mesh sieve). Then, they were stored at − 80 °C | Preparation of a 1:10 methanolic extract with a further shaking, ultrasonic bath, filtration, and concentration | α-Amylase from porcine pancreas | In vitro | -Red GP obtained the highest TPC and AOX activity than white and mixed pomace<br>-The α-amylase inhibition percentage of red GP was the highest reported (almost 94%) while the one from mixed GP was the lowest (72.69%) at 10 mg/mL of phenolic concentration<br>-Catechin and procyanidin B2 were the most predominant phenolic compounds, maybe responsible for the α-amylase inhibition activity |
| Fernández-Fernández et al. (2019) | Red (Tannat) grape pomace from winemaking | Seeds and skin were separated manually. Then, the skin was dried at 40 °C up to constant weight (24 h) with a further milling | Preparation of different extracts with ethanol at 95%, methanolic and formic acid with a further ultrasonic extraction, filtration, concentration, and lyophilization | Commercial α-glucosidase from *Saccharomyces cerevisiae* type I | In vitro | -Almost 50% of fiber content<br>-The hydro alcoholic acid extraction obtained higher total phenolic content than the methanolic and aqueous ones<br>-The hydro alcoholic acid extract obtained the best α-glucosidase inhibition capacity ($IC_{50}$ 889 µg/mL) with almost 90% inhibition percentage at 10 mg/mL of phenolic concentration |
| Hogan et al. (2010) | Red (Cabernet Franc) and white (Chardonnay) grape pomaces from winemaking | The samples were immediately freeze-dried upon receiving and then ground | The extraction was carried out with ethanol 80% (1:10 ratio) with a further shaking, filtration, and evaporation of the solvent | α-Glucosidase from yeast and rat intestine | In vitro | -Both GP extracts inhibited the intestinal α-glucosidase<br>-Red GP inhibited both α-amylases activity in a higher amount than white GP (almost 60 and 47% in the case of α-glucosidase from yeast and rat intestine, respectively) at 1.5 mg/mL of phenolic concentration |
| Kato-Schwartz et al. (2020) | Red (Merlot) grape pomace from winemaking | The pomace was dried in a convection oven at 80 °C for 36 h with a further milling | Preparation of different extracts (40% ethanol and 60% distilled water) with a 1:50 (m/v) ratio, with a further shaking, centrifugation concentration of the solvent, and lyophilization | Pancreatic and salivary α-amylase, intestinal α-glucosidase | Study in vitro, in silico, and in vivo | -The most abundant phenolic compounds found were epicatechin, catechin, quercetin, myricetin, isorhamnetin glycoside derivatives, malvidin-3-O-glucoside, and peonidin-3-O-glucoside<br>-Salivary α-amylase inhibition was stronger than pancreatic amylase ($IC_{50}$ values 90 and 143 µg/mL, respectively)<br>-No inhibition of α-glucosidase was observed |

**Table 2** (continued)

| References | Winery by-product | Stabilization protocol | Extraction method | Enzyme inhibition activity | Methods of study | Results |
|---|---|---|---|---|---|---|
| Kong et al. (2019) | Red (Cabernet Sauvignon) grape seeds from winemaking | The extract from the grape seeds was provided from the winery. The formation of inclusion complexes with sulfobutyl ether-β-cyclodextrin was performed in a ratio 1:10 (grape seed extract:sulfobutyl ether-β-cyclodextrin) | ND | α-Glucosidase and α-amylase from baker's yeast | In vitro | -At concentration higher than 2 mg/mL, the inclusion complex inhibited α-glucosidase activity stronger than acarbose with an $IC_{50}$ of 1.188 and 1.035 mg/mL, respectively<br>-At the same conditions, the $IC_{50}$ for inhibiting amylase activity was 0.513 and 0.587 mg/mL for the inclusion complex and acarbose, respectively |
| Kadouh et al. (2016) | Red (Chambourcin, Merlot, Norton, Petit Verdot, Syrah and Tinta Cão) grape pomaces from winemaking | The pomaces were immediately dried in a food dehydrator at 35 °C for 28 h and then separated from stems to be ground | The extraction with aqueous acetone (50%) at 0.1 g/mL (GP powder/solvent) was carried out with a further filtration, concentration, and lyophilization | α-Glucosidase from rat intestine | In vitro | -Merlot GP obtained the highest TPC (0.29 mg/mL) while Petit Verdot the lowest (0.06 mg/mL)<br>-Tinta Cão GP presented the highest concentration of malvidin chloride, delphinidin chloride, epicatechin gallate, and resveratrol, if compared with the rest of the varieties studied<br>-Tinta Cão grape pomace obtained the strongest α-glucosidase inhibition while Petit Verdot reached 7%, both at 0.5 mg/mL of dry extract |
| Lavelli et al. (2016) | White grape pomace from winemaking | The GP was sieved (5 mm) to separate the skins from the seeds. The skins were frozen and then dried at 55 °C for 48 h ($a_w < 0.3$). Then, it was ground and sieved | 1 g of grape skin was extracted with 20 mL of methanol/water/formic acid (70:29.9:0.1, v/v/v) for 2 h at 60 °C with continuous stirring. Then, a centrifugation (10000 *g* for 10 min) and a re-extraction was carried out twice | α-Glucosidase and α-amylase from intestine and pancreas, respectively | Study in model foods: tomato puree and bread | -Quercetin and kaempferol derivatives were identified in grape skin<br>-Enzyme inhibition by the enriched foods was higher than their respective controls |
| Lavelli et al. (2015) | Red (Barbera, Dolcetto, and Albarossa) and white (Chardonnay, Muller Thurgau, Cabernet Sauvignon, and Moscato Bianco) grape pomace from winemaking | The stalks were separated from the pomaces and then sieved (5 mm) to obtain the seeds. The seeds were dried at 55 °C for 48 h for a further grinding and then defatted by SC-$CO_2$ at a pressure of 500 bar at 50 °C | 1 g of grape seeds was extracted with 16 mL of methanol/0.1% HCl for 2 h at room temperature with continuous stirring. Then, a centrifugation was carried out at 10000 *g* for 10 min. A re-extraction was performed twice with 12 mL of the same solvent and then the 3 supernatants were collected | α-Glucosidase and α-amylase from intestine and pancreas, respectively | In vitro | -The major phenolic compounds found were proanthocyanidins<br>-The main factor for the α-glucosidase inhibition was the grape variety, Albarossa and Barbera obtaining the weakest inhibitory properties<br>-Good correlations were found between the content of phenolic/proanthocyanidin contents and the inhibition of α-amylase |

**Table 2** (continued)

| References | Winery by-product | Stabilization protocol | Extraction method | Enzyme inhibition activity | Methods of study | Results |
|---|---|---|---|---|---|---|
| Huamán-Castilla et al. (2021) | Red (Carménère) grape pomace from winemaking | The GP (skin and seeds) was reduced down (2 mm) using a blender | 5 g of GP was mixed with 110 g quartz sand. The mixture was placed in an hot pressurized liquid extraction (HPLE) device, using pure water, water-glycerol (15%), and water–ethanol (15%) at 90, 120 and 150 °C, applying 10 MPa, one extraction cycle, 150% washing volume, 250 s nitrogen purge time, and 5 min static extraction. The final matrix/solvent ratio was 1:10 | α-Glucosidase from *S. cerevisiae* and porcine pancreatic α-amylase | In vitro | -The higher the HPLE temperature, the higher the TPC, reaching 143% when using pure water as solvent<br>-The highest antioxidant activity was found when using water-glycerol as solvent (27% more than the control)<br>-1000 μg/mL of the water–ethanol extract at 90 °C decreased the activity of α-amylase and α-glucosidase by 56 and 98%, respectively<br>-Acarbose inhibited the activity of both enzymes by 56 and 73% for α-amylase and α-glucosidase, respectively, at the same concentration (1000 μg/mL) |

& Kong, 2016). In general, tannins have been reported to inhibit α-amylase, while α-glucosidase is inactivated by smaller phenolic compounds such as phenolic acids (Barrett et al., 2013; Oladiran & Emmambux, 2018). Besides the potential of phenolic compounds in this bioactivity, several factors such as the concentration in food, bioaccessibility, absorption, metabolism, and bioavailability can maximize the antidiabetic capacity of this compounds (Chen et al., 2019; de Paulo Farias et al., 2021). For example, factors such as pH and temperature may modify the interaction between the phenolic compounds and proteins (including the digestive enzymes), as reported by Martinez-Gonzales et al. (2017).

On the other hand, the molecular interactions mostly recognized between the enzymes and phenolic compounds are van der Waals, electrostatic forces, and hydrogen as well as hydrophobic binding (Martinez-Gonzalez et al., 2017), which have been related to inhibit the enzymes in a non-competitive way (Rocha et al., 2020; Yang & Kong, 2016). Therefore, the inhibitor can bind to either the free enzyme or the complex enzyme–substrate (Rocha et al., 2020). In addition, this kind of inhibition has been previously found in GP (Oladiran & Emmambux, 2018). Some phenolic compound inhibition has been observed to be in a competitive way, especially the one from quercetin and caffeoylquinic acid (Martinez-Gonzalez et al., 2017). However, non-covalent interactions are recognized to be the key of the enzymatic inhibition since they represent the basis of reversible inhibitions, which may be useful within some medical treatments (Martinez-Gonzalez et al., 2017). The number of galloyl ester groups and the polymerization degree are the main characteristics of phenolic compound structure that have an influence on their interactions with proteins (Lavelli et al., 2016).

Additionally, the α-amylase activity has been related to the insoluble fiber content and to the limited enzyme accessibility to the substrate, due to network of starch and enzyme by the fiber (Saikia & Mahanta, 2016). Moreover, insoluble dietary fiber has a higher inhibitory effect on α-glucosidase than on α-amylase, and this activity may be related to the inhibitors present on the surface of the fiber as well as the trapping capacity of the porous fiber network (Yang et al., 2019). However, the soluble dietary fiber is the most associated with the postprandial glucose response by reducing the glucose absorption (Oladiran & Emmambux, 2018).

GP has been identified as an α-glucosidase and α-amylase inhibitor (Table 2), showing, especially the red varieties, a possible potential in the management of diabetes (Fernandes et al., 2020a; Hogan et al., 2010; Kadouh et al., 2016; Kato-Schwartz et al., 2020). Table 2 shows that yeast α-glucosidases are usually employed in research (Kong et al., 2019); however, the mammalian enzymes are more biologically relevant since they are more comparable to those acting in the human intestinal tract (Kadouh et al., 2016). In addition, GP has lowered the starch digestibility rate and the estimated glycemic index (Oladiran & Emmambux, 2018; Rocchetti et al., 2021; Tolve et al., 2020). Moreover, GP was employed to fortify yogurt, showing a higher α-glucosidase inhibition activity (Fernández-Fernández et al., 2022; Iriondo-DeHond et al., 2020). Seeds present in GP powder as well as their extract have been described to inhibit α-amylase and α-glucosidase, respectively, the efficiency being comparable and higher than acarbose (Yilmazer-Musa et al., 2012). This activity was even more potent than the one exerted by isolated catechins in the case of α-amylase, while epigallocatechin gallate (EGCG) has reached a more significant effect on α-glucosidase inhibition (Yilmazer-Musa et al., 2012). On the other hand, the inhibition of α-glucosidase has shown to reduce the postprandial hyperglycemia in diabetic mice when they were fed with grape skins (Hogan et al., 2011), while a recent study has showed GP does not have an effect on glucose absorption, but inhibiting the amylase activity (Kato-Schwartz et al., 2020).

Another factor to consider when assessing the GP inhibitory activity is the type of study. After the preliminary in vitro screening, it is necessary to carry out an in vivo model to understand some factors such as the bioavailability and the physiological response to the GP components (Alongi & Anese, 2021; Gerardi et al., 2020; Kato-Schwartz et al., 2020). However, human clinical trials are mandatory required (Reg. (EU) n. 353/2008) for obtaining a health claim (Alongi & Anese, 2021).

## Conclusion

The present review has highlighted the importance of GP as a promising α-amylase and α-glucosidase inhibitor, due to the complexity of its components. Diverse phenolic compounds and fiber are the constituents more related to this bioactivity, beyond their traditional properties. In addition, the GP inhibition of α-amylase and α-glucosidase has been showed to remain also in the fortified food products with this ingredient. However, it is crucial to focus on the kind of study performed since the majority is preliminary at an in vitro level, clinical trials being necessary to reach stronger conclusions. Although the studies reported in this review were carried out in the GP extract, the use of the whole GP would be more convenient because it is easier to use and eco-friendly, and all the bioactive compounds involved in the α-amylase and α-glucosidase inhibition activity may remain. The GP capacity of inhibiting α-amylase and α-glucosidase along the time is another factor to take into consideration since several reactions between the internal GP components can take place during its storage, modifying its bioactivity. This review deals with the GP obtained after the winemaking process; however, scarce information is available regarding the utilization of the exhausted GP recovered after the production of distilled spirits, whose bioactivity was barely pointed out. The valorization of these by-products as functional ingredients within the food industry as α-amylase and α-glucosidase inhibitors could encourage the circular economy approach of a more sustainable production.

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## Declarations

**Conflict of Interest** The authors declare no competing interests.

## References

Alongi, M., & Anese, M. (2021). Re-thinking functional food development through a holistic approach. *Journal of Functional Foods, 81*, 104466. https://doi.org/10.1016/J.JFF.2021.104466

Alqahtani, S. N., Alkholy, S. O., & Ferreira, M. P. (2013). Antidiabetic and anticancer potential of native medicinal plants from Saudi Arabia. In *Polyphenols in Human Health and Disease* (Vol. 1, pp. 119–132). Elsevier Inc. https://doi.org/10.1016/B978-0-12-398456-2.00011-6

Álvarez, E., Rodiño-Janeiro, B. K., Jerez, M., Ucieda-Somoza, R., Núñez, M. J., & González-Juanatey, J. R. (2012). Procyanidins from grape pomace are suitable inhibitors of human endothelial NADPH oxidase. *Journal of Cellular Biochemistry, 113*(4), 1386–1396. https://doi.org/10.1002/jcb.24011

Antonić, B., Jančíková, S., Dordević, D., & Tremlová, B. (2020). Grape pomace valorization: A systematic review and meta-analysis. *Foods, 9*(11), 1627. https://doi.org/10.3390/foods9111627

Ain, B. U., H., Saeed, F., Khan, M. A., Niaz, B., Khan, S. G., Anjum, F. M., et al. (2019). Comparative study of chemical treatments in combination with extrusion for the partial conversion of wheat and sorghum insoluble fiber into soluble. *Food Science & Nutrition, 7*(6), 2059–2067. https://doi.org/10.1002/FSN3.1041

Banwo, K., Olojede, A. O., Adesulu-Dahunsi, A. T., Verma, D. K., Thakur, M., Tripathy, S., et al. (2021). Functional importance of bioactive compounds of foods with potential health benefits: A review on recent trends. *Food Bioscience, 43*, 101320. https://doi.org/10.1016/J.FBIO.2021.101320

Barba, F. J., Brianceau, S., Turk, M., Boussetta, N., & Vorobiev, E. (2015). Effect of alternative physical treatments (ultrasounds, pulsed electric fields, and high-voltage electrical discharges) on selective recovery of bio-compounds from fermented grape pomace. *Food and Bioprocess Technology, 8*(5), 1139–1148. https://doi.org/10.1007/S11947-015-1482-3/TABLES/2

Barrett, A., Ndou, T., Hughey, C. A., Straut, C., Howell, A., Dai, Z., & Kaletunc, G. (2013). Inhibition of α-amylase and glucoamylase by tannins extracted from cocoa, pomegranates, cranberries, and grapes. *Journal of Agricultural and Food Chemistry, 61*(7), 1477–1486. https://doi.org/10.1021/JF304876G

Berry, E. M. (2019). Sustainable food systems and the mediterranean diet. *Nutrients, 11*(9), 2229. https://doi.org/10.3390/NU11092229

Boath, A. S., Stewart, D., & McDougall, G. J. (2012). Berry components inhibit α-glucosidase in vitro: Synergies between acarbose and polyphenols from black currant and rowanberry. *Food Chemistry, 135*(3), 929–936. https://doi.org/10.1016/j.foodchem.2012.06.065

Campbell, I. (2007). Oral antidiabetic drugs: Their properties and recommended use. *The Prescriber, 18*(6), 56–74. https://doi.org/10.1002/PSB.48

Cardullo, N., Floresta, G., Rescifina, A., Muccilli, V., & Tringali, C. (2021). Synthesis and in vitro evaluation of chlorogenic acid amides as potential hypoglycemic agents and their synergistic effect with acarbose. *Bioorganic Chemistry, 117*, 105458. https://doi.org/10.1016/J.BIOORG.2021.105458

Carmona-Jiménez, Y., García-Moreno, M. V., & García-Barroso, C. (2018). Effect of drying on the phenolic content and antioxidant activity of red grape pomace. *Plant Foods for Human Nutrition, 73*(1), 74–81. https://doi.org/10.1007/S11130-018-0658-1/TABLES/2

Chen, L., Gnanaraj, C., Arulselvan, P., El-Seedi, H., & Teng, H. (2019). A review on advanced microencapsulation technology to enhance bioavailability of phenolic compounds: Based on its activity in the treatment of Type 2 Diabetes. *Trends in Food Science & Technology, 85*, 149–162. https://doi.org/10.1016/J.TIFS.2018.11.026

Cilli, L. P., Contini, L. R. F., Sinnecker, P., Lopes, P. S., Andreo, M. A., Neiva, C. R. P., et al. (2019). Effects of grape pomace flour on quality parameters of salmon burger. *Journal of Food Processing and Preservation, 44*(2), 1–11. https://doi.org/10.1111/jfpp.14329

Cisneros-Yupanqui, M., Rizzi, C., Mihaylova, D., & Lante, A. (2021). Effect of the distillation process on polyphenols content of grape pomace. *European Food Research and Technology*. https://doi.org/10.1007/S00217-021-03924-6

Cisneros-Yupanqui, M., Zagotto A., Alberton, A., Lante, A., Zagotto, G., Ribaudo, G., & Rizzi, C. (2020a). Study of the phenolic profile of a grape pomace powder and its impact on delaying corn oil oxidation. *Natural Product Research*, 1–5. https://doi.org/10.1080/14786419.2020a.1777414

Cisneros-Yupanqui, M., Zagotto, A., Alberton, A., Lante, A., Zagotto, G., Ribaudo, G., & Rizzi, C. (2020b). Monitoring the antioxidant activity of an eco-friendly processed grape pomace along the storage. *Natural Product Research, 35*(4), 1–4. https://doi.org/10.1080/14786419.2020.1815741

de Paulo Farias, D., de Araújo, F. F., Neri-Numa, I. A., & Pastore, G. M. (2021). Antidiabetic potential of dietary polyphenols: A mechanistic review. *Food Research International, 145*, 110383. https://doi.org/10.1016/J.FOODRES.2021.110383

de Sales, P. M., de Souza, P. M., Simeoni, L. A., Magalhães, P. de O., & Silveira, D. (2012). α-amylase inhibitors: A review of raw material and isolated compounds from plant source. *Journal of Pharmacy and Pharmaceutical Sciences*, *15*(1), 141–183. https://doi.org/10.18433/j35s3k

Ditano-Vázquez, P., Torres-Peña, J. D., Galeano-Valle, F., Pérez-Caballero, A. I., Demelo-Rodríguez, P., Lopez-Miranda, J., et al. (2019). The fluid aspect of the Mediterranean Diet in the prevention and management of cardiovascular disease and diabetes: The role of polyphenol content in moderate consumption of wine and olive oil. *Nutrients*, *11*(11), 2833. https://doi.org/10.3390/NU11112833

Dong, R., Liao, W., Xie, J., Chen, Y., Peng, G., Xie, J., et al. (2022). Enrichment of yogurt with carrot soluble dietary fiber prepared by three physical modified treatments: Microstructure, rheology and storage stability. *Innovative Food Science & Emerging Technologies, 75*, 102901. https://doi.org/10.1016/J.IFSET.2021.102901

Ebrahimi, P., & Lante, A. (2021). Polyphenols: A comprehensive review of their nutritional properties. *The Open Biotechnology Journal, 15*(1), 164–172. https://doi.org/10.2174/1874070702115010164

FAO. (2020). *Fruit and vegetables – your dietary essentials. Fruit and vegetables – your dietary essentials*. Rome. https://doi.org/10.4060/cb2395en

Fernandes, A. C., Martins, I. M., Moreira, D. K., & Macedo, G. A. (2020a). Use of agro-industrial residues as potent antioxidant, antiglycation agents, and α-amylase and pancreatic lipase inhibitory activity. *Journal of Food Processing and Preservation, 44*(4), 1–12. https://doi.org/10.1111/jfpp.14397

Fernandes, A. C., Santana, A. L., Martins, I., & sabela M., Moreira, D. K. T., Macedo, J. A., & Macedo, G. A. (2020b). Anti-glycation effect and the α-amylase, lipase, and α-glycosidase inhibition properties of a polyphenolic fraction derived from citrus wastes. *Preparative Biochemistry and Biotechnology, 50*(8), 794–802. https://doi.org/10.1080/10826068.2020.1737941

Fernández-Fernández, A. M., Dellacassa, E., Nardin, T., Larcher, R., Ibañez, C., Terán, D., et al. (2022). Tannat grape skin : A feasible ingredient for the formulation of snacks with potential for reducing the risk of diabetes. *Nutrients, 14*(419), 1–19.

Fernández-Fernández, A. M., Iriondo-DeHond, A., Dellacassa, E., Medrano-Fernandez, A., & del Castillo, M. D. (2019). Assessment of antioxidant, antidiabetic, antiobesity, and anti-inflammatory properties of a Tannat winemaking by-product. *European Food Research and Technology, 245*(8), 1539–1551. https://doi.org/10.1007/s00217-019-03252-w

Ferri, M., Rondini, G., Calabretta, M. M., Michelini, E., Vallini, V., Fava, F., et al. (2017). White grape pomace extracts, obtained by a sequential enzymatic plus ethanol-based extraction, exert antioxidant, anti-tyrosinase and anti-inflammatory activities. *New Biotechnology, 39*, 51–58. https://doi.org/10.1016/j.nbt.2017.07.002

Fontana, A. R., Antoniolli, A., & Bottini, R. (2013). Grape pomace as a sustainable source of bioactive compounds: Extraction, characterization, and biotechnological applications of phenolics. *Journal of Agricultural and Food Chemistry, 61*(38), 8987–9003. https://doi.org/10.1021/jf402586f

García-Lomillo, J., & González-SanJosé, M. L. (2017). Applications of wine pomace in the food industry: Approaches and functions. *Comprehensive Reviews in Food Science and Food Safety, 16*(1), 3–22. https://doi.org/10.1111/1541-4337.12238

García-Lomillo, J., Gonzalez-SanJose, M. L., Del Pino-García, R., Ortega-Heras, M., & Muñiz-Rodríguez, P. (2017). Antioxidant effect of seasonings derived from wine pomace on lipid oxidation in refrigerated and frozen beef patties. *LWT - Food Science and Technology, 77*, 85–91. https://doi.org/10.1016/j.lwt.2016.11.038

Garcia-Lomillo, J., González-SanJosé, M. L., Skibsted, L. H., & Jongberg, S. (2016). Effect of skin wine pomace and sulfite on protein oxidation in beef patties during high oxygen atmosphere storage. *Food and Bioprocess Technology, 9*(3), 532–542. https://doi.org/10.1007/S11947-015-1649-Y/FIGURES/6

Gerardi, G., Cavia-Saiz, M., Rivero-Pérez, M. D., González-Sanjosé, M. L., & Muñiz, P. (2020). The dose–response effect on polyphenol bioavailability after intake of white and red wine pomace products by Wistar rats. *Food & Function, 11*(2), 1661–1671. https://doi.org/10.1039/C9FO01743G

Gharravi, A. M., Jafar, A., Ebrahimi, M., Mahmodi, A., Pourhashemi, E., Haseli, N., et al. (2018). Current status of stem cell therapy, scaffolds for the treatment of diabetes mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 12*(6), 1133–1139. https://doi.org/10.1016/J.DSX.2018.06.021

Gonçalves, G. A., Soares, A. A., Correa, R. C. G., Barros, L., Haminiuk, C. W. I., Peralta, R. M., et al. (2017). Merlot grape pomace hydroalcoholic extract improves the oxidative and inflammatory states of rats with adjuvant-induced arthritis. *Journal of Functional Foods, 33*, 408–418. https://doi.org/10.1016/j.jff.2017.04.009

Gowd, V., Karim, N., Shishir, M. R. I., Xie, L., & Chen, W. (2019). Dietary polyphenols to combat the metabolic diseases via altering gut microbiota. *Trends in Food Science & Technology, 93*, 81–93. https://doi.org/10.1016/J.TIFS.2019.09.005

Gummidi, L., Kerru, N., Ebenezer, O., Awolade, P., Sanni, O., Islam, M. S., & Singh, P. (2021). Multicomponent reaction for the synthesis of new 1,3,4-thiadiazole-thiazolidine-4-one molecular hybrids as promising antidiabetic agents through α-glucosidase and α-amylase inhibition. *Bioorganic Chemistry, 115*, 105210. https://doi.org/10.1016/J.BIOORG.2021.105210

Hogan, S., Canning, C., Sun, S., Sun, X., Kadouh, H., & Zhou, K. (2011). Dietary supplementation of grape skin extract improves glycemia and inflammation in diet-induced obese mice fed a Western high fat diet. *Journal of Agricultural and Food Chemistry, 59*(7), 3035–3041. https://doi.org/10.1021/jf1042773

Hogan, S., Zhang, L., Li, J., Sun, S., Canning, C., & Zhou, K. (2010). Antioxidant rich grape pomace extract suppresses postprandial hyperglycemia in diabetic mice by specifically inhibiting alpha-glucosidase. *Nutrition and Metabolism, 7*(1), 1–9. https://doi.org/10.1186/1743-7075-7-71

Huamán-Castilla, N. L., Campos, D., García-Ríos, D., Parada, J., Martínez-Cifuentes, M., Mariotti-Celis, M. S., & Pérez-Correa, J. R. (2021). Chemical properties of vitis vinifera carménère pomace extracts obtained by hot pressurized liquid extraction, and their inhibitory effect on type 2 diabetes mellitus related enzymes. *Antioxidants, 10*(3), 1–14. https://doi.org/10.3390/antiox10030472

Ilyas, T., Chowdhary, P., Chaurasia, D., Gnansounou, E., Pandey, A., & Chaturvedi, P. (2021). Sustainable green processing of grape pomace for the production of value-added products: An overview. *Environmental Technology and Innovation, 23*, 101592. https://doi.org/10.1016/j.eti.2021.101592

International Diabetes Federation, F. (2021). IDF Diabetes Atlas. Retrieved December 2, 2021, from https://diabetesatlas.org/

Iriondo-DeHond, M., Blázquez-Duff, J. M., del Castillo, M. D., & Miguel, E. (2020). Nutritional quality, sensory analysis and shelf life stability of yogurts containing inulin-type fructans and winery byproducts for sustainable health. *Foods, 9*(9), 1199. https://doi.org/10.3390/foods9091199

José Jara-Palacios, M., Hernanz, D., Escudero-Gilete, M. L., & Heredia, F. J. (2014). Antioxidant potential of white grape pomaces: Phenolic composition and antioxidant capacity measured by spectrophotometric and cyclic voltammetry methods. *Food Research International, 66*, 150–157. https://doi.org/10.1016/j.foodres.2014.09.009

Kadouh, H. C., Sun, S., Zhu, W., & Zhou, K. (2016). α-Glucosidase inhibiting activity and bioactive compounds of six red wine grape pomace extracts. *Journal of Functional Foods, 26*, 577–584. https://doi.org/10.1016/j.jff.2016.08.022

Kato-Schwartz, C. G., Corrêa, R. C. G., de Souza Lima, D., de Sá-Nakanishi, A. B., de Almeida Gonçalves, G., Seixas, F. A. V., et al. (2020). Potential anti-diabetic properties of Merlot grape pomace extract: An in vitro, in silico and in vivo study of α-amylase and α-glucosidase inhibition. *Food Research International, 137*, 109462. https://doi.org/10.1016/j.foodres.2020.109462

Khalil, H. (2017). Diabetes microvascular complications—A clinical update. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 11*, S133–S139. https://doi.org/10.1016/J.DSX.2016.12.022

Khan, S. A., Al Kiyumi, A. R., Al Sheidi, M. S., Al Khusaibi, T. S., Al Shehhi, N. M., & Alam, T. (2016). In vitro inhibitory effects on α-glucosidase and α-amylase level and antioxidant potential of seeds of Phoenix dactylifera L. *Asian Pacific Journal of Tropical Biomedicine, 6*(4), 322–329. https://doi.org/10.1016/j.apjtb.2015.11.008

Kong, F., Su, Z., Zhang, L., Qin, Y., & Zhang, K. (2019). Inclusion complex of grape seeds extracts with sulfobutyl ether β-cyclodextrin: Preparation, characterization, stability and evaluation of α-glucosidase and α-amylase inhibitory effects in vitro. *LWT, 101*, 819–826. https://doi.org/10.1016/j.lwt.2018.12.007

Lavelli, V. (2021). Circular food supply chains – Impact on value addition and safety. *Trends in Food Science and Technology, 114*(2021), 323–332. https://doi.org/10.1016/j.tifs.2021.06.008

Lavelli, V., Sri Harsha, P. S. C., Ferranti, P., Scarafoni, A., & Iametti, S. (2016). Grape skin phenolics as inhibitors of mammalian α-glucosidase and α-amylase - Effect of food matrix and processing on efficacy. *Food and Function, 7*(3), 1655–1663. https://doi.org/10.1039/c6fo00073h

Lavelli, V., Sri Harsha, P. S. C., & Fiori, L. (2015). Screening grape seeds recovered from winemaking by-products as sources of reducing agents and mammalian α-glucosidase and α-amylase inhibitors. *International Journal of Food Science and Technology, 50*(5), 1182–1189. https://doi.org/10.1111/ijfs.12763

Li, X., Bai, Y., Jin, Z., & Svensson, B. (2022). Food-derived non-phenolic α-amylase and α-glucosidase inhibitors for controlling starch digestion rate and guiding diabetes-friendly recipes. *LWT, 153*, 112455. https://doi.org/10.1016/J.LWT.2021.112455

Lin, Y.-H., Huang, H.-W., & Wang, C.-Y. (2022). Effects of high pressure-assisted extraction on yield, antioxidant, antimicrobial, and anti-diabetic properties of chlorogenic acid and caffeine extracted from green coffee beans. *Food and Bioprocess Technology, 15*(7), 1529–1538. https://doi.org/10.1007/S11947-022-02828-X

Liu, J., Wang, M., Peng, S., & Zhang, G. (2011). Effect of green tea catechins on the postprandial glycemic response to starches differing in amylose content. *Journal of Agricultural and Food Chemistry, 59*(9), 4582–4588. https://doi.org/10.1021/JF200355Q

Lv, Y., Hao, J., Liu, C., Huang, H., Ma, Y., Yang, X., & Tang, L. (2019). Anti-diabetic effects of a phenolic-rich extract from Hypericum attenuatum Choisy in KK-Ay mice mediated through AMPK /PI3K/Akt/GSK3β signaling and GLUT4, PPARγ, and PPARα expression. *Journal of Functional Foods, 61*, 103506. https://doi.org/10.1016/J.JFF.2019.103506

Mahindrakar, K. V., & Rathod, V. K. (2021). Antidiabetic potential evaluation of aqueous extract of waste Syzygium cumini seed kernel's by in vitro α-amylase and α-glucosidase inhibition. *Preparative Biochemistry and Biotechnology, 51*(6), 589–598. https://doi.org/10.1080/10826068.2020.1839908

Maragkoudakis, P. A., Nardi, T., Bovo, B., D'Andrea, M., Howell, K. S., Giacomini, A., & Corich, V. (2013). Biodiversity, dynamics and ecology of bacterial community during grape marc storage for the production of grappa. *International Journal of Food Microbiology, 162*(2), 143–151. https://doi.org/10.1016/j.ijfoodmicro.2013.01.005

Marchiani, R., Bertolino, M., Ghirardello, D., McSweeney, P. L. H., & Zeppa, G. (2016). Physicochemical and nutritional qualities of grape pomace powder-fortified semi-hard cheeses. *Journal* *of Food Science and Technology, 53*(3), 1585–1596. https://doi.org/10.1007/s13197-015-2105-8

Martinez-Gonzalez, A. I., Díaz-Sánchez, Á. G., de la Rosa, L. A., Vargas-Requena, C. L., Bustos-Jaimes, I., & Alvarez-Parrilla, A. E. (2017). Polyphenolic compounds and digestive enzymes: In vitro non-covalent interactions. *Molecules, 22*(4), 669. https://doi.org/10.3390/MOLECULES22040669

Martínez-Maqueda, D., Zapatera, B., Gallego-Narbón, A., Vaquero, M. P., Saura-Calixto, F., & Pérez-Jiménez, J. (2018). A 6-week supplementation with grape pomace to subjects at cardiometabolic risk ameliorates insulin sensitivity, without affecting other metabolic syndrome markers. *Food & Function, 9*(11), 6010–6019. https://doi.org/10.1039/C8FO01323C

McGurnaghan, S. J., Weir, A., Bishop, J., Kennedy, S., Blackbourn, L. A. K., McAllister, D. A., et al. (2021). Risks of and risk factors for COVID-19 disease in people with diabetes: A cohort study of the total population of Scotland. *The Lancet Diabetes & Endocrinology, 9*(2), 82–93. https://doi.org/10.1016/S2213-8587(20)30405-8

Messina, C. M., Manuguerra, S., Catalano, G., Arena, R., Cocchi, M., Morghese, M., et al. (2019). Green biotechnology for valorisation of residual biomasses in nutraceutic sector: Characterization and extraction of bioactive compounds from grape pomace and evaluation of the protective effects in vitro. *Natural Product Research*. https://doi.org/10.1080/14786419.2019.1619727

Miao, M., Jiang, H., Jiang, B., Li, Y., Cui, S. W., & Zhang, T. (2014). Structure elucidation of catechins for modulation of starch digestion. *LWT - Food Science and Technology, 57*(1), 188–193. https://doi.org/10.1016/J.LWT.2014.01.005

Mildner-Szkudlarz, S., Bajerska, J., Zawirska-Wojtasiak, R., & Górecka, D. (2013). White grape pomace as a source of dietary fibre and polyphenols and its effect on physical and nutraceutical characteristics of wheat biscuits. *Journal of the Science of Food and Agriculture, 93*(2), 389–395. https://doi.org/10.1002/jsfa.5774

Muñoz-Bernal, Ó. A., Coria-Oliveros, A. J., de la Rosa, L. A., Rodrigo-García, J., del Rocío Martínez-Ruiz, N., Sayago-Ayerdi, S. G., & Alvarez-Parrilla, E. (2021). Cardioprotective effect of red wine and grape pomace. *Food Research International, 140*, 110069. https://doi.org/10.1016/j.foodres.2020.110069

Mwakalukwa, R., Amen, Y., Nagata, M., & Shimizu, K. (2020). Postprandial hyperglycemia lowering effect of the isolated compounds from olive mill wastes - An inhibitory activity and kinetics studies on α-glucosidase and α-amylase enzymes. *ACS Omega, 5*(32), 20070–20079. https://doi.org/10.1021/acsomega.0c01622

Nassar, M., Daoud, A., Nso, N., Medina, L., Ghernautan, V., Bhangoo, H., et al. (2021). Diabetes mellitus and COVID-19: Review article. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 15*(6), 102268. https://doi.org/10.1016/J.DSX.2021.102268

Oladiran, D. A., & Emmambux, N. M. (2018). Nutritional and functional properties of extruded cassava-soy composite with grape pomace. *Starch/staerke, 70*(7–8), 1–11. https://doi.org/10.1002/star.201700298

Papoutsis, K., Zhang, J., Bowyer, M. C., Brunton, N., Gibney, E. R., & Lyng, J. (2021). Fruit, vegetables, and mushrooms for the preparation of extracts with α-amylase and α-glucosidase inhibition properties: A review. *Food Chemistry*, *338*(September 2020), 128119. https://doi.org/10.1016/j.foodchem.2020.128119

Pérez-Jiménez, J., Serrano, J., Tabernero, M., Arranz, S., Díaz-Rubio, M. E., García-Diz, L., et al. (2009). Bioavailability of phenolic antioxidants associated with dietary fiber: Plasma antioxidant capacity after acute and long-term intake in humans. *Plant Foods for Human Nutrition, 64*(2), 102–107. https://doi.org/10.1007/S11130-009-0110-7/FIGURES/2

Petersen, K. F., & Shulman, G. I. (2006). Etiology of insulin resistance. *The American Journal of Medicine, 119*(5), S10–S16. https://doi.org/10.1016/J.AMJMED.2006.01.009

Rainero, G., Bianchi, F., Rizzi, C., Cervini, M., Giuberti, G., & Simonato, B. (2021). Breadstick fortification with red grape pomace: Effect on nutritional, technological and sensory properties. *Journal of the Science of Food and Agriculture*. https://doi.org/10.1002/JSFA.11596

Ribeiro, L. F., Ribani, R. H., Francisco, T. M. G., Soares, A. A., Pontarolo, R., & Haminiuk, C. W. I. (2015). Profile of bioactive compounds from grape pomace (Vitis vinifera and Vitis labrusca) by spectrophotometric, chromatographic and spectral analyses. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 1007*, 72–80. https://doi.org/10.1016/j.jchromb.2015.11.005

Rocchetti, G., Rizzi, C., Cervini, M., Rainero, G., Bianchi, F., Giuberti, G., et al. (2021). Impact of grape pomace powder on the phenolic bioaccessibility and on in vitro starch digestibility of wheat based bread. *Foods, 10*(3), 1–12. https://doi.org/10.3390/foods10030507

Rocha, L., Neves, D., Valentão, P., Andrade, P. B., & Videira, R. A. (2020). Adding value to polyvinylpolypyrrolidone winery residue: A resource of polyphenols with neuroprotective effects and ability to modulate type 2 diabetes-relevant enzymes. *Food Chemistry, 329*(June), 127168. https://doi.org/10.1016/j.foodchem.2020.127168

Rodríguez-Morgado, B., Candiracci, M., Santa-María, C., Revilla, E., Gordillo, B., Parrado, J., & Castaño, A. (2015). Obtaining from grape pomace an enzymatic extract with anti-inflammatory properties. *Plant Foods for Human Nutrition, 70*(1), 42–49. https://doi.org/10.1007/S11130-014-0459-0/FIGURES/3

Rodriguez Lanzi, C., Perdicaro, D. J., Antoniolli, A., Fontana, A. R., Miatello, R. M., Bottini, R., & Vazquez Prieto, M. A. (2016). Grape pomace and grape pomace extract improve insulin signaling in high-fat-fructose fed rat-induced metabolic syndrome. *Food & Function, 7*(3), 1544–1553. https://doi.org/10.1039/C5FO01065A

Rosak, C., & Mertes, G. (2012). Critical evaluation of the role of acarbose in the treatment of diabetes: Patient considerations. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 5*, 357. https://doi.org/10.2147/DMSO.S28340

Sáez-Almendros, S., Obrador, B., Bach-Faig, A., & Serra-Majem, L. (2013). Environmental footprints of Mediterranean versus Western dietary patterns: Beyond the health benefits of the Mediterranean diet. *Environmental Health: A Global Access Science Source, 12*(1), 1–8. https://doi.org/10.1186/1476-069X-12-118/FIGURES/3

Saikia, S., & Mahanta, C. L. (2016). In vitro physicochemical, phytochemical and functional properties of fiber rich fractions derived from by-products of six fruits. *Journal of Food Science and Technology, 53*(3), 1496–1504. https://doi.org/10.1007/s13197-015-2120-9

Sánchez-Alonso, I., Jiménez-Escrig, A., Saura-Calixto, F., & Borderías, A. J. (2007). Effect of grape antioxidant dietary fibre on the prevention of lipid oxidation in minced fish: Evaluation by different methodologies. *Food Chemistry, 101*(1), 372–378. https://doi.org/10.1016/j.foodchem.2005.12.058

Sáyago-Ayerdi, S. G., Brenes, A., & Goñi, I. (2009). Effect of grape antioxidant dietary fiber on the lipid oxidation of raw and cooked chicken hamburgers. *LWT - Food Science and Technology, 42*(5), 971–976. https://doi.org/10.1016/j.lwt.2008.12.006

Shobana, S., Sreerama, Y. N., & Malleshi, N. G. (2009). Composition and enzyme inhibitory properties of finger millet (Eleusine coracana L.) seed coat phenolics: Mode of inhibition of α-glucosidase and pancreatic amylase. *Food Chemistry*, *115*(4), 1268–1273. https://doi.org/10.1016/J.FOODCHEM.2009.01.042

Solari-Godiño, A., Lindo-Rojas, I., & Pandia-Estrada, S. (2017). Determination of phenolic compounds and evaluation of antioxidant capacity of two grapes residues (Vitis vinifera) of varieties dried: Quebranta (red) and Torontel (white). *Cogent Food & Agriculture, 3*(1). https://doi.org/10.1080/23311932.2017.1361599

Šporin, M., Avbelj, M., Kovač, B., & Možina, S. S. (2018). Quality characteristics of wheat flour dough and bread containing grape pomace flour. *Food Science and Technology International, 24*(3), 251–263. https://doi.org/10.1177/1082013217745398

Takahama, U., & Hirota, S. (2018). Interactions of flavonoids with α-amylase and starch slowing down its digestion. *Food and Function, 9*(2), 677–687. https://doi.org/10.1039/c7fo01539a

Tan, S. Y., Mei Wong, J. L., Sim, Y. J., Wong, S. S., Mohamed Elhassan, S. A., Tan, S. H., et al. (2019). Type 1 and 2 diabetes mellitus: A review on current treatment approach and gene therapy as potential intervention. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13*(1), 364–372. https://doi.org/10.1016/J.DSX.2018.10.008

Tan, Y., & Chang, S. K. C. (2017). Digestive enzyme inhibition activity of the phenolic substances in selected fruits, vegetables and tea as compared to black legumes. *Journal of Functional Foods, 38*, 644–655. https://doi.org/10.1016/J.JFF.2017.04.005

Tolve, R., Pasini, G., Vignale, F., Favati, F., & Simonato, B. (2020). Effect of grape pomace addition on the technological, sensory, and nutritional properties of durum wheat pasta. *Foods, 9*(354), 1–11.

Tuyen, D. T., Yew, G. Y., Cuong, N. T., Hoang, L. T., Yen, H. T., Hong Thao, P. T., et al. (2021). Selection, purification, and evaluation of acarbose−an α-glucosidase inhibitor from Actinoplanes sp. *Chemosphere, 265*, 129167. https://doi.org/10.1016/J.CHEMOSPHERE.2020.129167

Vadivel, V., Kunyanga, C. N., & Biesalski, H. K. (2012). Antioxidant potential and type II diabetes-related enzyme inhibition of Cassia obtusifolia L.: Effect of indigenous processing methods. *Food and Bioprocess Technology*, *5*(7), 2687–2696. https://doi.org/10.1007/S11947-011-0620-9/TABLES/8

Venkatakrishnan, K., Chiu, H. F., & Wang, C. K. (2019). Popular functional foods and herbs for the management of type-2-diabetes mellitus: A comprehensive review with special reference to clinical trials and its proposed mechanism. *Journal of Functional Foods, 57*, 425–438. https://doi.org/10.1016/J.JFF.2019.04.039

Wang, M., Chen, J., Ye, X., & Liu, D. (2020). In vitro inhibitory effects of Chinese bayberry (Myrica rubra Sieb. et Zucc.) leaves proanthocyanidins on pancreatic α-amylase and their interaction. *Bioorganic Chemistry*, *101*, 104029. https://doi.org/10.1016/J.BIOORG.2020.104029

WHO. (2021). Noncommunicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed 26 July 2022.

Wise, J. (2016). Type 1 diabetes is still linked to lower life expectancy. *BMJ, 353* https://doi.org/10.1136/BMJ.I1988

Xie, Y., Gou, L., Peng, M., Zheng, J., & Chen, L. (2021). Effects of soluble fiber supplementation on glycemic control in adults with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition, 40*(4), 1800–1810. https://doi.org/10.1016/J.CLNU.2020.10.032

Yang, B., Wu, Q., Song, X., Yang, Q., & Kan, J. (2019). Physicochemical properties and bioactive function of Japanese grape (Hovenia dulcis) pomace insoluble dietary fibre modified by ball milling and complex enzyme treatment. *International Journal of Food Science and Technology, 54*(7), 2363–2373. https://doi.org/10.1111/ijfs.14134

Yang, X., & Kong, F. (2016). Effects of tea polyphenols and different teas on pancreatic α-amylase activity in vitro. *LWT - Food Science and Technology, 66*, 232–238. https://doi.org/10.1016/J.LWT.2015.10.035

Yilmazer-Musa, M., Griffith, A. M., Michels, A. J., Schneider, E., & Frei, B. (2012). Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of α-amylase and α-glucosidase activity. In *Journal of Agricultural and Food Chemistry* (Vol. 60, pp. 8924–8929). NIH Public Access. https://doi.org/10.1021/jf301147n

Zhang, Y., Santosa, R. W., Zhang, M., Huo, J., & Huang, D. (2020). Characterization and bioactivity of proanthocyanidins during Malay cherry (Lepisanthes alata) fruit ripening. *Food Bioscience, 36*, 100617. https://doi.org/10.1016/J.FBIO.2020.100617