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**ABSTRACT:** Grape seed oil is rich in phenolic compounds, fatty acids, and vitamins, with economic importance to pharmaceutical, cosmetic, and food industry. Its use as an edible oil has also been suggested, especially due to its pleasant sensory characteristics. Grape seed oil has beneficial properties for health that are mainly detected by *in vitro* studies, such as anti-inflammatory, cardioprotective, antimicrobial, and anticancer properties, and may interact with cellular and molecular pathways. These effects have been related to grape seed oil constituents, mainly tocopherol, linolenic acid, resveratrol, quercetin, procyanidins, carotenoids, and phytosterols. The aim of this article was to briefly review the composition and nutritional aspects of grape seed oil, the interactions of its compounds with molecular and cellular pathways, and its possible beneficial effects on health.

**KEYWORDS:** grape seed extract, antioxidants, fatty acids, inflammation

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## Introduction

The berries of *Vitis vinifera* L. ssp. *sativa* grapes have been of interest worldwide due to the nutritional properties of the natural product (raw and dried fruit) and wine and the pharmaceutical properties of derivatives, such as peel and seed extracts.<sup>1</sup> For instance, grape seed extract (aqueous or alcoholic) has a high antioxidant potential; its beneficial effects include the modulation of antioxidant enzyme expression, protection against oxidative damage in cells, antiatherosclerotic and anti-inflammatory effects, and protection against some cancer types, in both humans and animal models.<sup>2–6</sup>

Grape seed is a by-product of winemaking process,<sup>7,8</sup> and its oil content is traditionally extracted using either an organic solvent or mechanical techniques.<sup>9</sup> Cold-pressing is a method of oil extraction that involves no heat or chemical treatment and hence may retain more health beneficial components.<sup>10</sup> Although the yield is usually lower than that with conventional solvent extraction, in cold-pressing, there is no concern about solvent residues in the oil, resulting in a safer and more consumer-desired product.<sup>11</sup>

Grape seed contains 8%–20% of oil (dry basis).<sup>12</sup> Oil yield depends on the extraction technique, type of solvent and operating conditions employed, the variety of cultivars, and the environmental factors during harvesting year.<sup>9</sup> In a study conducted in the state of Rio Grande do Sul, Brazil, three

varieties of *V. vinifera* (Moscato Giallo, Merlot, and Cabernet Sauvignon) and two of *V. labrusca* (Bordeaux and Isabel) harvested between 2005 and 2006 were analyzed for their seed oil content. The highest oil contents were obtained from the Bordeaux variety (15.4%) in 2005 and from the Merlot grape variety (14.7%) in 2006.<sup>13</sup>

The aim of this article is to briefly review the composition and nutritional aspects of grape seed oil, interactions of its compounds with cellular and molecular pathways, and its probable beneficial effects for health.

## Grape Seed Oil Constituents

The interest in grape seed oil as a functional food product has increased, especially because of its high levels of hydrophilic constituents, such as phenolic compounds, and lipophilic constituents, such as vitamin E, unsaturated fatty acids (UFAs), and phytosterols.<sup>14</sup> Grape seed oil composition is related to grape vine variety environmental factors and maturation degree of the seeds. Due to organoleptic properties of grape seed oil, including its aroma and pleasant flavor, the interest in its use in culinary preparations has increased. In Europe, for example, the product has been manufactured in Germany, France, and Italy since 1930 and has gained use as culinary oil.<sup>11</sup>

**Hydrophilic constituents of grape seed oil.** Grape seed oil contains a large amount of phenolic compounds, including



flavonoids, carotenoids, phenolic acids, tannins, and stilbenes.<sup>9</sup> It has also 59–360 mg of gallic acid equivalent/kg of phenols, which have been reported to be involved in a wide range of biological activities but are mostly known for their antioxidant properties.<sup>12</sup> The main polyphenols identified in grape seed oil are catechins, epicatechins, trans-resveratrol, and procyanidin B1.<sup>15,16</sup> The total amount of polyphenols, extracted from grape seed oil by cold-pressing method, is about 2.9 mg/kg, and minor amounts of catechin, epicatechin (1.3 mg/kg each), and trans-resveratrol (0.3 mg/kg) have been detected.<sup>16</sup>

However, considering the total amount of phenolic compounds, the content of polyphenols in grape seed oil is very low (0.013%–0.019% of total phenolic compounds). The low solubility of clear (filtered) oil in grape seed oil production could be attributed to the hydrophilic nature of polyphenols in oil.<sup>12</sup> In contrast, the (unfiltered) turbid oil, obtained after the oil recovery process (press residue), exhibited high amounts of polyphenols, and these sediments are a rich source of polyphenolic compounds with antioxidant activity.<sup>16</sup>

**Lipophilic constituents of grape seed oil.** Regarding the fatty acid (FA) composition, linoleic acid (LIA) is the most abundant FA in cold-pressed grape seed oils, contributing to between 66.0% and 75.3% of total FA.<sup>7</sup>

LIA belongs to the group of polyunsaturated FA (PUFA),<sup>8</sup> and it has been related to the promotion of human health.<sup>15</sup> Grape seed oil has a high content of PUFA, in the range of 85%–90%.<sup>11</sup> Oleic acid, a monounsaturated FA (MUFA), is also largely found in grape seed oil, and saturated fatty acids (SFAs) are present in lower quantities. Each grape variety and its oil have a different FA composition;<sup>11,17–19</sup> Table 1 shows the FA composition of grape (*V. vinifera* L.) seed oil in comparison with other fats.

Each type of oil has a characteristic tocopherol and tocotrienol content. In addition to exhibiting vitamin E activity, tocopherols occur in seed oils, such as  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -tocopherol, with  $\gamma$ -tocopherol as one of the most potent antioxidants.<sup>20</sup> Grape seed oils are richer in tocotrienols (unsaturated forms of vitamin E) than tocopherols though, among which  $\gamma$ -tocotrienol is the most abundant, followed by  $\alpha$ -tocotrienol.<sup>21</sup>  $\alpha$ -tocopherol and  $\gamma$ -tocotrienol have been reported to show the highest variability between grape varieties. In a study with grape seed oils from 10 traditional Portuguese varieties, it was found that Marufo has the highest concentration of both compounds.<sup>21</sup>

Grape seed oil has a great content of vitamin E, ranging from 1 to 53 mg per 100 g of oil,<sup>11,20</sup> and 148–358  $\alpha$ -tocopherol equivalents,<sup>21</sup> which is higher than that of soybean oil and olive oil. In addition to the type of grape, vitamin E content in grape seed oil also depends on environmental cultivation conditions.<sup>11,22</sup>

Vitamin E contributes to the beneficial effects of grape seed oil, because of its high antioxidant activity<sup>8</sup> and neuroprotective and antitumoral properties.<sup>21</sup> For this reason, the use of

**Table 1.** Fatty acid compositions\* of grape (*V. vinifera* L.) seed oil and other fats.<sup>18</sup>

FATTY ACIDS	GRAPE SEED OIL	OLIVE OIL	SUNFLOWER OIL	COCONUT OIL
C6:0	nd	nd	nd	0.52
C8:0	0.01	nd	nd	7.6
C10:0	nd	nd	nd	5.5
C12:0	0.01	nd	0.02	47.7
C14:0	0.05	nd	0.09	19.9
C15:0	0.01	nd	nd	nd
C16:0	6.6	16.5	6.2	nd
C17:0	0.06	nd	0.02	nd
C18:0	3.5	2.3	2.8	2.7
C20:0	0.16	0.43	0.21	nd
C22:0	nd	0.15	nd	nd
C16:1 (n-7)	0.08	1.8	0.12	nd
C17:1 (n-7)	nd	nd	nd	nd
C18:1 cis (n-9)	14.3	66.4	28.0	6.2
C18:1 trans (n-9)	nd	nd	nd	nd
C20:1 (n-9)	0.40	0.30	0.18	nd
C18:2 cis (n-6)	74.7	16.4	62.2	1.6
C18:3 (n-3)	0.15	1.6	0.16	nd
C18:3 (n-6)	nd	nd	nd	nd
SFAs	10.4	19.4	9.4	92.1
MUFAs	14.8	68.2	28.3	6.2
PUFAs	74.9	18.0	62.4	1.6
n-3 PUFAs	0.2	1.6	0.2	0.0
n-6 PUFAs	74.7	16.4	62.2	1.6

**Note:** \*Data are expressed as percentages of total fatty acid methyl esters (FAMES).

**Abbreviations:** nd, not determined; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.

grape seed oils has been suggested to delay the aging process and prevent the occurrence of some chronic diseases.

Other lipophilic constituents largely found in grape seed oil are phytosterols, which may prevent the release of proinflammatory mediators by oxidized low-density lipoprotein-stimulated macrophage during oxidative stress and eicosanoid synthesis.<sup>11,23</sup> Table 2 shows the phytosterol content of grape seed oil.

### Grape Seed Compounds and Bioactivity

Superoxide, hydrogen peroxide, and hydroxyl radicals are common reactive oxygen species (ROS). These ROS are physiologically produced to act as signaling molecules that assist the immune system and homeostasis regulation. This mechanism is controlled by antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase. An excessive ROS production leads to an imbalance between antioxidants and ROS, characterized by an oxidative stress,

**Table 2.** Main phytosterol content of grape (*V. vinifera* L.) seed oil.<sup>11,19</sup>

PHYTOSTEROLS	mg/kg/OIL
Cholesterol	nd–0.10
Cholestanol	nd
Brassicasterol	0.6–0.9
2,4 methylencholesterol	nd–0.18
Campesterol	0.1–9.3
Campestanol	–
Stigmasterol	10.2–10.8
$\Delta$ -7 campesterol	0.16–0.27
$\Delta$ -5 2,3 stigmastadienol	–
Clerosterol	0.90–0.94
$\beta$ -sitosterol	66.6–67.4
Sitostanol	3.92–4.70
$\Delta$ -5 avenasterol	1.98–2.09
$\Delta$ -5 2,4 stigmastadienol	0.41–0.47
$\Delta$ -7 estigmastenol	1.99–2.30
$\Delta$ -7 avenasterol	0.98–1.10

Abbreviation: nd, not determined.

which is related to cancer, type 2 diabetes mellitus (T2DM), pulmonary and cardiovascular diseases, and degenerative illnesses.<sup>24,25,28</sup> Therefore, grape and its by-products contain different phenolic compounds such as resveratrol, quercetin, procyanidins, and others, with anti-inflammatory and antioxidant capabilities.<sup>26</sup>

**Antioxidant capacity of grape seed oil.** The most notable bioactive property of phenolic compounds is their antioxidative capacity. This property has been widely studied in grape seed extracts whose compounds are capable of scavenging ROS and inhibiting lipid oxidation.<sup>27</sup> Xia et al<sup>26</sup> compared the antioxidant capacity of grape and its by-products, including leaves, skin, wine, and seeds. The highest antioxidant capacity, measured by oxygen radical absorbance capacity assay, was found in grape seeds (42.18 mmol of Trolox equivalent/g). This high antioxidant capacity is related to the high content of gallic acid, catechin, epicatechin, procyanidins, and proanthocyanidins in grape seed and seed oil<sup>28</sup> and may be a result of the synergistic combination of these phenolic compounds.<sup>29</sup>

The biological mechanism underlying the antioxidant property is associated with the removal of free radicals, mainly hydroxyl radical, and chelation of metals, which influence cell signaling and functioning of the immune system.<sup>30</sup> This is of particular importance when considering the capacity of grape seed extract to attenuate oxidative stress<sup>31</sup> and decrease low-density lipoprotein (LDL) levels,<sup>32</sup> and thereby reduce the inflammatory process related to some diseases.

Defatted milled grape seed, a wine by-product obtained from the oil extraction of grape seed, has been shown to protect the cell membrane from oxidative damage and consequently prevent protein and lipid oxidation.<sup>33</sup>

**The anti-inflammatory effect of grape seed oil.** Chronic diseases, which may be associated with increased mortality and morbidity rates worldwide, are generally accompanied by inflammation processes, which are often difficult to control with available therapies and interventions. In this context, the consumption of nutrients with anti-inflammatory capabilities would be beneficial in the treatment of chronic diseases. Olas et al<sup>34</sup> observed that grape seed oil decreased platelet adhesion in vitro, showing more effectiveness than pure resveratrol. This result, along with that reported by Sano et al,<sup>32</sup> showing a reducing effect of grape seed extract on oxidized LDL in 61 healthy subjects, suggests a cardioprotective potential of grape seed oil. The polyphenols present in grape seed oil are able to inhibit the release of arachidonic acid (AA), responsible for the production of leukotrienes and prostaglandins, which in turn activates the inflammatory response.<sup>35</sup>

Muscadine grape (*Vitis rotundifolia* Michx.) seed oil (MGSO) contains high amounts of  $\alpha$ - and  $\gamma$ -tocotrienol (mean of 40.1 and 50.8 mg, respectively, for each 100 g of oil) with minor seasonal changes.<sup>36</sup> In the study by Zhao et al,<sup>36</sup> differentiating primary human adipose-derived stem cells (hASCs) were treated with MGSO and tocotrienol rich fraction (TRF) from MGSO, and then compared with rice bran and olive oils. The accumulation of triglyceride was significantly lower in MGSO-treated hASCs when compared with rice bran and olive oils. The MGSO-derived TRF treatment significantly reduced mRNA and protein expression related to adipogenesis, such as peroxisome proliferator-activated receptor gamma and adipocyte protein 2 in hASCs. The LPS-induced proinflammatory gene expression in human adipocytes and cytokine (IL-6 and IL-8) secretion to the medium was also reduced by MGSO-derived TRF treatment. Thus, MGSO may constitute a dietary strategy to attenuate obesity (by attenuating the formation of new adipose cells) and its associated adipose inflammation.

**The role of grape seed oil in cell cycle control.** Some phenolic compounds of grape seed oil have anticancer activities and act in cell cycle modulation,<sup>37</sup> being cytotoxic to tumor cells without compromising healthy cells.<sup>38</sup> Proanthocyanidins are polymers of flavan-3-ol with antiproliferative effect on cancer cells.<sup>39</sup> The suggested biological mechanisms are attenuation of pro-angiogenic factor expression, such as the vascular endothelial growth factor and angiopoietins,<sup>37</sup> and the inactivation of phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) signaling pathway, leading to the induction of apoptosis of colon cancer cells.<sup>38</sup> Cheah et al<sup>40</sup> also showed that the low molecular weight procyanidins, present in ripe grape seeds, increased the toxicity of the chemotherapeutic agent 5-fluorouracil on these cells, suggesting that these components may be used as a supplement in the treatment of colon cancer.

Still experimentally, in cancer, grape seed oil has been evaluated as a nanocarrier, since the development of nano-dosage forms of phytochemicals may represent a significant



progress in the field of biomedical research. The effectiveness of lipid nanocarriers based on natural oils (grape seed oil and laurel leaf oil) in counteracting free radicals and combating certain tumor cells was evaluated between two tumor cells, MDA-MB 231 and HeLa cell lines, and two normal cells, L929 and B16 cell lines. In this study, nanocarriers based on a combination of grape seed and laurel leaf oils showed a capacity to scavenge about 98% of oxygen free radicals. A drastic decrease in tumor cell proliferation was detected with a dose of nanocarriers of 5 mg/mL even in the absence of an antitumor drug (about 50% viability for MDA-MB 231 cell line and 60% viability for HeLa cell line). Comparing the survival profile of normal and tumor cells exposed to a 2.5 mg/mL dose of lipid nanocarriers, a death rate of 20% was shown for normal B16 cells, while the MDA-MB 231 and HeLa tumor cells exhibited a 40% death rate. Thus, lipid nanocarriers based on grape seed oil in association with laurel leaf oil could be a candidate to reduce the delivery system toxicity and may significantly improve the therapeutic efficacy of antitumor drugs in clinical applications.<sup>41</sup> Some authors suggest that the diversity of bioactive compounds from grape seed and laurel oils may be responsible for the antitumor activity exerted by lipid nanocarriers, resulting from multiple cellular events and mechanisms (eg, antioxidant activity, induction of cell cycle arrest and apoptosis, modulation of antioxidant enzymes, etc.).<sup>42,43</sup>

**Antimicrobial features of grape seed oil.** Grape seed oil has also a toxicity effect on some pathogens, suggesting an antimicrobial feature. In fact, the oil extracted from grape seeds had an inhibitory effect on the growth of *Staphylococcus aureus* and *Escherichia coli*.<sup>44,45</sup> The antimicrobial activity displayed by phenolic compounds, such as resveratrol, involves the induction of oxidative damage to bacterial membrane, especially *E. coli*, without affecting the host cells. These findings suggest that the use of resveratrol would aid traditional therapies in which antibiotics are ineffective.<sup>46</sup>

Although the process of oil extraction from grape seeds may reduce to half its antioxidant capacity, other grape products, such as grape juice, wine, seed, and seed extract could be used as dietary supplements for their antioxidant properties.<sup>26</sup> As previously mentioned, the phenolic compounds present in the grape seed extract exert not only antioxidant activity but also antimicrobial, anticancer, cardioprotective, and antiaging effects.

Thus, these observations, primarily based on in vitro studies, in which different cells are incubated with grape seed oil and tested for different properties, have been extended to clinical and preclinical tests, exploring the potential therapeutic use of grape seed oil.

### Grape Seed Oil and Translation

Although the benefits of grape seed extract are well recognized, little is known about the use of grape seed oils in human health. Even in animal models, results may be conflicting regarding health outcomes, and in humans, results may be

different from those obtained in experimental (cell cultures and animal models) studies.

**Preclinical tests.** Thorn grape (*Vitis davidii* Foex.) seed oil (TGSO) has shown antiapoptotic effects on pancreatic  $\beta$ -cells in murine models. TGSO (87.02% UFAs) significantly reduced rattus pancreatic  $\beta$ -cell line RIN-m5F apoptosis and prevented insulin secretion impaired by high glucose levels. The expressions of proapoptotic genes such as inducible nitric oxide synthase (iNOS), Caspase-3, ATF-3, JNK, p38, and Fas were downregulated while the antiapoptotic genes Akt and Bcl-2/Bax were upregulated after TGSO treatment. The seed oil protective activity may be linked to mitochondrial pathway, endoplasmic reticulum stress pathway, and Fas signal pathway, suggesting that it may be an alternative, nonpharmacological treatment against T2DM.<sup>47</sup>

Although the polyphenols present in grape seeds are able to inhibit the release of AA, PUFAs may be converted into AA, and grape seed oil is considered an important LIA source. In small amounts, eicosanoids derived from AA are biologically active; however, when produced in large amounts, they may contribute to thrombus and atheroma formation, inflammatory disorders, and cell proliferation. Thus, excessive supplementation with grape seed oil could change the AA status from a physiologic condition to a prothrombotic and proinflammatory state.<sup>48,49</sup>

In fact, FA from grape seed oil may be a potent prooxidative agent<sup>50,51</sup> when compared with other fats such as olive oil (source of oleic acid). Stroke-induced Wistar rats were fed a diet containing 7% of commercial oils for 35 days. Grape seed oil showed a pro-oxidative and proinflammatory effect, by increasing the liberation of arachidonate and its transformation into prostaglandins. Olive oil diet was protective in terms of redox homeostatic balance, minor increases in lipid and protein damage, protective activation of nitric oxide synthase (NOS) in penumbra neurons, and apoptosis (caspase-3, milli- and microcalpains).<sup>52</sup> In another study, male Wistar rats were fed for 60 days on the same basal diet plus olive oil or grape seed oil, and the lipid FA composition of liver, enzymatic and nonenzymatic components of the antioxidant defense system, and the activity of enzymes involved in lipid metabolism were evaluated. The grape seed oil group showed significantly increased oxidative stress biomarkers, and the enzymatic and nonenzymatic components of the antioxidant defense system were increased in the olive oil group.<sup>53</sup>

In addition, pretreatment with grape seed oil exerted a neuroprotective effect against CCl<sub>4</sub>-induced brain injury in  $\gamma$ -irradiated rats, which was attributed to the ability of grape seed oil to scavenge free radicals, suppress inflammatory responses, improve the activity of antioxidant enzymes, and inhibit the xanthine oxidase and iNOS gene expression levels.<sup>54</sup> It has also been demonstrated that grape seed oil exhibits protective effects on CCl<sub>4</sub>-induced acute liver injury in  $\gamma$ -irradiated rats due to its antioxidant, anti-inflammatory, and antiapoptotic activities.<sup>55</sup>

In an experimental study,<sup>56</sup> long-term intake of a high-fat diet with grape seed oil resulted in increased leptin expression and high total cholesterol and high-density lipoprotein cholesterol (HDL-c) levels, suggesting that the leptin changes and the atherogenic impact of the oil may be related to an excessive, chronic consumption of fat. Thus, the deleterious effects of grape seed oil (PUFA)-derived eicosanoids have not been well established and may have an interaction with other lipids and/or components of daily diet.

**Studies in humans.** In 35,239 male participants of the VITamins and Lifestyle (VITAL) cohort, a study designed to investigate the associations of the use of vitamin, mineral, and specialty supplements with cancer risk, the regular use of grape seed extract was associated with a 41% (hazard ratio, 0.59; 95% confidence interval, 0.40–0.86) reduced risk of total prostate cancer.<sup>5</sup> On the other hand, different from experimental study results,<sup>38,40</sup> there was no significant association between the use of grape seed supplement and colorectal cancer or lung cancer in the same population.<sup>57</sup> The use of grape seed oil as a protective agent against cancer was not evaluated in the VITAL study.

In humans, the effects of grape seed oil consumption on inflammation and insulin resistance were evaluated in overweight/obese women.<sup>58</sup> The subjects ( $n = 44$ ) were randomly assigned into two groups, grape seed oil (consuming 15% of daily energy from grape seed oil) and sunflower oil (consuming 15% of energy from sunflower oil), through a weight loss diet for eight weeks. Homeostatic model assessment of insulin resistance scores, ultrasensitive C-reactive protein (us-CRP), and TNF- $\alpha$  decreased in the grape seed oil group, but only us-CRP was significantly lower than the sunflower oil group after the intervention ( $P < 0.03$ ). Since both groups were submitted to weight loss diets, it was not possible to confirm if grape seed oil exerted beneficial effects on body weight. Grape seed oil also showed a decrease of  $8.4\% \pm 1\%$  in platelet aggregation when compared with the peanut oil (rich in oleic FA) consumption, which decreased aggregation by  $10.4\% \pm 1\%$ .<sup>59</sup>

Nash<sup>60</sup> observed that the consumption of up to 45 g/day of grape seed oil seemed to increase HDL-c by 13% and reduce LDL-cholesterol levels by 7% in humans. In animal models, however, there are conflicting results regarding changes in serum, muscular, and hepatic lipid profile<sup>8,61,62</sup> after the use of grape seed oil. Well-designed, randomized clinical trials are needed to evaluate the effects of grape seed oil on lipid profile in humans.

## Conclusion

Grape seed oil is a by-product of winemaking industry, with good benefits to human health. Numerous in vitro and in vivo evidences suggest cardioprotective and anticancer effects of grape seed oil. However, the amounts of lipophilic and hydrophilic grape seed oil constituents with cardioprotective, anti-inflammatory, and anticancer activities are small, requiring the consumption of a large amount of oil for beneficial effects to be achieved. With respect to clinical studies, most studies

have an observational design and involve small sample sizes, and thus, caution must be exercised in the interpretation of the results. Further studies are needed on the beneficial effects of grape seed oil on human health and its use as an adjuvant agent in the prevention and treatment of chronic diseases.

## Author Contributions

Contributed to the writing of the manuscript, made critical revisions, and approved the final version: JG, MMM, AO, and AM. All authors reviewed and approved of the final manuscript.

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