Phytochemical Profile, Antioxidant and Antitumor Activities of Green Grape Juice

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Date Submitted: 2020-07-02

Keywords: antioxidant, anti-proliferative, unripe grape juice, pulmonary adenocarcinoma, phytochemicals, verjuice

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(1) Plants, due to their phytochemicals, have long been known for their pharmacological potential and medicinal value. Verjuice, the acidic juice of unripe green grape, is still poorly characterized in terms of its chemical composition and biological activities. (2) In this study, we characterized the chemical composition, antioxidant and antitumor potential of verjuice extract. Folin-Ciocalteu and aluminum chloride reagents were used to identify the total phenol and total flavonoid composition. Various conventional methods were used to quantify the alkaloids and tannins. DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay and Neutral Red assay were used to assess the antioxidant and antitumor activities, respectively. (3) We showed that the verjuice extract contains alkaloids, tannins, and a high quantity of total flavonoids and total phenols. Besides its antioxidant activity, verjuice significantly repressed human pulmonary adenocarcinoma (A549) cells' viability in both dose- and time-dependent manners. Moreover, verjuice extract significantly enhanced the anticancer potential of cisplatin. (4) Altogether, these observations suggest a potential use of verjuice as a natural antitumor remedy.

Record Type: Published Article

Submitted To: LAPSE (Living Archive for Process Systems Engineering)

Citation (overall record, always the latest version): LAPSE:2020.0774
Citation (this specific file, latest version): LAPSE:2020.0774-1
Citation (this specific file, this version): LAPSE:2020.0774-1v1

DOI of Published Version: https://doi.org/10.3390/pr8050507

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Phytochemical Profile, Antioxidant and Antitumor Activities of Green Grape Juice

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Received: 26 March 2020; Accepted: 21 April 2020; Published: 26 April 2020

Abstract: (1) Plants, due to their phytochemicals, have long been known for their pharmacological potential and medicinal value. Verjuice, the acidic juice of unripe green grape, is still poorly characterized in terms of its chemical composition and biological activities. (2) In this study, we characterized the chemical composition, antioxidant and antitumor potential of verjuice extract. Folin–Ciocalteu and aluminum chloride reagents were used to identify the total phenol and total flavonoid composition. Various conventional methods were used to quantify the alkaloids and tannins. DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging assay and Neutral Red assay were used to assess the antioxidant and antitumor activities, respectively. (3) We showed that the verjuice extract contains alkaloids, tannins, and a high quantity of total flavonoids and total phenols. Besides its antioxidant activity, verjuice significantly repressed human pulmonary adenocarcinoma (A549) cells’ viability in both dose- and time-dependent manners. Moreover, verjuice extract significantly enhanced the anticancer potential of cisplatin. (4) Altogether, these observations suggest a potential use of verjuice as a natural antitumor remedy.

Keywords: verjuice; phytochemicals; unripe grape juice; pulmonary adenocarcinoma; anti-proliferative; antioxidant

1. Introduction

Besides being a vital source of alimentation, nowadays, plants are being used for cosmetic, food processing, pharmaceutical, and medicinal purposes. Phytochemicals from traditional medicinal herbs have long been known for their therapeutic value in treating a vast array of critical health disorders, including cancer [1]. Nowadays, plant-derived bioactive molecules are used for designing novel remedies [1].

Cancer represents the second leading cause of mortality worldwide and includes many types. Pulmonary cancer, one of the most aggressive human tumors, exists in two forms: NSCLC (Non-Small Cell Lung Cancer) and SCLC (Small Cell Lung Cancer), representing 80–85% and 15–20% of cases, respectively [2]. Distinct strategies, including surgery, chemotherapy, radiation, hormones, and
immunotherapy can be employed for lung cancer prevention and treatment. Currently, chemotherapy is the most commonly used strategy. However, its application is challenged with its limited efficacy, toxic side effects, and cancer resistance [3]. Remarkably, medicinal plants have shown potential during pulmonary cancer therapy due to their ability to: (i) increase the sensitizing capacity of conventional agents, (ii) extend patients’ survival time, (iii) restrain chemotherapy side effects, and (iv) improve the quality of life of lung cancer patients [4]. In this context, various medicinal plants’ extracts as well as plant-derived phytochemicals have exhibited a significant capacity to inhibit lung cancer cell proliferation [5].

Lebanon, due to its geographic location, is characterized by a great variety of plant species known for their therapeutic value. More than ninety wild species encountered in Lebanon are endemics. Therefore, it is of great interest to characterize the biological and therapeutic potential of these endemic plants [6,7]. *Vitis vinifera* L. (the common grape vine) is one of the largest fruit crops worldwide. It is known for its antioxidant potential and ability to protect the cardiovascular system [8,9]. Verjuice (green grape juice or unripe grape juice), which is highly consumed in the Mediterranean region, corresponds to the acidic juice recovered upon mechanically pressing unripe green grape [10]. Although distinct studies have addressed the chemical composition and antioxidant activity of different fruits and seeds of grape [11,12], the chemical composition and biological properties of verjuice are still poorly characterized.

In this study, we aimed at investigating the phytochemical composition of verjuice extract and evaluating its antioxidant effect and anti-proliferative potential against the human pulmonary adenocarcinoma (A549) cell line.

2. Materials and Methods

2.1. Plant Collection and Preparation of the Samples

Unripe green grapes or immature white grapes were obtained in 2017 from Byblos (north-east direction from Beyrouth via Charles Helou station). The juice was collected after pressing the grapes. The main techniques used for green grape juice production were the “Hot press” (HP), “Cold press” (CP), and “Hot Break” (HB) processes [13]. The juice was centrifuged for 10 min (1000 rpm at room temperature). The pellet was discarded, and the supernatant was taken and stored at −80 °C for 48 h. The juice was then lyophilized for 72 h to be converted into powder and then stored in desiccators at room temperature. This powder was used for chemical measurements.

2.2. Qualitative Phytochemical Screening

2.2.1. Total Alkaloid Content (TAC) Determination

Alkaloid content was determined following the method of Harborne [14]. 1 g of dry powder of verjuice extract and 100 mL of 10% acetic acid (in ethanol) were incubated in a covered 250 mL beaker for 4 h. The extract was then filtrated and concentrated. Ammonium hydroxide was added drop by drop until the precipitation was complete. The obtained precipitates were then washed with diluted ammonium hydroxide and filtered with a Whatman filter paper. The residue was then dried (at 40 °C in an oven) and weighted. The alkaloids content was then determined based on the following equation:

\[
\% \text{ Alkaloid} = \frac{\text{Final weight of the sample}}{\text{Initial weight of the extract}} \times 100
\]  

2.2.2. Estimation of Total Tannins Content (TTC)

Tannins were determined by the Folin–Ciocalteu method [15–17]. The reaction mixture was prepared upon mixing 100 µL of verjuice (10 µL of verjuice in 90 µL of water) extract, 0.5 mL of Folin–Ciocalteu’s reagent, 1 mL of Na₂CO₃ (35%), and 8.4 mL of water. Verjuice extract absorbance versus the prepared blank was determined at 765 nm. The blank corresponded to 1 mL water and
1 mL of Na$_2$CO$_3$ (35%). Tannin content was expressed as mg Gallic Acid Equivalents (GAE)/g of dry weight extract.

$$\text{Total tannin content} = \frac{\text{GAE} \times V \times D}{m} \quad (2)$$

2.2.3. Estimation of Total Phenolic Content (TPC)

The method of Folin–Ciocalteu reagent was used to estimate the TPC [17,18]. One milligram (mg) of verjuice powder was dissolved in one milliliter (mL) of distilled water. Polyvinyl pyrrolidone was then added at a ratio of 0.1 mg to 1 mL of distilled water and extract of tannins. From this mixture, 100 µL was added to 0.5 mL of Folin–Ciocalteu’s phenol reagent (1/10 dilution in water) (Sigma-Aldrich Co. St Louis, MO, USA). 1.5 mL of a 2% Na$_2$CO$_3$ solution was added after 5 min (Fair Lawn, NJ, USA). The mixture was kept in the dark (30 min at room temperature). The absorbance of blue-colored solution of extract was measured at 765 nm upon utilizing a Gene Quant 1300 UV-Vis spectrophotometer (UV–Vis. Cary 4000, Agilent, UK). The extract was prepared in triplicates for each analysis, where the mean value of absorbance was then calculated. The same procedure was applied in the case of the standard solution of gallic acid (Sigma-Aldrich Co. St Louis, MO, USA) and the linear calibration graph was prepared.

The TPC, expressed as mg of gallic acid equivalents per g of extract (mg of GAE/g of extract), was deduced following extrapolation of the calibration curve.

$$\text{Total phenol content} = \frac{\text{GAE} \times V \times D}{m} \quad (3)$$

where GAE corresponds to the gallic acid equivalents (mg/mL), V represents the volume extract (mL), D represents the dilution factor, and m corresponds to the sample weight (g).

The blank was prepared upon mixing 0.5 mL water-MeOH and 1.5 mL of Na$_2$CO$_3$ (2%) (VWR, Fontenay-sous-Bois, France).

2.2.4. Estimation of Total Flavonoid Content (TFC)

The aluminum chloride method [19] was used for the determination of TFC. 1 mL of diluted verjuice extract (5 mg/mL) was mixed with 1 mL of 2% solution of the methanolic aluminum chloride (Fair Lawn, NJ, USA). The absorbance of verjuice extract versus that of the prepared blank was determined at 415 nm following incubation (1 h at room temperature in the dark). For each analysis, the extract was prepared in triplicate and the mean value of absorbance was then determined in mg per g of Rutin equivalents (RE).

$$\text{Flavonoids content} = \frac{\text{RE} \times V \times D}{W} \quad (4)$$

where RE corresponds to Rutin equivalents (µg/mL), V represents the total volume of the sample (mL), D corresponds to dilution factor, and W is the sample weight (g).

The blank was prepared upon mixing 1 mL water-MeOH and 1.5 mL of 2% methanolic aluminum chloride solution.

2.2.5. DPPH Assay

The antioxidant assay was performed as previously described in the literature [15,18]. Verjuice extract samples of increasing concentrations (1.5, 2.5, 3.5, and 4.5 mg/mL) were prepared. 1 mL of each diluted sample was mixed with 1 mL of the free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) (0.15 mM in methanol) reagent. The absorbance of each solution was determined at 517 nm by a Gene Quant 1300 UV-Vis spectrophotometer (UV–Vis. Cary 4000, Agilent, UK) following incubation (30 min at room temperature in the dark). For each analysis, samples were prepared in triplicates and the mean
The value of absorbance was calculated. The DPPH scavenging ability of each sample was calculated using the following equation:

\[
\text{\% Scavenging activity} = \left( \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}} \right) \times 100
\]  

(5)

The control sample was prepared upon combining 1 mL DPPH with 1 mL of the selected solvent. The blank corresponded to 1 mL of the water-methanol solution. The used positive control was ascorbic acid. The absorbance control was that of DPPH + water-methanol. Sample absorbance corresponded to the absorbance of DPPH radical + sample.

2.3. Cell and Cell Culture

Human lung adenocarcinoma cell line A549 was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and cultivated (at 37 °C under an atmosphere containing 5% CO₂) in DMEM (Dulbecco’s Modified Eagle Medium) medium (Sigma Chemical Company, St. Louis, MO, USA) containing 0.1 mg/mL streptomycin, 100 U/mL penicillin, and 10% fetal bovine serum.

2.3.1. Treatment of Cells

A stock solution of lyophilized verjuice extract was prepared at 10 mg/mL in DMEM culture. The stock solution was then diluted to obtain different concentrations that were used for treatments. Cells were plated in a 96-well microtiter plate, at a concentration of \(^{10^5}\) cells/well. Cell viability was assessed 24, 48, and 72 h after the treatment. Cells were treated with increasing concentrations of either cisplatin (4, 8, 12, and 80 µg/mL) (purchased from Ebewe, Austria) or verjuice extract (1, 2.5, 3, 3.2, 3.4, 3.6, 3.8, and 4 mg/mL). Moreover, A549 cells were simultaneously treated with combinations of verjuice extracts (3.6, 3.8, and 4 mg/mL) and cisplatin (4 µg/mL).

2.3.2. Evaluation of the Anti-Proliferative Activity

Assessment of cell viability was carried out upon applying the Neutral Red assay following a previously described protocol [20,21]. Neutral Red (chromogenic dye) was used as a lysosomal activity indicator in live cells. After 24 h of cultivation in a 96-well microtiter plate as described above, cells were exposed to increasing concentrations of verjuice extract and/or cisplatin and re-incubated for 24, 48, and 72 h. Untreated cells were considered as a negative control, whilst ethanol (0.5%, v/v)-treated cells were used as a vehicle control. Following 24, 48, and 72 h, the culture medium was replaced with 100 µL of fresh medium containing 40 µg/mL Neutral Red. Cells were then incubated for 3 h, during which the vital dye can enter the lysosomes of viable and undamaged cells. The media were then discarded, and cells were washed twice (100 µL of 1X PBS). 200 µL of a 50% ethanol–1% acetic acid lysing solution was used to extract the intracellularly accumulated Neutral Red dye. The eluted dye was then characterized in terms of its optical density at 490 nm using a microplate reader. The experiments were performed in triplicates.

2.4. Statistical Analysis

All presented results correspond to mean ± standard deviation (SD). Statistical analyses were carried out by the mean of GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). A two-way analysis of variance (ANOVA) test was employed to determine the p-values: * \( p < 0.05 \), ** \( p < 0.01 \), and *** \( p < 0.001 \). Duncan’s test means comparison test was used to compare the different treatments performed at the \( p < 0.05 \) probability level.

3. Results and Discussion

3.1. Phytochemical Screening

Given that the pharmacological potential and medicinal value of plants is attributed to their chemical composition, phytochemical analysis was carried out to identify the bioactive compounds
present in the verjuice extract. Our results showed that verjuice extract is rich in alkaloids, phenols, flavonoids, and tannins (Table 1). Interestingly, secondary metabolites such as phenols, particularly flavonoids, are well known for their anti-inflammatory and antimicrobial activities as well as their ability to inhibit cholesterol biosynthesis by the liver cells [22,23]. Moreover, phenols and alkaloids usually exert high antioxidant and antibacterial activities [24]. These molecules are well described for their pharmacological potential and are traditionally used to treat different diseases [24].

### Table 1. Bioactive compounds in verjuice extract.

<table>
<thead>
<tr>
<th>Active Compounds</th>
<th>Total Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total alkaloids content (TAC)</td>
<td>0.057 g (5.7%)</td>
</tr>
<tr>
<td>Total phenols content (TPC; mg GAE/mL)</td>
<td>2.82 mg/mL</td>
</tr>
<tr>
<td>Total flavonoids content (TFC; mg RE/mL)</td>
<td>2.6 mg/mL</td>
</tr>
<tr>
<td>Total tannins content (TTC)</td>
<td>19.9 mg/mL</td>
</tr>
</tbody>
</table>

GAE: Gallic Acid Equivalents; RE: Rutin Equivalents.

Different juices contain an array of secondary metabolites, including phenols, flavonoids, flavanones, tannins, terpenoids, diterpenes, quinones, glycosides, glucides, reducing sugar, and alkaloids. Comparison with other juices showed important differences. Indeed, verjuice contained 1.8, 2.1, and 7.4 times more TPC than grape materne, pomegranate, and pineapple juices, respectively [25,26]. The difference was more marked when considering TFC, in which case, verjuice exhibited 2.2 to 54.1 times more, depending on the species [25,26]. Total tannins comparison highlighted that verjuice presented 73.7, 62.2, and 3.8 times more than pineapple, pomegranate, and grape materne, respectively [25,26].

#### 3.2. Antioxidant Activity of Verjuice

The phytochemical arsenal in verjuice extract suggests potential biological properties for this plant. Therefore, we assessed, in a next step, the antioxidant capacity of the verjuice extract. DPPH free radical scavenging assay was performed to assess the cell-free antioxidant activities of different concentrations of verjuice. The antioxidant activity increased three-fold in a dose-dependent manner between the extreme concentrations of verjuice (Figure 1). This strong antioxidant activity could be explained by the significant phenolic compounds content. In cells, antioxidant molecules prevent the free radicals from causing damage, thus, they are known to reduce chronic diseases like cancer. The observed potent antioxidant capacity highlights potential therapeutic implications of verjuice for protecting cells against oxidative stress.

![Figure 1](image-url). Antioxidant activities of different concentrations of verjuice extract. The samples were prepared in triplicates. The results are expressed as the percentage of control (0 mg/mL verjuice). Each value represents the mean ± standard deviation (SD) of triplicates. *** p < 0.001.
3.3. Cytotoxic Effect of Verjuice Extract on A549 Cancer Cells

In order to assess the cytotoxic effect of verjuice extracts on lung cancer cells, the Neutral Red cell viability assay was carried out. A549 cells were treated with distinct concentrations of the verjuice extracts over 24, 48, and 72 h (Figure 2). After 24 h, cells’ viability was significantly decreased in a dose-dependent manner. It decreased by 20%, 41%, and 72% in cells treated with verjuice extract at concentrations of 3.2, 3.6, and 4 mg/mL, respectively (Figure 2A). After 48 and 72 h, comparable profiles of dose-dependent decreases in cells’ viability were obtained upon treating cells with increasing concentrations of verjuice. This inhibitory effect might be attributed to the high content of phenolic compounds in verjuice. In agreement with our observations, similar results against A549 and H129 cells were reported using grape seed proanthocyanidin extracts [27].

![Figure 2](image-url)  
**Figure 2.** Effect of different concentrations of verjuice on the survival of A549 after (A) 24 h, (B) 48 h, and (C) 72 h of treatment. The results are expressed as the percentage of control cell (0 mg/mL verjuice) viability (Ctrl). Each value represents the mean ± SD of triplicates obtained from five independent experiments. **p < 0.01; ***p < 0.001.

3.4. Co-Treatment with Cisplatin and Verjuice Has Superior Inhibitory Effects on A549 Cell Viability

Cisplatin is well known for its cytotoxic effect against different cancer cell lines, including A549 cells. Here, in a first step, we have confirmed, using the Neutral Red assay, the cytotoxic effect of cisplatin on the A459 cells after 24 and 48 h of treatment. As shown in Figure 3, cisplatin reduced cell
viability in a dose- and time-dependent manner. For instance, after 24 h of cisplatin treatment, the viability of the cells was reduced by 22%, 46%, 62%, and 78% at 4, 8, 12, and 80 μg/mL, respectively (Figure 3A). On the other hand, after 48 h, cells’ viability was reduced by 51%, 72%, 84%, and 90% (Figure 3B).

In a next step, and in order to determine whether the combination of cisplatin and verjuice may have a greater anticancer effect than cisplatin alone, cells were exposed to a unique low dose of cisplatin 4 μg/mL and different concentrations of verjuice (3.6, 3.8, and 4 mg/mL). The 4 μg/mL dose of cisplatin was chosen based on our above results showing a low level of toxicity at this indicated dose. Interestingly, Figure 4 shows that the verjuice extract significantly enhanced the cisplatin-dependent cytotoxic effect at both time points (24 and 48 h).

Cisplatin, a chemotherapy drug that contains platinum, is used to treat various types of cancer. However, cisplatin has severe side effects such as nephro- and hepato-toxicity [28,29]. One way to increase the efficacy of cisplatin and limit its side effects is the drug combination strategy [30]. Therefore, we studied the potency of verjuice as an anticancer natural product as well as its ability to enhance the anticancer effect of cisplatin. It is noteworthy that this is the first report to study the anticancer potential of verjuice. The major output of this study was that verjuice extract could suppress A549 cells’ viability where minor concentrations of this extract could strongly enhance cisplatin’s anticancer potential. In this context, various studies have previously reported the importance of the combination of cisplatin and plant-derived natural molecules to increase the anticancer potential of cisplatin [31,32]. Moreover, administration of verjuice was shown to reduce atherosclerotic and fibrinogen lesions in coronary arteries of rabbits [33]. Altogether, these observations suggest that verjuice extracts could increase the efficacy and tolerability of available anticancer chemotherapies.
Figure 4. Effect of different concentrations of verjuice (Verj) in combination with cisplatin (Cis) on the survival of A549 cells after (A) 24 h and (B) 48 h of treatment. The results are expressed as the percentage of control cell (0 mg/mL cisplatin) viability (Ctrl). Each value represents the mean ± SD of triplicates obtained in five independent experiments. *** p < 0.001.

The observed anticancer potential of verjuice could be related to its antioxidant capacity. In this context, grape antioxidants have been well reported for their potential anticancer effects. Distinct studies have suggested that high consumption of grape components could be correlated with the low risk of certain cancers, including breast and colon cancers [34]. Various grape antioxidants have been established to elicit cell cycle arrest, trigger apoptosis, and prevent cancer progression in rodent models [35]. Grape antioxidants have also been shown to alter estrogen receptor (ER) levels and are therefore important in the case of breast cancer [34]. Consistently, distinct grape antioxidants (such as resveratrol, quercetin, and catechin), and due to their structural similarity to the steroid hormone estrogen, exhibit both estrogenic and anti-estrogenic effects [36]. On the other hand, feeding grape products in the form of juice (50%) and raisins (10%) strikingly lowered the aberrant crypt foci in male rats. Grapes were also shown to exert a protective effect against chemically induced colon cancer due to their ability to induce Glutathione-S-tranferase enzyme [37]. Remarkably, grape antioxidants could significantly suppress the expression of epidermal growth factor receptor (EGFR), an essential factor accounting for the aggressive growth of cancer cells, in head and neck squamous cell carcinoma (HNSCC) [38]. Grape seed proanthocyanidins have also showed an in vitro potential against oral squamous cell carcinoma (OSCC). Other studies report that phenols extracts increase cell viability in the colon carcinoma cell line [39]. Moreover, grape extract was also shown to be protective against prostate cancer, in which it was shown to inhibit histone acetyltransferases (HATs), leading to decreased androgen-receptor (AR)-mediated transcription and cancer cell growth [40]. Further, one study revealed that grape antioxidants can elicit an antitumor activity due to their immune-potentiating activities via the enhancements of lymphocyte proliferation, natural killer (NK) cell cytotoxic activity, and IFN-γ (Interferon gamma) secretion [41]. By inhibiting genes for the migration of cells, the grape juice acts as an antimetastatic [42] and can be considered as a potential drug for cancer treatments [43,44].
4. Conclusions

Higher levels of phenols, flavonoids, alkaloids, and tannins were reported in the studied unripe grape juice. Besides its antioxidant activity, verjuice extract significantly repressed human pulmonary adenocarcinoma cells’ viability and also enhanced the anticancer potential of cisplatin. This is the first report highlighting correction between verjuice composition and its anticancer effects. This study reveals that verjuice contains significant amounts of bioactive molecules and can exert a significant antioxidant potential and prominent inhibitory effect on lung cancer cells’ viability. Verjuice could therefore hold therapeutic promise during cancer treatment. Determination of phenolic and alkaloid composition could help to understand if the effects induced by verjuice supply with cisplatin is due to one component of a synergetic impact. Further in vivo studies are needed to ascertain these results.


Funding: This study was funded by the Central Administration of the Lebanese University and by the French Foreign Ministry trough the Hubert Curien Project—Côedre No 42232RE.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

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