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Phenolic Compounds of Potato Peel Extracts: Their Antioxidant Activity and Protection against Human Enteric Viruses

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Potato peels (PP) contain several bioactive compounds. These compounds are known to provide human health benefits, including antioxidant and antimicrobial properties. In addition, these compounds could have effects on human enteric viruses that have not yet been reported. The objective of the present study was to evaluate the phenolic composition, antioxidant properties in the acidified ethanol extract (AEE) and water extract of PP, and the antiviral effects on the inhibition of Av-05 and MS2 bacteriophages, which were used as human enteric viral surrogates. The AEE showed the highest phenolic content and antioxidant activity. Chlorogenic and caffeic acids were the major phenolic acids. In vitro analysis indicated that PP had a strong antioxidant activity. A 3 h incubation with AEE at a concentration of 5 mg/ml was needed to reduce the PFU/ml (plaque-forming unit per unit volume) of Av-05 and MS2 by 2.8 and 3.9 $\log_{10}$, respectively, in a dose-dependent manner. Our data suggest that PP has potential to be a source of natural antioxidants against enteric viruses.

Keywords: Potato peel, antiviral, phenols, bacteriophages, antioxidants

Introduction

Potatoes (*Solanum tuberosum*) are, after maize, wheat, and rice, one of the most cultivated crops around the world. Potatoes are mostly confined to food use and feature heavily in diets of developed regions, particularly Europe and North America. The world production of potatoes in 2007 was 325,302 tons, of which only a few were destined for human consumption [1]. Their nutritional, agricultural, and toxicological properties have been described previously. Additionally, they are known to possess antihypertensive [2], anticancer [3], and antimicrobial [4] properties. The beneficial potato properties can be found both in the pulp and in the peel; however, the peel is often discarded.

In recent years, the study of by-products as natural source of antimicrobial and antioxidant properties has become a subject of worldwide interest. Previous reports have shown that potato peels (PP) (a waste by-product of potato processing) have antioxidant activity in several in vitro assay systems [5] and the aqueous extract of PP is rich in various phenolic acids, including hydroxycinnamic acids and flavonoids, which have strong antioxidant capacity [6] and offer therapeutic effect, including protection of erythrocytes, without having any mutagenic effects [5, 7].

In addition, most phenolic extracts possess antimicrobial activity. Potato tubers reduced the numbers of *Candida albicans*, *Rhizoctonia solani*, and coliform bacteria in the intestinal tract of pigs [4], and the potato aspartic protease (StAsp-PSI) exerts antimicrobial activity against human pathogens [8]. Additionally, PP demonstrated antibacterial activity toward *E. coli* and *S.* Typhimurium [7]. However, the effect of PP against human enteric viruses has not yet been reported. Each year, millions of people become sick from foodborne enteric infections of viral etiology. Noroviruses are the leading cause of viral foodborne illness in the United States [9]. Therefore, the antimicrobial components of PP could be considered as a natural resource to control foodborne viral infections.

Bacteriophages and enteroviruses have similar structural properties, and phages have therefore become a useful viral surrogate for the evaluation of antiviral substances on the basis of the ease of handling them in a laboratory environment [10]. Recently, extracts from grape seed and grape skin by-products were reported to have antiviral activities against viral surrogates and human enteric viruses [11].

In this context, the aims of this study were to characterize the phenolic compounds from potato peels using HPLC-DAD and to determine their antioxidant activity and antiviral effects using two bacteriophages, MS2 and Av05, as human viral surrogates.

Materials and Methods

Chemical Reagents

Potassium persulfate, 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), Folin-Ciocalteu reagent, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), sodium carbonate, gallic acid, quercetin, chlorogenic acid, ferulic acid, caffeic acid, and rutin were purchased from the Sigma Chemical Co. (USA). All other nonspecified reagents and solvents were purchased from J.T. Baker (Baker-Mallinckrodt, México).

Virus Strain and Bacterial Hosts

The bacteriophages MS2 and Av-05 and the hosts *E. coli* O157:H7 (ATCC 4076) and *E. coli* (ATCC 15597-B1) were obtained from the viral and bacterial collection of the Laboratorio Nacional para la Investigación en Inocuidad Alimentaria at the Centro de Investigación en Alimentación y Desarrollo (CIAD) in Culiacán, Sinaloa, México.

Extraction Process

Potatoes (*S. tuberosum*) of the Fianna variety was obtained from Yaqui Valley, Sonora, México, during the harvest of 2014. The tubers were washed with distilled water and manually peeled to a depth of ~1 mm. The peels were dried at 45°C for 24 h and then powdered and passed through a No. 20 sieve (WS Tyler, USA). The peel extracts were obtained according to the following procedure: 35 g of dried material was mixed with 350 ml of absolute ethanol with 5% acetic acid (95:5 ratio) and macerated with constant stirring for 72 h. To obtain the first supernatant, the sample was vacuum-filtered by using Whatman No. 1 paper, (Whatman, UK). The obtained residue was subjected to sonication for 20 min (Branson 3510; Branson Ultrasonic Corp., USA) with 50 ml of the extraction solution at 20°C. The sample was filtered to obtain the second supernatant, which was then mixed with the first supernatant. The resulting extract was concentrated in a rotatory evaporator (Büchi water bath B-490, Büchi rotator evaporator R-200; Switzerland), and the resulting concentrated extract was designated the acidified ethanol extract (AEE). The water extract (WE) was obtained by mixing 10 g of dried material in 150 ml of distilled water and stirring for 72 h. The samples were filtered and concentrate by freeze-drying (Freeze zone 4.5; Labconco Corporation, USA) instead of evaporation. Both extracts were evaluated for the phenolic compounds, and antioxidant and antiviral activities. The experiments were carried out in triplicates, and the results are reported as the mean ± standard deviation.

Phenolic Compounds

Total phenolics. The concentration of the total phenolic compounds was determined using the methods described by Singleton and Rossi [12], with some modifications. The extract was dissolved in absolute methanol, and 15 µl of the extract was mixed with 750 µl of 1 N Folin-Ciocalteu reagent (1:10). After 5 min of equilibration time, 60 µl of Na_2CO_3 (7.5% (w/v)) was added to this mixture. Following incubation for 20 min at room temperature, the absorbance was read at 765 nm using a Fluostar Omega multi-mode microplate reader (BMG Labtech, Germany). The results were expressed as milligrams of gallic acid equivalents (GAE) per gram (mg GAE/g).

Total flavonoids. The total flavonoid content was measured by the method described by Chen *et al*. [13], with modifications. The reaction mixture contained 100 µl of the PP extract and 430 µl of 5% $NaNO_2$, which was incubated for 5 min. After incubation, 30 µl of $AlCl_3$ (10%) and 440 µl of NaOH (1 mol/l) were added to the reaction. The absorbance was read at 496 nm with a Fluostar Omega multi-mode microplate reader (BMG Labtech). The results were expressed as mg of quercetin equivalents (QE) per gram (mg QE/g).

HPLC Analysis

The chromatographic analysis was carried out using a Waters HPLC 2690 (USA) with a diode array detector equipped with an automatic injector and automatic degassing system and a 4.6 mm ID × 250 mm Zorbax SB-C_{18} column. Ten microliters of the sample was injected. The conditions for analysis were in accordance with

Albishi *et al*. [6], using 1% (v/v) formic acid in water (A) and methanol HPLC grade (B) at a flow rate of 1 ml/min. The absorbance was recorded at 254 to 324 nm. The phenolic content was calculated using standard curves and was expressed as mg/100 g dry weight (DW).

Antioxidant Capacity

Trolox equivalent antioxidant capacity. The analysis was performed according to Al-Weshahy and Venket-Rao [14]. The ABTS radical cations were generated by combining 7 mmol ABTS with a 0.139 mmol $K_2S_2O_8$ solution. The extracts were diluted with absolute ethanol, and 5 µl of each extract was mixed with 245 µl of the ABTS solution. Trolox was used as the reference standard. The absorbance was read at 734 nm after the initial mixing (Abs_i) and every minute thereafter for 7 min (Abs_f) using a Fluostar Omega microplate reader spectrophotometer (BMG Labtech). The value of the results was expressed as mmol Trolox equivalents (mmol TE/g).

DPPH free-radical scavenging assay. A 280 µl aliquot of a solution of DPPH radicals (0.025 mg/ml in absolute methanol) was mixed with 20 µl/ml of each extract diluted in absolute ethanol. After 30 min, a control reaction mixture was prepared without any extract, and Trolox was used as the reference standard. The changes of absorbance (BMG Labtech) were measured at 515 nm using a Fluostar Omega microplate reader spectrophotometer. The results were expressed as mmol Trolox equivalents (mmol TE/g).

Oxygen radical absorbance capacity (ORAC). The ORAC was determined according to López-Cobo *et al*. [15], using a Fluostar Omega microplate reader spectrophotometer (BMG Labtech). The AAPH reagent was used as the peroxyl radical generator, fluorescein (FL) as the fluorescent indicator, phosphate buffer as the blank, and Trolox as the standard. The reaction mixture contained 100 µl of PP extract, 1.65 µl of phosphate buffer (pH 7.4), 150 µl of 0.8M AAPH, and 100 µl of 0.106 µM FL. The samples were pre-incubated at 37°C for 15 min, and AAPH was then added. Fluorescence was monitored at 484–515 nm. Each extract measurement was repeated 3 times. The final ORAC values were expressed as mmol Trolox equivalents per gram (mmol TE/g).

Propagation of MS2 (RNA) and Av-05 (DNA) Bacteriophages

The Av-05 and MS2 bacteriophages were propagated using *E. coli* O157:H7 (ATCC 4076) and *E. coli* (ATCC 15597-B1) as the host bacteria, respectively. Single host bacterial colonies were cultured in TSB at 37°C for 24 h. One milliliter of the bacterial culture was mixed with 100 µl of bacteriophages and 3 ml of TSB containing 0.4% agarose. The suspension was transferred to a Petri dish with a TSA layer and solidified [16]. The titers of the phage stock lysates were determined using the agar overlay technique.

Antiviral Activity

The extracts were dissolved in 5% DMSO and filtered through a 0.45 µm membrane filter. The concentrations tested were 1, 3, and 5 mg/ml. An aliquot of 100 µl of each bacteriophage was separately added to 3 ml of the extract and the mixtures were evaluated at intervals of 0, 1, and 3 h. At each time point, a neutralizing solution was added according to De-Siqueira *et al*. [17]. The suspensions for each treatment were serially diluted, and the reduction of the titer of bacteriophages was determined by soft agar overlay technique. The effect of each treatment on MS2 and Av-05 was determined separately. The viral reductions were compared with untreated control that consisted of 0.1 M phosphate-buffered saline (PBS).

Statistical Analyses

The results are expressed as the mean ± standard deviation (SD). The study was analyzed by analysis of variance (ANOVA) and Tukey comparisons were applied. The confidence limits were set at 0.95. The data were analyzed using Statgraphic for Windows ver. 4.0. The analysis model used to evaluate the survival of the phages was random. Two independent experiments, each performed in duplicates, were performed to assess the effects of the treatments. We used Statgraphic for Windows ver. 4.0 to perform the ANOVA.

Results

Biochemical Evaluations

Table 1 shows the total flavonoids content estimated as quercetin equivalents and total phenols as gallic acid equivalents. The AEE showed higher levels of total phenolics (14.031 ± 1.881 mg GAE/g) than the WE (4.160 ± 0.974 mg GAE/g). Additionally, the AEE showed high levels of total flavonoids with 3.310 ± 0.331 mg QE/g. The WE showed a lower level with a value of 1.016 ± 0.116 mg QE/g. In addition, identification of the phenolic compounds was performed using HPLC with photodiode array detection. Fig. 1 shows the chromatogram of the phenolic compounds in the PP as well the retention times for each compound. The components identified were four phenolic acids (gallic

Table 1. Total flavonoids and phenolic compounds in potato peel extracts.

Extract	Total flavonoids (mg QE/g)	Total phenols (mg GAE/g)
Acidified ethanol extract	3.310 ± 0.331[a]	14.031 ± 1.881[a]
Water extract	1.016 ± 0.116[b]	4.160 ± 0.974[b]

Data are expressed as the mean ±SD (n = 3); QE, quercetin equivalent; GAE, gallic acid equivalent.

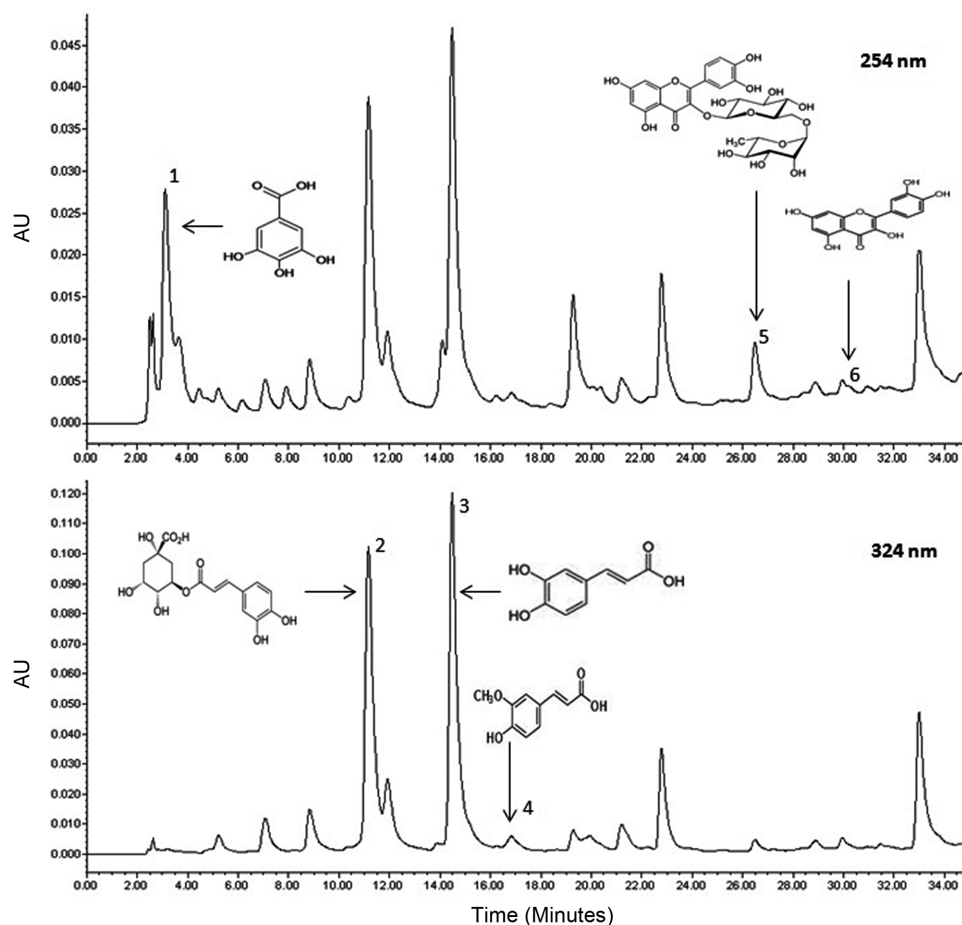

Fig. 1. HPLC chromatogram of phenolic compounds present in potato peel extracts.
Peaks: (1) gallic acid, (2) chlorogenic acid, (3) caffeic acid, (4) ferulic acid, (5) rutin, and (6) quercetin.

acid detected at 254 nm, and chlorogenic, caffeic, and ferulic acids detected at 324 nm) and two flavonoids (rutin and quercetin detected at 254 nm). The results were compared with authentic standards.

The phenolic contents are shown in Table 2. The individual constituents showed significant differences ($p < 0.05$) between the samples and the types of extraction (AEE and WE). The results indicated that PP contained three predominant compounds, specifically chlorogenic > caffeic > gallic acids, with levels of 346.03 ± 2.14, 332.58 ± 3.67, and 233.49 ± 9.78 mg/100 g DW, respectively, for AEE. In contrast, the predominant compounds in WE were chlorogenic > caffeic > and gallic acid with levels (159.99 ± 1.05, 56.99 ± 3.23, and 39.99 ± 3.03 mg/100 g DW), respectively. The acidified ethanol extracts showed low levels of the flavonoids rutin and quercetin as well as ferulic acid. In contrast, WE did not contain ferulic acid or the flavonoid rutin.

The PP extracts (AEE and WE) were able to neutralize the ABTS, DPPH, and peroxyl (ORAC assay) radicals (Fig. 2). The values obtained for the AEE (1.40, 0.38, and 4.00 mmol

Table 2. Phenolic composition of different potato peel extracts.

Extract	Gallic acid	Chlorogenic acid	Caffeic acid	Ferulic acid	Rutin	Quercetin
	(mg/100 g DW)					
Acidified ethanol extracts	233.49 ± 9.78[a]	346.03 ± 2.14[a]	332.58 ± 3.67[a]	3.29 ± 0.05[a]	5.01 ± 1.03[a]	11.22 ± 0.09[a]
Water extract	39.99 ± 3.03[b]	159.99 ± 1.05[b]	56.99 ± 3.23[b]	NA[b]	NA[b]	2.18 ± 0.07[b]

Data shown are the means of at least three HPLC experiments ± standard deviation (SD). NA = No detected.

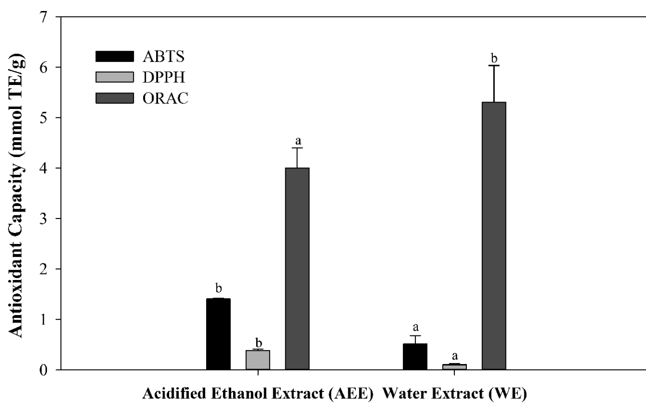

Fig. 2. Antioxidant capacity of potato peel extracts.
Each datum is expressed as mmol Trolox equivalent per gram.

TE/g, respectively) and WE (0.51, 0.10, and 5.31 mmol TE/g, respectively) indicated that the AEE was more effective in neutralizing the ABTS and DPPH radicals. The higher antioxidant capacity of the AEE could be associated with its high content of phenolic compounds as shown in the HPLC analysis (Fig. 2).

Antiviral Activity

The AEE of PP was used to evaluated the virus survival rate of the Av-05 and MS2 bacteriophages at titers of ~8 and 9 log PFU/ml. Each treatment was evaluated using the standardized plaque assay. Fig. 3 shows the reduction in the viral titers of the bacteriophages following incubation with the PP with contact times of 0, 1.0, and 3.0 h and concentrations of 1.0, 3.0, and 5.0 mg/ml at room temperature in complete darkness. The virus titers were compared with the untreated control (PBS), to determine the virus inactivation efficacy after different contact times. According to this analysis, PP showed significant differences compared with the control (p > 0.05), and the reduction of the viral titer was dependent on the contact time and the concentration of PP. Similar behavior was reported by Su *et al.* [18, 19], whose study showed that the reduction in the titer of enterovirus surrogates is a function of the contact time and the concentration of chemical compounds.

Av-05 was the most sensitive bacteriophage (Fig. 3A) as indicated by the inhibition of its multiplication by ~3.93 log PFU/ml after 3 h of contact time and 5.0 mg/ml of extract. In addition, an instantaneous reduction greater than 1 log PFU/ml was observed, and the replication of this phage continued to drop until 3 h. In contrast, the replication of the RNA bacteriophage MS2 was less inhibited by PP: a maximum reduction of ~2.8 log PFU/ml after 3.0 h of treatment at 5.0 mg/ml of PPE was observed (Fig. 3B).

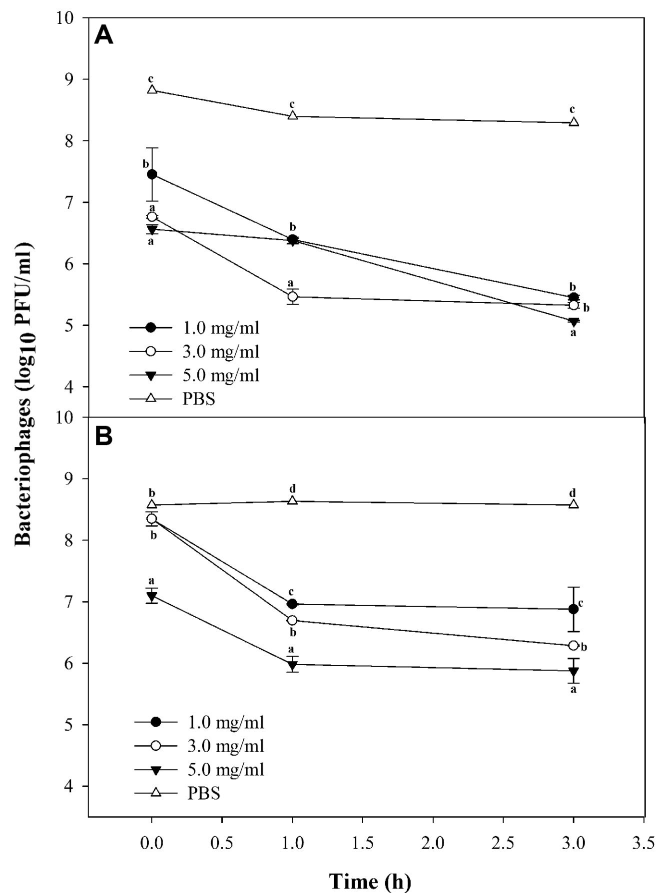

Fig. 3. Reduction (log PFU/ml) of Av-05 (**A**) and MS2 (**B**) after treatment with potato peel extracts for different contact times (0, 1, and 3 h) at three concentrations (1, 3, and 5 mg/ml).

Additionally, at concentrations 1.0 and 3.0 mg/ml, MS2 demonstrated a minimal reduction of the viral titer (<1 log PFU/ml) at the first contact time. After 1.0 h of treatment with PP, the reduction was approximately >1 log PFU/ml. Interestingly, the effects on the replications of MS2 and Av-05 in response to 5.0 mg/ml of PP and a contact time of 1 h were found to be similar: ~2.6 and ~2.3 log PFU/ml were recorded for MS2 and Av-05, respectively. However, at later contact times, the analysis showed that MS2 was more resistant to PP, whereas the DNA bacteriophages continued to decrease.

Discussion

Biochemical Evaluations

Higher extraction yields of phenolic compounds from PP was obtained using acidified ethanol. These results are in agreement with those found by Albishi *et al.* [6] for purple

potato peel, where they reported values of 4.64–13.85 mg GAE/g dried PP. On the other hand, Alvarez *et al*. [20] and Arun *et al*. [21] reported values higher than those of our study, with levels of 20 to 83 mg GAE/g in potato peel, using subcritical water extraction. The difference in the total phenol content could depend on the potato variety or method of extraction. Additionally, the differences could be attributed to the mixture of solvents employed. Ethanol was the solvent that extracted the most phenolic compounds, but the differences could be related to the presence of hydroxylated aglycone forms of phenolic compounds that are soluble in alcohols such as methanol or ethanol [22]. In addition, others studies have shown that most of the phenolics compounds are located in peel, whereas very few are found in the potato flesh [6].

To evaluate the possible relationship between the antiviral activity and the chemical composition of PP extracts, individual phenolic compounds were analyzed. Al-Weshahy and Venket-Rao [14] and Al-Weshahy *et al*. [23] evaluated the peel samples of six potato varieties, in which they detected four phenolic compounds. In contrast, in our study, only chlorogenic acid and caffeic acid were found. However, in the previous reports, the presence of quercetin and rutin derivates, and isomers of chlorogenic acid, such as *p*-couramic and ferulic acid, as well as derivatives of benzoic acid, such as gallic acid, and other phenolic compounds were also detected [6, 24].

Previous reports have evaluated the phenolic compounds from different varieties of PP and showed that chlorogenic and caffeic acids are the two major compounds found in PP [6, 23]. Although flavonoids such as rutin and quercetin were only present at low concentrations, PP could be considered to be a good source of flavonoids on the basis of the high potato consumption rate. Previous reports have shown that chlorogenic acid and caffeic acid are components with beneficial health effects. For example, studies showed that chlorogenic acid has a radioprotective effect, can reduce liver inflammation and fibrosis, and, in a complex with oxyvanadium, is a promising antioxidant and anticancer agent for human breast cancer [25, 26]. Furthermore, caffeic acid has both antitumor activity and an antihypertensive effect and has low cytotoxic manifestations compared with a conventional hypertension drug [27, 28].

Numerous studies have reported on the antioxidant capacity of potatoes [6, 21]. In addition, the use of PP as a source of antioxidants has been evaluated [5]. We evaluated the antioxidant capacity in PP using various assays, and the results were expressed as mmol TE/g as shown in Fig. 2. The reducing power towards free radicals such as DPPH, ABTS, and peroxy radical has been reported previously for PP ethanolic extracts and WE [6, 23]. However, our results are higher than those reported in these investigations [6, 23]. The high antioxidant activity might be due to high content of phenolic compounds, especially the presence of chlorogenic and caffeic acids in the PP. A high antioxidant activity of these compounds has already been reported [22]. Moreover, it is possible that the high antioxidant capacity was obtained owing to the use of sonication and vigorous stirring in the extraction process.

Antiviral Activity

The effectiveness of PP as an antiviral agent was evaluated using Av-05 and MS2 bacteriophages, two foodborne virus surrogates. Av-05 is a DNA bacteriophage for which the morphology and genetic characteristics have previously been studied by López-Cuevas *et al*. [16]. These authors showed a lytic effect in *Salmonella* serotypes and *E. coli* O157:H7. Our study showed that Av-05 was more sensitive, as indicated by the observation that our extract had only a small effect on the RNA bacteriophage MS2. This finding is in agreement with that reported by Su *et al*. [19], which demonstrated that MS2 is less susceptible, decreasing by ~1 log PFU/ml when the phages were exposed to cranberry juice. This resistance might be because MS2 is a lipid-free icosahedral virus and is therefore more resistant to stress [29]. Another study showed an inhibition of viral infection by phenolic compounds using foodborne viral surrogates. The authors argued that the inhibition may occur at the initial stage of viral replication [30]. A similar phenomenon was observed in this study. Additionally, our research group studied tomato leaf extracts and observed that Av-05 bacteriophage was inhibited early in its viral replication; that is, in the first contact time [31].

Recently, the inactivation of enteric viruses by phenolic compounds and their potential application in the food industry have been studied. These studies used bacteriophages as viral surrogates [30]. In the present study, the inhibition of bacteriophages was probably due to the high levels of hydroxycinnamic acids such as chlorogenic and caffeic acids, which are known to inhibit viruses, in the PP extracts [32]. Gallic acid was also detected in the PP, and this compound has been reported to cause moderate inhibition of viral replication [30]. Therefore, we hypothesized that these compounds could be closely associated with the inhibition of the viral replication of the phages MS2 and Av-05. Additionally, some phenolic compounds from other plant sources, including resveratrol, quercetin, gallic acid, chlorogenic acid, and caffeic acid, exhibited antiviral

activities [30, 32, 33], and several mechanisms have been suggested for inactivation of the viruses. Phenolic compounds such as quercetin interfere with the processing of RV polyproteins by the RV proteases that are essential for inactivation of the RNA polymerase. Thus, these compounds may interfere with viral replication by more than one mechanism [33]. Additionally, caffeic and chlorogenic acids inhibit the viral capsid [32], and it has been suggested that this activity could result from free hydroxyl and ester groups [34].

Potato peels clearly demonstrate a high content of phenolic compounds and a high antioxidant capacity. In addition, the AEE of PP effectively reduced the viral titers of the MS2 and Av-05 bacteriophages. The result that polyphenols are present in the PP extracts provides motivation for examining the potential use of this material in the food or pharmaceutical industries. Further studies of the individual phenolic compounds must be performed as well as studies of the mechanism of action against human enterovirus surrogates.

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