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Antioxidant Potential and Polyphenolic Profile of Endophytic Fungi *Aspergillus Sydowii* Strain AV5L and *Penicillium Verrucosum* AV6L Isolated from *Aloe Vera*

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Abstract Endophytic fungi are an important and underexplored source of multifunctional bioactive metabolites. In this study, we investigated the antioxidant potential of ethyl acetate extracts from *Aspergillus sydowii* AV5L and *Penicillium verrucosum* AV6L isolated from *Aloe vera*. The extracts exhibited strong concentration-dependent antioxidant activity in phosphomolybdenum, DPPH, and hydrogen peroxide scavenging assays. Notably, *P. verrucosum* AV6L demonstrated superior activity, showing phosphomolybdenum antioxidant capacity comparable to ascorbic acid (88.3 ± 2.3 AAE/mL at 1000 μg/mL) and exceeding it in hydrogen peroxide scavenging (78% at 1000 μg/mL). High levels of phenolic compounds and flavonoids were detected, and LC–MS/MS analysis revealed a diverse profile of polyphenols, including compounds with known antioxidant and urease inhibitory activity. These results highlight the potential of *Aloe vera*-associated endophytic fungi as a source of dual-function bioactive metabolites targeting both oxidative stress and enzyme-mediated pathogenicity.

Keywords Endophytes, Urease, Metabolites, Antioxidant activity, Phenols, Flavonoids

1. Introduction

Endophytic microorganisms are increasingly recognized as an important source of biologically active secondary metabolites with potential relevance in pharmaceutical and biomedical research [1-3]. These microorganisms inhabit plant tissues without causing apparent harm and often establish complex symbiotic relationships with their host plants. As a result of co-evolution, endophytes can produce structurally diverse metabolites, including compounds similar to those synthesized by their host, as well as unique bioactive molecules that may possess notable pharmacological properties [4,5].

Among medicinal plants, *Aloe vera* has attracted considerable attention due to its reported antioxidant, anti-inflammatory, antimicrobial, and gastroprotective properties [6,7]. These biological activities have been associated with the presence of phenolic compounds, flavonoids, and polysaccharides, which may contribute to reactive oxygen species (ROS) scavenging and modulation of inflammatory signaling pathways [8,9]. Endophytic microorganisms associated with *Aloe vera* may serve as alternative, sustainable sources of such compounds, as well as of potentially novel metabolites with diverse biological activities [10-11].

One of the important molecular targets associated with infectious and inflammatory diseases is the enzyme urease. Urease is a nickel-dependent metalloenzyme that catalyses the hydrolysis of urea into ammonia and carbon dioxide [12-14]. This reaction contributes to the pathogenicity of several urease-producing microorganisms, including *Helicobacter pylori* infection, *Proteus* spp., and *Yersinia enterocolitica* [18-20]. Ammonia production may result in local pH elevation, epithelial damage, disruption of mucosal integrity, and activation of immune responses, including increased generation of reactive oxygen species.

Thus, urease functions not only as metabolic enzyme but also as an important virulence factor associated with chronic inflammation, tissue damage, and increased risk of carcinogenesis. In the case of *H. pylori* infection, urease activity facilitates bacterial survival under acidic conditions while contributing to oxidative stress and activation of pro-inflammatory signalling pathways, including NF-κB. Infection with *H. pylori* stimulates innate immune responses, leading to the generation of reactive oxygen species (ROS) such as superoxide anion (O2−), hydrogen peroxide (H2O2), hydroxyl radicals (˙OH), and hypochlorous acid (HOCl). Increased ROS production in gastric cells and phagocytes following *H. pylori* exposure has been reported [22-23]. Elevated ROS levels in the gastric mucosa of infected

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patients may contribute to oxidative damage of proteins, DNA and lipids.

Notably, many naturally occurring urease inhibitors belong to phenolic compounds, flavonoids, and related polyphenols [24]. These molecules may inhibit urease activity through interactions with Ni^{2+} ions located in the enzyme active site while also exhibiting antioxidant and anti-inflammatory properties. Therefore, metabolites possessing both urease inhibitory and antioxidant activities may represent promising candidates for reducing enzymatic virulence and oxidative stress simultaneously.

Endophytic fungi associated with *Aloe vera* may represent a valuable source of multifunctional metabolites. In our previous studies, ethyl acetate extracts of *Aspergillus sydowii* strain AV5L and *Penicillium verrucosum* AV6L exhibited notable urease inhibitory activity, reaching up to 88,1% [25] inhibition. However, the antioxidant properties of these bioactive extracts have not yet been comprehensively investigated.

Therefore, the present study aimed to evaluate the antioxidant activity of these endophytic fungal extracts using multiple *in vitro* assays, and to establish a possible relationship between their chemical composition and biological activity. A comprehensive approach combining antioxidant assays and LC–MS/MS analysis was applied to elucidate the bioactive potential of secondary metabolites produced by these endophytes.

2. Materials and Methods

2.1. Fungal Strains and Cultivation

Endophytic fungi *Aspergillus sydowii* strain AV5L and *Penicillium verrucosum* AV6L were isolated from healthy leaves of *Aloe vera* collected in Tashkent, Uzbekistan. The isolates were previously identified by molecular methods and deposited in the NCBI GenBank database under accession numbers strain PQ726933 and strain PV065897 respectively.

The endophytic fungi were cultivated under submerged fermentation conditions in 500 mL flasks containing 250 mL of potato dextrose broth and incubated for 7 days at 28 ℃ on a rotary shaker.

2.2. Extraction of Secondary Metabolites

5 g of fungal biomass of endophyte was homogenized and transferred to a conical flask containing 50 ml of ethyl acetate, and left for 48 hours on the rotary shaker at room temperature. The mixture was filtered through filter paper (Whatman #1), after which the extract was dried on a rotary evaporator and redissolved in 1 ml of ethyl acetate. The resulting crude extract was used as a stock solution and stored at 4 ℃ until further use.

2.3. Determination of Total Antioxidant Capacity

2.3.1. Phosphomolybdenum Assay

Total antioxidant capacity (TAC) was evaluated by phosphomolybdenum assay according to Prieto et al (1999) [26], based on the reduction of Mo (VI) to Mo (V) and the formation of green phosphate/Mo(V) complex., with the refence to updated methodological overviews (Gulcin 2020) [27] with minor modifications. Briefly, 0.1 mL of each extract was mixed with 1 mL of reagent solution containing 0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate.

The reaction mixtures were incubated at 95 ℃ for 90 min. After cooling to room temperature, absorbance was measured at 695 nm against a blank using a UV–Vis spectrophotometer (UV-5100, China). Results were expressed as ascorbic acid equivalents (AAE). All experiments were performed in triplicate.

2.3.2. DPPH Radical Scavenging Assay

The free radical scavenging activity of the extracts was determined using the DPPH assay according to Blois [28]. Briefly, 1 mL of extract solution at different concentrations (100–1000 µg/mL) was mixed with 1 mL of 0.2 mM DPPH solution in ethanol. The reaction mixtures were incubated in the dark at room temperature for 30 min. Absorbance was measured at 517 nm. Ascorbic acid was used as a standard. The percentage of radical scavenging activity was calculated using the following equation: Scavenging activity (%) = (Ac − As) / Ac × 100, where Ac is the absorbance of the control and As is the absorbance of the sample.

2.3.3. Hydrogen Peroxide Scavenging Assay

Hydrogen peroxide (H2O2) scavenging activity was determined according to the method of Ruch et al. [29] based on the ability of antioxidants to neutralize H2O2. A 40 mM hydrogen peroxide solution was prepared in phosphate buffer (50 mM, pH 7.4). Extract solutions (100–1000 µg/mL) were added to the H_2O_2 solution, and absorbance was measured at 230 nm after 10 min. The percentage of scavenging activity was calculated as: H_2O_2 scavenging (%) = [(Ai − At) / Ai] × 100, where Ai is the absorbance of the control, and At is the absorbance of the sample.

2.4. IC_{50} Values Determination

IC_{50} values (the concentration required to inhibit 50% of radical activity) were calculated using nonlinear regression analysis based on concentration–response curves.

2.5. LC–MS/MS Analysis

Chemical profiling of the extracts was performed using reversed-phase nano-liquid chromatography coupled with a Q-TOF mass spectrometer (Agilent 1200 LC system with CHIP-Q-TOF 6520B, Agilent Technologies). Separation was carried out on a Zorbax SB-C18 chip column (5 µm, 75 µm × 43 mm). The mobile phases consisted of: (A) 0.1% formic acid in 5% acetonitrile and (B) acetonitrile with 0.1% formic acid and 10% water. A gradient elution program (0–60% B) was applied. The flow rate was 0.6 µL/min. All experiment were carried out in triplicate.

2.6. Statistical Analyses

Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Turkey's post hoc test. Data were expressed as mean ±standard deviation (SD). Differences were considerate statistically significant at $p < 0.05$.

3. Results

Compounds combining urease inhibitory and antioxidant activities may provide a dual therapeutic effect by simultaneously suppressing enzymatic virulence and oxidative stress.

In essence, having antioxidant activity ensures that the inhibitor not only works on the urease enzyme itself but also alleviates the oxidative damage that the pathogen has already inflicted on the host [30-32].

The presented study was focused on the evaluation of the antioxidant activity of ethyl acetate extracts of *Aspergillus sydowii* strain AV5L and *Penicillium verrucosum* AV6L secondary metabolites, whose urease inhibitory activity reached 88%. The antioxidant activity was assessed through three different assays (TAC, DHPP, H2O2).

The total antioxidant capacity assessed by the phosphomolybdenum method revealed a clear concentration -dependent increase in reducing power for both extracts. At the highest concentration (1000 µg/mL), *P. verrucosum* AV6L exhibited antioxidant activity (88.3 ± 2.3 AAE/mL) comparable to that of ascorbic acid (87.9 ± 2.4 AAE/mL), while *A. sydowii* strain AV5L showed slightly lower activity (76.0 ± 2.5 AAE/mL) (Figure 1).

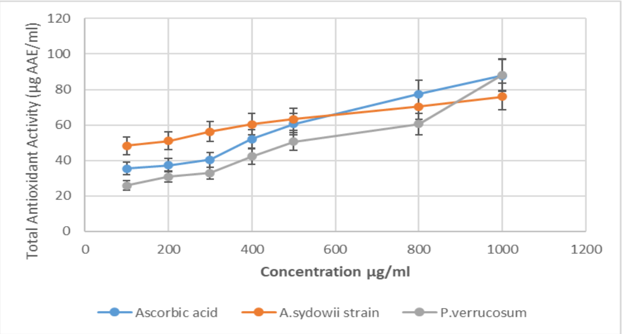

Figure 1. The total antioxidant capacity of *A. sydowii strain* AV5L and *P. verrucosum* AV6L by the phosphomolybdate assay (n=3)

These findings indicate that the reducing capacity of *P. verrucosum* AV6L extract was slightly higher, while *A. sydowii* strain AV5L extract was lower than that of a standard antioxidant, highlighting their potential as natural antioxidant sources.

The DPPH radical scavenging assay reveal the strong antioxidant potential of the studied extracts. A concentration-dependent correlation in radical scavenging activity was observed for both strains. At 1000 µg/mL, *P. verrucosum* AV6L achieved 81.5% inhibition, which is close to the activity of ascorbic acid (89.0%) and significantly higher than that of *A. sydowii* strain AV5L (57.6%) (Figure 2).

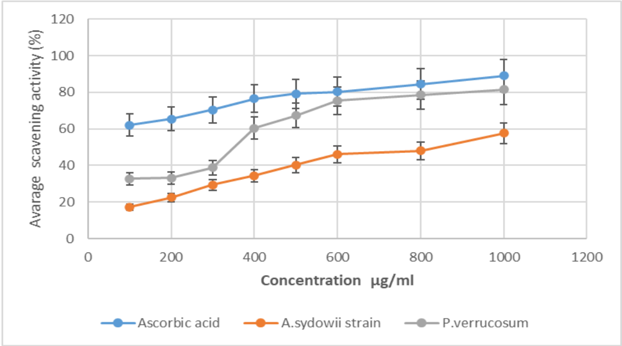

Figure 2. Free radical scavenging activity of endophytic fungi *A. sydowii* strain AV5L and *P. verrucosum* AV6L π measured by the DPPH assay (n=3)

The activity of hydrogen peroxide capture additionally confirmed the superiority of the antioxidant activity of *P. verrucosum* AV6L. At a concentration of 1000 µg/ml, the extract demonstrated 78.2% inhibition, exceeding both *A. sydowii* strain AV5L (51.4%) and ascorbic acid (76.4%). This result is especially significant because hydrogen peroxide plays a key role in oxidative stress and cell damage. Effective compounds capable of neutralizing reactive oxygen species were identified in the *P. verrucosum AV6L* extract (Figure 3).

The higher accumulation of phenolic compounds in *P. verrucosum* AV6L correlates well with its superior antioxidant activity observed in subsequent assays, suggesting a direct relationship between polyphenol content and radical scavenging capacity.

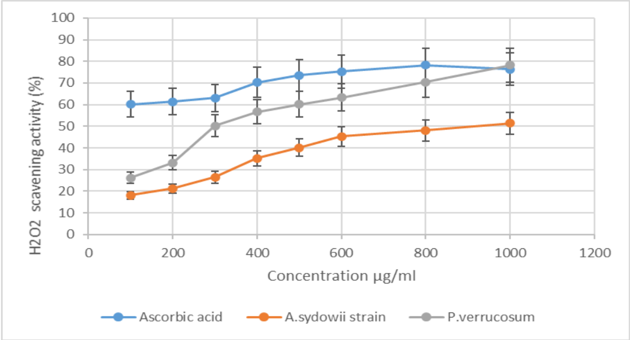

Figure 3. Hydrogen peroxide (H_2O_2) radical scavenging activity of *A. sydowii* strain AV5L and *P. verrucosum* AV6L (n=3)

These results demonstrate that *P. verrucosum* AV6L has a significantly higher ability to capture radicals, in compare with which is probably due to its higher content of phenolic compounds.

Quantitative analysis revealed that both endophytic strains accumulate substantial amounts of phenolic compounds and flavonoids. Notably, *P. verrucosum* AV6L exhibited higher levels of these metabolites, with total phenolic content reaching 92.1 ± 0.41 µg GAE/mg extract and total flavonoids 98 ± 0.56 µg QE/mg extract. In contrast, *A. sydowii* strain AV5L showed lower but still significant values (78.6 ± 0.24 µg GAE/mg and 82 ± 0.24 µg QE/mg, respectively) (Table 1).

Table 1. Polyphenols Content of Ethyl Acetate Extracts of *A. Sydowii* Strain AV5L and *P. Verrucosum* AV6L

№	Strain	Total phenols (µg of GAE/mg dry extract)	Total flavonoids (µg of QE / mg dry extract)
1	*A. sydowii strain* AV5L	78.6 ± 0.24	82.3 ± 0.24
2	*P.verrucosum* AV6L	92.1 ± 0.41	98.2 ± 0.56

Values are expressed as mean ± standard deviation (n = 3). GAE, garlic acid equivalents; QE, quercetin equivalents.

Table 2. IC_{50} of Antioxidant Activity of *A. Sydowii* Strain AV5L and *P. Verrucosum* AV6L extracts

№	Tested sample	TAC IC_{50}, (µg/ml)	DPPH IC_{50}, (µg/ml)	H_2O_2 IC_{50}, (µg/ml)
1	Ascorbic acid	529 ± 12.09	414 ± 9.03	397 ±8.04
2	*A. sydowii strain* AV5L	688 ± 15.13	347 ±7.15	390 ±9.03
3	*P. verrucosum* AV6L	631 ± 14.03	365 ± 8.13	335 ±6.05

Table 3. Mass Spectrometry Analysis of Endophytic Fungi Extracts *A. sydowii* Strain AV5L

№	Putatively identified compound	Molecular formula	RT (min)	Mode of ionization (m/z) [M+H] +	Molecular weight (g/mol)	Compound class	Reference database
1	Psoralen (6,7-furanocoumarin)	$C_{11}H_6O_3$	2.012	187.032	186.16	Furanocoumarins	http://phenol-explorer.eu/compounds
2	Pyrogallol	$C_6H_6O_3$	2.054	127.016	126.02	Phenolics	http://phenol-explorer.eu/compounds
3	Putative Indole-3-acrylic acid derivative	$C_{11}H_{13}NO_2$	9.085	208.145	207.22	Indole derivatives	http://phenol-explorer.eu/compounds
4	Nepetin	$C_{16}H_{12}O_7$	11.662	317.259	316.26	Flavones	http://phenol-explorer.eu/compounds
5	Sinapaldehyde	$C_{11}H_{12}O_4$	12.838	209.213	208.21	Phenylpropanoids	http://phenol-explorer.eu/compounds
6	4-Feruloylquinic acid	$C_{17}H_{20}O_9$	13.319	369.106	368.31	Hydroxycinnamic acid	http://phenol-explorer.eu/compounds
7	1,4-Naphthoquinone	$C_{10}H_6O_2$	14.320	159.153	158.15	Quinones	http://phenol-explorer.eu/compounds
8	Resveratrol (3,5,4'-trihydroxystilbene)	$C_{14}H_{12}O_3$	14.757	229.209	228.24	Stilbenes	http://phenol-explorer.eu/compounds
9	Tetradecanamide	$C_{14}H_{29}NO$	14.797	228.491	227.39	Fatty acid amides	http://phenol-explorer.eu/compounds
10	Curcumin	$C_{21}H_{20}O_6$	16.856	369.130	368.38	Curcuminoids	http://phenol-explorer.eu/compounds

Table 4. Mass Spectrometry Analysis of Endophytic Fungi Extracts *Penicillium verrucosum* AV6L

№	Putatively identified compound	Molecular formula	RT (min)	Mode of ionization (m/z) [M+H] +	Molecular weight (g/mol)	Compound class	Reference database
1	Pyrogallol	$C_6H_6O_3$	1.639	127.030	126.02	Phenolics	http://phenol-explorer.eu/compounds
2	Piceatannol	$C_{14}H_{12}O_4$	2.054	245.244	244.24	Stilbenes	http://phenol-explorer.eu/compounds
3	Coumarin	$C_9H_6O_2$	10.505	147.137	146.14	Coumarins	http://phenol-explorer.eu/compounds
4	1,4-Naphthoquinone	$C_{10}H_6O_2$	13.404	159.153	158.15	Quinones	http://phenol-explorer.eu/compounds
5	Curcumin	$C_{21}H_{20}O_6$	14.047	369.409	368.38	Curcuminoids	http://phenol-explorer.eu/compounds
6	Cyanidin glycoside	$C_{25}H_{20}O_{17}$	16.885	592.891	593.43	Flavonoids	http://phenol-explorer.eu/compounds

The higher accumulation of phenolic compounds in *P. verrucosum* AV6L in compare with *A. sydowii* AV5L correlates well with its superior antioxidant activity observed in subsequent assays, suggesting a direct relationship between polyphenol content and radical scavenging capacity.

A similar trend was observed in the hydrogen peroxide scavenging assay, where *P. verrucosum* AV6L exhibited the lowest IC_{50} value (335 µg/mL), confirming its superior antioxidant efficiency (Table 2).

The IC_{50} values confirm the antioxidant potential of the extracts. In the DPPH test, *P. verrucosum* AV6L and *A. sydowii* strain AV5L showed lower IC_{50} values (347 and 365 µg/ml, respectively) compared with ascorbic acid (414 µg/ml), indicating a stronger radical absorbing activity.

A similar trend was observed in the hydrogen peroxide capture test, where *P. verrucosum* AV6L demonstrated the lowest IC_{50} value (335 µg/ml), confirming its excellent effectiveness.

LC–MS/MS analysis revealed a diverse spectrum of secondary metabolites, predominantly belonging to polyphenolic classes, including flavonoids, stilbenes, phenolic acids, and quinones. Among the identified compounds were resveratrol, quercetin derivatives, catechins, curcumin, and naphthoquinones, all of which are well-documented antioxidants (Table 3 and 4).

Importantly, many of these compounds have also been reported as urease inhibitors, suggesting that the observed biological activity of the extracts may result from multifunctional metabolites capable of both enzyme inhibition and oxidative stress modulation.

4. Discussion

The results obtained in this study clearly demonstrate that ethyl acetate extracts of the endophytic fungi *Aspergillus sydowii* strain AV5L and *Penicillium verrucosum* AV6L possess pronounced antioxidant activity, which is concentration-dependent and assay-specific.

Among the investigated strains, *P. verrucosum* AV6L consistently exhibited superior antioxidant potential across all applied methods, particularly in hydrogen peroxide scavenging and DPPH assays.

The observed antioxidant activity is strongly associated with the high content of phenolic compounds and flavonoids detected in the extracts.

Numerous studies have demonstrated that phenolic compounds play a key role in neutralizing reactive oxygen species through electron donation and radical stabilization mechanisms (Shahidi & Ambigaipalan, 2015; Rice-Evans et al., 1997) [33,34].

In the present study, the higher total phenolic and flavonoid content in *P. verrucosum* AV6L directly correlates with its enhanced antioxidant capacity, supporting the widely reported relationship between polyphenol content and radical scavenging activity.

Similar trends have been reported for endophytic fungi isolated from medicinal plants. For example, endophytes from *Calotropis procera* demonstrated a strong positive correlation between total phenolic content and antioxidant activity, including DPPH scavenging capacity and enzyme inhibition (Khiralla et al., 2015) [35]. These findings are consistent with our results and further confirm that phenolic -rich endophytic extracts represent a promising source of natural antioxidants.

An important aspect of this study is the demonstrated link between antioxidant activity and urease inhibition. It is well established that many phenolic compounds, including flavonoids and stilbenes, exhibit dual biological activity, functioning both as antioxidants and enzyme inhibitors (Al-Rooqi et al., 2023) [36]. These compounds can chelate metal ions in the active site of urease while simultaneously reducing oxidative stress, which plays a critical role in the pathogenesis of infections caused by urease-producing microorganisms such as *Helicobacter pylori*.

In this context, the dual functionality of the studied extracts is of particular interest. The combination of urease inhibitory and antioxidant activities suggests a synergistic therapeutic potential, where both enzymatic virulence and oxidative damage are targeted simultaneously. This concept has been previously described for plant-derived phenolics, but remains relatively underexplored for endophytic fungi.

LC–MS/MS analysis revealed the presence of a diverse spectrum of putatively identified polyphenolic compounds, including resveratrol, flavonoids, phenolic acids, and quinones, which are widely recognized for their antioxidant and enzyme-inhibitory properties. Compound annotation was primarily based on LC-MS/MS fragmentation patterns and database comparisons. Compouds such as resveratrol and curcumin have been extensively reported to exhibit both antioxidant and urease inhibitory activity, further supporting the potential multifunctional nature of the detected metabolites (Bhat et al., 2021; Sharma et al., 2021) [37,38]. Overall, the results suggest that the observed biological activity of the studied endophytes may be associated with the synergistic interactions among multiple secondary metabolites rather than a single dominant compound. This synergistic effect is a well-known characteristic of natural extracts and often contributes to enhanced biological activity compared to isolated constituents.

5. Conclusions

The present study demonstrates that endophytic fungi associated with *Aloe vera*, particularly *Penicillium verrucosum* AV6L, represent a promising source of biologically active secondary metabolites with significant antioxidant potential. The extracts exhibited strong concentration dependent radical-scavenging activity, reducing power, and hydrogen peroxide neutralization capacity.

The observed biological activity is associated with the relatively high content of phenolic compounds and flavonoids, as indicated by quantitative analysis and LC–MS/MS profiling. The detected polyphenolic metabolites, some of with have been previously reported to exhibit antioxidant and urease inhibitory activities may contribute to the overall bioactivity of the extracts.

Importantly, the combined antioxidant and urease inhibitory effects suggest that these endophytic fungi could be a dual-activity bioactive compounds acting on both oxidative stress enzyme-mediated pathogenic processes. However, further studies, including isolation of individual compounds and confirmation using authentic reference standards are required substantiate these activities and clarify their mechanisms on action.

Further studies are needed to isolate and characterized individual compounds, clarify their mechanisms of action, and evaluate their biological effects in vivo. The present findings indicate that endophytic fungi isolated from *Aloe vera*, particularly *Penicillium verrucosum* AV6L, represent a potential source of biologically active secondary metabolites with significant antioxidant potential. The extracts demonstrated concentration-dependent radical-scavenging activity, hydrogen peroxide-neutralizing capacity, and reducing power, with some activities comparable to those of ascorbic acid under the tested condition.

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