

The effect of natural phenolic compounds on reducing oxidative stress

Avani Kaur¹, Michael Norris²

¹ Mills E. Godwin High School, Richmond, Virginia

² Department of Chemistry, University of Richmond, Richmond, Virginia

SUMMARY

Oxidative stress is caused by oxidation-reduction dysregulation between free radicals and antioxidants, damaging cellular components. Research implicates this phenomenon in the pathophysiology of various diseases, notably cancer and neurodegenerative conditions, which are becoming more prevalent due to environmental pollutants and unhealthy lifestyle choices. Therefore, we aimed to identify a natural phenolic compound exhibiting potency in reducing oxidative stress. By investigating the antioxidant capacities of these phenolic compounds, this research contributes to our understanding of natural antioxidants and their potential applications in preventing and managing oxidative stress-mediated diseases. We used cyclic voltammetry, an electrochemical technique, to measure the oxidation potential of different compounds. We hypothesized that curcumin would exhibit the smallest oxidation potential compared to cinnamic acid, epigallocatechin gallate (EGCG), and resveratrol, due to its extensive conjugation system and electron-donating functional groups that facilitate electron delocalization. We found that EGCG was the easiest to oxidize and most effective in alleviating oxidative stress, followed in decreasing effectiveness by cinnamic acid, resveratrol, and curcumin. Our findings did not support our hypothesis, as curcumin exhibited the highest oxidation potential among the tested compounds. This contrasts with the predicted outcome based on its structural features. The results highlight the importance of molecular structure in determining the antioxidant effectiveness and suggest that EGCG may be a more promising candidate for reducing oxidative stress than other commonly studied phenolic compounds.

INTRODUCTION

Free radicals are highly reactive molecules that contain one or more unpaired electrons. Free radicals form through normal metabolic processes, such as those in the mitochondrial electron transport chain and phagocytic immune cells, as well as from external sources including pollution, heavy metals, and unhealthy lifestyle choices (1). In low to moderate concentrations, free radicals play crucial roles in biological functions like cellular signaling and immune defense (1). However, an excessive production of free radicals can result in oxidative stress, which disrupts the equilibrium between these molecules and the body's antioxidant mechanisms (1). This imbalance results in damage to crucial cellular components like lipids, proteins, and DNA, contributing to the

development of conditions such as cancer, cardiovascular diseases, neurodegenerative disorders, and diabetes (1).

The human body employs endogenous antioxidants like superoxide dismutase (SOD) and glutathione peroxidase (GPx) to combat oxidative stress (1). A diet rich in exogenous antioxidants, particularly natural phenolic compounds found in fruits and vegetables, is essential for enhancing the body's defense mechanisms (1). Epidemiological studies have linked the consumption of antioxidant-rich foods to a reduced incidence of oxidative stress-related diseases, highlighting the importance of understanding how these compounds function in health promotion (1).

In this study, we compared the antioxidant properties of different natural phenolic compounds. Among the various classes of dietary antioxidants, phenolic compounds have garnered attention for their potent antioxidant properties (1). These secondary metabolites, prevalent in the plant kingdom, not only protect plants from environmental stressors but also offer health benefits when consumed (1). Their antioxidant mechanisms involve scavenging reactive species and inhibiting the activity of enzymes that produce free radicals, such as NAD(P)H and xanthine oxidase (2). The structural diversity of phenolic compounds, identified by their aromatic rings and hydroxyl groups, influences their antioxidant capacity, with simpler compounds generally demonstrating higher bioavailability compared to larger, polymerized structures (2).

Our aim was to determine the oxidation potential of various phenolic compounds to evaluate their ability to act as effective antioxidants. We compared four compounds: curcumin, cinnamic acid, epigallocatechin gallate (EGCG), and resveratrol (**Figure 1**). Curcumin was chosen for its potent antioxidant activity in modulating enzymatic antioxidants like SOD and GPx (3). Cinnamic acid was chosen for its strong free radical scavenging and antipathogenic properties (4). EGCG, a catechin in green tea, has metal-chelating abilities that prevent free radical production and is effective in cancer prevention (5). Resveratrol was included for its proven effects in alleviating oxidative stress and modulating signaling pathways (6). Oxidation potential indicates a molecule's ability to lose electrons, with lower potentials suggesting greater antioxidant efficacy through enhanced electron donation and free radical neutralization (7).

Using cyclic voltammetry (CV) with an Ag/AgNO₃ reference electrode, we measured the redox behavior of these compounds (**Figure 2**). We hypothesized that curcumin would have the lowest oxidation potential due to its complex structure featuring electron-donating functional groups and extensive conjugation system, as supported by studies linking it to cancer mitigation (8). However, our results showed that

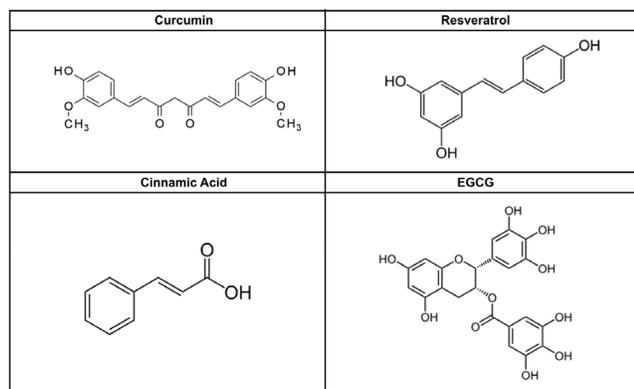


Figure 1: Chemical structures of the phenolic compounds tested for antioxidant capacity. Structures of curcumin, cinnamic acid, epigallocatechin gallate (EGCG), and resveratrol, showing their varying functional groups and conjugation patterns which influence their oxidation potential and antioxidant properties. These structures were used to predict and analyze the compounds' effectiveness in reducing oxidative stress.

EGCG actually had the lowest oxidation potential and was the most effective antioxidant, followed by cinnamic acid, resveratrol, and curcumin.

RESULTS

To test the effect of natural phenolic compounds on reducing oxidative stress, we measured their oxidation potentials using CV at a scan rate of 100 mV/s and then calculated the mean oxidation potential for each compound based on their CV curves (Figure 3-4). We hypothesized that curcumin would have the smallest oxidation potential. The oxidation potentials were determined to be 1.227 V for curcumin, 1.008 V for cinnamic acid, 0.962 V for EGCG, and 1.031 V for resveratrol. EGCG exhibited the lowest oxidation potential, while curcumin demonstrated the highest. This indicates that EGCG has the greatest capacity to donate electrons and, therefore, the highest efficiency in scavenging reactive oxygen species (ROS). Both resveratrol and cinnamic acid showed intermediate oxidation potentials suggesting moderate antioxidant capacity compared to EGCG and curcumin. Curcumin was found to be least effective as a ROS scavenger.

In addition, in reference to the CV, we did not detect any cathodic peaks at a 100 mV/s scan rate (Figure 3). The absence of significant cathodic peaks suggests these compounds undergo irreversible oxidation, indicating they permanently neutralize free radicals rather than reversibly binding them.

DISCUSSION

We aimed to determine the oxidation potentials of selected natural phenolic compounds as an indicator of their antioxidant capacity. We employed CV to gain insight into the electrochemical properties of each compound. We hypothesized that curcumin would have the smallest oxidation potential and thus be the most effective at reducing oxidative stress. However, the results showed that EGCG would most likely have the greatest impact on alleviating oxidative stress because it exhibited a smaller oxidation potential compared

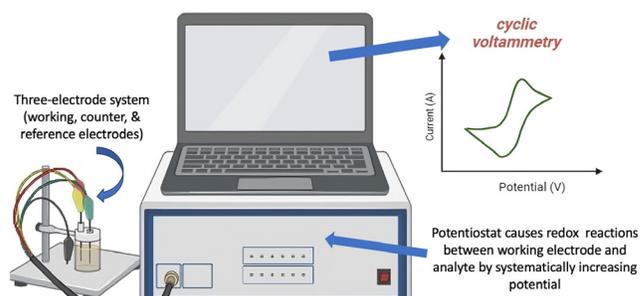


Figure 2: Experimental setup for measuring oxidation potentials of phenolic compounds. Schematic diagram showing the three-electrode configuration used for all cyclic voltammery measurements, comprising a glassy carbon working electrode, platinum wire counter electrode, and Ag/AgNO₃ reference electrode in a TBAPF6 and acetonitrile solution.

to curcumin, cinnamic acid, and resveratrol. This implies that EGCG has the highest antioxidant ability and capacity to mitigate oxidative stress. Although our hypothesis was refuted, our finding is valuable because it reveals that EGCG is the most effective antioxidant among the compounds tested, highlighting its potential importance in reducing oxidative stress.

Other researchers have investigated curcumin, cinnamic acid, EGCG, and resveratrol as methods of reducing oxidative stress, specifically through the electrochemical determination of oxidation potentials. Reported oxidation potentials include 0.66 V for curcumin, 0.570 V for resveratrol, and two oxidation peaks at 0.29 V and 0.38 V for EGCG that correspond to different hydroxyl groups on the molecule (5, 6, 9). No previous oxidation potential measurements for cinnamic acid were found in literature, though its derivative caffeic acid showed an oxidation potential of 0.45 V (4). These reported values align with the trends observed in this experiment, where curcumin had the highest oxidation potential and EGCG the lowest, with resveratrol and cinnamic acid falling in between. There are minor differences in the magnitudes of measured oxidation potentials, but these discrepancies likely stem from variations in electrode materials and configurations across studies (4, 7). For instance, while this experiment used a glassy carbon working electrode and an Ag/AgNO₃ reference electrode, other studies used gold and graphene pastes as working electrodes or Ag/AgCl reference electrodes (4-6, 9). The choice of electrode material is essential in CV because different electrodes possess varying surface properties, which can lead to slight differences in these electrochemical experiments (7). However, despite these differences, the overarching trends and relative comparisons between the phenolic compounds based on their oxidation potentials remains consistent among studies. This consistency suggests that the broader trends regarding the antioxidant capacities of these compounds remain intact, even if specific electrode configurations introduce subtle variations in the recorded values.

There are a number of possible explanations for the results of this experiment, which revealed that EGCG was superior in mitigating oxidative stress when compared to cinnamic acid, resveratrol, and curcumin. We hypothesize that structural differences among the compounds might

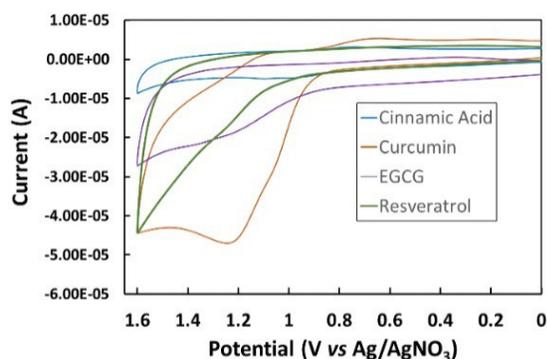


Figure 3: Electrochemical characterization of phenolic compounds using cyclic voltammetry. Representative cyclic voltammograms of curcumin, cinnamic acid, epigallocatechin gallate (EGCG), and resveratrol were recorded using a three-electrode setup in TBAPF6 and acetonitrile solution at a scan rate of 100 mV/s. Distinct anodic peaks indicate oxidation events, with peak positions corresponding to each compound's oxidation potential.

explain their varying oxidation potentials. Curcumin has the most complex structure when compared to the other tested phenolic compounds. Its extensive presence of a conjugated system consisting of alternating double and single bonds allows for electron delocalization, attributing to curcumin's reactivity and molecular properties (9). In addition, curcumin consists of electron-donating groups such as the hydroxyl and methoxyl functional groups, which distribute the positive charge throughout the molecule and prevent it from localizing in a singular atom. This enhances stability and minimizes undesirable side reactions (6). However, when curcumin undergoes oxidation, its conjugation system is disrupted, leading to structural changes, degradation through autoxidation, and the formation of new chemical species. Unfortunately, this autoxidation can potentially cause pro-oxidant effects through the generation of free radicals, ultimately resulting in oxidative stress (10).

Furthermore, resveratrol was observed to have the second-largest oxidation potential because of its structure. Resveratrol, consisting of two phenolic rings connected by an ethylene bridge, has a less extensive conjugation system than curcumin. A smaller conjugation system typically indicates reduced electron delocalization capability, which could result in a smaller relative oxidation potential value. Resveratrol contains two phenolic hydroxyl groups that can participate in electron donation and hydrogen bonding, potentially contributing to its oxidation behavior (6).

Cinnamic acid showed a lower oxidation potential than resveratrol in our measurements. This may be largely due to its molecular structure, which contains a phenyl ring and a carboxyl functional group. While cinnamic acid has a limited conjugated system, its oxidation potential was higher than EGCG's. This is likely due to EGCG's greater number of electron-donating hydroxyl groups and more extensive conjugation network. The presence of multiple hydroxyl groups in EGCG's structure may contribute to electron delocalization and stabilization during oxidation processes (4, 5). The extended conjugation of EGCG, particularly from these functional groups, may provide resistance to oxidation reactions, the ability to stabilize free radicals, and ensures charge equilibrium within the molecule.

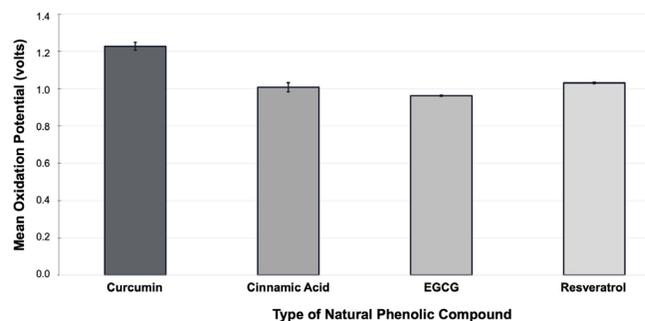


Figure 4: Mean oxidation potentials of natural phenolic compounds. The mean oxidation potential for curcumin, cinnamic acid, epigallocatechin gallate (EGCG), and resveratrol (n=5). Cyclic voltammograms were recorded from 0 to 0.5 V versus Ag/AgNO₃ at scan rates of 10, 25, 50 and 100 mV/s.

There were several potential sources of error in our experiment. Firstly, the evaluation and analysis of the CV was challenging and may have yielded errors in the determination of the compounds' oxidation potential. In our voltammograms, we observed that some oxidation peaks of different compounds appeared at similar potentials and partially overlapped, making it challenging to precisely determine individual oxidation potentials. Additionally, we found that the oxidation reactions were not chemically reversible, meaning we did not observe corresponding reduction peaks in the reverse scan. This irreversibility makes it more difficult to confirm the exact oxidation potential values, as reversible reactions typically provide more reliable electrochemical measurements through the comparison of oxidation and reduction peaks. Therefore, further studies are needed to optimize experimental parameters such as scan rate. While our measurements used 100 mV/s, testing slower scan rates could improve peak resolution by allowing more time for the electrochemical reactions to occur, potentially leading to more defined and separated peaks.

Despite these limitations, this research displays the value of CV in characterizing antioxidant activity and shows that EGCG, having the lowest oxidation potential among tested compounds, may have strong antioxidant properties. Future studies should examine these compounds *in vitro* to directly measure their ability to reduce ROS levels. Subsequently, these compounds should be investigated in living organisms, where factors like metabolism, absorption, and bioavailability could affect their antioxidant activity. Additional studies focusing on EGCG's ability to reduce ROS are needed to validate our CV data and demonstrate its effectiveness as an antioxidant. Our study demonstrates that among the four phenolic compounds tested, EGCG exhibited the lowest oxidation potential, suggesting superior electron-donating capacity and antioxidant potential compared to curcumin, resveratrol, and cinnamic acid. These findings support the utility of CV as a rapid electrochemical screening method for comparing the relative antioxidant capacities of natural phenolic compounds, providing a foundation for future *in vitro* and *in vivo* validation studies.

MATERIALS AND METHODS

Reagents and materials

Curcumin, resveratrol, cinnamic acid, and EGCG powders were obtained as solid powders. Tetrabutylammonium hexafluorophosphate (TBAPF6) served as the supporting electrolyte.

Preparation of phenolic compound solutions

Each compound was prepared as a 0.001 M solution in acetonitrile. To each solution, 194.70 mg of TBAPF6 was incorporated to create a 0.1 M electrolyte concentration. All solutions were prepared fresh on the day of experimentation and kept at room temperature during measurements. Each compound was added to its respective vial and sonicated in an ultrasonic water bath for approximately 5 seconds to ensure proper dissolution and homogenization.

Electrode preparation

A conventional three-electrode cell was employed, consisting of a glassy carbon working electrode, a platinum wire counter electrode, and a Ag/AgNO₃ reference electrode. Before inserting the working electrode, a polishing procedure was followed: a polishing pad was prepared with a small amount of distilled water (no additional polishing compounds were used), and the working electrode was placed on the pad with moderate pressure. It was polished using circular motions for one minute, after which it was rinsed with acetonitrile and placed into the glass vial through the cap's designated hole.

Cyclic voltammetry

CV measurements were performed using a three-electrode configuration. We recorded CVs using a potentiostat (CH Instruments), with parameters set for scans ranging from 0 to 0.5 V vs. Ag/AgNO₃ at scan rates of 10, 25, 50, and 100 mV/s. The Ag/AgNO₃ electrode served as a control reference. We exported the CV data to Excel and identified the x-coordinate to indicate the oxidation potential corresponding to the maximum current peak to determine the oxidation potential.

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