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Understanding Antioxidant Abilities of Dihydroxybenzenes: Local and Global Electron Transfer Properties

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Abstract: In the current work, globally based on Koopmans' approximation, local electron transport characteristics of dihydroxybenzenes have been examined using the density functional theory for understanding their antioxidant activity. Our experimental and theoretical studies show that hydroquinone has better antioxidant activities when compared to resorcinol and catechol. To identify the antioxidant sites for each dihydroxybenzene molecule, an average analytical Fukui analysis was used. The typical Fukui analytical results demonstrate that dihydroxybenzene oxygen atoms serve as antioxidant sites. The experimental and theoretical results are in good agreement with each other; therefore, our results are reliable.

Keywords: quantum chemical descriptors; analytical Fukui; DFT; antioxidant

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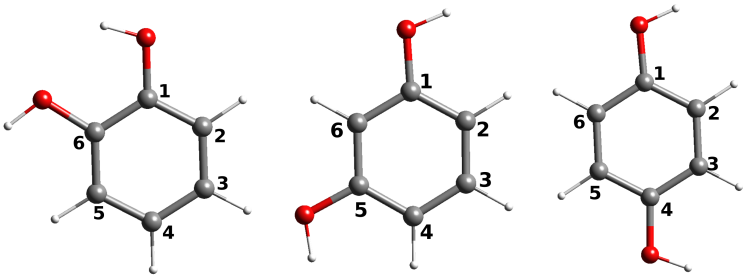
1. Introduction

The relationship between the structure and property of compounds is a great requirement of the modern biochemistry world. For this purpose, quantitative structure–activity, and structure–property relationship (QSAR/QSPR) studies can easily reveal the treasure hidden inside compounds. Once we understand the working rhythm of every structure of a specific compound, we can easily access the properties. Thus, it is possible to develop such molecules which can act as a panacea for diseases by developing highly effective drugs at the industrial level [1]. To meet this aspect of understanding the correlation between structure and properties of a compound, every description, whether in terms of theory or other experimental characteristics of that compound, must be considered. Once the relationship is understood it can be analyzed in mathematical terms and then with the help of efficient algorithms assisted with computational hardware and a new aspect can be added to the quantum chemical molecular system [2]. Recent research successfully established a relation between structures and property and then analyzed a computational system by applying density functional theory (DFT) studies [3]. H. Djeradi et al. have used conceptual DFT methods such as the Fukui indices to analyze the radical scavenging properties of flavonoids. The results prove that conceptual DFT methods are useful for understanding the relation between carbonyl atoms and the antioxidant activity of flavonoids [4]. V. P. Petrović et al. used DFT to assess pyrazolone antioxidant capacity. The results indicate that pyrazolone's radical scavenging abilities depend on substituents present on the phenyl rings [5]. E. Bendary et al. have used DFT for comparing the antioxidant properties of phenolic and aniline compounds. Their studies confirm that aniline derivatives have better

antioxidant activities than phenolic compounds of O–H bond dissociation energies than N-H [6].

Phenols are considered a central molecule in the organic chemistry world [7]. Phenolic compounds possess potent antibacterial [8], anticancer [9], and antiviral activity with the presence of high antioxidants in comparison to alines and flavonoids [6]. Thus, phenols are a major class of highly antioxidant compounds, and they should be explored according to the need of the present time for drug development. Phenols possess antioxidants in high amounts, and thus a computational study about the structure of gallic acid was performed for analysis of antioxidant activity with DFT-B3LYP. The physiochemical properties and pharmacological effects of a compound are consequences of its structure. It is confirmed in the previous studies that the antioxidant activities increase with an increase in the OH group of phenols and increase their radical scavenging activity [10]. Even the presence of the OH group at different positions has a different effect on the antioxidant properties of phenols.

Considering the above-mentioned reasons and as an extension of previous work, we attempted an experiment and evaluated the antioxidant radical scavenging potential in this study. With this, the computational determination was also performed for radical scavenging activity via hydrogen atoms present in the ortho, meta, and para position versus electron transfer. The DFT method is used to calculate the mathematical values and their analysis for inhibiting ability. Ionization potential (IP), distribution of HOMO orbitals, and LUMO orbitals were particularly calculated for three members of the phenol family viz. catechol, resorcinol, and hydroquinone with the presence of OH group on their structures at ortho (A), meta (B), and para (C) positions, respectively, as shown in Figure 1.



(**a**) Catechol (**b**) Resorcinol (**c**) Hydroquinone

Figure 1. Structures of dihydroxy benzenes [H = white, C = grey, and O = red].

2. Experimentation

2.1. Computational Methods

The molecular structures of all models were plotted using the Sinapsis tool [11]; as shown in Figure 1, geometry optimization was carried out using density functional theory (DFT) implemented in deMon2K code [12] with PBE [13] correlation functionals and TZVP [14] basis sets. The Fukui function was calculated for all species by an analytic method [15,16] implemented in deMon2K code [12].

The energy of frontier orbitals ϵ_{HOMO} and ϵ_{LUMO} was used to approximate the reactivity descriptors [17] electron affinity (EA), ionization potential (IP), hardness, and softness [18] using the following equations:

$$IP \approx -\epsilon_{HOMO} \quad (1)$$

$$EA \approx -\epsilon_{LUMO} \quad (2)$$

$$\eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{\nu} = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{\nu} = \frac{1}{2}(IP - EA) \tag{3}$$

$$S = \frac{1}{2\eta} \tag{4}$$

The Fukui function can be defined according to Equation (5) [19].

$$f^{\pm}(\mathbf{r}) \equiv \lim_{\Delta N \to 0^{\pm}} \frac{\rho_{N+\Delta N}(\mathbf{r}) - \rho_N(\mathbf{r})}{\Delta N} \tag{5}$$

where $\rho(\mathbf{r})$ is the electron density, N is the number of electrons in the system, and $+$ and $-$ signs correspond to addition or remotion of electrons, respectively. Equation (5) has been used to compute analytical Fukui functions. The average Fukui value ($f^o(\mathbf{r})$) can be used to predict regioselectivity in the addition of free radicals. In this work, Fukui functions were calculated analytically [15,16].

$$f^o(\mathbf{r}) = \frac{f^-(\mathbf{r}) + f^+(\mathbf{r})}{2} \tag{6}$$

Global electron transfer properties are calculated using DFT as implemented in ORCA 4.2.1 [20] with the functional B3LYP [21] with TZVP basis set. The solvent effects were included via the conductor-like polarizable continuum model (CPCM) [22].

2.2. Chemicals

DPPH, (1,1-diphenyl-2-picryl-hydrazyl), catechol, resorcinol, hydroquinone, methanol: all the chemicals used were obtained from Himedia and are of analytical grade.

2.3. DPPH Assay

The radical scavenging activity of all the three selected phenolic compounds was analyzed and was compared with the radical scavenging activity of ascorbic acid, which is used as standard in the present study. A purple-colored crystalline powder of DPPH (reagent) is dissolved in methanol and a stable radical solution is prepared for spectrophotometric analysis of the hydrogen atoms donating capacities of phenolic compounds [23]. For the analysis of free radical scavenging activity of selected compounds, the method of Blios (1958) was followed with slight modifications. DPPH radical absorbs light at 517 nm and as the percentage of antioxidant reagent increases the absorption decreases [24]. The DPPH stock solution was prepared in methanol by adding 2 mg of DPPH crystals in 100 mL of methanol; 20 mg of each compound is dissolved in 1ml of methanol separately. Aliquots of 1 mL of each sample freshly prepared in methanol were collected at four different concentrations 20 µg/mL, 40 µg/mL, 40 µg/mL 60 µg/mL, 80 µg/mL, and 100 µg/mL. In each concentration, the methanolic dilution of DPPH was added to get 1 mL of the final solution. From this 1 mL of solution, 100 µL of the solution was pipetted out and 2 mL of DPPH solution was added. All the prepared solutions were mixed properly in a vortex machine and then kept in dark for 30 min for incubation. A half-hour later, the absorbance was measured at 517 nm against blank samples lacking scavenger in a UV-spectrophotometer. The blank sample was prepared with the methanolic dilution of DPPH. A standard curve was prepared using different concentrations of DPPH. The inhibition percentage was calculated according to the following formula:

$$\text{Radical scavenging activity}(\%) = \frac{\text{Control} - \text{Sample}}{\text{Control}} \times 100 \tag{7}$$

where Control = absorbance of DPPH and Sample = absorbance of test compounds.

3. Results and Discussion

3.1. Global Electron Transfer Properties of Dihydroxybenzenes

The global reactive descriptor values of different dihydroxybenzenes in the vacuum medium are shown in Table 1. The reactive descriptors (IP and η) give information related to the oxidation process and will tell the capacity of a molecule to show antioxidant properties. As shown in Table 1, catechol and resorcinol have comparatively higher antioxidant power when compared to hydroquinone. The reactive descriptors (EA and S) give information related to the reduction process. As shown in Table 1, hydroquinone has higher oxidation power when compared to catechol and resorcinol.

Table 1. Reactivity descriptors of dihydroxybenzenes

Model	IP (Vacuum) eV	IP (Solvent) eV	EA (Vacuum) eV	EA (Solvent) eV	η (Vacuum) eV	η (Solvent) eV	S (Vacuum) eV	S (Solvent) eV
Catechol	5.124	6.022	0.964	0.267	2.080	2.875	0.240	0.173
Resorcinol	5.271	6.171	0.952	0.298	2.159	2.936	0.231	0.170
Hydroquinone	4.901	5.795	1.225	0.517	1.838	2.639	0.272	0.189

3.2. Local Electron Transfer Properties of Dihydroxy Benzenes

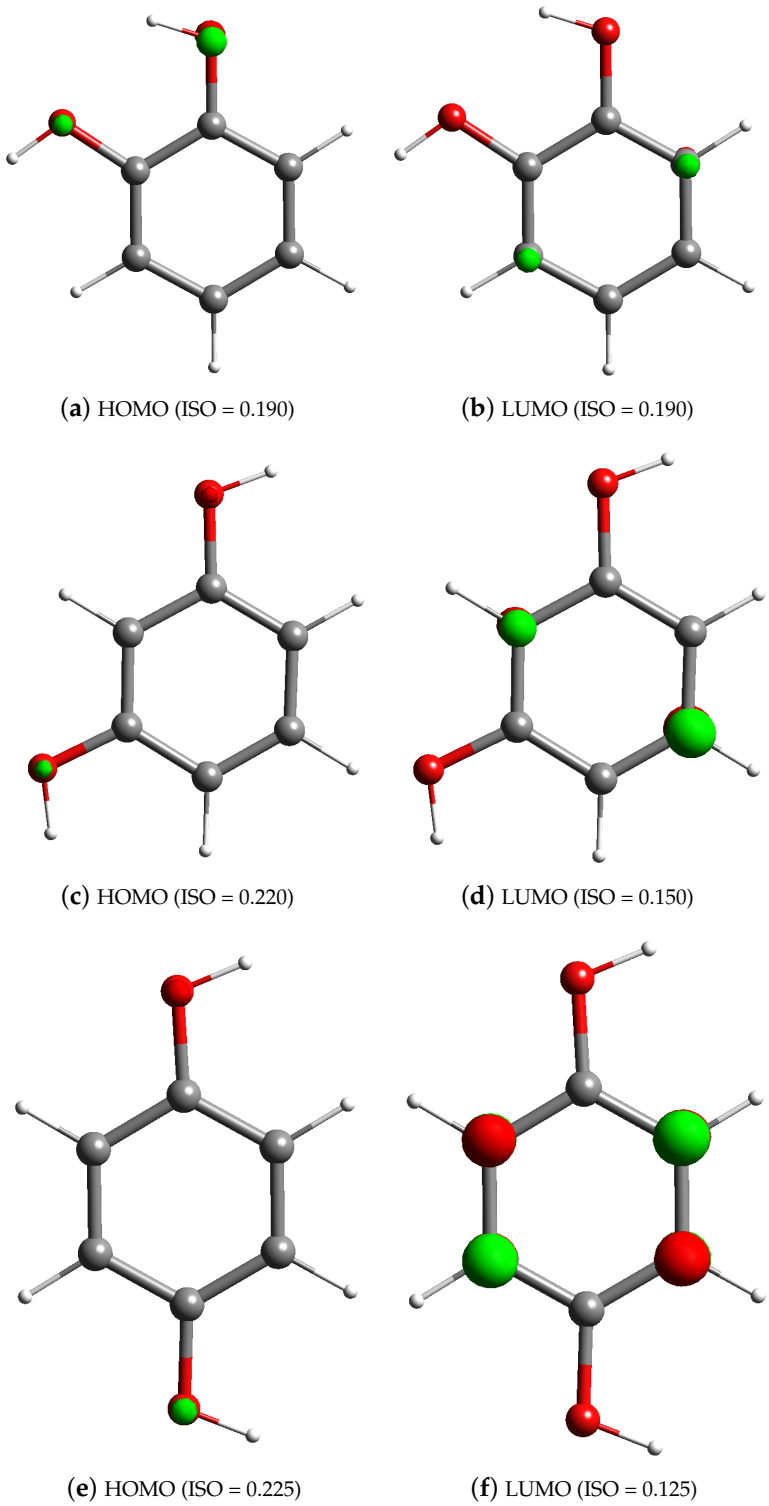
3.2.1. Frontier Molecular Orbital Analysis

To compare the local electron transfer properties of different atoms within the same molecule we are using frontier molecular orbitals and analytical Fukui function as discussed in our previous articles [25–28].

The frontier molecular orbital analysis of each dihydroxybenzene is shown in Figure 2. The highest occupied molecular orbitals (HOMO) of catechol, resorcinol, and hydroquinone are shown in Figure 2a,c,e. As shown in Figure 2, all dihydroxybenzene HOMO orbitals are located on their hydroxyl group.

The lowest unoccupied molecular orbitals (LUMO) of catechol, resorcinol, and hydroquinone are shown in Figure 2b,d,f. As shown in Figure 2, all dihydroxybenzene LUMO orbitals are located on ortho C atoms. From the obtained results, we can say that the ortho-positioned carbon atom concerning the hydroxyl group plays a major role in comparing the antioxidant properties of these dihydroxybenzenes. Additionally, the HOMO is located on the oxygen atom of the hydroxyl group (presence of 2 lone pairs), while the LUMO is located on the ortho-carbon atoms; thus, polarization effects by the C-O bond and carbon acquire a partial positive charge.

In the case of catechol, there are two ortho-positioned carbon atoms; therefore, we can say two atoms can contribute to LUMO and can act like electron-deficient sites. Additionally, if we pass a mirror plane in between the adjacent carbon atoms containing hydroxyl groups, the molecule forms mirror images; thus, both these electron-deficient sites become identical, but in the case of resorcinol, there are three ortho-positioned carbon atoms out of which one lies in between carbon atoms attached to the hydroxyl groups, while two are surrounded by the CH group from one side and by a carbon atom having an OH group from one side. Therefore, we can say that the carbon atom positioned in between the carbon-containing hydroxyl group is more likely to contribute to LUMO as polarization produced in both the C-O bonds will cause an electron shift away from carbon, making it more electron deficient. In hydroquinone, there are four ortho carbon atoms and all are in the same environment. Three mirror planes, one passing through both the carbon atoms containing a hydroxyl group and two planes perpendicular to it, confirm the formation of mirror images. So, all four carbon atoms are equivalent, and therefore, with hydroquinone, four atoms can contribute to LUMO.



(**a**) HOMO (ISO = 0.190) (**b**) LUMO (ISO = 0.190)

(**c**) HOMO (ISO = 0.220) (**d**) LUMO (ISO = 0.150)

(**e**) HOMO (ISO = 0.225) (**f**) LUMO (ISO = 0.125)

Figure 2. Frontier molecular orbitals of dihydroxybenzenes.

3.2.2. Hirshfield Charges

The polarization effects of each carbon atom present in hydroxybenzene rings can be easily analyzed by calculating the Hirshfield charges [29,30]. Hirshfield charges of all the three compounds were measured and compiled in Table 2, and it can be easily seen that the all the carbon atoms of dihydroxybenzenes which are bonded to oxygen atoms have high electron charges. With the higher electron charges present among all the six carbon atoms

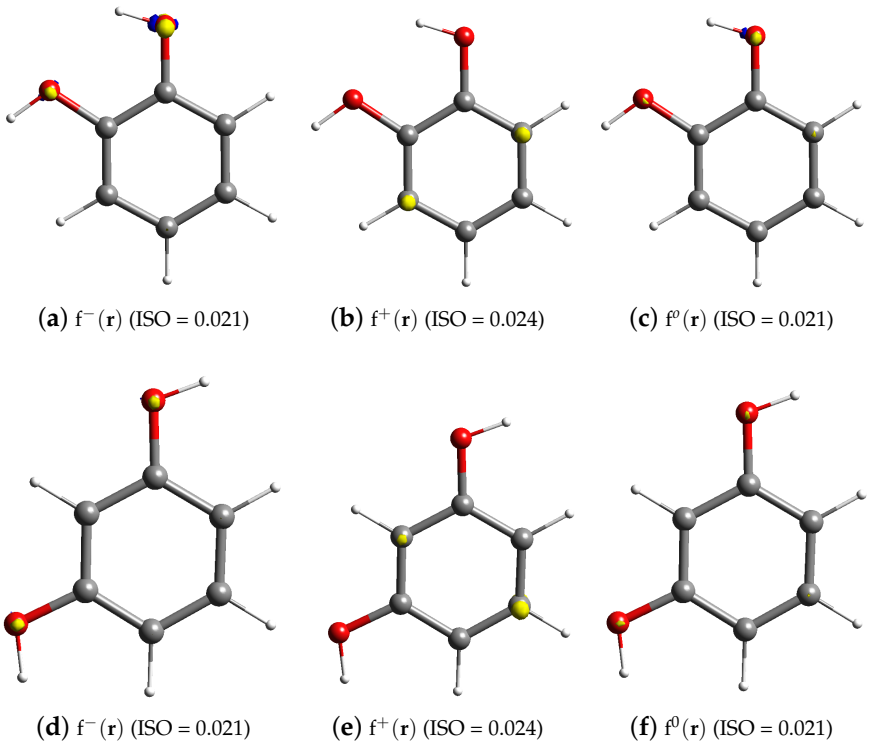
of the respective hydroxybenzenes, carbon is more prone to polarization effects, leading to the occurrence of polarization at C-O sites.

Table 2. Atomic charge on carbon atom at ground state with respect to their position numbers in catechol, resorcinol, and hydroquinone.

Model	C1	C2	C3	C4	B	C6
Catechol	0.0561	−0.0589	−0.0546	−0.0581	−0.0713	0.0468
Resorcinol	0.0722	−0.0844	−0.0445	−0.0845	0.0716	−0.0772
Hydroquinone	0.0574	−0.0685	−0.0689	0.0576	−0.0561	−0.0544

3.2.3. Analytical Fukui Analysis

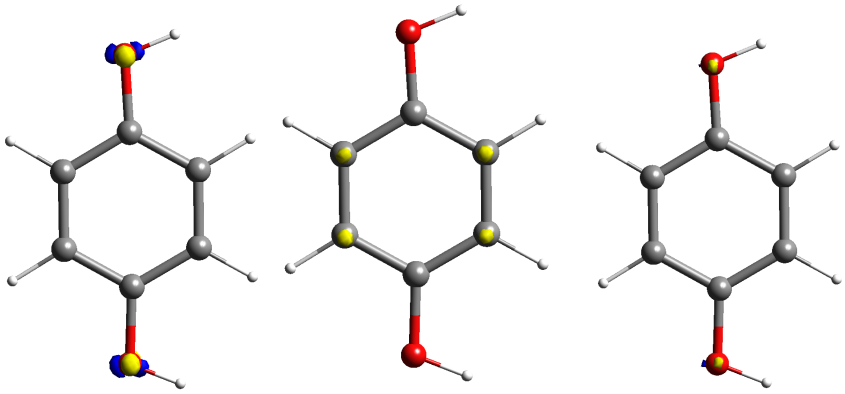
The analytical Fukui analysis of each dihydroxybenzene is shown in Figure 3. The $(f^{-}(\mathbf{r})$ of catechol, resorcinol, and hydroquinone is shown in Figure 3a,d,g. As shown in Figure 3, for all dihydroxybenzenes, HOMO orbitals are located on their hydroxyl group. Therefore, O atoms are higher antioxidant sites on the dihydroxybenzenes. The $(f^{+}(\mathbf{r})$ of catechol, resorcinol, and hydroquinone is shown in Figure 3b,e,h. As shown in Figure 3, LUMO orbitals are located on ortho C atoms. Therefore, ortho C atoms are reduction sites in dihydroxybenzenes. To predict the antioxidant sites on dihydroxybenzenes, we have also computed the average Fukui value, as shown in Figure 3. The $(f^{o}(\mathbf{r})$ of catechol, resorcinol, and hydroquinone are shown in Figure 3c,f,i. The average Fukui results are almost similar to $(f^{-}(\mathbf{r})$.



(a) $f^{-}(\mathbf{r})$ (ISO = 0.021) **(b)** $f^{+}(\mathbf{r})$ (ISO = 0.024) **(c)** $f^{o}(\mathbf{r})$ (ISO = 0.021)

(d) $f^{-}(\mathbf{r})$ (ISO = 0.021) **(e)** $f^{+}(\mathbf{r})$ (ISO = 0.024) **(f)** $f^{0}(\mathbf{r})$ (ISO = 0.021)

Figure 3. *Cont.*



(g) $f^{-}(\mathbf{r})$ (ISO = 0.021) **(h)** $f^{+}(\mathbf{r})$ (ISO = 0.024) **(i)** $f^{0}(\mathbf{r})$ (ISO = 0.021)

Figure 3. Analytical Fukui results of dihydroxy benzenes.

3.3. Antioxidant Activity (DPPH) of Chemical Compounds

The radical scavenging activity of chemical compounds varied from 24.5% to 68.8%, as shown in Table 3. In chemical compounds, hydroquinone showed higher (68.8 %) percent inhibition at concentration 100 µg/mL and the IC_{50} value was 10.96 µg/mL. In the previous study, the IC_{50} value of pyrocatechol was 20.13 µM [31]. An experiment on the estimation of scavenging activity of phenolic compounds by using the ABTS assay and percent radical scavenging activity (RSA) for catechol was 65.1%. For resorcinol, the minimum percent inhibition was shown at 20 µg/mL concentration, followed by an increase at 40 µg/mL, 60 µg/mL, and 80 µg/mL, and the maximum percentage inhibition was 77.38% at 100 µg/mL concentration [32].

The IC_{50} values of all dihydroxybenzenes are shown in Figure 4. Our studies confirm that hydroquinone has the highest and resorcinol has least antioxidant activities. The experimental results are in good agreement with the theoretical results.

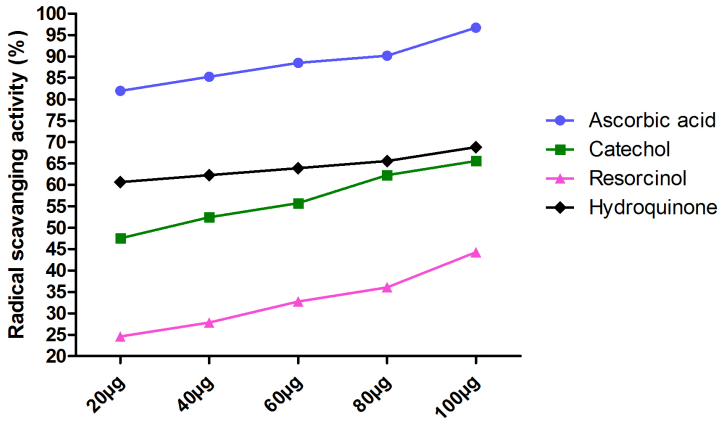


Figure 4. Inhibition radical scavenging activity of phenolic compounds in comparison to ascorbic acid.

Table 3. Antioxidant activity of chemical compounds.

Compound Name	Varying Concentration of Dihydroxy Benzenes for Determining Free Radical Scavenging Activity (%)					IC_{50} µg/mL
	20 µg/mL	40 µg/mL	60 µg/mL	80 µg/mL	100 µg/mL	
Catechol	47.55 ± 0.005	52.40 ± 0.006	55.74 ± 0.009	62.22 ± 0.009	65.54 ± 0.008	12.42
Resorcinol	24.59 ± 0.005	27.87 ± 0.006	32.79 ± 0.008	36.06 ± 0.007	44.27 ± 0.005	17.67
Hydroquinone	60.66 ± 0.005	62.30 ± 0.006	63.90 ± 0.007	65.50 ± 0.005	68.85 ± 0.005	10.96
Ascorbic acid	81.96 ± 0.005	85.27 ± 0.005	88.52 ± 0.005	90.16 ± 0.006	96.72 ± 0.005	6.34

The compounds examined in this study were selected based on structural characteristics, which means the number and position of the hydroxyl groups. Phytochemicals such as phenols are the main compounds responsible for antioxidant activity. Phenols have OH groups in their chemical structure and are very well known to reduce the rates of oxidation of organic matter by the transfer of hydrogen atoms from the OH group present in their structure [33].

In phenols, the hydrogen atoms and electrons get donated from the hydroxyl group, and this is because of presence of an aromatic ring in structure of phenols which allows stability to the relocation of unpaired electrons. The substitution of hydroxyl (OH) groups at 2, 3, and 4 positions in the chemical structure of compounds plays an important role in antioxidant activity. Due to the use of these compounds as a source of phototherapeutic products at the industrial level, the study of the antioxidant activity of such compounds has surged in recent research. All the compounds showed moderate results for the antioxidant assay. The IC_{50} values of the samples were compared with that of the standard value of ascorbic acid at 517 nm. It is clear from the table and the graph that the % inhibition of the methanolic sample and ascorbic acid was highest for the 100 μg/mL concentration, followed by the 80 μg/mL and 60 μg/mL,and 40 μg/mL concentrations. In the present study, the antioxidant activity test was found to be positive for all phenolic chemical compounds.

In the comparison between catechol, resorcinol, and hydroquinone, the hydroquinone possesses the minimum IC_{50} value, showing that hydroquinone has the highest antioxidant property, followed by the catechol and resorcinol; this is due to the lower ionization potential values.

The energy and electron density distributions of HOMO and LUMO for the studied phenolic compounds are given in Figure 2. The HOMO energy is an important aspect when evaluating the electron-donating ability in antioxidant studies [34]. Lower ionization potential means more capacity of donating electrons by disassociating bonds, thus ultimately leading to the higher antioxidant potential of compounds. It is clear from previous studies that the presence of the OH group on the structure of compounds leads to an increase in antioxidant power [35]. Ionization potential values were given by negative HOMO energies [36]. From Table 1, all dihydroxybenzenes have almost similar electron-donating properties. This is due to the presence of the same number of OH groups on the benzene ring for catechol and resorcinol.

4. Conclusions

The experimental results showed that the presence of hydroxyl groups in phenol at the para position possesses the highest antioxidant activity, followed by the ortho and meta positions. The presence of OH groups at the para position decreases the ionization potential; as a result, hydroquinone can donate the electron more easily when compared to catechol and resorcinol. Therefore, the dihydroxybenzene hydroquinone has the highest antioxidant properties when compared to others. The local electron transfer properties in terms of HOMO and LUMO also confirm that the hydroxyl groups in dihydroxybenzenes have a high ability to donate electrons because of the presence of an oxygen atom that has a lone pair of electrons in it. The results of the present study can directly help the therapeutic and food industries for the analysis of phenolic compounds on a structural basis.

Author Contributions: P.C.: experimental methodology and original draft preparation; G.K.J.: conceptualization, Fukui analysis, writing—review and editing; I.S.: experimental validation and original draft preparation; M.S.: experimental validation and original draft preparation; J.P.M.-S. and P.N.: solvent models and validation; S.R.: validation and review. All authors have read and agreed to the published version of the manuscript.

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