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# The Influence of Non-Covalent Complexation of ε-Viniferin on Its Antioxidant Activity: A Computational Investigation

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**Abstract**

We carefully selected a stable conformation of ε-viniferin as a representative model within the oligostilbene family to evaluate the influence of non-covalent association on its antioxidant activity, using Density Functional Theory (DFT). We calculated the Bond Dissociation Enthalpies (BDEs) in different positions and in both gaseous and methanol phases. We noted that non-covalent complexation enhanced the antioxidant potential of ε-viniferin, particularly at positions where hydrogen bonding interactions are prevalent. Conversely, an increase in BDE values has been observed at positions where hydrogen bonding hinders effective electron donation, indicating reduced antioxidant activity upon complexation. We also found that positions that do not actively participate in hydrogen bonding within the complex maintain stable BDE values, preserving the antioxidant activity. Additionally, we explored the electro-molecular characteristics of ε-viniferin as single and complex forms. We found that non-covalent complexation has a limited impact on the molecule's electronic structure and reactivity. Our results emphasize the remarkable potential of non-covalent associations involving ε-viniferin as an enhanced antioxidant. This finding is anticipated to significantly contribute to the exploration and discovery of new, potent antioxidants.

**Keywords:**

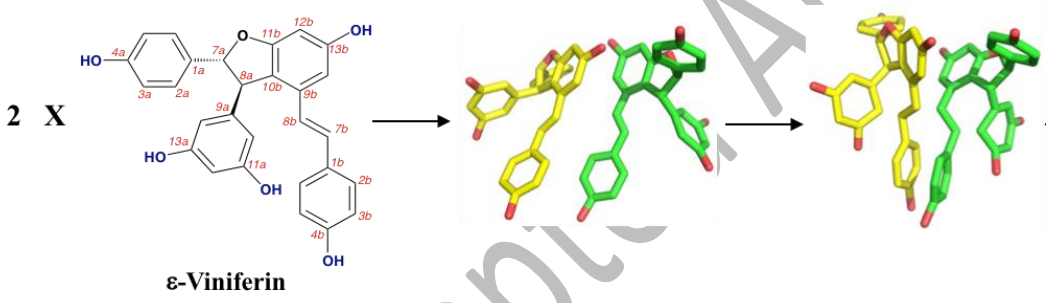
ε-Viniferin, non-covalent complexation, antioxidant activity, Bond Dissociation Enthalpies, spin density distribution, optoelectronic properties.

## Introduction

Antioxidants continue to play a vital role in scavenging free radicals and reducing oxidative stress. These compounds, commonly found in nature, hold significant promises in both preventive and therapeutic medicine [1]–[9]. They continue to intrigue researchers and health professionals for their potential in addressing various health concerns, including aging, inflammation, and the management of chronic illnesses such as cancer and cardiovascular diseases [4], [7], [10]–[13]. Among the different types of antioxidants, there is growing interest in oligostilbenes, which can be found in the Dipterocarpaceae family [14]. They are often characterized by the presence of many hydroxyl groups in their structures, to which the antioxidant activity is associated. This derives from their ability to inhibit the oxidative degradation of membranes by scavenging the peroxyl radicals of phospholipids responsible for propagating the autoxidation chain reaction. Antioxidants function by transferring a hydrogen atom to peroxyl oxygen, which is a widely recognized and extensively discussed mechanism in the literature [15]–[17]. The complex structures and multiple reactive hydroxyl groups in polyphenolic antioxidants present challenges in establishing a direct correlation between their molecular geometries and antioxidant efficacy. Nevertheless, an essential factor contributing to the evaluation of polyphenolic antioxidants is attributed to the relatively low bond dissociation enthalpy (BDE) of the O-H bond, which facilitates hydrogen atom transfer [18]–[22].

Within this expanding field of research, our study focused on the non-covalent complex of ε-viniferin, a prominent member of the oligostilbene family that is abundant in a variety of plant species, including grapes and peanuts [23], [24]. Due to its potent antioxidant activity and original molecular architecture, ε-viniferin garnered recognition and has been considered as fascinating subject for investigation, that could serve as a representative for oligostilbenes [25]. The primary objectives of the present study are twofold. Firstly, we aim to explore how non-covalent complexation impacts the antioxidant activity of ε-viniferin (Figure 1). In a previous study, we provided a new explanation on the biosynthesis of ε-viniferin, especially for the dimerization mechanism [14]. We proved that supramolecular self-assembly of species through non-covalent interactions is a significant driving force in some key-steps of oligostilbene biosynthesis [14]. Natural oligostilbenes could form non-covalent complexes with π-stacking and H-Bonding playing key stabilizing roles. In this prior study [14], we explored eight possible conformations of non-covalent complexes, and through rigorous analysis, identified the most stable conformation. In this current study, we have selected this highly stable complex as a model of a real-world polyphenol dimer to evaluate the accuracy of dispersion-corrected calculations [26]. Building upon our previous findings that underscore ε-viniferin's capacity to form non-covalent complexes [14], our central goal is to determine, computationally, whether such complexation enhances or reduces the overall antioxidant activity of the resultant complex in comparison to the individual molecule. We used Density functional theory (DFT), which is considered as an effective tool to better

understand the antioxidant activity of polyphenols and to bring evidences on the structure-activity relationship [6], [27]–[30]. Secondly, we extend our investigation to study the spin density distribution of the phenoxy radical within ε-viniferin, coupled with an exploration of the molecular orbitals associated with this compound. These additional analyses provided deeper insights into the electronic structure and reactivity of ε -viniferin, shedding light on the molecular complexities that govern its antioxidant activity. In summary, by this study, we sought to unravel the possible relationship between molecular structure, non-covalent complexation, and antioxidant potential of ε-viniferin, that could be extended to many other oligostilbenes. Simultaneously, we seek to contribute to the development of novel antioxidants, exploring opportunities for improved efficacy and broader applications in the field of health and wellness.




(a) (b)

Figure 1. (a) Chemical structure of ε-viniferin (monomer) and (b) two views for the optimized geometries of the non-covalent complex (dimer).

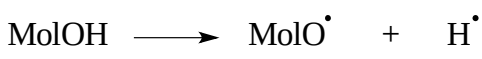
**Methods of calculation**

Density Functional Theory (DFT) has become an adequate and powerful tool for elucidating a wide array of molecular properties over the years [31]–[34]. For example, B3P86 is well adapted to study medium size chemical systems of polyphenols [14], [26]. However, this functional as all other hybrid functionals failed to describe non-covalent interactions. Consequently, including dispersive terms in calculations is imperative to accurately describe non-covalent complexes. One of the most used approaches that include dispersive terms in the calculations is known as DFT-D [35], which is crucial to describe non-covalent complexes. For DFT-D2 calculations, the refined dispersive DFT-D2 method [36] with the parametrized scaling factor s6 = 0.78 was validated for polyphenol derivatives [37]. It has been used with def2-SVP//QZVP basis set to perform geometry optimization of the investigated molecules.[26] This basis set was selected due to its good compromise between accuracy and computational time, and the BSSE (Basis Set Superposition Error) can be neglected [38]. Within DFT formalism, two distinct functionals, B3P86[39] and ωB97XD, [40] were employed to evaluate the

antioxidant activity and other optical properties. The former well described single oligostilbene (monomer) while the later that includes dispersive corrections, was specifically chosen to investigate long-range interactions, particularly when studying dimers (non-covalent complex). With both functionals, 6-31+G(d,p) basis was used to consider diffuse and polarization functions. Frequency calculations have been performed at the same level of theory in order to confirm the structures as true minima (no imaginary frequency).

For the TD-DFT study, ωB97XD/6-31+G(d,p) was selected as it is adequate to describe non-covalent interactions [40]. All calculations were performed with Gaussian 09 [41] and ORCA [42]. For the visualization of molecules, both GaussView [43] and Visual Molecular Dynamics (VMD) [44] were used.

The Bond Dissociation Enthalpy (BDE) of the molecule is defined as the enthalpy difference for the reaction, at 298 K and 1 atm:



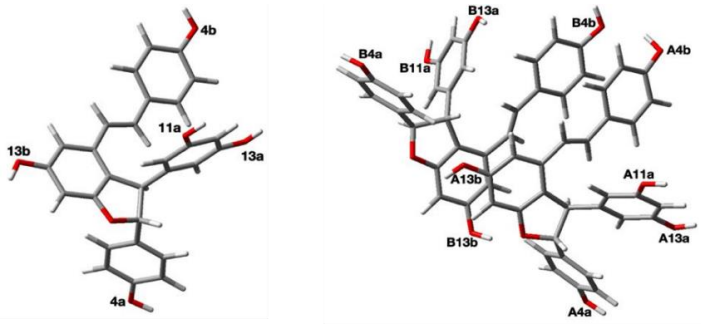
All Calculations were executed both in the presence and absence of the solvent, Methanol ($\varepsilon_{MeOH}$= 32.61), corresponding to the solvent used for the extraction of the selected oiligostilbene heartwood of *Neobalanocarpus heimii* (Dipterocarpaceae). The solvent effect was taken into account implicitly using the polarizable continuum model (PCM).

**Results and discussions**

**1. BDE:**

Oligostilbenes are known to act as free radical scavengers most probably by following hydrogen atom transfer (HAT) mechanism according to the following equation:

Based on the optimized geometries (Figure 2), BDEs were calculated for the single molecule (monomer) and non-covalent complex (dimer), within both the gas and methanol environments. The outcomes of our investigation revealed a compelling narrative of heightened antioxidant potential facilitated by complexation, albeit with intriguing variations among specific positions (Table 1).




(a) (b)

Figure 2. Optimized geometries including atomic numbers for the (a) monomer and (b) non-covalent complex.

Table 1. Calculated BDEs of the studied molecules (in kcal/mol).

| | Position | Gas | | Methanol | |
|---|---|---|---|---|---|
| | | ωB97XD | B3P86 | ωB97XD | B3P86 |
| Monomer | 13b | 84.14 | 85.69 | 82.24 | 83.67 |
| | 4a | 84.57 | 86.39 | 84.25 | 84.02 |
| | 11a | 85.08 | 86.74 | 83.94 | 85.39 |
| | 13a | 84.43 | 85.64 | 83.67 | 85.11 |
| | 4b | 80.60 | 81.31 | 79.33 | 79.65 |
| Dimer | A13b | 82.98 | 81.31 | 79.92 | 81.92 |
| | A4a | 85.68 | 87.64 | 81.63 | 83.53 |
| | A11a | 85.29 | 86.46 | 83.96 | 84.94 |
| | A13a | 84.72 | 85.63 | 82.02 | 83.45 |
| | A4b | 77.16 | 75.76 | 76.72 | 75.98 |
| | B13b | 83.27 | 83.38 | 80.16 | 80.67 |
| | B4a | 85.05 | 86.71 | 81.21 | 82.89 |
| | B11a | 86.60 | 87.73 | 83.04 | 84.14 |
| | B13a | 84.17 | 85.36 | 81.80 | 82.99 |
| | B4b | 77.41 | 75.57 | 77.12 | 76.03 |

The weakest BDE value is found for 4b-OH in both single species and non-covalent complexes, which makes this group the most antioxidant. However, 11a-OH bond exhibits the highest strength, resulting in the lowest antioxidant activity for this group.

We noted that in general the non-covalent interaction slightly reduces the BDE values, especially at 4b, followed by 13b. As it could be seen from the complex geometry, these two hydroxyl groups are involved in intermolecular hydrogen bonding, which significantly weakens the O-H bond. For instance, at positions 13b and 4b, characterized by their role as hydrogen donors in hydrogen bonding (HB) interactions within the non-covalent complex, we observed a significant reduction in BDE values for the dimer compared to the monomer. This marked reduction in BDEs signifies an elevated tendency for electron donation, and consequently, an enhanced capacity to neutralize free radicals. This observation resonates deeply with established principles of antioxidant behavior, where a lower BDE correlates with a superior ability to quench free radicals and mitigate oxidative stress. It underscores the pivotal role of hydrogen bonding in reinforcing ε-viniferin's antioxidant prowess.

Conversely, at position 4a, which serves as a hydrogen acceptor in hydrogen bonding within the complex, we find a contrasting trend. Complexation in this case leads to an increase in BDE values, indicative of reduced antioxidant activity. This phenomenon aligns with the principles of antioxidant action, where electron-donating capacity is paramount. Here, the formation of the non-covalent complex appears to disrupt the molecule's ability to donate electrons efficiently, resulting in diminished antioxidant potential.

Intriguingly, for positions 11a and 13a, which are not directly involved in hydrogen bonding within the complex, we observe that complexation leaves antioxidant activity largely unchanged. These positions play a passive role in the non-covalent complex, and as such, their BDE values remain relatively stable between the dimer and monomer configurations. Moreover, these results contribute to the growing body of evidence that underscores the pivotal role of molecular structure, particularly hydrogen bonding interactions, in dictating antioxidant potency. The intricate interplay of hydrogen bonding, π-π interactions, and steric effects inherent in non-covalent complexes emerges as a key determinant in governing the efficacy of ε-viniferin as an antioxidant.

The current findings are consistent with previous studies, such as the work of Amorati and Valgimigli, which emphasized the pivotal role of non-covalent interactions, particularly hydrogen bonding, in modulating the reactivity of phenolic antioxidants with radical species. The intricate discussion in their research underscores the varying effects of intra- or inter-molecular hydrogen bonding on antioxidant activity, depending on the specific roles of the -OH moiety. Moreover, their analysis highlights the nuanced impact of remote intra- and inter-molecular hydrogen bonding on the reactivity of antioxidants, shedding light on the complex chemistry of natural polyphenolic antioxidants and paving the way for future research directions [45]–[48].

**2. Spin Density:**

The Spin Density Distribution is a fundamental aspect of comprehending the electronic structure and reactivity of ε-viniferin's phenoxy radical, and a crucial element for understanding its antioxidant activity. It refers to the difference between alpha (spin-up) and beta (spin-down) electrons at each point within the molecule. This disparity is of particular significance in the realm of antioxidants as it illuminates the molecule's capability to provide electrons to free radicals, ultimately stabilizing them and preventing oxidative damage [49]–[52]. As illustrated in Figure 3, our study's findings indicated that the blue regions signify areas within the phenoxy radical exhibiting positive spin density. These regions are electron-rich, characterized by an excess of unpaired electrons. They are pivotal for antioxidant activity due to their readiness to donate electrons to electron-deficient free radicals, effectively neutralizing them and preventing oxidative damage. Conversely, the red regions represent areas within the phenoxy radical with negative spin density, indicating that they are electron-poor. While these regions may not directly participate in electron donation to free radicals, they possess their significance. They may exhibit different reactivity patterns compared to electron-rich regions, potentially influencing ε-viniferin's behavior in biological contexts. Additionally, these regions may be more susceptible to attack by electron-deficient species. Our study's findings based on the Spin Density Distribution provide valuable insights into ε-viniferin's antioxidant activity at the molecular level. These results highlight specific areas of the molecule actively involved in electron transfer processes, a fundamental aspect of its role as an antioxidant. Electron-rich regions enhance its ability to neutralize free radicals, while electron-poor regions introduce distinct reactivity nuances. Thus, our results represent a critical parameter for understanding how ε-viniferin functions as an antioxidant and reveal the spatial distribution of unpaired electrons within the molecule, providing valuable insights into its reactivity with free radicals and other species. This information enhances our understanding of ε-viniferin's antioxidant properties and its potential applications in protecting biological systems from oxidative damage.

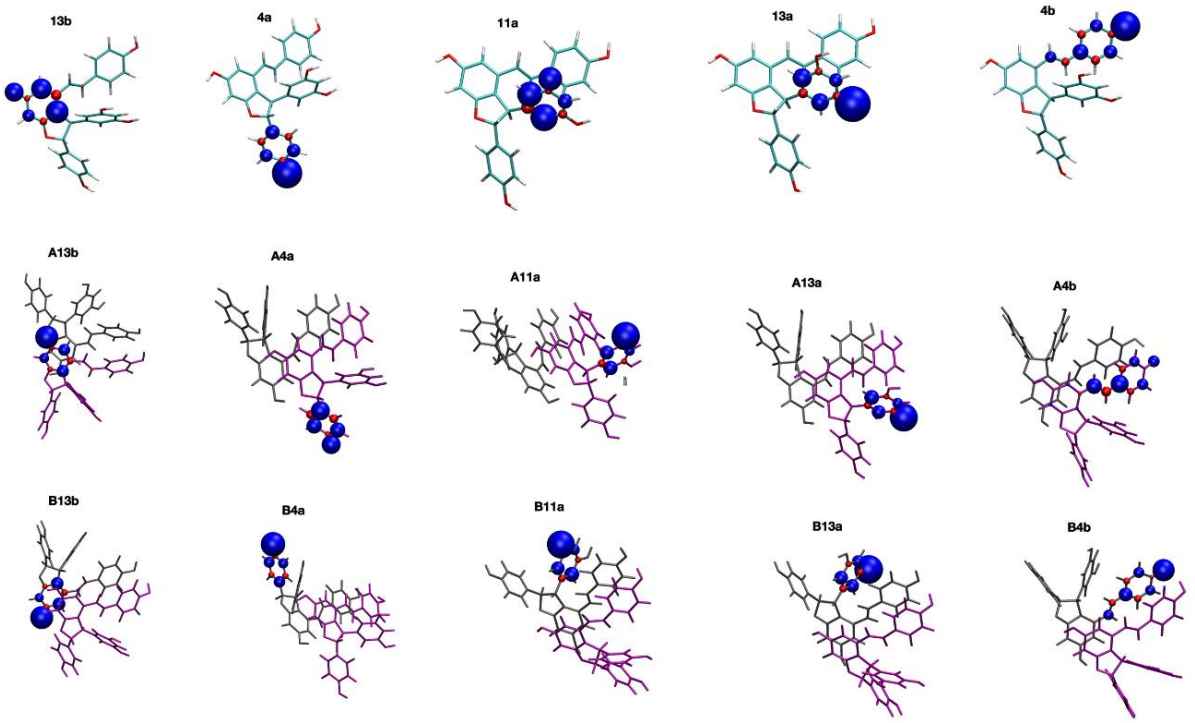



Figure 3. Calculated spin density distribution of the phenoxy radical. Blue and red colors refer to regions of positive and negative spin density, respectively.

**3.TD-DFT:**

The energy gap ($E_{gap}$), representing the difference in energy between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), is an important parameter to describe the reactivity of molecules toward free radicals. As can be seen from Table 2, the calculated $E_{gap}$ was found to be similar in both the monomer and dimer forms. This similarity implies that primary electronic features governing reactivity are preserved upon non-covalent complexation. Additionally, the energies of the HOMO and LUMO were investigated. We found that the LUMO energy was approximately 0.21 eV for the monomer and 0.33 eV for the dimer, while the HOMO energies were -7.23 and -7.12, for the monomer and dimer, respectively. This examination of the HOMO and LUMO energies revealed that the dimer configuration demonstrates a slightly higher LUMO energy compared to the monomer, suggesting increasing in the electron accepting capability. Additionally, the comparable HOMO energies indicated similar electron-donating potential for both the monomer and dimer. These findings implied that the dimer form may possess enhanced reactivity and potential for electron transfer processes compared to the monomeric form.

Moreover, analysis of ionization potential (IP) and electron affinity (A) revealed that both monomer and dimer forms maintain similar IP and A values. This suggested that dimerization does not significantly alter the molecule's ability to donate or accept electrons.

Furthermore, electro-molecular characteristics such as hardness (η), chemical potential ($\mu_p$), electrophilicity (ω), and softness (S) remained relatively constant upon dimerization. These characteristics provide insights into reactivity and stability, and being unchanged suggested that dimerization does not significantly impact these parameters.

The dipole moment (μ), which measures charge distribution within the molecule, was found to be similar in both forms, indicating that dimerization does not lead to significant changes in charge distribution.

Thus, our computational analyses indicates that non-covalent complexation of ε-viniferin has a limited effect on its electronic structure and reactivity. Both the monomer and dimer forms maintain comparable reactivity profiles, suggesting that the fundamental electronic features are preserved. These findings are pertinent in evaluating ε-viniferin's potential as an antioxidant, as they suggest that its role in electron transfer processes remains intact upon dimerization, making it a viable candidate for antioxidant applications.

Table 2. Calculated electro-molecular characteristics of both monomer and dimer. All energies are expressed in eV while the dipole moment in Debye (D).

| Egap | $\varepsilon_{HOMO}$ | $\varepsilon_{LUMO}$ | $E_{gap}$ | IP | A | η | $\mu_p$ | ω | S | μ (D) |
|---|---|---|---|---|---|---|---|---|---|---|
| Monomer | -7.23 | 0.21 | 7.44 | 7.23 | -0.21 | 3.72 | -3.51 | 3.31 | 0.21 | 4.28 |
| Dimer | -7.12 | 0.33 | 7.44 | 7.12 | -0.33 | 3.72 | -3.39 | 3.10 | 0.27 | 5.87 |

Furthermore, we have calculated the 3D plots of the HOMO and LUMO for both the monomer and dimer forms of ε-viniferin, along with the corresponding energy diagram (Figure 4). These visual representations provide a comprehensive view of the molecular orbitals and their energy levels in both forms.

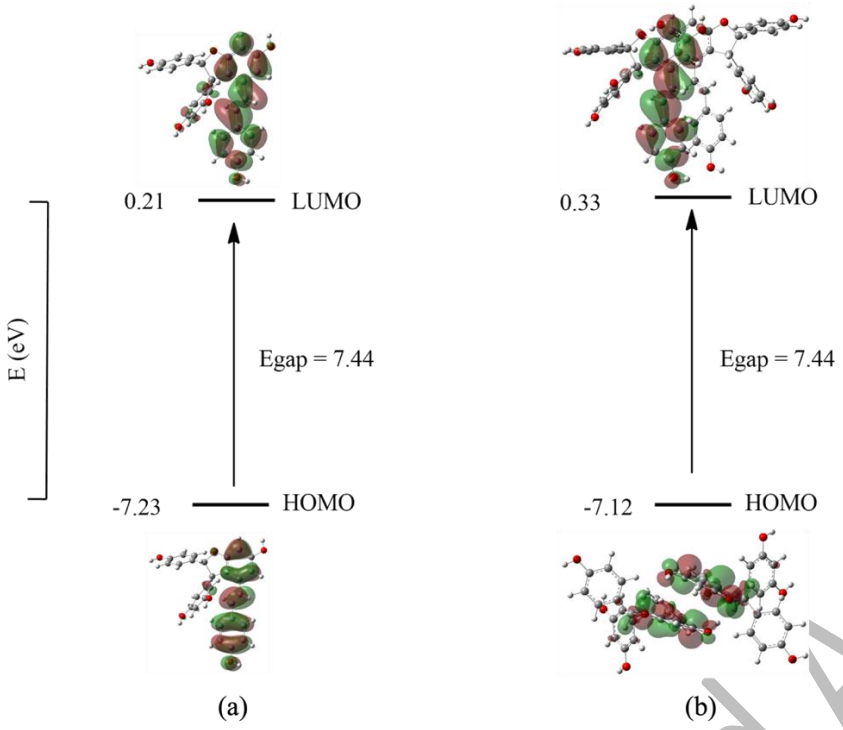



Figure 4. Calculated MOs Diagram for both (a) the monomer and (b) the dimer



**Conclusion**

In conclusion, our investigation has highlighted the influence of non-covalent complexation on the antioxidant activity of ε-viniferin, providing insights into its behavior in both monomeric and dimeric forms. Non-covalent interactions, particularly at positions 4b and 13b, demonstrate a slight reduction in BDE values, signifying an enhanced electron donation capacity and reinforcing ε-viniferin's antioxidant potential. Conversely, at position 4a, complexation hinders effective electron donation, leading to reduced antioxidant activity. Positions 11a and 13a, less affected by structural changes induced by dimerization, maintain stable BDE values, preserving their antioxidant activity. Additionally, our analysis of the electro-molecular characteristics suggests that non-covalent complexation has limited effects on the molecule's electronic structure and reactivity. This study enriches our understanding of the ε-viniferin's antioxidant properties, highlighting the significance of hydrogen bonding in enhancing its free radical neutralizing capacity and solidifying its potential for diverse applications as a natural antioxidant.

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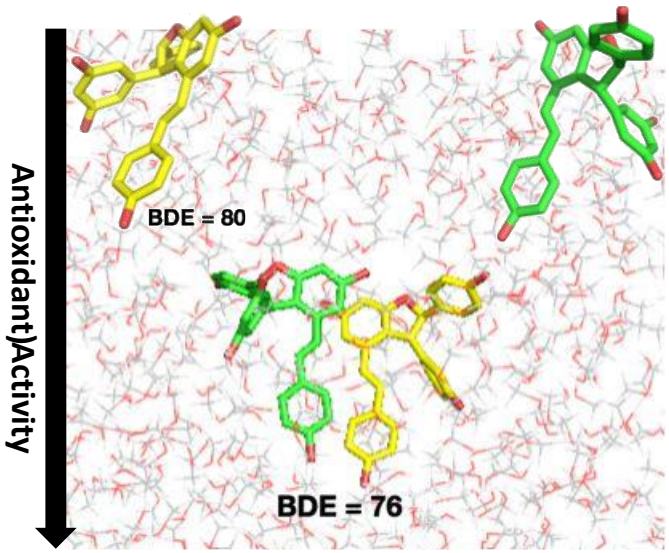
Graphical TOC

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