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Study on the Molecular Characteristics and Pharmacological Activity of Polyphenols as Antioxidants

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Abstract

Polyphenols are the largest group of phytochemicals widely used as biologically active compounds in pharmacology, medicine, and as potential agents for the prevention and treatment of oxidative stress-related diseases. Many of them have been found in plant-based foods and some are structurally and functionally related to flavonoids phenolic compounds.

In this project, thermodynamic and stereochemical properties of several types of biochemical molecules that can be used as a biological antioxidant were studied. Computational and biomedical simulations were used, and have been proven useful in assessing the physicochemical stability of molecules. Molecular editing programs were used to model, optimize, and compare the resulting molecular optimization energies of the phenolic compounds. Various polyphenols were tested when OH groups and functional groups were differently attached to the molecules: those with more OH groups and substituents, and those attached farther apart, or were with less functional groups. For all the types of functional groups attached, the optimization energy of the compounds in which the clusters attached were distanced is usually lower than that of the isomer in which the functional groups are close to each other.

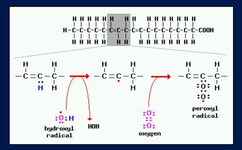
Introduction

Scientists have used computer simulations to model nano-scaled complexes that can virtually attach large quantities of protons and donate electrons to ROS-affected cells. The free radicals and oxidation negatively affect the immune system, causing increased susceptibility to illness. Oxidation may especially be accelerated by stress, alcohol, sunlight, pollution and other factors, to which the vast majority of individuals are exposed their entire lives. A common misconception is that Polyphenols are difficult to find in common foods, and their potential benefits may be questioned. Surprisingly, however, many kinds of foods are actually high in Polyphenols, including apples, peaches, grapes, broccoli, and tofu, all of which are readily available.

Polyphenols are plant secondary metabolites containing antioxidant properties, which help in preventing free radical damage, and its potential for causing chronic conditions in humans. As Polyphenols are included in Antioxidant food, many similar traits of Antioxidants are also seen on Polyphenols.

Reactive oxygen species should not necessarily be perceived as harmful, as they possess beneficial effects such as fighting off pathogens or acting as mitogens in moderation, although in excess, the effect is imminent. The unpaired electrons possess high electron affinity which can be highly reactive to all macromolecules such as lipids, proteins and nucleic acids. For instance, a well known toxicity of reactive oxygen species is lipid peroxidation, where peroxidation reaction occurs at the “kink” in unsaturated fatty acids.

This peroxidation can result in an increase in membrane rigidity, a decrease of membrane-bound enzyme activity, activity alteration in membrane receptors, and altered permeability. In addition, the radicals can also directly attach membrane proteins, including lipid-lipid, lipid-protein, and protein-protein crosslinking.



In this project, we assessed the thermodynamical and stereochemical safety of several types of biochemical molecules that can be used as a biological antioxidant. We used a molecular editing program to model, optimize, and compare the resulting molecular optimization energies of the fullerene derivatives.

Materials and Methods

The Chemcraft, Gaussian and Avogadro software programs are designed for open-source molecular editing, and are equipped with an auto-optimization feature to determine the theoretical values of pharmaceutical products’ atomic and chemical properties, through the Density Functional Theory (DFT). This software allows users to build virtually any molecule and optimize its geometry according to various force field options.
The Auto Optimize Tool and other tools were used for each molecule and other derivatives modeled in this project to determine their optimization energy. The Universal Force Field (UFF) option was selected for all the derivatives modeled. A timer was also used in each trial to record the time it took for the corresponding molecules to be optimized.
The three factors for their efficiencies of the nanoparticles were checked:

1. Thermodynamic stability
- Measure optimized energy (the value must be small to be stable)
- The smaller the optimized energy, the better in thermodynamic stability

2. Reactivity, Activity, or Conductivity
- Measure dipole moments (higher values are better)
- The higher the dipole moments , the better in activity

3. Electrostatic potential map
- Blue and red, or colorful → higher electrostatic potential → better in activity

Van der Waals Spheres

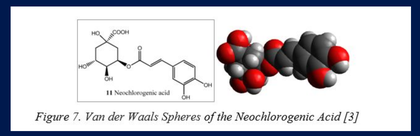


Figure 7. Van der Waals Spheres of the Neochlorogenic Acid [3]

Figure 3 through Figure 6 above depict chemical structures of different compounds. Each compound forms a different amount of biofilm mass. Studies show that there were significant differences in anti-biofilm activity between procyanidin B5 and B2, which suggests that even the smallest structural changes can play an important role in inhibiting biofilm formation. Research shows that Neochlorogenic acid is a more active biofilm inhibitor than chlorogenic acid against *B. cereus* but not *E. coli*. [3]

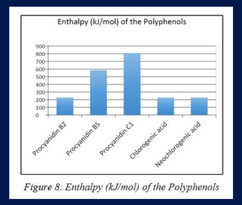


Figure 8. Enthalpy (kJ/mol) of the Polyphenols

As shown in Figure 8, Procyanidin C1 has the highest optimization energy since it is doped with many groups, Procyanidin B5 the second-highest, and the other three the lowest.

Polyphenol

A recent boom in biofilm research focuses on the development of alternative approaches, avoiding the use of antimicrobials altogether, or combining alternative treatments with more traditional antimicrobial drugs to potentially eliminate all biofilm formation on, e.g., indwelling devices. The aronia plant (Aronia melanocarpa) has gained in popularity because its berries contain a high percentage of polyphenols with antioxidant activity. The berries contain chlorogenic and neochlorogenic acids, as well as high levels of flavonoids; primarily proanthocyanidins and anthocyanins. Aronia is now used not only for nutritional supplements but also as an important source of ingredients used for juice, wine, and jam. It constitutes a rich source of natural food colorants.

Previous research on controlling biofilm infections included the effect of cranberry extracts on oral biofilms, biofilms produced on contact lenses, and biofilms produced by E. coli strains. The studies concluded that cranberry juice can lead to a decrease in pathogenic bacteria’s ability to develop biofilm, perhaps because cranberry contains A-type proanthocyanidins—active constituents that prevent the attachment of bacteria.

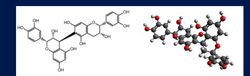


Figure 3. Procyanidin B5 [3]

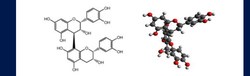


Figure 4. Procyanidin B2 [3]

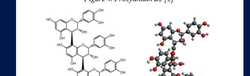


Figure 5. Procyanidin C1 [3]

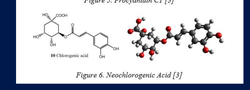


Figure 6. Neochlorogenic Acid [3]

Flavonoids

Flavonoids are phytonutrients that can help slow tooth decay. The cocoa bean, the main ingredient in chocolate, contains many strong antioxidants including flavonoids that are beneficial for the teeth. Cocoa flavanols combined with other related oligomers can have an impact on reducing the risk of disease. The thermodynamic property of Querceti was determined by using stereochemical analysis. Its optimized shape and time are as follows:

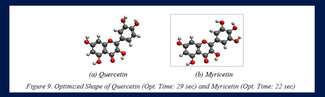


Figure 9. Optimized Shape of Quercetin (Opt. Time: 29 sec) and Myricetin (Opt. Time: 22 sec)

The thermodynamic properties of Kaempferol and other Flavanols derivatives were determined by using stereochemical analysis:

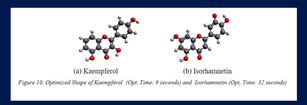


Figure 10. Optimized Shape of Kaempferol (Opt. Time: 9 seconds) and Isorhamnetin (Opt. Time: 32 seconds)

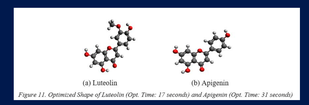
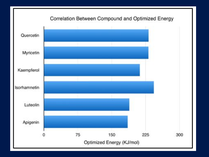
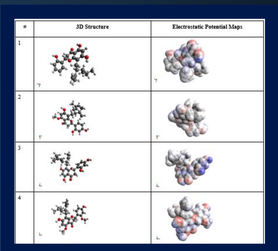


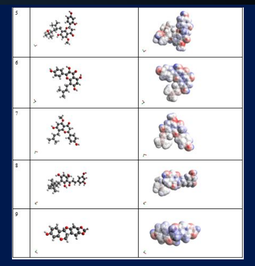
Figure 11. Optimized Shape of Luteolin (Opt. Time: 17 seconds) and Apigenin (Opt. Time: 31 seconds)

The purpose of this was to determine whether there was any noticeable difference in the molecular energies of the different molecules or structural isomers. For all the types of functional groups attached, the optimization energy of the compounds in which the clusters were attached, were distanced lower than that of the isomer in which the functional groups were close. The time it took for the compounds to be optimized was also noticeably lower for the compounds with distant functional groups.



Optimized shapes and Electrostatic potential map of flavonoids





Analysis procedure

TABLE I. OPTIMIZED ENERGY OF THE FLAVONOIDS

Flavonoids	Compound	Energy (kJ/mol)
1	Kushenol A	349.282
2	(-)-kurarinone	319.599
3	Sophoraflavanone G	342.340
4	2’-methoxykurarinone	342.414
5	kurarinol	433.344
6	8-prenylkaempferol	341.136
7	isoxanthohumol	292.711
8	kuraridin	418.075
9	maackiain	428.165

TABLE II. DIPOLE MOMENTS(DEBYE)

Flavonoids	Compound	Dipole Moments
1	Kushenol A	5.207
2	(-)-kurarinone	2.529
3	Sophoraflavanone G	3.733
4	2’-methoxykurarinone	1.082
5	kurarinol	3.565
6	8-prenylkaempferol	0.914
7	isoxanthohumol	2.466
8	kuraridin	1.722
9	maackiain	3.172

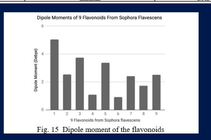


Fig. 15 Dipole moment of the flavonoids

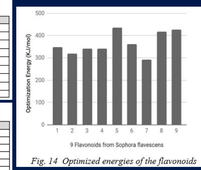


Fig. 14 Optimized energies of the flavonoids

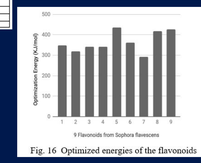


Fig. 16 Optimized energies of the flavonoids

Conclusion

In this project, the thermodynamic stability of polyphenol derivatives were studied in light of their promising role in treating cancer. Avogadro software was used to measure the optimization energy of each compound tested in the computational experiment.

1. Generally, a compound that stabilizes with the least energy is the most stable. Complexes with less substituted molecules were optimized in a relatively short period of time, which were also predicted to be more thermodynamically stable, as short optimization times generally equate to spontaneous converging.

2. Quantum chemical calculations were helpful in determining whether the compound modeled is stable enough to exist naturally as a compound. Models presenting extremely high optimization energies and/or extremely long optimization times were eliminated from the initial list of possible compounds.

3. Various polyphenols were tested when OH groups and functional groups were differently attached to the molecules: ones with more substituents and more OH groups, and others with less functional groups or attached farther apart. The purpose of this was to determine whether there was any noticeable difference in the molecular energies of the different molecules or structural isomers.