

## **Determination Functional Theory Investigation of Polyphenolic Compounds Reactions: NMR study**

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Received June 2011; Accepted June 2011

### **ABSTRACT**

Over the past decade, the chemical behavior of flavonoids as antioxidants has become the subject of intense experimental research. In this paper, we use a quantum-chemical approach to shed light on the reactivity of four poly phenols, Benzoic acid, vanilic acid, gallic acid and flavone. In order to establish the most efficient theoretical methodology, different methods, either Hartree–Fock-based or derived from density functional theory, and different basis sets from 6-31G(d) to 6-31G and 3-21G were tested on Benzoic acid, vanilic acid, gallic acid and flavone that it is phenolic compounds. This research showed oxygen atoms have very important role in these molecules.

**Keywords:** Polyphenols; DFT; NMR; Antioxidant activity; Flavonoids

### **INTRODUCTION**

The calculation of NMR parameters using semi-empirical and ab initio techniques has become a major and powerful tool in the investigation to look at how variations in the molecular structure occurs. The ability to quickly evaluate and correlate the magnitude and orientation of the chemical shielding anisotropy tensor with variations in bond length, bond angles and local coordination and nearest neighbor interactions has seen a number of recent applications in the investigation of molecular structure. The calculations also provide valuable information for exploring the experimental NMR chemical shifts with the molecular geometry and environment. Also NMR chemical shifts are quite sensitive to intermolecular interactions (1,2).

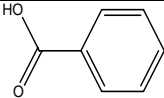
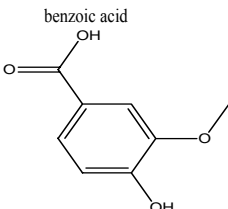
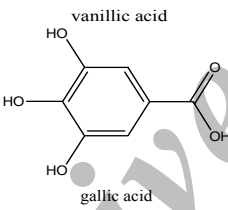
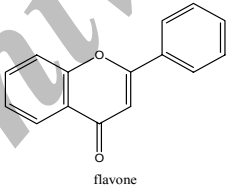
Structurally they have phenolic groups which as a source of readily available hydrogen atoms such that the subsequent radicals produced can be delocalized over the phenolic structure (figure 1). The interest in these compounds is due to their pharmacological activity as radical scavengers. They have been proved to have potential preventive and therapeutic effects in many diseases, where the

oxidative stress has been implicated, including cardiovascular diseases, cancer, neurodegenerative disorders and in aging(3). The phenolics are also of interest in food, cosmetic and pharmaceutical industries, as substitutes for synthetic antioxidants. These four phenolics widely distribute in the plant kingdom. Phenolic antioxidants such as hydroxybenzoates and flavonoids are important classes of natural antioxidants. The antioxidant efficiency of the phenolic acids and flavonoids have been related to the number of hydroxyl groups in the molecule and also to their hydrogen radical donating abilities(4) Phenolic acids present in plants are hydroxylated derivatives of benzoic and cinnamic acids. Flavonoids and phenolic acids have many functions in plants. Structurally, phenolic compounds comprise an aromatic ring, bearing one or more hydroxyl substituents, and range from simple phenolic molecules to highly polymerised compounds. Despite this structural diversity, the group of compounds is often referred to as - polyphenols. Flavonoids are low

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molecular weight compounds, consisting of fifteen carbon atoms, arranged in a C6–C3–C6 configuration. Essentially the structure consists of two aromatic rings A and B, joined by a 3-carbon bridge, usually in the form of a heterocyclic ring, C (table 1). The aromatic ring A is derived from the acetate/malonate pathway, while ring B is derived from phenylalanine through the shikimate.

**Table 1.** Some of the polyphenol structure

Entry	Compound name	Compound structure
1	Benzoic acid	
2	Vanillic acid	
3	Gallic acid	
4	Flavone	

pathway. Variations in substitution patterns to ring C result in the major flavonoid classes, i.e., flavonols, flavones, flavanones, flavanols. Phenolic compounds—especially phenolic acids and flavonoids—are ubiquitously present in vegetables, fruits, seeds, tea, wines and juices; thus they are an integral part of the human diet. Recently, they have received much attention since many epidemiological studies suggest that consumption of polyphenol-rich foods and beverages is associated with a reduced risk of cardiovascular diseases, stroke and certain forms of cancer. These protective effects have partly been ascribed to the antioxidant properties especially of flavonoids(5). Polyphenols are

common constituents of foods of plant origin and major antioxidants in the human diet. These compounds possess diverse biological activities such as antioxidation, apoptosis, antiaging, anticancer, anti inflammation, antiatherosclerosis, cardiovascular protection, improvement of the endothelial function, as well as inhibition of angiogenesis and cell proliferation activity (6). The imbalance between production and consumption of reactive oxygen species, leading to oxidative stress, is implicated in the pathophysiology of a plethora of genetic and acquired disorders, such as cancer, arteriosclerosis, malaria and rheumatoid arthritis, as well as neurodegenerative diseases and aging processes. Epidemiology studies have shown an inverse association between the daily consumption of fruits and vegetables and the risk to suffer from degenerative and chronic diseases.

The protective effects of fruits and vegetables have long been attributed to their antioxidant compounds, such as polyphenols, carotenoids, and vitamins C and E. Antioxidants act in various ways, which include the complexation of redox-catalytic metal ions, scavenging of free radicals and decomposition of peroxides(7). Polyphenols are the most abundant antioxidants in the diet. Their total dietary intake could be as high as 1 g/d, which is much higher than that of all other classes of phytochemicals and known dietary antioxidants. For perspective, this is ~10 times higher than the intake of vitamin C and 100 times higher than the intakes of vitamin E and carotenoids (8,9). Their main dietary sources are fruits and plant-derived beverages such as fruit juices, tea, coffee, and red wine. Vegetables, cereals, chocolate, and dry legumes also contribute to the total polyphenol intake. Despite their wide distribution in plants, the health effects of dietary polyphenols have come to the attention of nutritionists only rather recently. Until the mid-1990s, the most widely studied antioxidants were antioxidant vitamins, carotenoids, and minerals. Research on flavonoids and other polyphenols, their antioxidant properties, and their effects in disease prevention truly began after 1995. The main factor that has delayed research on

polyphenols is the considerable diversity and complexity of their chemical structures(10).

One of the most remarkable properties of flavonoids rises from their behavior as antioxidants acting through a variety of ways, including direct inhibition of formation or activity of reactive oxygen species and interaction, inhibition, with enzymes (11) Thus, this family of molecules has a remarkable pharmacological importance as therapeutic agents. They have been directly used, or through some of their derivatives, in the treatment of diseases ranging from allergies(12) to microbial, viral or bacterial infections processes, or even for cancer therapies(13).The study of flavonoids is therefore of great practical and theoretical importance. Nevertheless, the constant investigation of flavonoids has not led to a clear relationship between their molecular structure and properties. Nonetheless, the physiological activity of these molecules has been related to their structure and geometry (14, 15).

## COMPUTATIONAL METHOD

The term "Ab Initio" is given to computations which are derived directly from theoretical principles, with no inclusion of experimental data. The most common type of ab initio calculation is called a Hartree Fock calculation (abbreviated HF), in which the primary approximation is called the central field approximation. A method, which avoids making the HF mistakes in the first place, is called Quantum Monte Carlo (QMC). There are several flavors of QMC variational, diffusion and Green's functions. These methods work with an explicitly correlated wave function and evaluate integrals numerically using a Monte Carlo integration. These calculations can be very time consuming, but they are probably the most accurate methods known today. In general, ab initio calculations give very good qualitative results and can give increasingly accurate quantitative results as the molecules in question become smaller .There are three steps in carrying out any quantum mechanical calculation in HyperChem 7.0 program package [14].First, prepare a molecule with an appropriate starting geometry. Second, choose a calculation method

and its associated options. Third, choose the type of calculation with the relevant options.

### Langevin dynamics (LD) simulation

The Langevin equation is a stochastic differential equation in which two force terms have been added to Newton's second law to approximate the effects of neglected degrees of freedom . These simulations can be much faster than molecular dynamics.The molecular dynamics method is useful for calculating the time dependent properties of an isolated molecule. However, more often, one is interested in the properties of a molecule that is interacting with other molecules.

### Molecular mechanics (Monte Carlo simulation)

The Metropolis implementation of the Monte Carlo algorithm has been developed by studying the equilibrium thermodynamics of many-body systems. Choosing small trial moves, the trajectories obtained applying this algorithm agree with those obtained by Langevin's dynamics [16]. This is understandable because the Monte Carlo simulations always detect the so-called "important phase space" regions which are of low energy . Because of imperfections of the force field,this lowest energy basin usually does not correspond to the native state in most cases, so the rank of native structure in those decoys produced by the force field itself is poor.In density function theory the exact exchange (HF) for a single determination is replaced by a more general expression the exchange correlation functional, which can include terms accounting for both exchange energy and the electron correlation, which is omitted from Hartree-Fock theory:

$$E_{ks} = \nu + \langle hp \rangle + 1/2 \langle P_j(\rho) \rangle + E_{\chi(\rho)} + E_{C(\rho)} \quad (1)$$

Where  $E_{\chi(\rho)}$  is the exchange function and  $E_{C(\rho)}$  is the correlation functional. The correlation function of Lee, Yang and Parr is includes both local and non-local term .

The calculation procedures are as follows. First, the geometries of Benzoic acid, Gallic acid, Vanillic

acid and Flavone were fully optimized by DFT and B3LYP functional with 3-21G,6-31G and 6-31g(d), Gaussian basis set. Also, we calculated NMR chemical shielding tensors data that shown in Table 2.

If  $|\sigma_{11}-\sigma_{iso}| \geq |\sigma_{33}-\sigma_{iso}|$ ,  $\Delta\sigma$ , Chemical Shift Anisotropy,  $\eta$ , Asymmetry Parameter,  $\Omega$ , Shielding Tensor Anisotropy for molecule and  $\kappa$ , slop are shown as below:

$$\Delta\sigma = \sigma_{22} - \frac{\sigma_{22} + \sigma_{33}}{3} \quad (4)$$

$$\eta = \frac{\sigma_{22} + \sigma_{33}}{\sigma} \quad (5)$$

$$\delta = \sigma_{11} - \sigma_{iso} \quad (6)$$

but if  $|\sigma_{11}-\sigma_{iso}| \leq |\sigma_{33}-\sigma_{iso}|$ :

$$\Delta\sigma = \sigma_{33} - \frac{\sigma_{22} + \sigma_{11}}{2} \quad (7)$$

$$\eta = \frac{\sigma_{22} + \sigma_{11}}{\sigma} \quad (8)$$

$$\delta = \sigma_{33} - \sigma_{iso} \quad (9)$$

$$\Omega = \sigma_{33} - \sigma_{11} \quad (10)$$

$$\kappa = \frac{3(\sigma_{iso} - \sigma_{22})}{\Omega}$$

Chemical shifts of the considered compounds were calculated at the same level using the Gauge-Included Atomic Orbital (GIAO) approach(16,17).

## RESULTS AND DISCUSSIONS

we calculated NMR chemical shielding tensors data that shown in Table 2.the figure of isotropic determinant for Benzoic acid ,denoted that the most chemical shift is belong to oxygen atom number 8 . it shows , the oxygen atom is the very sensitive part of Bnzoic acid which located in chemical reaction.isotropic shielding show the tensor, 8<sup>th</sup> atoms in Benzoic Acid have more electronic density than other atoms.8<sup>th</sup> atoms are characterized in (Fig 1-5 and table 2).

Turning point in the oxygen atom number 8 can be seen. This spot is right in that the atomic is that has the most chemical shift.in the range of 8<sup>th</sup> atom, the atomic charge is strongly negative,

which the chemical shift caused this properties.the figure of isotropic determinant for gallic acid ,denoted that the most chemical shift is belong to oxygen atoms numer 5,7,9,11and 12 . it shows , the oxygen atoms is the very sensitive part of Gallic acid which located in chemical reaction.isotropic shielding show the tensor, 5<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup>, 11<sup>th</sup> and 12<sup>th</sup> atoms in Gallic acid have more electronic density than other atoms.8<sup>th</sup> atoms are characterized in (Fig1-5 and table 2 ).Turning point in the oxygen atom number 5,7,9 ,11and 12 can be seen. This spot is right in that the atomic is that has the most chemical shift.in the range of 5<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup>, 11<sup>th</sup> and 12<sup>th</sup> atoms, the atomic charge is strongly negative, which the chemical shift caused this properties.the figure of isotropic determinant for vanillic acid, denoted that the most chemical shift is belong to oxygen atoms numer 5,8,11 and 12. it shows, the oxygen atoms is the very sensitive part of Gallic acid which located in chemical reaction.isotropic shielding show the tensor, 5<sup>th</sup>, 8<sup>th</sup>, 11<sup>th</sup> and 12<sup>th</sup> atoms in vanillic acid have more electronic density than other atoms.8<sup>th</sup> atoms are characterized in (Fig 1-5 and tab. 2).Turning point in the oxygen atom number 5,8,11and 12 can be seen. This spot is right in that the atomic is that has the most chemical shift.in the range of 5<sup>th</sup>, 8<sup>th</sup>, 11<sup>th</sup> and 12<sup>th</sup> atoms, the atomic charge is strongly negative, which the chemical shift caused this properties.the figure of isotropic determinant for flavone, denoted that the most chemical shift is belong to oxygen atoms numer 4, and 11. it shows, the oxygen atoms is the very sensitive part of flavone which located in chemical reaction.isotropic shielding show the tensor, 4<sup>th</sup>and 11<sup>th</sup> atoms in flavone have more electronic density than other atoms. 4<sup>th</sup>and 11<sup>th</sup> atoms are characterized in Fig. Turning point in the oxygen atom number 5,7,9 and 10 can be seen. This spot is right in that the atomic is that has the most chemical shift.in the range of 5<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup> and 10<sup>th</sup> atoms, the atomic charge is strongly negative, which the chemical shift caused this properties(Fig. 1-5 and table 2).

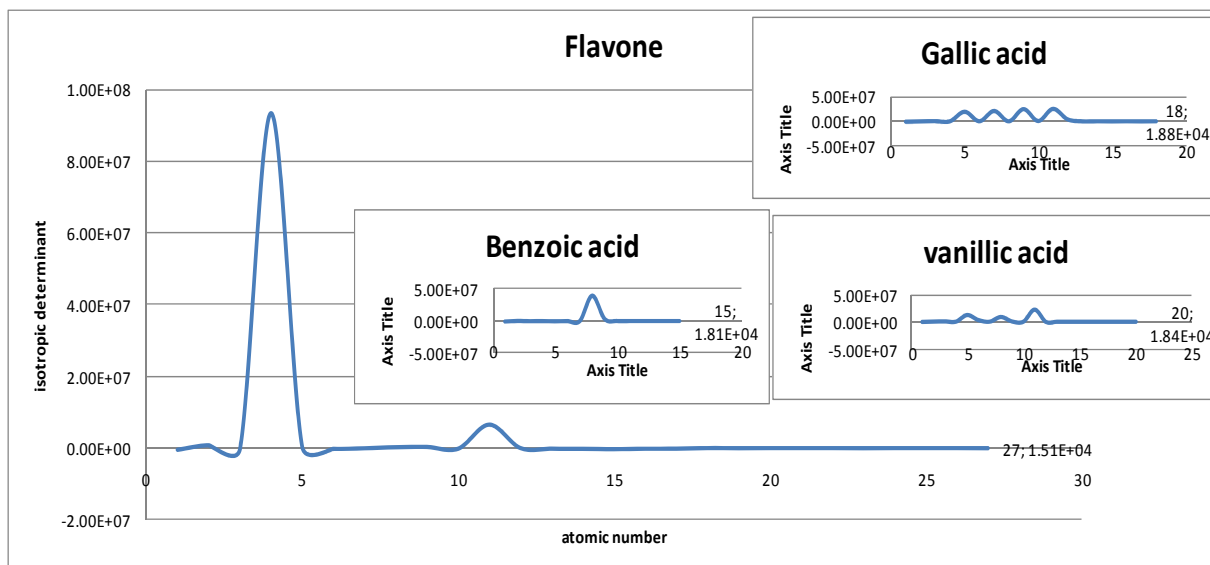


Fig. 1. Isotropic determinant versus number of atom.

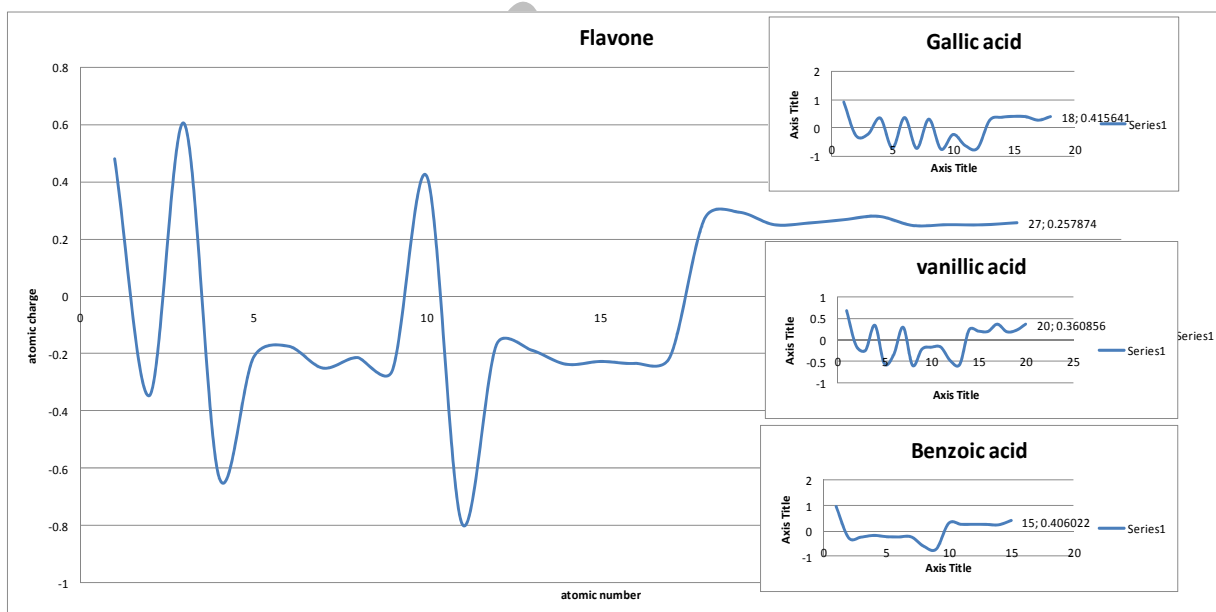


Fig. 2. Atomic charge versus number of atom.

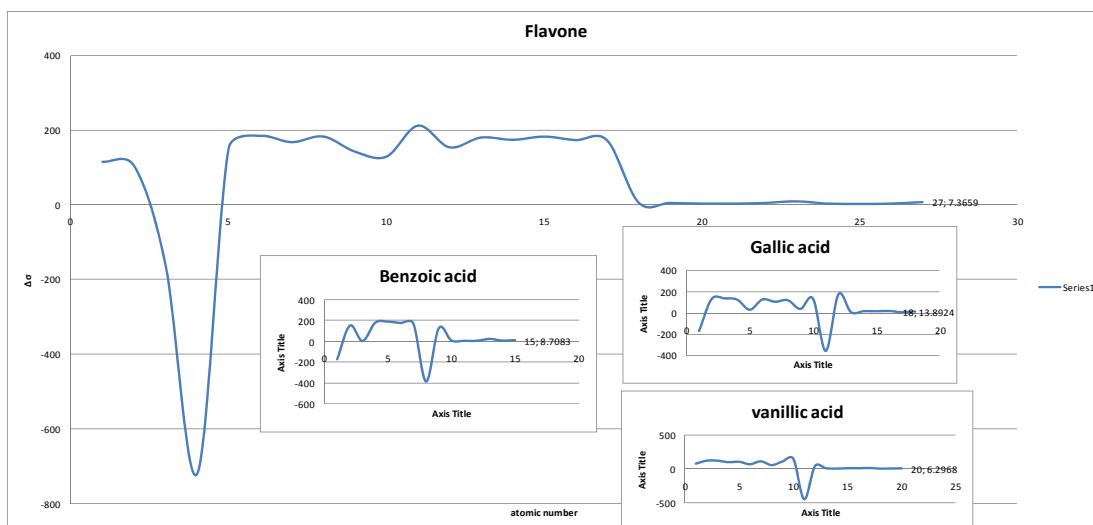


Fig. 3.  $\Delta\sigma$ (changes of chemical shift anisotropy) versus to number of atom.

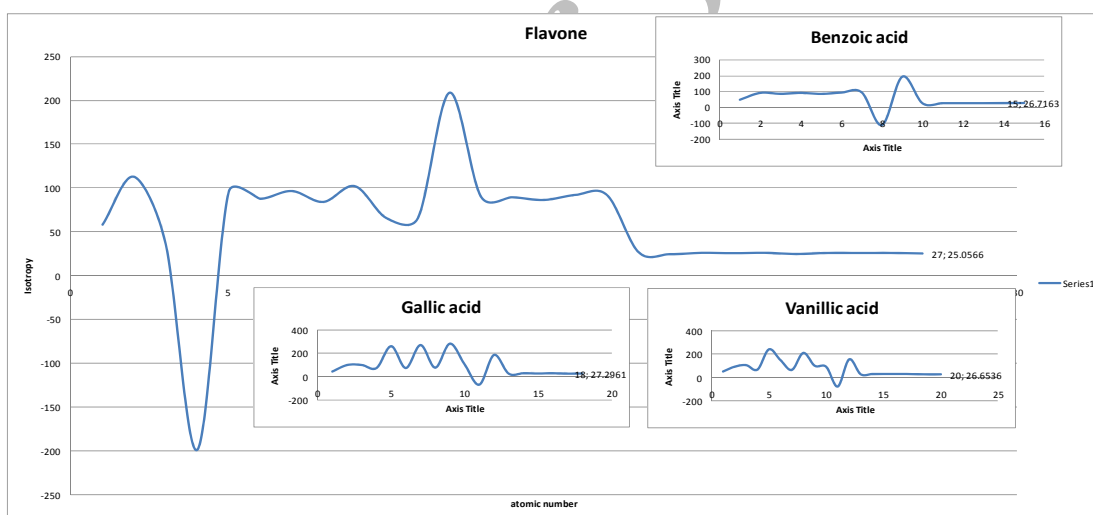


Fig. 4. Isotropy versus to number of atom.

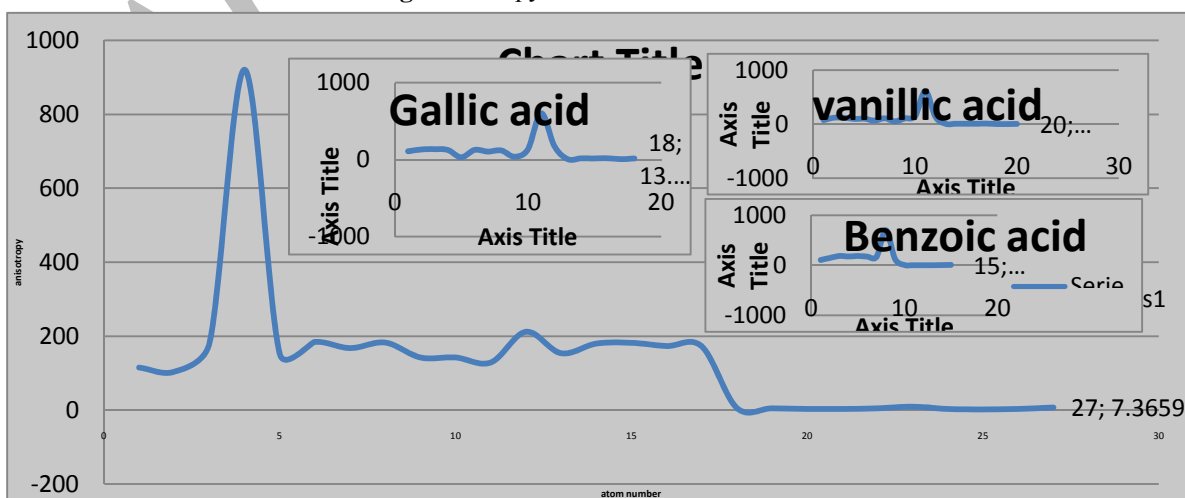


Fig. 5. Anisotropic data versus to number of atom.

**Table 2.** NMR chemical shielding tensors data of polyphenol compound

Name	atoms	HF/NMR																					
		3-2IG					6-31G					6-31G*											
Benzoinc	C1	0.947310	-115.73	0.2209	-173.599	5.3350e+005	-415.969154	5.66335	0.813585	-107.8256	0.722	23.2493	-5.4398e+005	-418.3029791	5.5317	0.846938	-107.8256	0.722	23.2493	-5.4398e+005	-418.3029791	5.5317	
	C2	-0.264433	98.85	0.7631	146.2873	-3.350e+004		-0.178042	106.6434	0.773	155.9651	-2.3807e+005		-0.144725	106.6434	0.773	159.9651	-2.3807e+005					
	C3	-0.221033	124.28	0.7189	186.4425	-3.1647e+005		-0.179243	129.5764	0.731	147.2876	-4.3678e+005		-0.181832	129.5764	0.731	147.2876	-4.3678e+005					
	C7	-0.229063	112.17	0.7442	168.2607	-3.9836e+004		-0.180251	119.4405	0.766	146.4933	-3.2690e+005		-0.215133	119.4405	0.766	148.4933	-3.2690e+005					
	O8	-0.590625	-327.86	1.8622	-389.035	3.945e+007		-0.561001	118.6099	0.746	177.9148	2.6004e+007		-0.741961	118.6099	0.746	177.9148	2.6004e+007					
	O9	-0.703901	82.19	2.6500	123.2990	3.1392e+006		-0.741961	-292.9364	1.870	435.4046	1.7089e+006		-0.741961	-292.9364	1.870	439.4046	1.7089e+006					
	O9	0.295833	3.64	1.388	5.4666	1.4917e+004		0.263292	83.3623	2.524	125.0434	1.2726e+004		0.263292	83.3623	2.524	125.0434	1.2726e+004					
	H10	0.256363	1.68	2.5359	2.5359	1.6489e+004		0.218283	2.6637	2.159	4.671	1.4798e+004		0.218283	2.6637	2.159	4.1671	1.4798e+004					
	H12																						
	Gallic acid	C1	0.934132	112.8911	0.281	-169.334	6.055e+005	-639.3008011	3.7712	0.411347	0.031762	146.7761	-3.9413e+005	-646.2721764	3.2179	0.821762	-101.0206	0.324	-151.5309	-4.5119e+005	-642.8779978	3.736	
		C2	-0.262385	166.2029	0.411	132.0050	3.0452e+003		0.241678	88.4222	0.506	132.6333	6.9507e+004		-0.153698	96.388	0.819	144.5819	-6.1799e+004				
		C4	0.362160	83.0037	0.639	124.5056	7.2166e+004		-0.599843	76.438	0.488	114.6569	7.6074e+003		0.373597	88.3294	0.656	132.4940	-8.5670e+004				
O5		-0.708941	19.9239	0.430	29.8838	1.8324e+007		0.281846	23.2667	2.838	34.9001	9.0536e+005		-0.743846	23.2667	0.214	35.7757	1.7945e+007					
C6		0.379788	83.8031	0.446	125.7346	1.2296e+005		-0.593236	75.6615	0.119	113.4922	5.2419e+004		0.358013	84.7912	0.515	127.1867	8.1954e+003					
O7		-0.719800	69.5794	0.844	104.3691	1.2296e+005		0.294150	92.6859	0.335	135.0288	9.6382e+006		-0.75093	83.7368	0.411	93.8052	1.9506e+007					
O8		0.323303	79.045	1.578	118.5675	5.9434e+004		-0.62304	73.2134	0.629	105.6200	-2.0378e+006		0.331743	83.7368	0.794	125.6517	-1.0412e+005					
O9		-0.749316	24.7852	0.655	37.1778	2.3360e+007		-0.419749	28.3393	1.849	42.8089	1.2491e+007		-0.798398	26.8976	1.499	40.3014	2.0232e+007					
O11		-0.623946	-	2.371	-37.258	2.3360e+007		-0.574658	-235.921	2.214	-35.3913	2.2348e+007		-0.590757	-220.5808	2.188	-330.8689	2.7729e+007					
O12		-0.714049	238.1726	1.4271	174.521	3.6399e+006		0.162598	126.7563	1.428	190.1344	-5.4589e+005		-0.737579	112.4571	1.379	168.6856	2.7729e+006					
H13		0.293800	116.0344	1.860	3.4443	1.6309e+004			4.014	1.142	6.0216	1.6588e+004		0.246581	4.6402	1.250	6.9603	1.4501e+004					

Table 2. Continued ...

Name	atoms	HF/NMR																					
		3-21G					6-31G					6-31G*											
Atomic charge	$\delta$	$\eta$	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	$\delta$	$\eta$	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	$\delta$	$\eta$	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment			
Vanillic	C1	0.669122	51.675	2.4018	77.5155	-3.2643e+005	-607.1762266	4.5343	0.810707	51.675	2.401	77.5125	-8.0006e+005	-606.7675948	4.3621	0.842738	-108.857	-210	-143.3136	-5.5750e+005	-607.0248496	4.4324	
	C2	-0.129313	80.5151	0.6976	120.7721	3.3761e+005		-0.190318	80.5147	0.697	120.7721	-1.4644e+005		-0.135314	97.2392	0.828	145.8387	-153.3136	-1.0960e+005				
	C4	0.333661	65.7718	0.4331	98.6577	1.4839e+005		0.379139	112.9012	0.252	69.3580	-8.9941e+004		-0.403511	85.544	0.611	128.316	73.8893	-6.7340e+004				
	O5	-0.538889	45.0855	1.6215	104.2196	1.3141e+007		-0.732037	68.3931	1.623	104.2196	1.8344e+007		-0.665682	49.0882	1.934	78.8993	2.1377e+007	2.9806e+006				
	O6	-0.337832	36.9063	0.2228	55.3594	3.2371e+006		-0.150582	45.0855	0.222	67.8228	1.4017e+006		-0.189153	43.2808	0.155	64.9212	1.3618e+007	1.3618e+007				
	O8	-0.581341	72.2617	1.4602	109.1426	9.3371e+006		-0.744475	36.9063	0.310	55.3568	1.1579e+007		-0.745453	22.4196	2.749	33.6294	1.3618e+007	8.0088e+004				
	O9	-0.208201	-301.796	0.9111	452.694	5.3478e+005		-0.218208	72.2617	1.187	109.1876	2.2548e+007		-0.272285	90.7888	0.806	136.1787	-290.4015	2.5473e+007				
	O11	-0.471991	70.925	1.7183	40.3954	2.4372e+005		-0.538411	43.61254	1.887	45.6580	5.4189e+007		-0.564015	92.8739	1.935	-436.2773	124.3109	1.9316e+006				
	O12	-0.561490	5.2816	3.2333	7.9474	-2.4372e+005		-0.737732	90.9626	2.587	136.4429	-2.3984e+005		-0.746891	82.8739	2.398	124.3109	9.2037	1.9316e+006				
	H13	0.181571	0.7424	0.7424	0.7424	1.9390e+004		0.228176	5.2816	0.742	7.9324	1.7997e+004		0.220091	6.3371	0.711	9.2037	1.6332e+004					
	Flavone	C1	0.480733	76.7723	1.5925	115.1584	-4.4630e+005	-723.5775433	4.6066	0.473409	-110.8833	1.195	133.7669	-5.4677e+005	-723.3025719	4.5802	0.494521	-106.8829	-0.555	-160.3243	-5.0449e+005	-723.5775433	4.6066
		C2	-0.343939	69.3641	1.1781	104.1978	8.1117e+005		-0.277939	77.4509	1.077	116.1762	1.0782e+008		-0.383311	70.3675	1.137	105.5526	-4.0395e+005				
C4		-0.627866	479.4667	1.5383	-719.2100	9.3512e+007		-0.608838	479.3706	-1.642	719.0559	-3.7098e+005		-0.630382	-415.9544	1.536	-658.9931	6.9755e+007					
C5		-0.212979	101.2432	0.2891	151.8648	3.6416e+005		-0.147388	113.5942	0.278	170.7811	-2.7491e+005		-0.173921	108.3801	0.284	162.5701	8.1886e+004					
C6		-0.173216	122.9762	0.6426	184.4643	-1.8394e+005		-0.147710	135.742	0.626	203.6141	-2.4571e+006		-0.163746	131.203	0.639	196.8044	-3.44810e+005					
C10		0.418416	85.9433	0.9088	128.9149	1.4808e+005		0.418680	97.3665	0.912	146.0498	2.8181e+005		0.439350	207.2066	1.345	136.8092	-2.5784e+005					
O11		-0.790383	141.2271	1.1720	211.8406	6.5781e+006		-0.790383	159.4041	0.155	229.1057	-4.6684e+005		-0.751353	111.5718	0.100	216.4599	4.1642e+006					
C12		-0.168316	108.6267	0.6574	153.94	4.0802e+004		-0.130970	115.8433	0.724	175.756	1.7015e+004		-0.087796	126.1765	0.721	167.3577	-2.4739e+005					
C15		-0.226657	121.3393	0.7225	182.4639	-2.6425e+005		-0.177052	132.9255	0.724	199.3883	-4.6684e+005		-0.188665	126.1765	0.740	189.2674	-4.1839e+005					
H18		0.271943	3.9849	1.7300	5.3773	1.7916e+004		0.239058	4.5334	1.391	6.8001	1.5913e+004		0.238890	5.2144	1.278	7.8216	1.6795e+004					
H25		0.250835	1.4538	2.8074	2.3339	1.6666e+004		0.212938	2.0551	1.769	3.8826	1.5913e+004		0.213617	2.6274	1.819	3.9410	1.4995e+004					



## CONCLUSION

Computational chemistry methods are one of the most powerful tools to achieve advances in this field, and several studies may be found in the literature on this subject. They provide very valuable information at moderate economical costs, prior to time-consuming and expensive experimental or clinical studies, and allow inferring the effects of different molecular features on compounds' properties. Phenolic acids

present in plants are hydroxylated derivatives of benzoic and cinnamic acids. Flavonoids and phenolic acids have many functions in plants. Structurally, phenolic compounds comprise an aromatic ring, bearing one or more hydroxyl substituents, and range from simple phenolic molecules to highly polymerised compounds. This research showed oxygen atoms have very important role in these molecules.

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