

Determination Functional Theory Investigation of Polyphenolic Compounds Reactions: NMR study

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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).

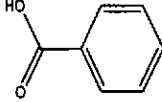
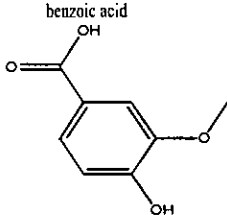
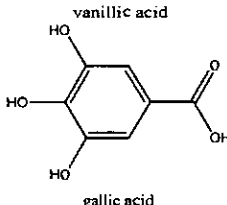
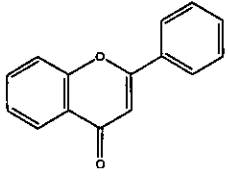
Structurally they have phenolic groups which as a source of readily available hydrogen atoms such that the subsequent radicals produced can be delocalized over the phenolic structure (figure 1). The interest in these compounds is due to their pharmacological activity as radical scavengers. They have 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:

$$E_{ks} = v + \langle hp \rangle + 1/2 \langle P_j(\rho) \rangle + E_{x(\rho)} + E_{c(\rho)} \quad (1)$$

Where $E_{x(\rho)}$ 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, η , Asymmetry Parameter, Ω , Shielding Tensor Anisotropy for molecule and κ , 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, 8th atoms in Benzoic Acid have more electronic density than other atoms.8th 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 8th 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, 5th, 7th, 9th, 11th and 12th atoms in Gallic acid have more electronic density than other atoms.8th 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 5th, 7th, 9th, 11th and 12th 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, 5th, 8th, 11th and 12th atoms in vanillic acid have more electronic density than other atoms.8th 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 5th, 8th, 11th and 12th 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, 4thand 11th atoms in flavone have more electronic density than other atoms. 4thand 11th 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 5th, 7th, 9th and 10th atoms, the atomic charge is strongly negative, which the chemical shift caused this properties(Fig. 1-5 and table 2).

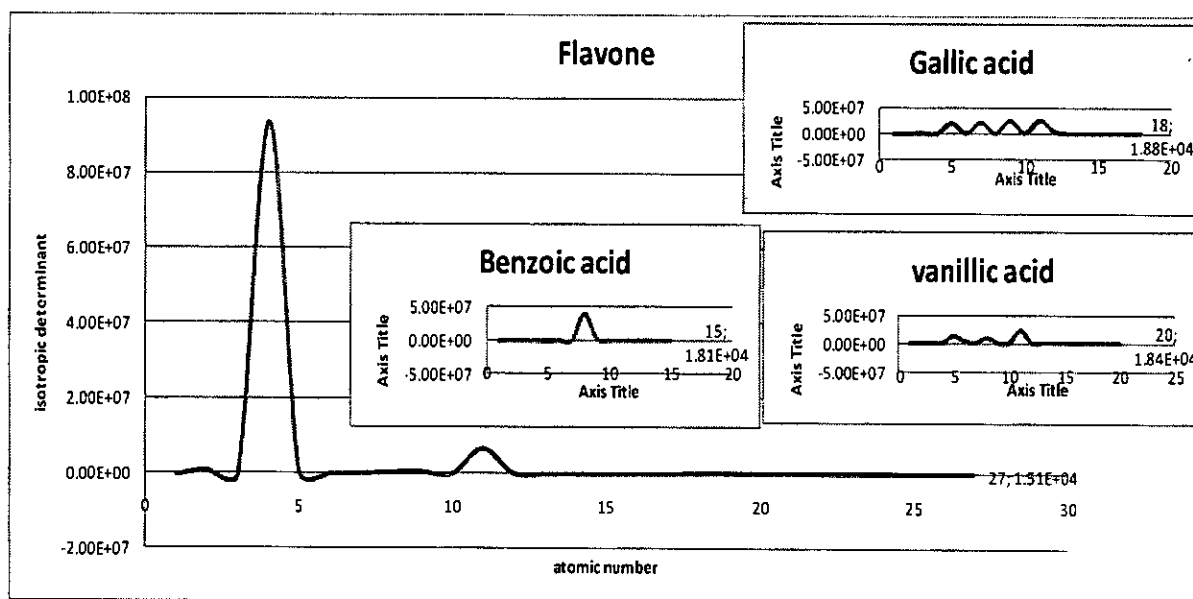


Fig. 1. Isotropic determinant versus number of atom.

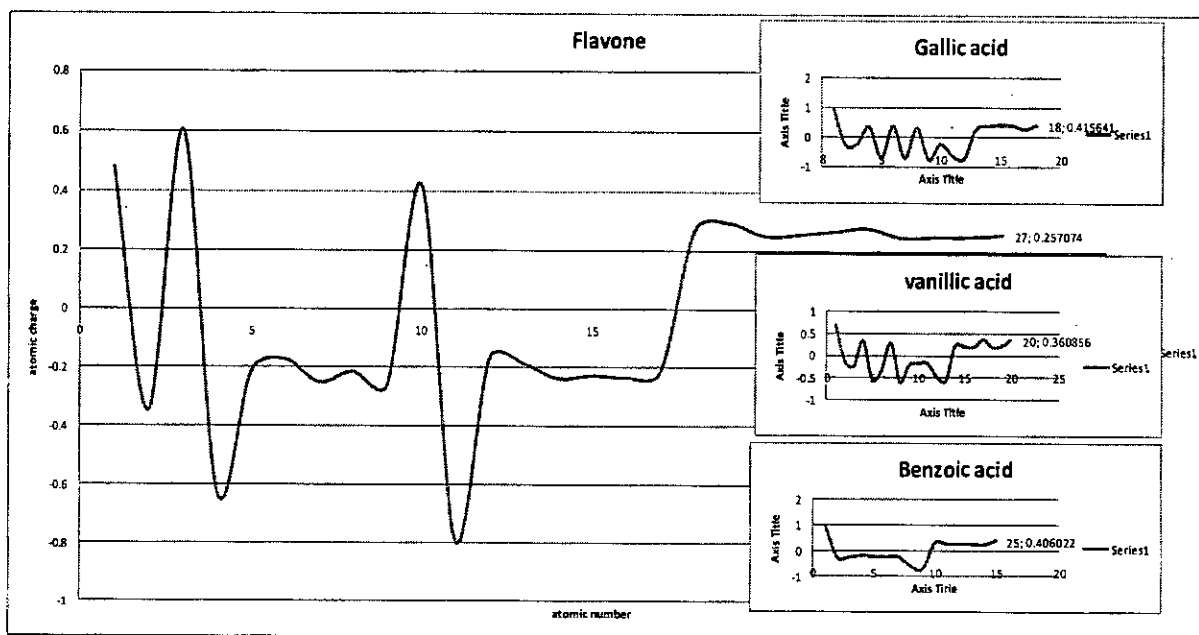


Fig. 2. Atomic charge versus number of atom.

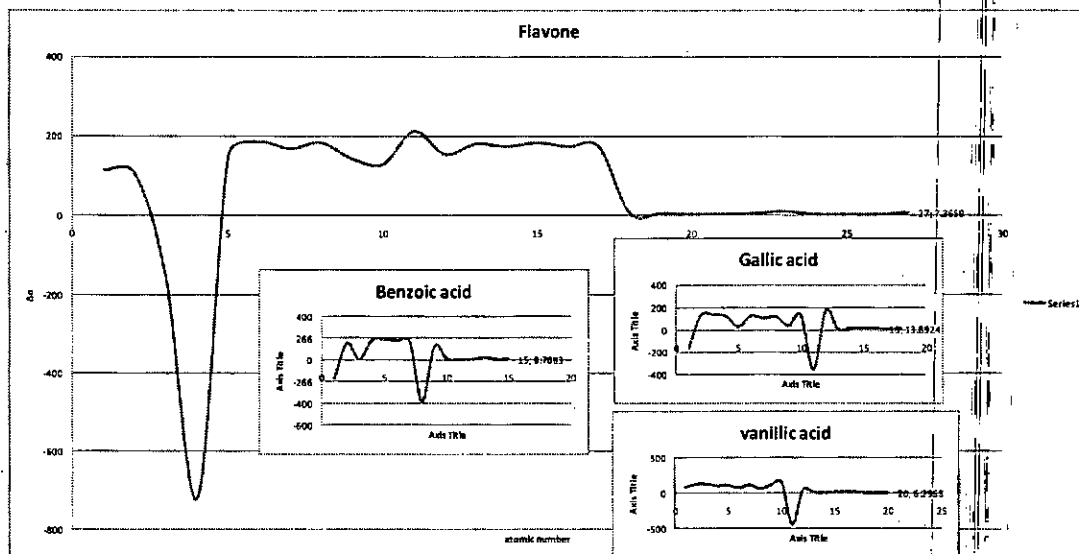


Fig. 3. $\Delta\sigma$ (changes of chemical shift anisotropy) versus to number of atom.

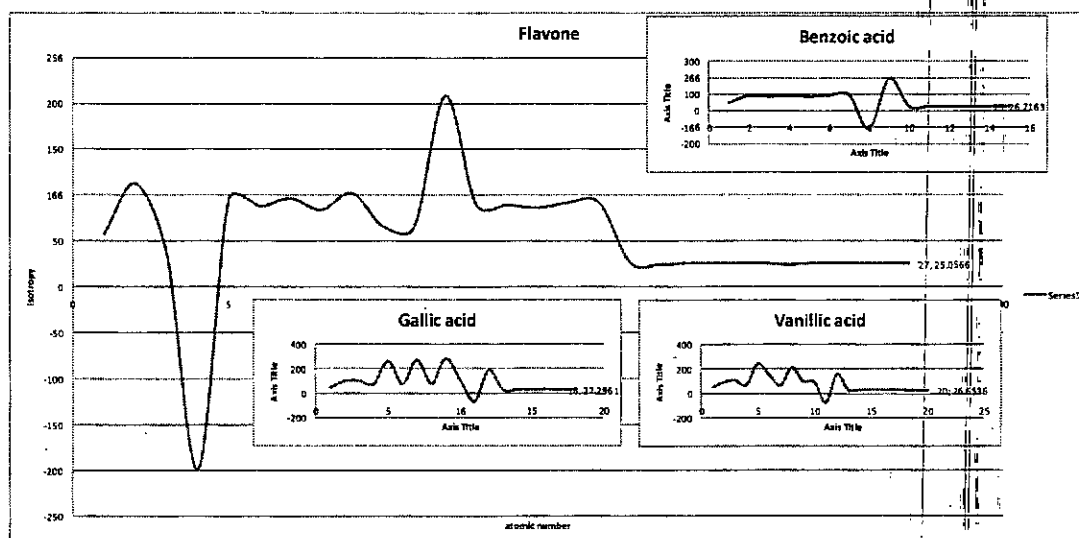


Fig. 4. Isotropy versus to number of atom.

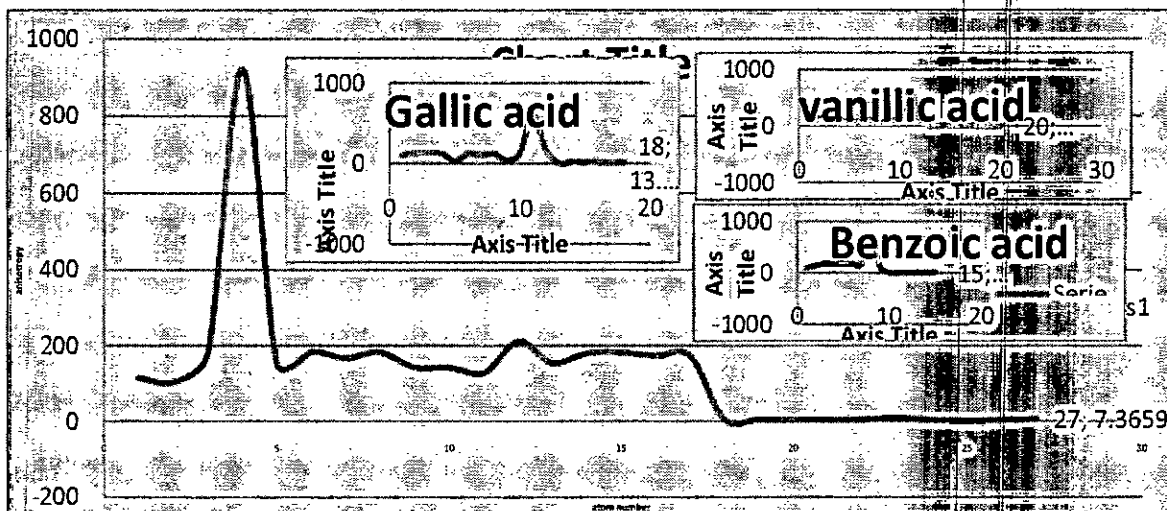


Fig. 5. Anisotropic data versus to number of atom.

Table 2. NMR chemical shielding tensors data of polyphenol compound

Name	atoms	HF/NMR																						
		3-2IG						6-3IG						6-3IG*										
		Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment		
Benzoc	C1 C2 C5 C7 O8 O9 H10 H12	0.947310 -0.264477 -0.221033 -0.229063 -0.590625 -0.703901 0.295833 0.256367	-115.73 98.85 124.28 112.17 -327.96 82.19 3.64 1.68	0.2209 0.7631 0.7189 0.7442 1.8622 2.6500 1.388 2.5339	-173.599 148.2873 186.4425 168.2607 -389.035 123.2990 5.4666 2.5339	-7.3659e+005 5.3550e+004 -3.1457e+005 -3.9876e+004 3.9945e+007 3.1962e+006 1.4047e+004 1.6489e+004	-415.960154 5.6635	0.813585 -0.180342 -0.175403 -0.180251 -0.561001 -0.741961 0.262829 0.218283	-107.8256 106.6434 129.5264 119.4405 118.6099 -292.9364 83.3623 2.6637	0.722 0.773 0.731 0.766 0.746 1.870 2.524 2.159	23.2493 159.9551 147.2876 148.4933 177.9148 439.4046 125.0434 4.1671	-5.4389e+005 -2.3507e+005 -4.3678e+005 -3.2690e+005 7.6004e+007 1.7089e+006 1.7226e+004 1.4798e+004	-418.302791 5.5317	0.840938 -0.144725 -0.181832 -0.215133 -0.561001 -0.741961 0.262829 0.218283	-107.8256 106.6434 129.5264 119.4405 118.6099 -292.9364 83.3623 2.6637	0.722 0.773 0.731 0.766 0.746 1.870 2.524 2.159	23.2493 159.9551 147.2876 148.4933 177.9148 439.4046 125.0434 4.1671	-5.4389e+005 -2.3507e+005 -4.3678e+005 -3.2690e+005 7.6004e+007 1.7089e+006 1.7226e+004 1.4798e+004	-418.302791 5.5317	0.840938 -0.144725 -0.181832 -0.215133 -0.561001 -0.741961 0.262829 0.218283	-107.8256 106.6434 129.5264 119.4405 118.6099 -292.9364 83.3623 2.6637	0.722 0.773 0.731 0.766 0.746 1.870 2.524 2.159	23.2493 159.9551 147.2876 148.4933 177.9148 439.4046 125.0434 4.1671	-5.4389e+005 -2.3507e+005 -4.3678e+005 -3.2690e+005 7.6004e+007 1.7089e+006 1.7226e+004 1.4798e+004
Gallicacid	C1 C2 C4 O5 O6 O7 O8 O9 O11 O12 H13	0.934132 -0.262385 0.362160 -0.708241 0.379788 -0.719800 0.323303 -0.749316 -0.623246 -0.714049 0.287800	112.8911 166.2029 83.0037 19.9239 83.8031 69.5794 79.045 24.7852 79.045 238.1726 116.0344 3.6295	0.281 0.411 0.639 0.430 0.446 0.844 1.578 0.655 2.371 1.4271 1.860	-169.334 132.0050 124.5056 29.8858 125.7346 104.3691 118.5675 37.1778 -357.258 174.521 5.4443	6.6055e+005 3.0452e+003 7.2066e+004 1.8324e+007 1.2296e+005 1.9841e+007 5.9434e+004 2.3360e+007 2.3865e+007 3.6390e+006 1.6303e+004	-639.3008011 3.7712	0.411747 0.031762 0.241678 -0.599843 0.281464 -0.593236 0.234150 -0.662404 -0.419749 -0.574658 0.162598	-99.1841 88.4222 76.438 23.2667 75.6615 92.6859 73.2134 28.3393 -235.921 126.7563 4.0144	0.173 0.506 0.458 2.838 0.119 0.335 0.629 1.849 2.214 1.428 1.142	148.7761 132.6333 114.6569 34.9001 113.4922 9.6392e+006 109.8200 42.5089 -352.9813 190.1344 6.0216	-3.9413e+005 6.9507e+004 7.6074e+003 9.0536e+006 5.2419e+004 -2.0338e+004 -2.491e+007 2.2348e+007 -5.4589e+005 1.6568e+004	-646.2721764 3.2175	0.821762 -0.153698 0.373597 -0.743846 0.350813 -0.750903 0.251743 -0.798398 -0.590757 -0.735737 0.248581	-101.0206 96.398 88.3294 238.8505 84.7912 62.5368 83.7697 26.8976 -230.5808 112.4571 4.6402	0.324 0.819 0.656 0.214 0.515 0.411 0.794 1.499 2.188 1.379 1.250	-151.5709 144.5819 132.4940 35.7757 127.1867 93.8022 125.6517 40.3014 -104.12e+005 168.6056 6.9603	-4.5119e+005 -6.1799e+004 -8.670e+004 1.7345e+007 8.1954e+003 1.9506e+007 -1.0412e+005 2.0232e+007 1.2772e+007 2.7788e+006 1.4901e+004	-643.8775978 79978	3.5736				

Table 2. Continued ...

Name	atoms	Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment	Atomic charge	δ	η	$\Delta\sigma$	Isotropy determinant	HF Energy	Dipole moment
C1	C1	0.669122	51.675	2.408	71.5155	-3.2641+005	-607.1762266	4.5343	0.810297	51.675	2.401	71.5125	-8.0096+005	-606.7675948	4.3321	0.802738	-108.857	-210	-163.116	-5.5726+005	-607.0442436	4.4324
C2	C2	-0.128913	80.5151	0.6976	120.7721	3.7016+005			-0.190518	80.5147	0.697	120.7321	-1.4644+005			-0.155514	97.232	0.828	145.897	-1.0922+005		
C4	C4	0.331661	63.7718	0.4731	98.6777	1.4632+005			0.371519	112.8012	0.232	69.3880	-8.9981+004			0.004317	85.344	0.611	128.316	-6.7324+004		
C5	C5	-0.335899	69.4798	0.4731	104.2196	1.3141+007			-0.732057	69.3931	1.623	104.2196	1.8344+007			-0.665672	49.062	1.934	73.873	2.1371+007		
C6	C6	-0.335782	45.0855	0.2228	67.6283	3.2371+006			-0.150582	45.0855	0.222	67.6228	3.4017+006			-0.189153	43.208	0.155	64.972	1.3864+006		
C8	C8	-0.381341	36.9063	0.2228	55.3594	9.3771+006			-0.744475	36.9063	0.310	55.3568	1.1579+007			-0.743453	22.4196	2.749	31.6284	1.6184+007		
C9	C9	-0.202801	72.2017	1.4902	109.1926	5.3478+005			-0.218078	72.2017	0.903	109.1876	2.2549+004			-0.212285	50.7658	0.806	116.1787	8.0388+004		
O1	O1	-0.471991	-301.736	0.9111	403.694	-2.3378+005			-0.539411	-436.1254	1.187	-452.6580	-2.5864+005			-0.564015	-290.4015	1.935	-431.6273	2.5471+007		
O12	O12	-0.561490	70.925	1.7183	129.925	-2.8272+005			-0.733733	90.9656	2.567	136.4439	-2.8864+005			-0.744891	82.8719	2.389	124.1099	1.9312+005		
H13	H13	0.181571	5.2816	0.7426	7.9774	1.9390+004			0.228176	5.2816	0.742	7.9724	1.9971+004			0.220391	6.3371	0.711	9.5297	1.6312+004		
C1	C1	0.480733	76.7723	1.5925	115.1584	-4.4630+005			0.473409	-110.8833	1.195	133.7669	-5.4671+005			0.434521	-106.6259	-0.0555	-160.3243	-5.0109+005		
C2	C2	-0.345939	69.3641	1.1781	104.1928	8.1112+005			-0.275797	77.4509	1.077	116.1762	1.0782+008			-0.283311	70.3673	1.137	102.5526	4.0706+005		
C4	C4	-0.627866	479.4667	1.5388	151.8468	9.3532+007			-0.606888	-479.3706	-1.682	719.0539	6.2988+004			-0.620392	-415.9954	1.536	-658.9931	6.9715+007		
C5	C5	-0.212979	0.2891	0.2891	1.31.8468	3.6416+005			-0.147388	113.5882	0.278	170.8111	-3.7088+005			-0.173221	103.3801	0.284	162.5701	8.1896+004		
C6	C6	-0.173216	101.7432	0.6402	128.9149	-1.8594+006			-0.147310	135.742	0.626	203.6141	2.9731+006			-0.163746	131.203	0.619	196.8034	-3.4810+005		
C10	C10	0.418116	863.9433	0.9088	211.82495	6.7818+006			-0.418800	97.7465	0.912	146.0498	-2.8143+005			-0.433320	-80.2041	1.545	-135.3092	-2.5789+005		
O11	O11	-0.793083	141.2271	0.1720	153.94	4.6802+006			-0.793083	159.4031	0.716	229.1057	4.6658+005			-0.751353	207.2066	0.100	216.4259	4.1618+006		
C12	C12	-0.168316	102.6267	0.6374	182.4639	4.6802+006			-0.130970	115.8213	0.774	173.76	1.7015+004			-0.087766	111.5718	0.721	169.3171	-2.4729+005		
C15	C15	-0.212943	121.3339	0.7225	158.4639	-2.6425+005			-0.232908	4.5334	1.391	159.2883	1.9935+004			-0.186895	126.1765	0.740	189.2674	-4.1826+005		
H18	H18	0.271943	1.7300	1.7300	2.3339	1.1976+004			0.232908	2.0351	1.769	6.8001	1.9935+004			0.235890	5.2144	1.278	7.8216	1.6795+004		
H25	H25	0.259835	1.4538	1.8074	2.3339	1.6666+004			0.212398	2.0351	1.8074	3.0826	1.9935+004			0.213617	2.6274	1.819	3.9410	1.6995+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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