

Theoretical investigation of flavonoids naringenin and genistein

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Abstract

The structural and electronic properties of the flavonoids naringenin (NG) and genistein (GS) have been investigated theoretically by performing semi-empirical and ab initio molecular orbital theory calculations. The geometry of the systems have been optimized considering the semi-empirical molecular orbital theory at the level of AM1, and the electronic properties of the systems have been calculated by ab initio RHF including full MP2 correlation correction in their ground state. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Flavonoids are a group of phenolic compounds with wide distribution in the plant kingdom. The antioxidant activities of flavonoids are related to their ability to chelate metal ions and scavenge singlet oxygen, superoxide radicals, peroxy radicals, hydroxyl radicals, and peroxynitrite [1,2]. These reactive oxygen and nitrogen species can react with critical cellular components such as DNA, lipids, and proteins leading to tissue injury and contributing to chronic disease. A high intake of flavonoids has been associated with a lower incidence of cardiovascular diseases the leading cause of death [3]. Consumption of fruits, vegetables, and certain teas and beverages such as black tea and grape juice is associated with a lowered risk of cardiovascular disease [4,5]. On the other hand, the dietary components such as flavonoids

have recently been shown in epidemiological studies to be protective for heart disease [6]. Recently, several flavonoids have been identified [7–9] and their ability to bind lipoproteins in plasma and protect them from ex vivo oxidation have been examined [5,10]; the antioxidant properties mostly attributed to their ability to inhibit Cu²⁺-mediated oxidation of the low-density lipoprotein (LDL) class. Oxidation of LDL is thought to play a central role in atherosclerosis.

In this study, we have investigated the structural and electronic properties of two flavonoids, naringenin (NG) and genistein (GS), theoretically, by performing semi-empirical molecular orbital and ab initio calculations because of their biological and medical importance.

2. Method of calculation

In the present study, the NG and GS molecules have been considered theoretically by performing both semi-empirical molecular orbital theory and ab initio calculations. The Austin Model 1 (AM1)

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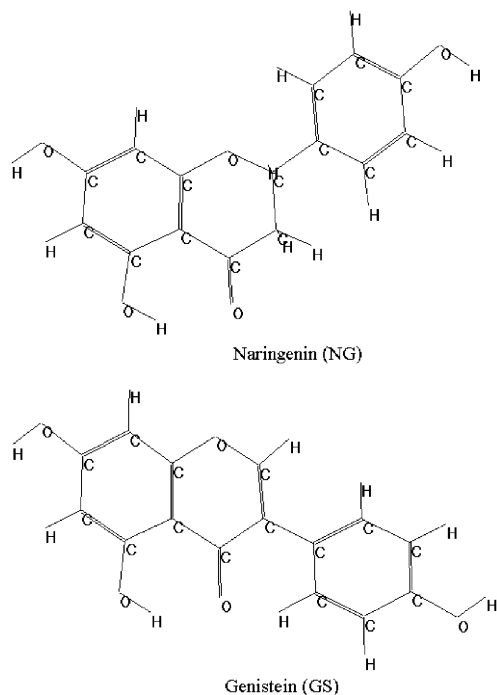


Fig. 1. The structures of naringenin (NG) and genistein (GS) molecules. The structures are non-planar with C_1 symmetry. Optimizations have been performed by AM1 method.

semi-empirical method [11] within the Restricted Hartree–Fock (RHF) [12] formalism has been considered to optimize the geometry of the systems considered.

Geometry optimization is carried out by using a conjugate gradient method (Polak–Ribiere algorithm [13]), then the electronic structure of the system has been calculated by applying the ab initio RHF including full MP2 correlation correction [14] in the ground

Table 1

Some of the molecular properties of NG and GS in their ground state (according to ab initio calculation)

Quantity	NG	GS
No. of electrons	142	140
No. of doubly occupied levels	71	70
No. of total orbitals	112	110
No. of primitive Gaussians	336	330
Multiplicity	Singlet	Singlet
Molecular point group	C_1	C_1

state. The minimum basis set (STO-3G) [15] has been used in the calculations, which may give qualitative but reliable information about the systems considered. The SCF convergency is set to 0.00001 kcal/mol in the calculations. We have performed all the calculations by using the HyperChem-5.1 packet.

3. Results and discussion

The closed formula of the NG and GS molecules are in the form $C_{15}H_{12}O_5$ and $C_{15}H_{10}O_5$, respectively. The optimized structures of the systems considered are shown in Fig. 1. The AM1 geometry optimization yields a non-planar structure as the stable form of isolated NG and GS molecules. There is a slight torsion and bending between the double hexagon ring part and the single hexagon ring part of both NG and GS. Some of the molecular properties of the systems considered are given in Table 1.

The calculated excess charge on the atoms by the ab initio method are given in Fig. 2. All carbon atoms

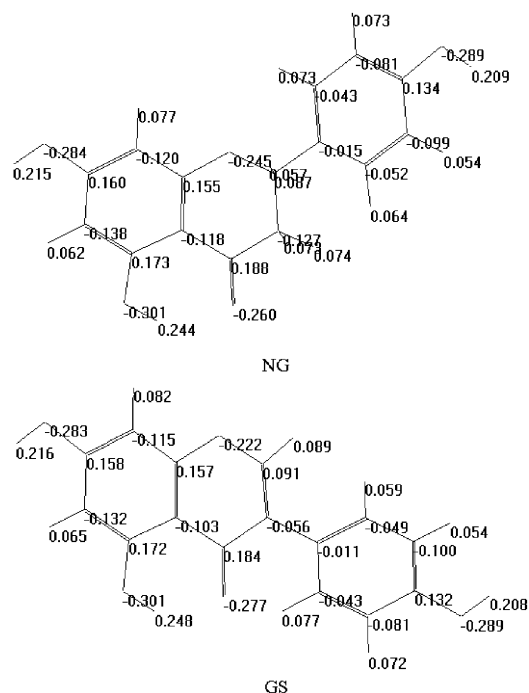


Fig. 2. Calculated excess charge (by ab initio method) on the atoms (in units of electron charge) of NG and GS molecules in their ground state with singlet symmetry.

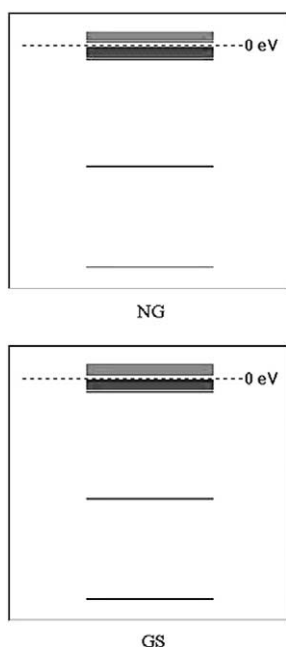


Fig. 3. The molecular orbital energy spectra of NG and GS molecules in their ground state with singlet symmetry, ab initio calculation result.

making bond with oxygen atom have positive excess charge, the rest of the carbon atoms have negative excess charge accumulation. The net excess charge on the atoms of the single hexagon part of NG is about +0.028 electron charge, the same quantity on GS is about +0.029 electron charge; they almost have the same amount of positive excess charge accumulation. Double bonded oxygen atom in NG has -0.260 electron charge; however, in GS, it has -0.277 electron charge. This means that the double bonded oxygen in GS is more reactive than that of NG. On the other hand, the oxygen atom in the hexagon ring of NG has the excess charge of amount -0.245 unit, the corresponding quantity in GS is -0.222 unit.

The molecular orbital energy (eigenvalue) spectra of the systems studied are shown in Fig. 3. The calculated energy values of the systems studied are given in Table 2. The highest occupied and the lowest unoccupied molecular orbital (HOMO and LUMO, respectively) energies and the inter-frontier molecular orbital energy gap (LUMO–HOMO energy difference, ΔE) with the lowest and highest level energy values are also given in Table 2. According to AM1

Table 2
Some of the calculated energy values and dipole moments of NG and GS molecules in their ground state with singlet symmetry

Quantity	NG	GS
<i>AM1 calculation results</i>		
Total energy (kcal/mol)	−85,032.668	−84,380.758
Binding energy (kcal/mol)	−3639.053	−3512.749
Isolated atomic energy (kcal/mol)	−81,393.615	−80,868.009
Electronic energy (kcal/mol)	−513,194.630	−497,618.800
Core–Core interaction (kcal/mol)	428,161.962	413,238.042
Heat of formation (kcal/mol)	−152.684	−130.584
<i>Ab initio calculation results</i>		
Total energy (kcal/mol)	−588,805.578	−588,071.453
MP2 correlation contribution (kcal/mol)	−667.220	−681.326
eK, ee and eN energy (kcal/mol)	−1,505,305.714	−1,484,769.861
Nuclear repulsion energy (kcal/mol)	917,167.356	897,379.734
Lowest level energy (eV)	−552.669	−554.120
HOMO (eV)	−6.558	−5.893
LUMO (eV)	5.620	5.356
ΔE (gap) (eV)	12.178	11.249
Highest level energy (eV)	30.807	31.340
μ_x (Debyes)	−1.317	−0.599
μ_y (Debyes)	−0.756	1.687
μ_z (Debyes)	0.259	−0.502
μ (Debyes)	1.540	1.859

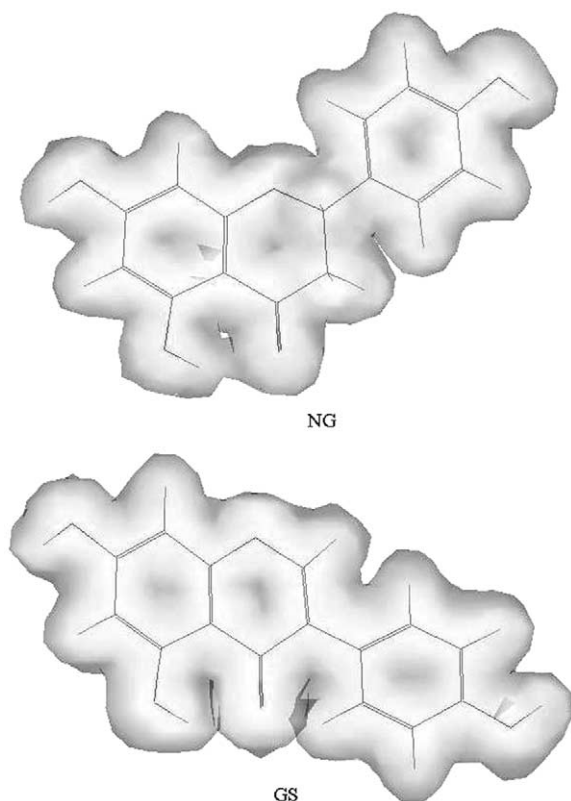


Fig. 4. Three-dimensional pictures of total charge density (ab initio result) of NG and GS molecules in their ground state with singlet symmetry.

calculation binding energy of NG is lower than that of GS; the difference between the binding energies of NG and GS is about 126 kcal/mol. On the other hand, the heat of formation of both systems are exothermic, NG has about 22 kcal/mol larger heat of formation with respect to GS. According to ab initio calculation, HOMO–LUMO gap of NG is larger than that of GS. This means that in any excitation process GS needs less (ca. 0.93 eV) energy than NG. The calculated dipole moment values of the systems considered are also given in Table 2. GS has relatively larger dipole moment than that of NG. One may conclude that GS is more polar than NG, therefore GS may interact with its environment especially other polar molecules in the cell stronger with respect to NG. On the other hand, NG is more apolar, leading to its possibly more accelerated interaction with lipids. Miranda et al. [10] have shown NG to be

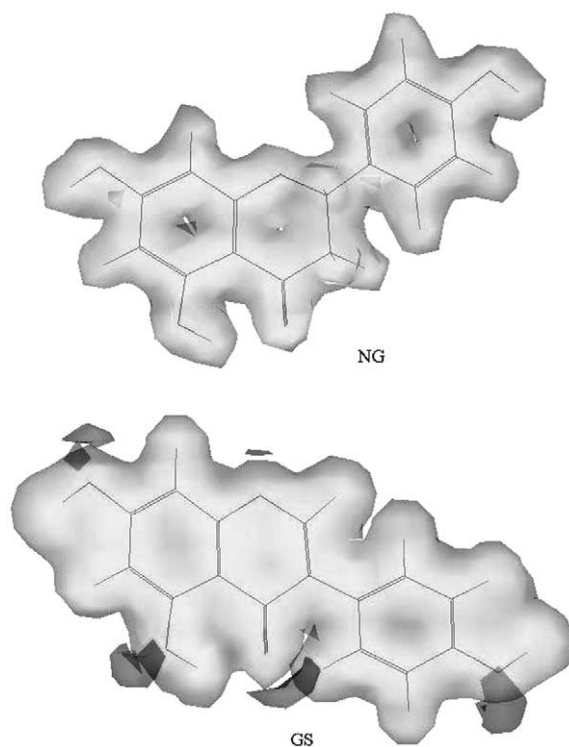


Fig. 5. Three-dimensional pictures of electrostatic potential (ab initio result) of NG and GS molecules in their ground state with singlet symmetry.

exert prooxidant effects on LDL oxidation experimentally.

Three-dimensional pictures of total charge densities and electrostatic potentials of NG and GS are shown in Figs. 4 and 5, respectively. These pictures also show that GS molecule looks like more linear and might have larger dipole moment, as the calculations reveal.

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