Theoretical Insight on Structural Activities and Targets of Kaempferol Glycosides

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Perspectiva teórica sobre las actividades estructurales y los objetivos de los glucósidos de kaempferol

Perspectiva teòrica sobre les activitats estructurals i els objectius dels glucòsids de Kaempferol

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ABSTRACT.

Metabolite profile always hold important place for flavonoids as they are the major promoters of secondary metabolism in human body. For decades numerous flavonoids are explored for their structural activities which in turn helped them to meet various health promoting applications such as radical scavenging activity. Apart from conventional flavonoids their derivatives are also tend to exhibit similar kind of structural activity. Therefore in the present work afzelin and juglanin – the glycosyl derivatives of kaemepferol an established flavonoid are subjected to structural activity relationship analysis using density functional theory. The structures of the two kaempferol glycosides are optimized and the optimized geometry is simulated to obtain frontier orbitals, electrostatic potential energy and molecular descriptors. The obtained results suggest that maximum amount of charge is accumulated over B-ring of two flavonoids, thus prefers to act as better electron donating region. Target predicted for two flavonoids over *homosapien* class reveal that the flavonoid highly prefers *lyase* and enzymatic targets for inhibition purpose.

Keywords: Kaempferol glycosides, structural activity, target prediction.

RESUMEN.

Los flavonoides siempre ocupan un lugar importante para el perfil de los metabolitos, ya que son los principales promotores del metabolismo secundario en el cuerpo humano. Durante décadas, se exploraron numerosos flavonoides por sus actividades estructurales que a su vez les ayudaron a cumplir con diversas aplicaciones promotoras de la salud, como la actividad de eliminación de radicales. Aparte de los flavonoides convencionales, sus derivados también tienden a exhibir un tipo similar de actividad estructural. Por lo tanto, en el presente trabajo, los derivados glicosílicos del kaemepferol, un flavonoide, la afzelina y la juglanina, se sometieron a un análisis de relación de actividad estructural utilizando la teoría funcional de la densidad. Se optimizaron las estructuras de los dos glucósidos de kaempferol y se simulo la geometría optimizada para obtener orbitales de frontera, energía potencial electrostática y descriptores moleculares. Los resultados obtenidos sugieren que la cantidad máxima de carga se acumula sobre el anillo B de dos flavonoides, por lo que prefiere actuar como una mejor región donante de electrones. La diana predicha sobre la clase *homosapien* para los dos flavonoides revela que prefieren a *lyasa* como diana enzimática con fines de inhibición.

Palabras clave: glucósidos de kaempferol, actividad estructural, predicción de objetivos.

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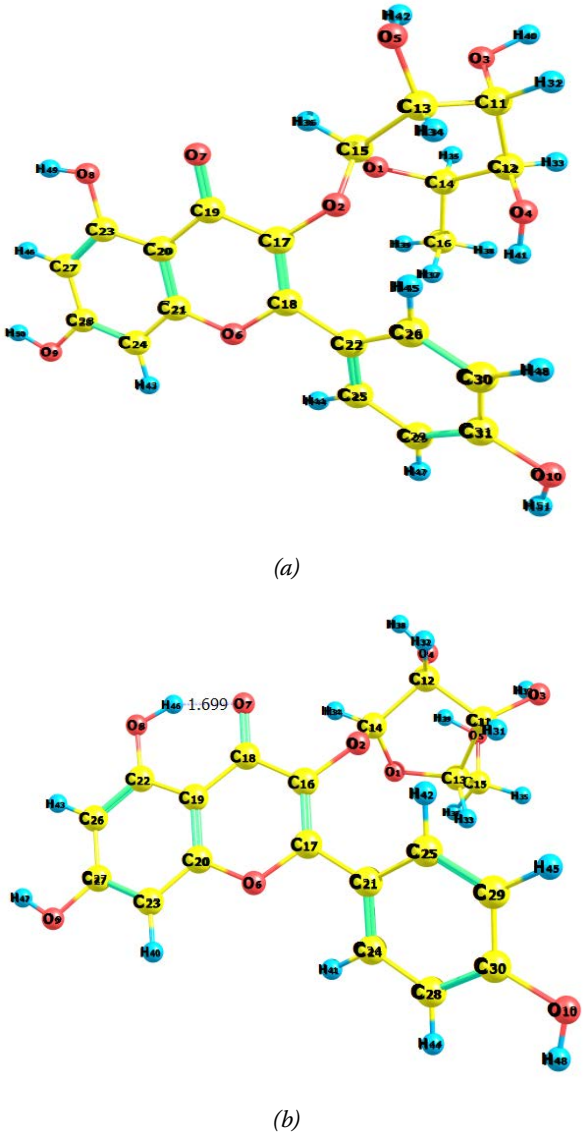
INTRODUCTION

Flavonoids are ubiquitous group of naturally occurring polyphenolic compounds derived from plants, vegetables and fruits considered as health promoting as well as disease preventing dietary supplements. Epidemiological, clinical and animal studies reveal that flavonoids act as protective shield against various disease conditions including cardiovascular disease and cancer that are revealed in epidemiological, clinical and animal studies [1]. They have dominant impact over parameters associated with atherosclerosis, including lipoprotein oxidation, blood platelet aggregation, and vascular reactivity which makes them to be the focus of much current nutritional and therapeutic interest. Of all, well known flavonoids kaempferol containing plants have superior antioxidant activity not only in vitro but also in vivo [2]. Kaempferol significantly decreases superoxide levels at low concentrations, making it to be a potential antioxidant, since the formation of superoxide anion is required for the production of reactive oxygen and nitrogen species involved in oxidative stress. Structural features that support their antioxidant property are the presence of a double bond at C2-C3 in conjugation with an oxo group at C4, and the presence of hydroxyl groups at C3, C5 and C4′ positions. At present scientific community is showing much interest over the derivatives of several high potent antioxidants, as they also mimic the same properties similar to their parent due to some important structural similarities with their parent. Best examples are glycosyl derivatives of flavonols and flavon-3-ols[3]. The present work portrays the theoretical investigation of structural activity of kaempferol afzelin derivatives and juglanin based on orbitals, electrostatic potential, molecular descriptors and identification of the potential targets using in-silico method.

COMPUTATIONAL DETAILS

In the present work, the geometries of afzelin and juglanin are optimized to their ground state using the hybrid density functional of a B3LYP parameter (Beckes-three parameter reformulated by Lee Yang and Parr) using the triple zeta valence basis set 6-311G(d,p) and polarization functions ++ are also been considered, due to high delocalization [4]. All the simulations were supported by the quantum chemical software Gaussian 09 and visualizations are aided by Gauss view 5.0 and chemcraft software. Initially the structures are been optimized to attain the ground state energy minimum through potential energy scan. The optimized structure of afzelin with energy -1564.8771034 Hartree is obtained from the simulation. Whereas optimized structure of juglanin possess a intra molecular hydrogen bond of length 1.699 A° and energy -1525.5879351 Hartree. Energetically afzelin seems to be of active than juglanin even though it lags intra molecular hydrogen bonding between. Target prediction for the respective compounds is supported by Swissadme.



(a)

(b)

Figure 1. *Optimized structure of (a) Afzelin and (b)Juglanin*

RESULT AND DISCUSSION

Frontier Molecular Orbital Analysis

Frontier orbitals provide an insight on organic reactions based on how orbitals interact to control the outcome of reactions [5]. Here they are been used to understand the characteristic nucleophilic and electrophilic components by visualizing the occupied and unoccupied molecular orbitals. From Figure 2.it is observed that molecular orbitals of both HOMO and LUMO are found to be spread all over both the molecules. C3-C6-C3´ skeleton possess bonding type of orbitals in both occupied and unoccupied energy levels. Similarly hydroxyl units possess anti-bonding orbitals. Herein considering molecular orbital energy levels both afzelin and juglanin possess same kind of occupancies, A and B ring in both molecules possess high charge density which is shown by increased number of positive and negative lobes there. Another important

observation is energy gap between HOMO and LUMO for afzelin and zuglanin. For afzelin energy difference of about 4.14 eV is observed and for zuglanin energy difference of about 4.06 eV is observed, since there is no any appreciable variation that is in line with previous observations. Hence both molecules exhibit same kind of antioxidant activity.

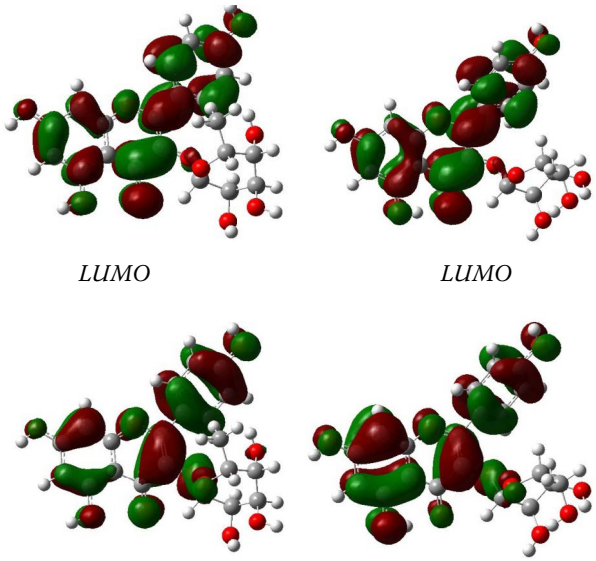


Figure 2.*Molecular orbital occupancies for (a)Afzelin and (b)Juglanin*

Molecular Electrostatic Potential(MEP) analysis

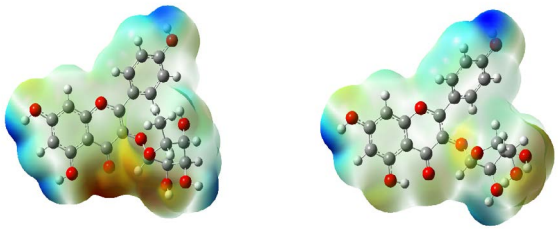


Figure 3.*Electrotatic potential diagrams of (a) Afzelin and (b) Juglanin*

MEP diagrams (Figure 3.) are helpful in understanding the charge distribution in a molecule. Here this analysis is been done to understand the electrostatic potential properties of the two studied molecules [6]. For afzelin highest electrostatic potential regions are been witnessed near hydroxyl units present in b and a ring hence they act as active electron donating sites. Similarly for the hydroxyl units of juglanin, the same observation is witnessed. Lower electrostatic potential regions are witnessed over the glycosyl region for both the molecules, indicating its electron acceptor property hence said to be highly delocalized. From the above observation, it can be concluded that the molecules act as electron donors since they possess more number of higher electrostatic potential regions.

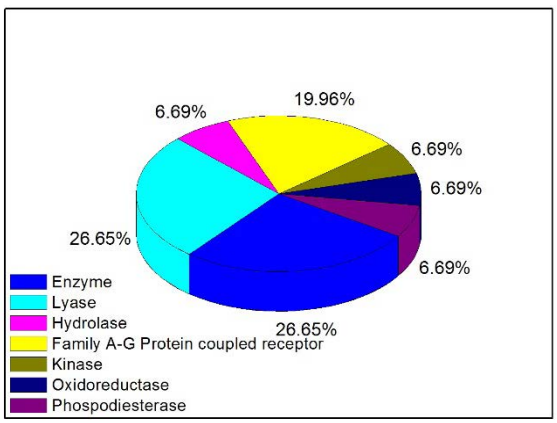
MOLECULAR DESCRIPTORS

Table 1.*Molecular descriptive parameters for afzelin and juglanin*

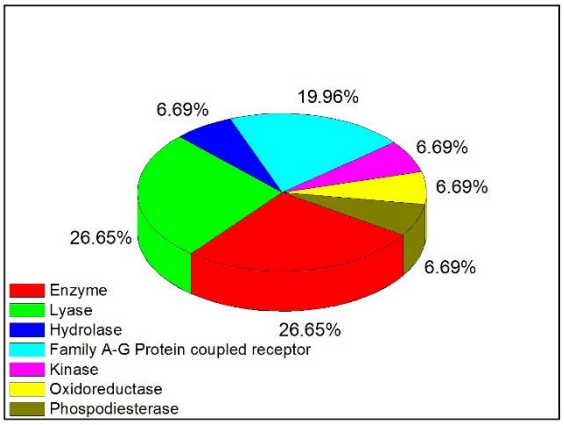
Molecular descriptors	E_o (eV) of Afzelin	E_o (eV) of Juglanin
IP (eV)	5.66	6.12
EA (eV)	1.51	2.05
ω (eV)	2.07	2.03
S (eV)	0.24	0.24
X (eV)	3.59	4.08
η (eV)	3.11	4.10

To characterize the antioxidant property of a flavonoid, it is vital to compute χ, IP, EA, η, S and ω [7]. Ionization potential(IP) portrays electron donating ability, likewise chemical hardness(η) is a measure of resistance to charge transfer, while the electronegativity (χ) is a measure of the tendency to attract electrons in a chemical bond and is defined as the negative of the chemical potential in DFT . The maximum electron flow between a donor and an acceptor is governed by the decomposition of binding energy between the atoms and it is determined by the factor electrophilicity index (ω). The above molecular descriptor values obtained from the total orbital energy method for the investigated compounds are displayed in Table 1. Ionization energy profile shows that electron removal is more facilitated by afzelin than juglanin with a difference of 0.54 eV in magnitude. Both the molecules display lesser hardness and increased smoothness which facilitate enhanced structural activity to change its electronic configuration. The electron attracting ability for afzelin is quite easier than juglanin which is represented by the electronegativity values. The calculated molecular properties clearly confirm that afzelin and juglanin prefer to act as electron donor rather than electron acceptors. This is also an indicator of their antioxidant capability.

Target prediction analysis



(a)



(b)

Figure 4. *Target prediction chart for (a) Afzelin and (b) Juglanin*

Screening of targets for the lead compounds is considered to be an essential step in in-silico analysis, as it helps for easier identification for the potential target for inhibitory action [8]. Out of 500 hundred studied targets both afzelin and juglanin prefers lyase as well as enzymatic targets (Figure 4.) under homosapien class in higher percentages. Since inhibiting lyase and enzyme based target regulates imbalance in metabolisim thereby facilitates good health and improves secondary metabolism in human body.

CONCLUSION

In the present work structural activity identification of kaempefrol glycosides afzelin and juglanin through theoretical mode with the help of density functional theory is been carried out. Molecular geometry (bond length, bond angle, dihedral angle and minimum ground state energy conformer) are achieved with the hybrid density functional of a B3LYP parameter and triple zeta valence basis set 6-311G(d,p) adopted in the present investigation. The following results are arrived from observations made in result and discussion section.

Frontier molecular orbital analysis supports the well-known fact about reactivity of B-ring which here is characterized by bonding type of orbitals in highest occupied state for both the molecules. The energy gap is in the order of 4 eV for the two flavonoids resulting that both exhibit same kind of reactivity towards invading free radicals. Molecular electrostatic potential analysis depicts the presence if highest electrostatic potential regions over hydroxyl units in both the compounds. Henceforth these –OH units readily scavenges the free radicals through H-atom transfer mechanism.

Molecular descriptive parameter gives a deep insight regarding structural activity where both the compounds acts as electron donors rather than electron acceptors. Electron donation is the major concerned property of flavonoids, so in that way the flavonoids under study are potential antioxidants nominated for radical scavenging process.[9]

Target prediction analysis sheds light over lyase and enzymatic targets for azelin and juglanin thereby depicting their inhibitory action over pathogens through non-covalent interaction or electron donation.

Based on the above observations it is validated that both afzelin and juglanin exhibit better structural activity and are also suitable for inhibition of the targets.

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