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Research paper

Modelling of Flavanoid Derivatives from *Leucaena leucocephala* as Anti-UV

Pemodelan Turunan Flavanoid dari *Leucaena leucocephala* sebagai Anti-UV

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ABSTRACT

Excessive exposure to UV light can have negative effects on humans, including the risk of cancer. To address this, the search for anti-UV materials is ongoing. One potential source is the extract from Leucaena leucocephala leaves. In this study, eight flavone-derived compounds from the leaf extract were modeled using a semi-empirical approach with the PM3 method, and their electronic transitions were calculated using ZINDO/S. The geometry optimization results indicated that while the bond lengths between carbon atoms in flavonoid derivatives did not change significantly with different functional groups, there was a notable difference in the dihedral angle due to repulsion between functional groups. Electronic transition calculations showed that all flavonoid derivatives 1-8 are active in the UV A, UV B, and UV C regions, suggesting their potential as anti-UV agents. Furthermore, the energy levels of the HOMO-LUMO compounds were calculated, revealing that flavonoid 1 has the smallest Eg while flavonoid 8 has the largest Eg. Overall, the position of functional groups in flavone derivatives does not significantly change the bond length but does affect the dihedral angle between the rings. These findings highlight the potential of flavone-derived compounds from Leucaena leucocephala as promising candidates for further development as anti-UV agents based on their maximum wavelength in UV spectra.
Keyword: Flavonoid, semi-empiric, ZINDO/S, anti-UV

INTRODUCTION

UV radiation is a form of non-ionizing radiation that is emitted by the sun and artificial sources, such as tanning beds. Based on their wavelengths, UV radiation is divided into three main categories: ultraviolet A (UV-A) in range 320-400 nm, ultraviolet B (UV-B) in range 280-320 nm, and ultraviolet C (UV-C) in range 100-280 nm (Manikrao Donglikar & Laxman Deore, 2016). Though some UV-B radiation does reach the earth, the majority of UV energy that does is UV-A. Health concerns from UV-A and UV-B sunlight include skin cancer, aging skin, and snow blindness. The interaction of ultraviolet radiation (UVR) with human skin is important in a few fields, including medicine (Hamouda et al., 2022), the food-cosmetic industry (Nitulescu et al., 2023; Vasuja & Kumar, 2018), biology (Rastogi et al., 2014) , physics (Kobkam & Dangudom, 2023), research, and forensics (Kearse, 2020). However, both natural and artificial sources can expose people to ultraviolet radiation (UVR). Depending on the safety precautions that have been followed for protection, the known effects of (UVR) on man can be either harmful or beneficial. The skin and eyes may be the main targets of negative effects. Cataracts are a result of excessive UV exposure to the eyes (Mahendra & Andari, 2022). If the sunburn is severe enough, it can cause blisters and the surface of the skin to be damaged (Stump et al., 2023).

According to a substantial body of scientific research, photoprotectors, especially sunscreens, are essential for lowering the incidence of skin illnesses brought on by UV radiation (Fivenson et al., 2021). Sunscreens are cosmetic products that shield skin from deterioration caused by ultraviolet radiation from the sun. Topical sunscreen that either absorbs or reflects radiation to shield skin from its harmful effects is unable to fully protect organs like the eyes and lips from the sun's rays. While there are also marketable oral sunscreen solutions or ingredients that can be consumed to prevent skin harm (Manikrao Donglikar & Laxman Deore, 2016). Since they were first made available for purchase about a century ago, sunscreens have become widely recognized as a crucial part of sun protection plans (Guan et al., 2021). Because of their ability to absorb, reflect, and deflect sun rays, they are effective at preventing and reducing the harmful effects of UV light. In terms of their active components as well as their cosmetic formulation, sunscreens have seen gradual advancements over time (Geoffrey et al., 2019; Ngoc et al., 2019).

The organic active ingredients in sunscreens can derived from benzophenone, aminobenzoate, and cinnamic acid, which are chromophores and auxochromes that can absorb specific wavelengths in the UV range (Gunia-Krzyżak et al., 2018; Kim & Choi, 2014). Organic sunscreen (also known as herbal sunblock, suntan lotion) is a lotion, spray or topical product containing herbal ingredients which helps to protect from the UV radiations of the sun and hence lowering the risk of skin cancer (Tahir et al., 2021).

Most organic sunscreens are made of organic compounds connected by a carbonyl group, such as in flavonoid structure. Flavonoids are a class of plant secondary metabolites that are known for their diverse biological activities. They consist of a 15-carbon skeleton that is arranged in three rings (A, B, and C) with a heterocyclic ring (B ring) fused to a benzene ring (A ring) and another heterocyclic ring (B ring) attached to the C ring (Singh et al., 2014). Flavone, one of type flavonoid, have potency to absorb UV light because the presence of conjugated double bonds in their structure. The conjugated double bonds allow an organic compound to absorb light in the UV-visible range (Lin et al., 2021). The absorption of UV light by organic compounds influenced many factors such as the number and position of hydroxyl groups and the presence of other functional groups in the molecule (Anderson et al., 1975).

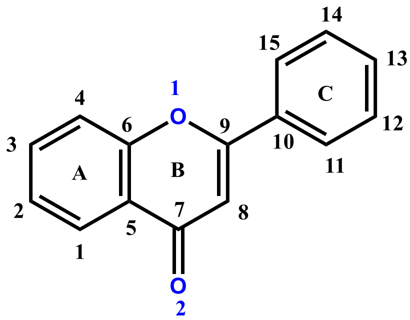

Figure 1. Structure of flavon

Sun protection properties can be found in many organic materials. Extracts of the leaves of *Leucaena leucocephala* is one of them. Extracts of *L. leucocephala* leaves have a wide range of biological effects, including those that are antimicrobial, anticancer, cancer preventive, diuretic, anti-inflammatory, antioxidant, antitumor, antihistaminic, nematicide, pesticide, antiandrogenic, hypocholesterolemic, and hepatoprotective (Elbanoby et al., 2022; Umaru et al., 2018; Zarina et al., 2017; Zayed & Samling, 2016). *L. leucocephala* extract can be employed as an active ingredient in sunscreen cream compositions, according to Anggraini et al.'s research (Zyuri Anggraini et al., 2019). The maximum sunscreen activity of the extract is SPF 20.53% in the ultra category, 0.6667% in the total block category, and 5.1167% in the total block category at 0.5% extract concentration. The maximum sunscreen activity of the lamtoro seed extract cream is SPF 7.0908% in the extra category, 14.163% in the fast-tanning category, and 26.6608% in the total block category at 7% concentration. Based on that reason, the investigation of each derivative of flavonoid contains in *L.Leucana* is investigated to determine the potency of each compound as a sunscreen protection.

METHODS

The computational study was conducted using a laptop with an Intel Core™ i5-7200 processor, CPU @2.5 GHz, 8Gb RAM, and 2 Gb NVidia Geforce 930 MX GPU. The software used included Avogadro to describe the molecule and generate input to Orca with the .inp extension, Orca 4.2.1. to perform compound structure optimization calculations and electron excitation calculations, and IboView used to represent HOMO-LUMO orbitals.

Modeling of molecular geometry optimization and energy calculations used the PM3 semi-empirical method. The geometry optimization process is carried out to obtain a stable molecular geometry. Then the geometry that has been optimized is then calculated the electronic transition using semi-empirical ZINDO/S method. This method is used to determine the electron transition data and molecular orbital energy modeling of the compound. Modeling of molecular orbitals is used to determine the HOMO-LUMO level. The

list of functional groups in falvonoid derivatives used in this investigation was obtained from Xu's research (Xu et al., 2018), which is provided in **Table 1**.

Table 1. Functional group in flavonoid derivatives

Comp	C1	C2	C3	C4	C8	C11	C12	C13	C14	C15
1	OH	H	OH	H	H	H	H	OH	OH	H
2	OH	H	OH	H	OH	H	H	OH	OH	H
3	H	H	OH	H	H	H	H	OMe	OH	H
4	OH	H	OH	H	H	H	H	OH	H	H
5	OH	H	OH	H	H	H	H	OMe	OH	H
6	OH	H	OH	H	OH	H	H	OH	H	H
7	H	H	OH	H	H	H	H	OH	OH	H
8	OH	H	OH	H	OH	H	OH	OH	OH	H

RESULTS AND DISCUSSION

Geometry Optimization of flavonoid derivatives from L.leucocephala

L. leucocephala leaf extract has various bioactive ingredients such as flavonoids, alkaloids, and phenolics (Haggag et al., 2011). However, in this study, flavanoids are the main focus in identifying its electronic properties. This is related to its potential as an anti-UV agent because it has carbonyl functional groups, benzene rings, and several auxochrome groups around it that can affect its properties related to UV light absorption.

Optimization of the molecular geometry of falvonoids was performed using the semi-empirical ZINDO/s method. The purpose of geometry optimization is to obtain stable molecules that are close to the actual state in nature.

Geometrical optimization preceding Density Functional Theory (DFT) calculations is imperative as it allows atoms to relax into a stable configuration, ensuring accurate electronic structure calculations. This step guarantees that initial atomic positions are close to the true equilibrium positions, enhancing the reliability of predicted properties such as energies, geometries, and electronic properties.

Figure 1 shows the basic structure of flavonoids which consists of a benzene and six member ring (heteroatom) with carbonyl groups and oxygen atoms in the six-member ring. Table 1 shows the differences in functional groups found in 8 flavonoid-derivative compounds. The difference in functional groups lies in the combination of methoxy ($-OCH_3$), hydroxy (-OH), and hydrogen atoms (-H). The results of optimization through semiempirical method of PM3 show that the bond between carbon atoms (C) in the flavonoid ring system is not so affected by the presence of different functional groups bound. The length slightly differences between C9-C10. In flavanols that have an -OH group at the C8 atom (compounds **2**, **6**, and **8**), have shorter bonds than falvonoids without hydroxy groups at C8 (compounds **1**, **3**, **4**, **5**, and **7**). However, significant difference occurs in the dihedral angle between flavon with -OH group in C8 and without -OH group. Flavonoids **2**,**6** and **8** have dihedral angles of 90^{o} between their rings, while compounds **1,3,4,5**, and **7** only 30^{o}. This is possible because the presence of the -OH group at the C8 atom causes the repulsion of the electron cloud to be stronger so that the benzene ring undergoes a rotation from 30º to 90º to minimize the repulsion of the electron cloud. The complete geometry parameter optimization results is available in table 2.

Table 2. Three dimensional optimized geometry of flavon from *L.leucocephala* leaves extracted

Optimized Geometry	Atom	Compound							
		1	2	3	4	5	6	7	8
Bond Length (Å)	C_1-C_2	1.396	1.395	1.395	1.396	1.396	1.395	1.396	1.396
	C_1-C_5	1.398	1.395	1.395	1.397	1.397	1.397	1.397	1.397
	C_5-C_7	1.471	1.471	1.471	1.471	1.471	1.471	1.471	1.471
	C_7-O_2	1.223	1.224	1.223	1.223	1.223	1.224	1.223	1.224
	C_9-C_{10}	1.477	1.474	1.477	1.477	1.477	1.474	1.477	1.474
Dihdral angle (º)	$C_{8,9}$–$C_{10,11}$	30	90	30	30	30	90	30	90

Electronic transition and UV spectra of flavonoid dervatives

Electron transition modeling is performed using the ZINDO/S semi-empirical method with the analyzed parameters being molecular orbital (MO) level, HOMO-LUMO energy, maximum wavelength and intensity. Based on the wavelength data, the potential of a compound as an anti-UV (suncreen) material can be determined. Each flavonoid compound derivative has 3 peaks in the wavelength range between 250-350 nm in the UV region. The UV spectra of the modeling results are presented in Figure 2 and the wavelength data is available in Table 3.

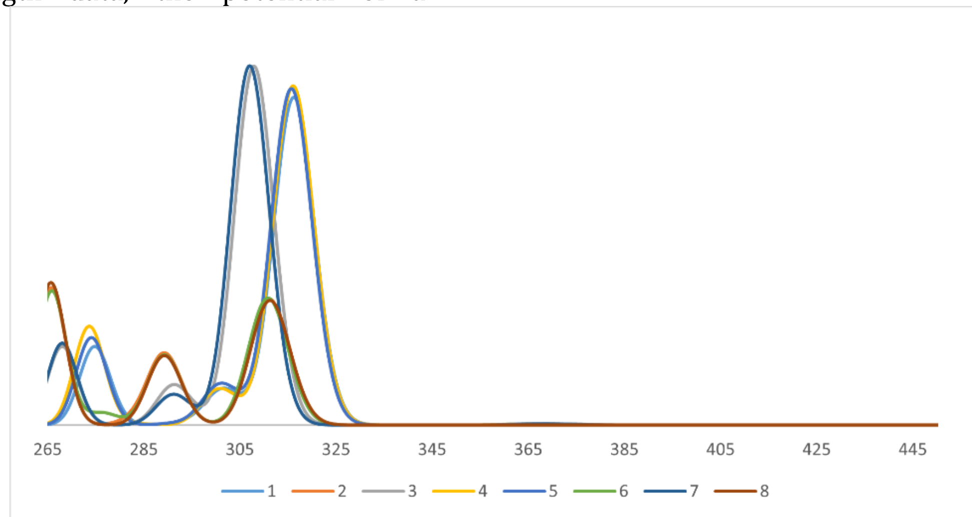

Figure 2. UV Spectra of flavon derivatives

Table 3. Maximum peak and electronic transition type

Compound	λ_{peak} (nm)
1	275, 301, 316
2	268, 290, 311
3	268, 292, 308
4	274, 300, 316
5	274, 301, 316
6	266, 290, 311
7	269, 292, 307
8	266, 289, 311

Based on its wavelength, UV light is divided into 3 categories, namely UV A (315-400 nm), UV B (280-325 nm), and UV C (100-280 nm). Based on the UV spectra data from electron transition modeling, each flavonoid has 3 peaks and the three peaks are respectively in the UV A, UV B, and UV C regions. So it can be said that flavonoids from L. leucocephala are active as anti-UV A, anti-UV B, and anti-UV C. Further analysis can be done by determining the type of transition that occurs in flavonoids. The transitions that occur in each flavonoid are n to π* and π to π* type transitions. The n to π* electron transition occurs due to the chromophore contained in the aromatic ring. The π to π* electron transition indicates the presence of auxochrome on the aromatic ring.

One of the parameters calculated in this study is the molecular orbital level associated with HOMO and LUMO. Higest Occupied Molecular Orbital (HOMO) is the highest level of molecular orbital that contains electrons, while

Lowest Unoccupied Molecular Orbital (LUMO) is the lowest energy level that is not filled by electrons. The energy difference between HOMO and LUMO is known as the energy gap (E_g), which is the minimum energy required by electrons to undergo excitation. E_g in each compound can vary and can be measured in the form of its wavelength. In this calculation, it is found that the lowest E_g is owned by flavon **1** and the largest E_g is owned by flavon **8**. Complete data on the level of HOMO, LUMO and Eg can be seen in Table 4.

Based on these data, the -OH group at position C8 affects the HOMO value of the compound. hydroxy groups as electron donor groups cause electron density to increase. This results in an increase in the level value of HOMO. In this study, it can be seen in the calculation results that compounds **3, 6**, and **8** the HOMO value of these compounds has a higher value than the others.

Table 4. Energy Level of Molecular Orbital flavon derivative

Compound	HOMO	LUMO	E_g
1	-8.75	-1.20	7.54
2	-9.04	-1.12	7.92
3	-8.64	-1.06	7.59
4	-8.73	-1.16	7.57
5	-8.73	-1.17	7.56
6	-9.03	-1.10	7.93
7	-8.69	-1.08	7.61
8	-9.06	-1.14	7.91

CONCLUSSION

Modeling of flavonoid-derived compounds from L. leucocephala leaves using the PM3 semi-empirical method aimed to determine the most stable compound and achieve a geometric structure resembling its natural state. The study revealed that while the C-C bond length remained relatively stable across different groups, the dihedral angle was significantly influenced by the presence of functional groups, particularly -OH groups near the inter-ring bridge (C8), which caused a large dihedral angle due to electron cloud repulsion. Electronic transition calculations using the ZINDO/s semiempirical method showed that all test compounds exhibited absorption peaks in UV A, UV B, and UV C types, indicating their potential as anti-UV agents with λ_{max} around 265 nm-325 nm. Analysis of the HOMO-LUMO levels indicated no significant difference between the test compounds, with flavonoid 1 having the smallest Eg value and flavonoid 8 having the largest Eg value. The value of HOMO-LUMO is influenced by the presence of electron-driving groups in the structure. Based on calculations, compounds 3, 6, and 8 (-9.04 eV, -9.03 eV, and -9.06 eV) have high HOMO values compared to the others due to the presence of hydroxy groups in the compound structure. Based on that, flavonoid derivatives in *L. Leucocephala* has potential for anti-UV.

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