Turkish Computational and Theoretical Chemistry

Turkish Comp Theo Chem (TC&TC)

Volume(Issue): 6(2) – Year: 2022 – Pages: 18-21

e-ISSN: 2602-3237

https://doi.org/10.33435/tcandtc.1055649

Received: 02.08.2021 **Accepted:** 21.03.2022 *Research Article*

A theoretical study of oleuropein derivatives as drugs

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Abstract: *Oleuropein is a natural product revealing a large variety of biological activity. The natural products are functionalized to increase the activity in the pharmaceutical industry. Theoretical calculations were carried out for oleuropein derivatives to display the target compound exhibiting the most biological effects. Hence, synthetic chemists are able to get inspired to synthesize the most active oleuropein derivatives. The chemical properties of oleuropein derivatives have been investigated theoretically. Gaussian method was used for quantum calculations of these compounds. The properties of compounds were presented and the utilization of these compounds in pharmaceutical industries was investigated. The quantum calculations revealed that 2H-oleuropein (3) and 4-aminobutyl-2-oleuropein (2) were unstable and were prone to react to the radical compounds.*

Keywords: *Oleuropein, 2H-oleuropein, 4-aminobutyl-2-oleuropein, Gaussian*

1. Introduction

Natural products, especially plant derived-compounds play a prominent role in drug invention and progressing stage due to the revealing a broad spectrum of biological effects [1-8] .The olive tree, which belongs to the Oleaceae family, is also known as Olea europaea. The habitat of this plant is usually warm regions of the world. The products obtained from olive and its leaves have been used in traditional medicine since ancient times. Recently, these mentioned products are recognized as an important supplement to a healthy diet. It has been determined that phenolic and fatty acid components in olive fruit and oil have very beneficial effects in terms of health. Epidemiological researches reveal that olive oil consumption protects the human being against various diseases and notably decreases the risk of cancer. In addition, It has been understood that high olive oil consumption significantly reduces the risk of breast and digestive system cancer growth.[9].

A review report including 25 epidemiological studies presented that high intake of olive oil decreased the breast cancer risk and reduced the upper aero-digestive tracts cancers.[10] A recent study found that adherence to the Mediterranean diet in relation to high olive oil consumption was associated with a reduced risk of cancer. Moreover, olive oil consumption caused the decrease risk of respiratory system, pancreatic, head, neck, liver, gastric, colorectal, breast, and prostate cancer.[11] The main phenolic compounds of olive oil are; phenolic acid and its derivatives, phenolic alcohols, lignans, secoiridoids and flavonoids. [12] Oleuropein is found in high levels in olives and leaves as an effective active product. The structure of oleuropein consists of an oleosidic skeleton and a carbohydrate group. Phytochemical studies have revealed that Oleuropein has antioxidant, anticancer, anti-inflammatory, cardioprotective and hepatoprotective effects.[13-15]

Due to the revealing a large number of biological effects of oleuropein, functionalisations of oleuropein to increase the activity attract the great interest in synthetic chemistry. Hence, oleuropein derivatives were carried out hypothetically. Theoretical calculations were executed on these derivatives to present the most active compound. As a consequence, synthetic chemists could find a framework to synthesize the bioactive derivatives of oleuropein.

2. Computational Method

The chemical properties of oleuropein (1), 4-aminobutyl-2-oleuropein (2), 2H-oleuropein (3) 4-

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aminobutylimino-oleuropein (4), 2-hydroxy-oleuropein (5) were determined as theoretical. The molecules were drawn by ChemDraw Ultra 11.0. Theoretical calculation was executed by Gaussian functions bases in Gaussian 09W [21] programme.

3. Results and discussion

The calculation of oleuropein derivatives on Gaussian 09 with RHF/STO-3G presented that compound 3 has the most energy with the highest HOMO-LUMA differences among the derivatives. Hence, the reaction can proceed from compound 1 to compound 3 spontaneously. The energy values of compounds were 3 > 2 > 1 > 4 > 5 order. High E_{HOMO} value presents the electron releasing ability of a compound. Oleuropein(1) had the most E_{HOMO} value (-0.22977). Hence, this natural product (1) had a potency to exhibit the most antioxidant activities than that of the derivatives of oleuropein. An effective antioxidant compound is able to release the electron of hydrogen to the radical compound easily.

The electron releasing capability of the molecule is expressed by chemical parameter as E_{HOMO}. If a molecule has the high HOMO value it is interpreted as the donation of electron to an appropriate acceptor the molecule of low empty molecular orbital energy.[16]

The amount of energy required to remove an electron from a molecule is determined as the ionization potential (I).[17] It is related to the energy of the E_{HOMO} through Eq. (1): $I = -E_{HOMO}$

If a molecule has the large HOMO–LUMO the stability of it good and a high chemical hardness.[18] On the other hand ıf a small has frontier orbital gap it will be more polarizable and showed a high chemical reactivity, As known Koopman's theorem: $\eta = \varepsilon LUMO - \varepsilon HOMO$ can be determined Global hardness (η). In the reaction scheme (Figure 1), compound 5 had the lowest HOMO–LUMO gap. Hence this compound has a tendency to react the other compounds i.e. radicals and has an ability to chelate the metal. This compound (5) can be synthesis by hydrolysis of oleuropein (1). The compound 2 and compound 3 are alike but only difference is lack of double bond between C-2 and C-3 in compound 3. The lack of double bond provides the compound flexibility. Butyl amine group gains the flexibility around C-2 carbon. Hence, NH2 group can bind to DNA easily. The possible reaction pathway of oleuropein is given in Figure 1.

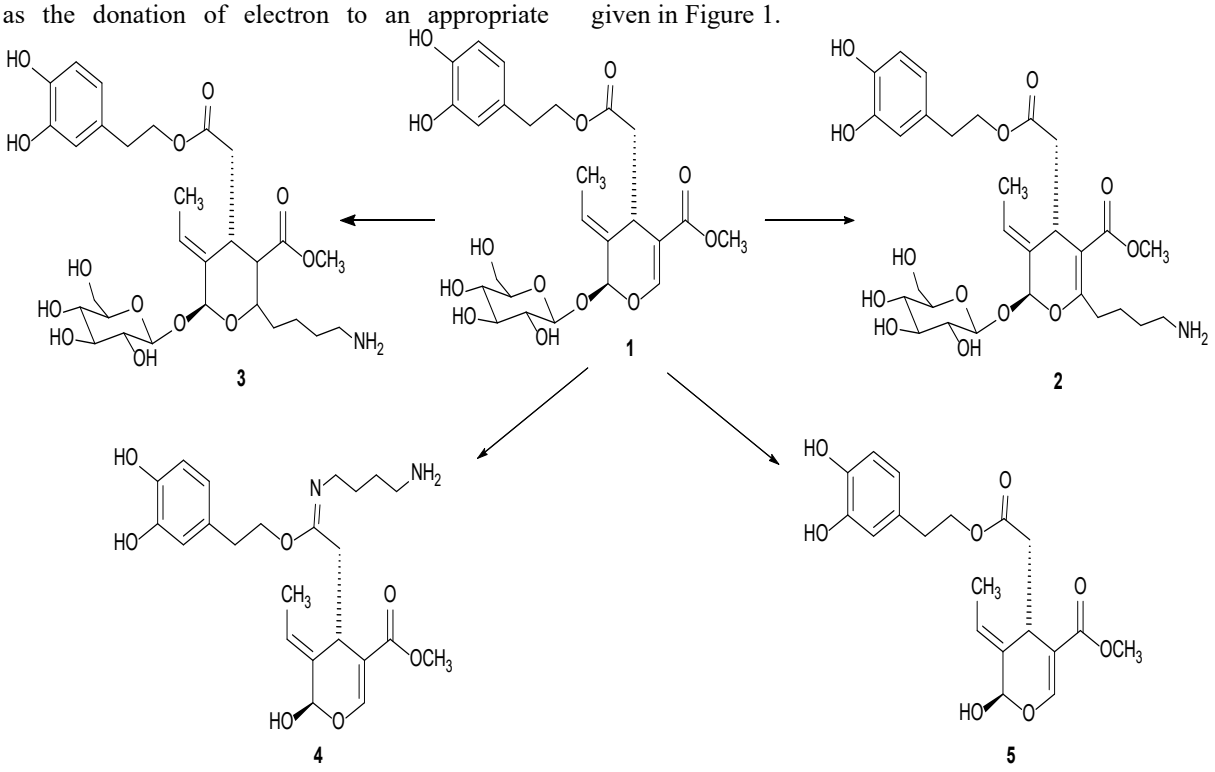

Figure 1. Theoretical calculation was executed for the oleuropein derivatives

The theoretical values of oleuropein derivatives by using RHF/STO-3G is given in Table 1. The theoretical values of oleuropein derivatives by using b3lyp/6-311+g(d,p) is given in Table 2. The theoretical values of oleuropein derivatives by using hf/6-311+g(d,p) is given in Table 3.

Table 1. HF, HOMO, LUMO, Δ (HOMO-LUMO) and Dipol Moment values of oleuropein derivatives using RHF/STO-3G

Compounds	**E (Hartree)**	**HOMO (eV)**	**LUMO (eV)**	**GAP (eV)**	**Dipole moment (Debye)**
1	-1913.6360022	-0.22977	0.24389	0.47366	2.0753
2	-2122.1555563	-0.22878	0.25390	0.48268	1.7976
3	-2123.4710485	-0.22499	0.26236	0.48735	1.2808
4	-1503.2406461	-0.22289	0.24924	0.47213	2.8613
5	-1314.1903003	-0.22608	0.23942	0.46550	3.8781

Table 2. HF, HOMO, LUMO, Δ (HOMO-LUMO) and Dipole Moment values of oleuropein derivatives using b3lyp/6-311+g(d,p)

Compounds	**E (Hartree)**	**HOMO (eV)**	**LUMO (eV)**	**GAP (eV)**	**Dipole moment (Debye)**
1	-1949.794419	-0.02104	-0.00422	0.01682	2.9825
2	-2162.253986	-0.02096	-0.00439	0.01657	2.5835
3	-2163.594328	-0.02061	-0.00454	0.01607	1.8407
4	-1531.599431	-0.01743	-0.00384	0.01359	4.5150
5	-1339.022108	-0.02390	-0.00460	0.01930	5.0273

Table 3. HF, HOMO, LUMO, Δ (HOMO-LUMO) and Dipole Moment values of oleuropein derivatives using b3lyp/6-311+g(d,p)

Compounds	**E (Hartree)**	**HOMO (eV)**	**LUMO (eV)**	**GAP (eV)**	**Dipole moment (Debye)**
1	-1938.513270	-0.36081	0.04847	0.40928	3.0602
2	-2149.486521	-0.35925	0.05046	0.41140	2.6507
3	-2150.818856	-0.35330	0.05215	0.40545	1.8887
4	-1522.290625	-0.35076	0.05242	0.40318	4.4490
5	-1331.115586	-0.36412	0.04499	0.40911	5.4069

Table 4. HF, HOMO, LUMO, Δ (HOMO-LUMO) and Dipole Moment values of oleuropein derivatives using m062x/6-311+g(d,p)

Compounds	**E (Hartree)**	**HOMO (eV)**	**LUMO (eV)**	**GAP (eV)**	**Dipole moment (Debye)**
1	1948.0814704	-0.31295	-0.01231	0.3064	3.2150
2	2160.354356	-0.31160	-0.01282	0.29878	2.7848
3	2161.693527	-0.30643	-0.01325	0.29318	1.9842
4	-1530.971846	-0.30042	-0.01140	0.28902	5.0899
5	-1338.492022	-0.31115	-0.01316	0.29799	5.1166

The olive phenolic structures and their activities were related the formation of the sable derivatives [19,20]. When we look at the calculation base sets (Rhf/Sto-3g, HF, B3lyp, and m062x) at different levels in Tables 1,2,3, and 4; The most stable structure is compound 3 from the derivatives of oleuropein and it has also high energy. The reaction direction is possible to compound 3 from oleuropein.

Dipol moment order of oleuropein derivatives compounds from high to low as;

5 > 4 > 1 > 2 > 3

Compound 5 had high chemical activity as mentioned above ıt had also the highest dipole moment. The polarity of it is more than the other oleuropein derivatives.

4. Conclusions

Oleuropein(1) had the most EHOMO value (-0.22977). Hence, this natural product (1) had a potency to exhibit the most antioxidant activities than that of the derivatives of oleuropein. The reaction pathway from oleuropein to compound 3 due to having high the energy and the broad gap. Compound 5 from derivatives of oleuropein had high chemical activity because of having the low HOMO-LUMO gap and the high polarity.

Acknowledgements

The authors report no conflict of interests in this work. Thanks for the contribution of Kırıkkale University to be used Gaussian program (BAP-2016/016).

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