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An update on docking analysis of some pharmacological activity in Japanese knotweed leaf compounds

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Abstract: The proof of concept presents the results of molecular docking analysis of Japanese knotweed leaf compounds interacting with the four different proteases 4GQQ, 2B17, 2FW3 and 1ZB6 from the Protein Data Bank. Several of these compounds exhibit binding energies for the various proteases and according to our data, compare favorably to known antibacterial, anti-inflammatory, antidiabetic and antioxidant drugs. The advancement of improved docking techniques has also made it possible to more accurately predict the biological activity of substances. This paper provides compounds of Japanese knotweed leaf to determine the result of gas chromatography-mass spectrometry for calculation of binding energy in comparison to standard drugs. The lowest value of binding energy for good biological activity. The compound Undecane had a higher negative binding energy than cyclohexanecarboxylic acid 2-hydroxyethyl ester. As we can see from the docking results, by comparing the values of the binding energies of the four proteins from the Protein Data Bank (4GQQ, 2B17, 2FW3 and 1ZB6), we propose that the Undecane compound is better antibacterial, anti-inflammatory, antidiabetic and antioxidant nature then cyclohexanecarboxylic acid 2-hydroxyethyl ester compound. The density function theory (DFT) results of the energy difference between the highest molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (ΔE = -0.44 eV) showed that the compounds were more reactively.

Keywords: Japanese knotweed, DFT, 4GQQ, 2B17, 2FW3, HOMO and LUMO

1. Introduction

Plants are considered dietary supplements and have long been important to human life due to their nutritional and health benefits. Despite the expansion of the pharmaceutical industry, complementary therapies are still widely used. Additionally, people are now more aware of the benefits of consuming foods that support balance and can improve and promote health. This is because of the impact that food can have on human health [1]. Analysis of the properties and chemical composition of a *Japanese knotweed* leaf show as Figure.1 [2]. One of the main categories of molecules thought to be bioactive substances includes the compounds found in roots, stems, leaves and flowers such as flavanoids, stilbenes, anthraquinones, coumarins and lignans. It is important to remember that environmental factors such as climate and harvest time have a major impact on plant chemistry [3]. *Fallopia japonica* has been used in traditional medicine around the world for many years. Numerous investigations have focused on it as its chemical compositions promise therapeutic properties [4]. Alcoholic, hydroalcoholic and aqueous extracts from plant roots, rhizomes and other parts such as leaves, stems and flowers have antibacterial activity, antioxidant effects, anticancer, anti proliferative apoptotic properties, anti-inflammatory properties, antiviral activity and many other bioactive properties [5]. The unique therapeutic properties of *Fallopia japonica* are primarily attributed to the abundant sources of physiologically active compounds found within [6]. The study of herbal

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antimicrobials has attracted researchers interested in how different plants and their morphological extracts relate to therapeutic effects and how they might be used as natural preservatives or additives for specific medicinal purposes [7]. According to this theory, the significant antibacterial abilities of *Polygonum cuspidatum* are mainly due to its bioactive components, particularly stilbenes and anthraquinones [8]. The most popular methods for assessing antimicrobial activity are disk diffusion, well diffusion, broth or agar dilution, minimal inhibitory concentration, and minimal bactericidal value. The main components of *Fallopia japonica*, known as polyphenols, have beneficial therapeutic effects related to their antioxidant capacity and may be linked to the modulation of a number of receptors and metabolic processes. They can trigger oxidative reactions in the body that can lead to a variety of diseases, especially cancer, as they act as free radical inhibitors [9]. Numerous approaches adapted to different matrices are used to analyze antioxidant activity [10].

Figure 1. *Japanese knotweed* leaf

2. Computational Method

2.1 Preparation of leaf extract

100 g of fresh leaves of *Japanese knotweed* leaves were collected. They were cleaned with running tap water to remove particles of various infected natural ingredients and then dried in the sun for three to four days. The dried 5g leaves are then ground into a high quality powder form using a pestle and mortar. The leaves were crushed and placed in a beaker containing 50 ml of ethanol, where they were left at room temperature for 24 hours. After filtering the extract using Whatman #1 filter paper, it was packaged and shipped for characterization.

2.2. GC-MS-analysis

An Elite 5 fused silica column was used for the GC-MS assessment on a Varian CP 3800. The oven was configure red to go from 60 °C at a rate of 300 °C/min to 240 °C with a hold time of 2 min, then go from there at a ramp rate of 10 °C to 310 °C with a final preservation time of 1 min. Hydrogen was utilized as the input gas at a rate of 1 ml/min on normal sliding, and the injector and detector were both set to a temperature of 30 °C with a cut ratio of 100. Dichloromethane was used to arrange the samples, and in the phase following the GC procedure, a 0.04 L sample was manually injected into a split and splitless injector GC/MS utilising a PerkinElmer Clarus 680 GC linked to an 8 C-square mass spectrometer.

2.3 Molecular docking studies

Using Argus Lab 4.0, molecular docking is performed to determine the specific binding position of ligands on proteins. After downloading the protein in PDB format from http://www.rcsb.org/pdb, the structure of two chemicals extracted from *Japanese knotweed* was sketched using chemdraw extremely 7.0 and saved as a.mol file. The proteins were added and converted into binding sites in Argus lab 4.0 by choosing the Making binding site for this protein option. The Dock a ligand option was then utilized to compute the ligand and the shape-based search technique was employed to carry it out. 4.5 of Discovery Studio allowed viewers to see interactions.

2.4 Density functional theory studies

The B3LYP/6-31G (d,p) set implemented in the Gaussian 03 software package, the DFT approach is employed to carry out complete geometric optimizations of the molecules under study [11]. This method produces advantageous geometry for a number of different structures. High-quality geometry optimizations are produced by this base set. Unrestricted optimization has been applied to the geometric structure. The optimized structure was used to calculate the energy difference (ΔE), electronegativity (χ), electron affinity (A), global hardness (η), global softness (σ) and ionization potential (I) as well as the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}).

3. Results and discussion

Molecular docking is one of the most widely used methods in shape-based full drug design [12] because it can predict the binding conformation of small molecule ligands at the ideal target binding site [13]. The explanation of fundamental physiological processes as well as the rational design [14] of drugs depends on the ability to characterize binding behavior. The target protein shown as Figure.3 form was downloaded from RCSB in PDB format. The prepared analysis to the GC-MS chromatogram of the ethanolic extract of the composite leaf of *Japanese knotweed* shows that Figure. 2 these spectral data explain different compounds shown as Figure. 4 - 7.

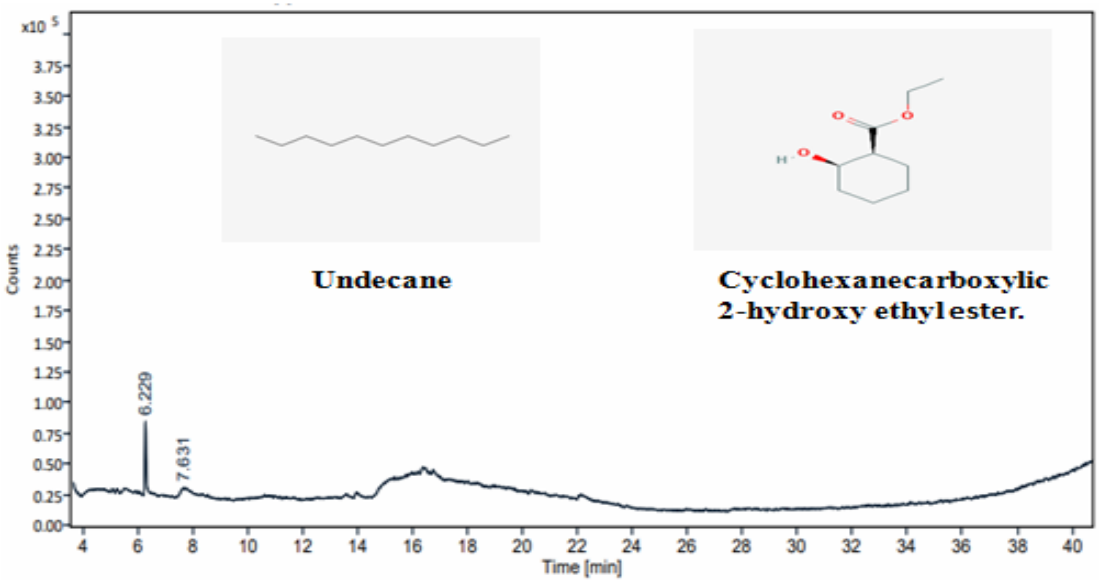

Figure 2. GC-MS chromatogram of ethnological extract of *Japanese knotweed* leaf

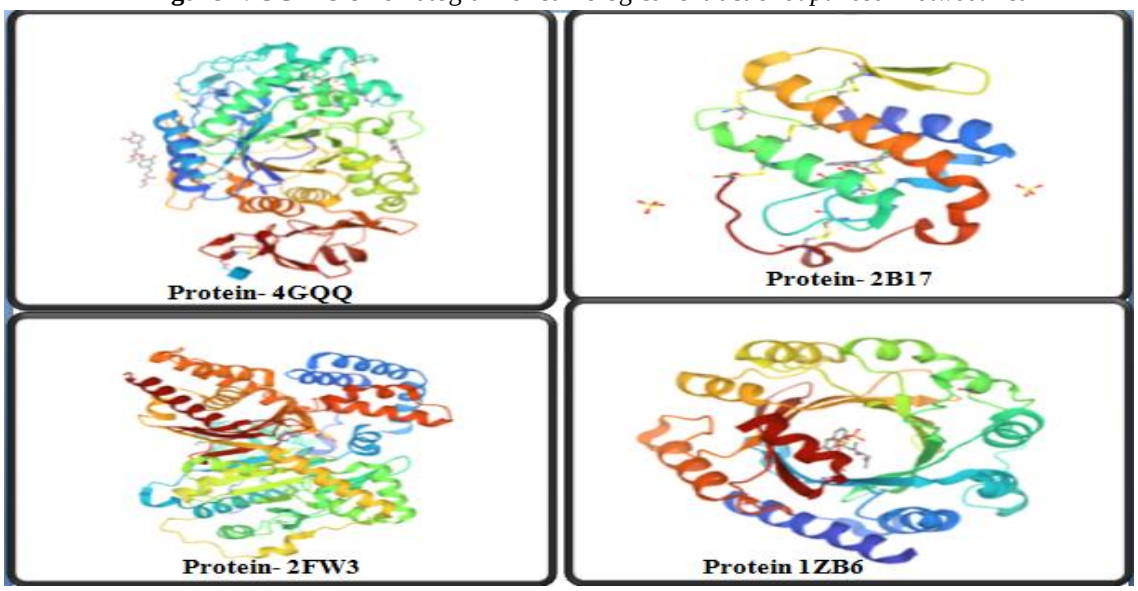

Figure 3. Four different protein structures

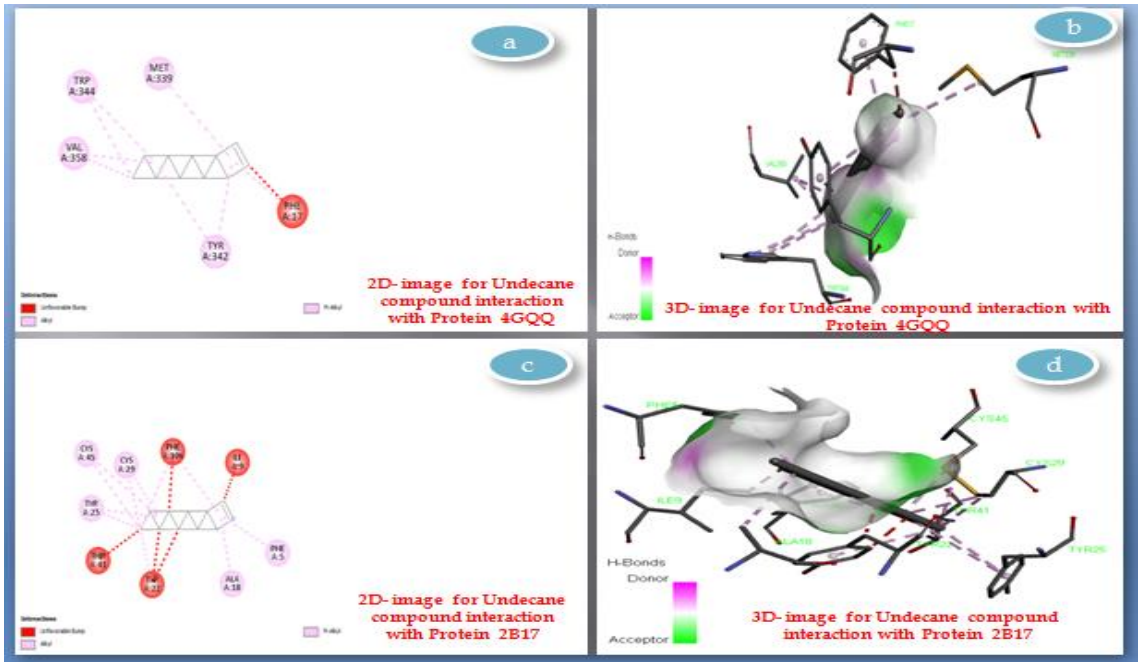

Figure 4. Representation of the 2-D and 3-D images of a & b Undecane interaction with Protein 4GQQ and c & d Undecane interaction with Protein 2B17

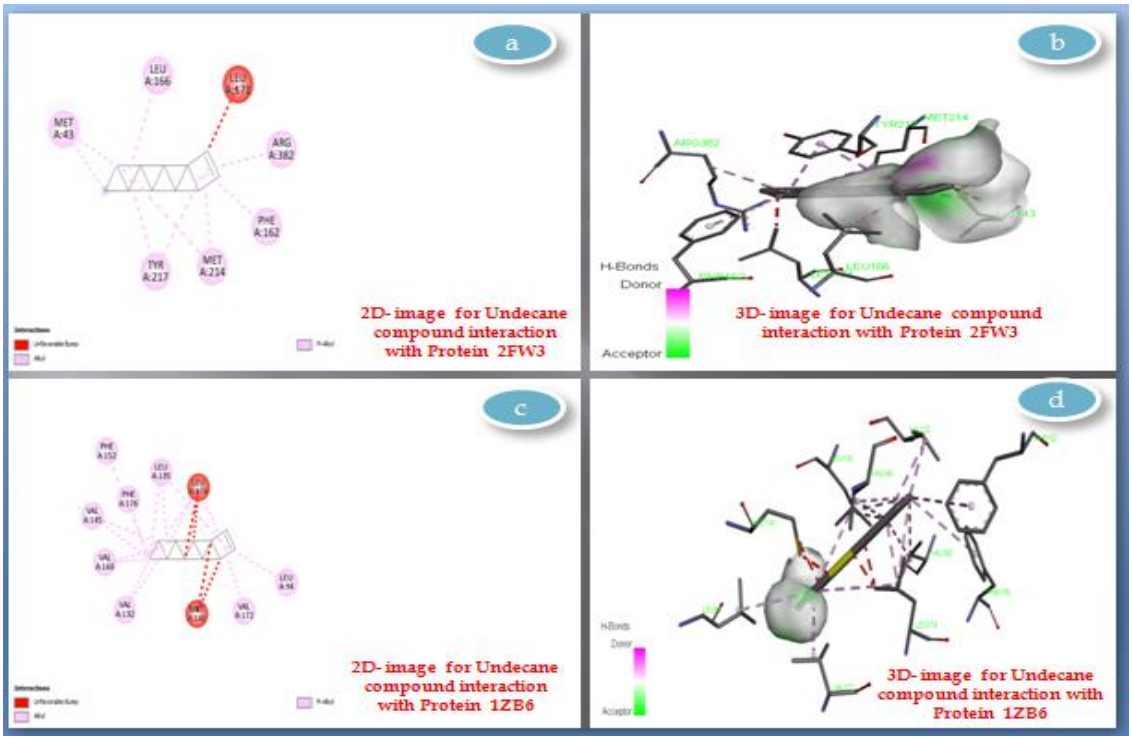

Figure 5. Representation of the 2-D and 3-D images of a & b Undecane interaction with Protein 2FW3 and c & d Undecane interaction with Protein 1ZB6

The connection of the leaves of Japanese knotweed shows that Undecane and Cyclohexane carboxylic acid 2-hydroxy ethyl ester can be compared in terms of their binding energies, shown as Table 1. This first compound shows Undecane interaction with various proteins with binding energies of -9.9720 for 4GQQ, -11.9914 for 2B17, -12.0047 for 2FW3 and -12.2273 for IZB6. In addition, 4GQQ, 2B17, 2FW3 and IZB6 interact Cyclohexane carboxylic acid 2-hydroxy ethyl ester (-9.4928, -8.67208, -9.887019 and -9.63691, respectively). For optimal pharmacological effectiveness, the

lowest binding energy value. Since the compounds with a higher negative binding energy value are more stable, the biological activity is also increased at the same time.

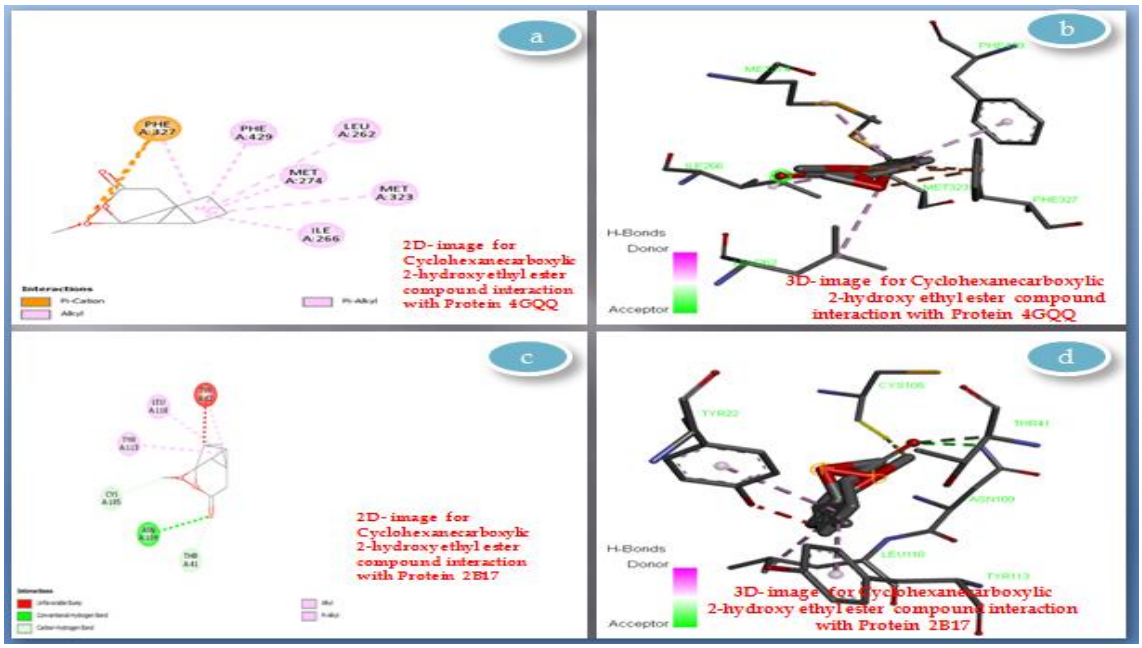

Figure 6. Representation of the 2-D and 3-D images of a & b Cyclohexanecarboxylic acid 2-hydroxy ethyl ester interaction with Protein 4GQQ and c & d interaction with Protein 2B17

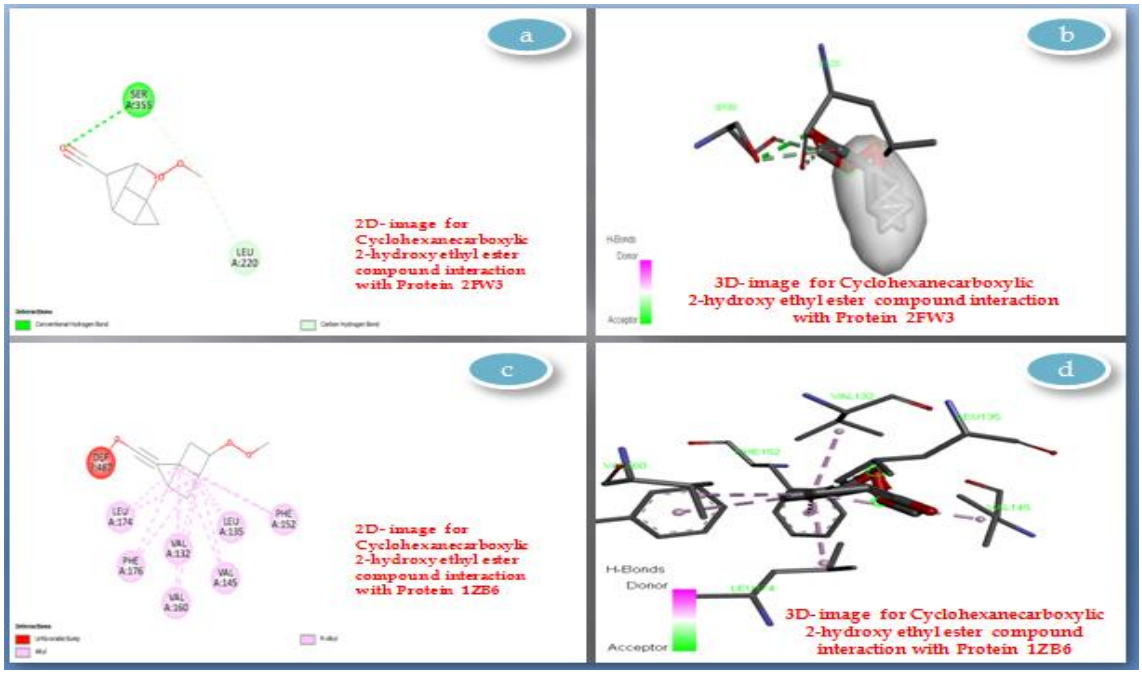

Figure 7. Representation of the 2-D and 3-D images of a & b Cyclohexanecarboxylic acid 2-hydroxy ethyl ester interaction with Protein 2FW3 and c & d interaction with Protein 1ZB6

The antibacterial activity interacts with the 4GQQ protein for two compounds by comparing their respective binding energies, cyclohexanecarboxylic acid 2-hydroxyethyl ester binding energy value -9.49428 and Undecane binding energy value -9.9720 as indicated in the table. 1, so low binding energy better antibacterial activity. Then anti-inflammatory compounds Undecane Cyclohexane carboxylic acid 2-hydroxy ethyl ester have a bond energy values of -11.9914 and -8.67208, respectively, both of which are lower than the anti-inflammatory properties of the

Undecane molecule. When the binding energy value of both compounds is related to another antidiabatic activity (2FW3) of the chemical, the results are -12.0047 and -9.887019. The antioxidant activity of the 1ZB6 proteins is 12.2273 and 9.63691, respectively. Finally, the two connections are compared in all exercises. As the binding energy value of Undecane is a more active binding energy value when it interacts with various proteins. Undecane molecules have better activity in antioxidant, anti-inflammatory, anti-diabetic and anti-inflammatory agents due to maximum binding energy value obtained. The energy disparity between HOMO and LUMO energies in the DFT analyzes of Japanese knotweed compounds was compared with this report study as shown in Table 2. The function B3LYP/6-31G (d,p) of the DFT method program was used for all calculations. In less time and with less computational effort, these methods can achieve levels of accuracy comparable to previous methods. It has been shown that this method creates favorable geometries for a large number of systems [15]. These basis set optimizations for the geometry are good. The geometry structure was optimized without restrictions [16]. The optimal structure was calculated using the following quantum chemical parameters the ionization potential (I), electronegativity (χ), electron affinity (A), global hardness (η), global softness (σ) and the energy difference (ΔE) between the highest occupied molecular orbital (EHOMO) and the lowest unoccupied molecular orbital (ELUMO) [17]. The chemical stability and electrical transport properties of molecules are determined by the energy difference between the HOMO and LUMO molecular orbitals [18]. The cyclohexanecarboxylic acid 2-hydroxyethyl ester molecule has strong chemical stability and reactivity, corresponding to the HOMO-LUMO energy of 0.44 eV. The global softening ionization potential, another DFT parameter and all other factors indicate that they are more active than other chemicals.

Table 1. Computational of Binding values of *Japanese knotweed* leaf compounds

Sl. no	Name of the compounds	Protein name	Binding value
1.	Undecane	(a) 4GQQ	-9.9720
		(b) 2B17	-11.9914
		(c) 2FW3	-12.0047
		(d) 1ZB6	-12.2273
2.	Cyclohexane carboxylic acid 2-hydroxy ethyl ester	(a) 4GQQ	-9.49428
		(b) 2B17	-8.67208
		(c) 2FW3	-9.887019
		(d) 1ZB6	-9.63691

Table 2. Quantum chemical values of *Japanese knotweed* leaf compounds

Sl. No	Parameters	Name of the Compounds	
		Undecane	**Cyclohexane, carboxylic acid, 2-hydroxy ethyl ester.**
1	E_{HOMO} (eV)	-0.40656	-0.40583
2	E_{LUMO} (eV)	0.13065	0.03968
3	Δ E	0.53721	0.44551
4	I= -E_{HOMO} (eV)	0.40656	0.40583
5	A= -E_{LUMO} (eV)	-0.13065	-0.03968
6	$\chi=\frac{I+A}{2}$	0.341235	0.38599
7	$\eta=\frac{I-A}{2}$	0.471885	0.42567
8	$\sigma=\frac{I}{\eta}$	0.86156	0.9534

4. Conclusions

The binding energy result was compared to standardized drugs. The lowest binding energy required for good biological activity. Molecular docking studies showed that Undecane has a higher negative binding energy than cyclohexanecarboxylic acid 2-hydroxyethyl ester. As we can see from the docking results, by comparing the values of the binding energies of the four proteins obtained from the PDB (4GQQ, 2B17,

2FW3 and 1ZB6), we suggest that the Undecane molecule has better antioxidant activity, anti-inflammatory, antidiabetic and anti-inflammatory agents. The density function theory results of the energy difference between the highest molecular orbital and the lowest unoccupied molecular orbital (ΔE = -0.44 eV) showed that the compounds were more reactively.

Author Contribution

Methodology, Investigation, Resources, Writing-Original draught preparation, Synthesis chemicals Conceptualization, Validation, Supervision, Writing-Reviewing and Editing are all responsibilities of K.Raja and K.Tharini.

Declaration of competing interest

The authors declare that they are not aware of any competing financial interests or personal relationships that may have influenced the work described in this document.

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