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Quantum Chemical Calculation and *in silico* Molecular Modelling Studies on Some Multi-targeting Anti-Inflammatory Inhibitors

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Problem Statement: Inflammation plays a key role in many chronic diseases, including autoimmune disorders and arthritis. There are some of the natural compounds, which possess anti-inflammatory properties and offer significant therapeutic potential. Computer-aided molecular design helps to discover the Quantitative Structure Activity Relationship (QSAR) of the molecules.
Aims: This study aims to provide a deeper understanding of the electronic structure and reactivity behaviour of natural compounds to design novel leads with enhanced biological activity.

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Methodology: Natural anti-inflammatory molecules from plant and marine sources were identified through an extensive literature review. Compounds such as Oleocanthal, Viridicatin, Liquiritin, and Nobiletin were selected for analysis. Their electronic structures were studied using Density Functional Theory (DFT) with the B3LYP functional and 6-311G(d,p) basis set to calculate geometric and electronic parameters, reactivity descriptors, and molecular electrostatic potential (MEP) maps. Physicochemical properties and drug-likeness were assessed through *in silico* ADMET studies. Finally, molecular docking simulations were performed to evaluate the binding affinities and interactions of the selected compounds with key inflammatory targets, including IL-17, MAPK, TNF-α, and MMP-9.
Results: The DFT calculations revealed critical insights into the electronic distribution and reactivity patterns of the compounds, identifying potential interaction sites. ADMET predictions confirmed favourable drug-likeness and safety profiles, while docking studies highlighted significant binding affinities, particularly for Liquiritin, which demonstrated the highest binding efficiency among the tested compounds.
Conclusion: By integrating quantum chemical calculations and molecular modelling, this study provides a comprehensive framework for exploring the QSARs of natural anti-inflammatory compounds. The findings contribute to the rational design and discovery of novel anti-inflammatory drugs with improved therapeutic potential.

Keywords: Quantum chemical calculation; ADMET; molecular docking; anti-inflammatory natural compounds etc.

1. INTRODUCTION

A joint is an area where two different bones meet and help to move the body parts connected by its bone. Arthritis is a general term that refers to inflammation of one or more joints (Coutant & Miossec, 2020). Symptoms may include pain, stiffness, swelling, redness in and around one or more joints and decreased range of motion of that particular joint. Joint pain can be caused by injury affecting any of the ligaments, bursae, or tendons surrounding the joint (Stone et al., 2021). This wound can also affect the cartilage, ligaments, and bones within the joint. Extremely rarely but it can be a cause of joint cancer (Clézardin et al., 2021).

These symptoms can be developed gradually or suddenly. Various internal organs and immune system of the body may also get affected by certain rheumatic conditions such as rheumatoid arthritis and lupus (SLE), cause diverse effect on multiple organs and cause widespread symptoms. In general arthritis is common among adults aged 64 years or older, but it can also affect people of all ages, including children (Coutant et al., 2021).

There are >100 different types of arthritis with different causes and treatment methods for example osteoarthritis, rheumatoid arthritis, gout and fibromyalgia. Osteoarthritis, the most common type of arthritis which involve wear-and-tear damage to your joint's cartilage (joint forming hard, slick coating providing a cushion support to the ends of the bones and allows nearly frictionless joint motion), which can lead to bone grinding, ultimately results in arthritis (Bandyopadhyay, 2018). Osteoarthritis can affect the entire joint. It can also cause the deterioration of connective tissues that attach muscle to bone and hold the joints together. It also causes inflammation of the joint lining. In rheumatoid arthritis, body's immune system attacks the lining of the joint capsule (A tough synovial membrane that encloses all the joint parts). This lining becomes inflamed and puffed and eventually arthritic process can destroy cartilage and bone within the joint (Beasley, 2012).

According to World Health Organization (WHO) approximately 1.71 billion people have musculoskeletal conditions worldwide. Musculoskeletal conditions significantly limit mobility and dexterity, thus leading contributor to enormous expenditures in healthcare and poor work (www.who.int/news-room/fact-sheets/ detail/ musculoskeletal-conditions). In 2019, 18 million and 528 million people worldwide were living with rheumatoid arthritis and osteoarthritis respectively, which is an increase of 113% since 1990. About 70% of people living with arthritis are women, and 55% are older than 55 years. With a prevalence of 365 million, the knee is the most frequently affected joint, followed by the hip and the hand (www.who.int/news-room/fact-sheets/detail/osteoarthritis, www.who.int/news-room/fact-sheets/detail/rheumatoid-arthritis). As

stated by the Centres for Disease Control and Prevention (CDC), during 2019–2021, 21.2% of U.S. adults (53.2 million) have received a diagnosis of some form of arthritis. In developing countries like India, Arthritis is a serious public health problem.

Although the exact aetiology of RA is not known yet, many factors are considered to trigger the inflammation of the joints, including environmental factors, genetic factors, infections such as viral and hormonal changes and unusual autoimmune disorder (Bandyopadhyay, 2018). Mostly the B cells and the T cells commonly associated in causing the inflammation. Inflammation is a process by which body deals with infections and tissue damage, but there is a good balance between the benefits of inflammation cascades and their potential for long-term tissue destruction. If they reach beyond control or resolution, inflammation pathways may lead to the development of diseases such as rheumatoid arthritis, chronic asthma, multiple sclerosis, inflammatory bowel disease and psoriasis (Beasley, 2012; Qiu et al., 2021). Within many inflammation cascades there are often pivotal molecular targets that, when neutralized or antagonized, block the output of the pathway (Fang et al., 2020). Some endogenous pro-inflammatory mediators include leukotrienes, prostaglandins and histamines. Anti-inflammatory inhibitors target their synthesis or activity to reduce inflammation and associated symptoms (Simmons, 2006). These inhibitors work by interfering with signalling pathways or enzymes that promote inflammation. Cyclooxygenase 1 and 2 (COX-1 and COX-2) (Liu et al., 2019), 5-Lipoxygenase (LOX) (Liu et al., 2019), Nuclear Factor-kB (NF-kB) (Farrugia & Baron, 2016), Interleukin (IL)-17, 18 (Gracie, 2004), Cytokines such as tumor necrosis factor (TNFα) (Farrugia & Baron, 2016), IL-1, IL-6 (Dayer &, Choy, 2010), IL-1β (Gracie, 2004), Mitogen activated protein kinases (MAPKs) (Ganguly et al., 2023) and Matrix Metalloproteinases (MMPs) as MMP-2 and MMP-9 (Itoh, 2017) are some of these targets. In the modern era of high-throughput sequencing to screening biology, it is expected that targets can be identified, validated and translated into clinical candidates in ever decreasing periods of time. However, it should be acknowledged that it often takes many years to know the complete biology of a particular target and to select the best utility of this in specific diseases. For example in the early 90s, a pioneering clinical trial in rheumatoid arthritis demonstrated, for the first time, the valuable effects of blocking TNF-α in autoimmune disease (Farrugia & Baron, 2016). This later lead to several approved therapies, either monoclonal antibodies blocking TNF-α (Simmons, 2006).

The Conceptual-Density Functional theory (DFT) is a powerful computational chemistry tool used to study the molecular and electronic properties of anti-inflammatory inhibitors, making it highly relevant in drug discovery, especially for ligand-target interactions (Alghuwainem et al., 2023). DFT has been appreciated by tremendous achievements during the 1990s for the estimations of electronic structure of the molecules and solids. The system's response varies as the number of electrons (***N)*** changes at a constant external potential, $\boldsymbol{v}(\vec{r})$ described by reactivity descriptors and may be considered as response functions (Pucci & Angilella, 2022). In light of the Hohenberg and Kohn Theorem, DFT has emerged as a quantum synthesis framework that facilitates the examination of matter's structure and the calculation of reactivity descriptors for molecular systems. The descriptors may be global reactivity descriptors or local reactivity descriptors (Geerlings et al., 2003). The overall reactivity of a molecule measured by global reactivity descriptors and these are Electronic chemical potential (μ), Electronegativity (χ), Global hardness (η) and global softness (S), Electrophilicity index (ω), Donor index (Rd) and acceptor index (Ra). The local properties may vary from point to point in space and are one-point ($\vec{r}$) functions, hence they play the key role in determining the most reactive points in a compound or lead. Some of the local reactivity descriptors are Fukui function ($f(\vec{r})$), Local softness ($s(\vec{r})$), Relative nucleophilicity, relative electrophilicity, Local electrophilicity index ($\omega(\vec{r})$), Local hardness ($\eta(\vec{r})$) andi Dual reactivity descriptor. The explanation and formulas of each of these descriptors have been illustrated in supplementary methods (Supplementary Material).

In-silico molecular docking studies involve use of computational techniques to predict the binding interactions between small molecules called ligand (natural compound) and target protein (Ali et al., 2023). The binding between biologically active molecule such as, carbohydrates, proteins, nucleic acid and lipids play important role in signal transduction. This interaction decides the type of signal produced. Thus, it is shown that the docking is a good way to evaluate the strength and signal produced in the

interaction. Molecular docking is employed so that we can predict the structure of the intermolecular complex composed between these two molecules. There are several possible mutual conformations in this binding, and these are commonly called binding modes. Besides this property it not only predicts the binding strength, the types of signals generate, the energy of the intricate but also calculate the binding affinity between two molecules utilizing scoring functions (Agu et al., 2023). There are several offline as well as online tools for molecular docking studies. (e.g., AutoDock (Valdés et al., 2020), Molegro Virtual Dockers [molegro-virtual-docker], Patch Dock [bio.tools/patchdock], Swiss Dock [www.swissdock.ch] etc.). Following this The *In Silico* prediction of ADMET (adsorption, distribution, metabolism, excretion and toxicity) property is essential to determine physiological behavior of compound. ADMET studies aid in assessing the safety profiles of inhibitor molecule, revealing drug likeness with no violation to Lipinski's rule of five or Weber's parameters (Nandu & Jithesh, 2024) Prediction of an ADMET property is essential for active lead discovery and development with the main purpose of pharmaceuticals. ADMET studies can be performed in terms of molecular descriptors such as logP, H-bond donors and acceptors, drug likeness, molar refractivity and total polar surface area (TPSA). Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, kinase inhibitor, ion channel modulator, nuclear receptor protease inhibitor and enzyme inhibitor.

Natural products have always offered a great opportunity in identification of natural leads to address various ailments/diseases. In recent past, some molecules have been isolated from the various natural sources and found to possess anti-inflammatory activity. for example Gallic acid and it's derivative, curcumin (from turmeric), resveratrol (red grapes, cranberries and peanuts) (Shakibaei et al., 2008), tea polyphenols, genistein (soy), quercetin (onions) (Khanna et al., 2007) and calycosin which is one of the components of *Angelica sinensis*, (Huang et al., 2014) has been indicated to have an important role in the treatment of rheumatoid arthritis.

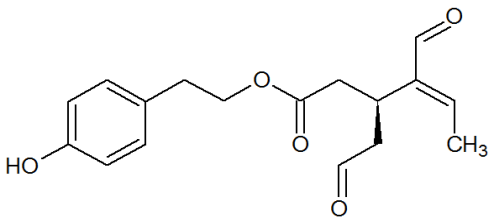
The objective of this study is to gain a deeper understanding of the electronic structure of natural anti-inflammatory compounds and explore their reactivity behaviour and structure-activity relationships. This knowledge aims to guide the design of new leads with potential biological activity. To achieve this, the following strategy is proposed: (1) identify molecules from plant or marine sources with reported anti-inflammatory activity, (2) perform electronic structure calculations to elucidate the molecular nature and reactivity, and (3) conduct *in-silico* ADMET and docking studies to establish a structure-activity relationship, which can support the development of novel therapeutic agents.

2. MATERIALS AND METHODS

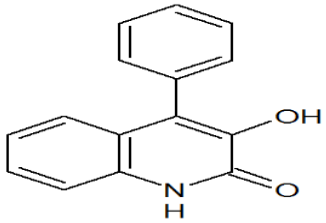
The materials and methods used for this study are presented in the following sections.

Data Set: Literature survey have been done to search for natural compounds possessing anti-inflammatory activity and then four sets of compounds as shown in Fig. 1., have been selected to perform further studies. Of which compound 1 is Oleocanthal, phenolic compound (secoiridoids) which is found in extra virgin Olive (*Olea europaea*) oil (Francisco et al., 2019), compound 2, Viridicatin is found in shark gill-derived fungus *Penicillium polonicum* AP2T1 and act as MMP2 inhibitor (Liang et al., 2019) Compound 3, Liquiritin is present in *Glycyrrhiza uralensis* and attenuates rheumatoid arthritis via reducing inflammation, supporting angiogenesis, and inhibiting MAPK signaling pathway (Zhai et al., 2019) and Compound 4, Nobiletin, a citrus flavonoid, found in vegetables and fruits (Potue et al., 2019).

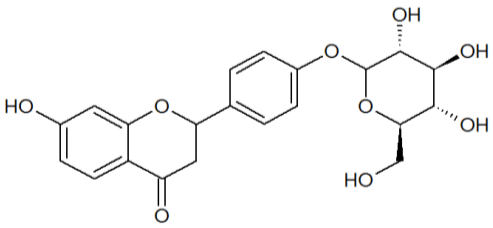
Methodology: The molecular structures of compound have been optimized at the density functional theory (DFT) level using the B3LYP functional (combination of Becke's three parameter (B3) gradient corrected hybrid exchange functional (Wang et al., 2021), with the dynamical correlation functional of Lee, Yang and Parr (LYP) (Domagała et al., 2022). All the calculations including optimized geometrical parameters, fundamental vibrational frequencies and frontier molecular orbitals have been calculated using Gaussian 03W/09 package (Frisch et al., 2009). All the atoms were described with highest 6-311G (d,p) set, which contains sufficient basis functions to describe the molecular properties of the compound. The absence of imaginary frequencies in a harmonic frequency calculation is being carried out at the same level of theory. It indicates that on the potential energy surface the calculated geometry



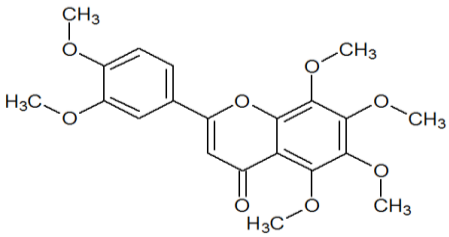
1. Oleocanthal



2. Viridicatin



3. Liquiritin



4. Nobiletin

Fig. 1. Structures of anti-inflammatory inhibitors (compound 1-4) used for the electronic structure calculations and *In Silico* drug designing studies

of the compound (1-4) is truly minimum. The atomic charges of all selected atoms are evaluated by employing Mulliken Population Analysis (MPA), Natural Population Analysis (NPA) and Hirshfeld Population Analysis (HPA) schemes at the same level of theory. A very good correlation is found in these three different schemes, and they lead us to acquire better understanding of the charge distribution. The energies of HOMO-LUMO frontier molecular orbitals have been calculated using finite approximation (whereby, Single Point Energy (SPE) calculation was performed for the Neutral (N), Anion (N+1) and Cation (N-1) systems of each compound (1-4) of the data set and Koopmans's approximation (Geerlings et al., 2003); The DFT based global and local reactivity descriptors have been calculated at the selected atoms of all compounds using the formulas enlisted in methods section of Supplementary Material. The molecular electrostatic potential maps and visualization of all results done using Gauss View 5.0 (Frisch et al., 2009).

***In silico* ADMET studies:** *In Silico* ADMET studies of compound (1-4) of the data set have been done using an open-source web program molinspiration. For this, firstly the structures of compounds have been drawn by using an open source ACD labs ChemSketch version 2019.12.0 (Hassan et al., 2022) and saved as molecule_number.mol [(MDL molfiles (*.mol) (V2000)]. To generate the SMILES notation of each compound an open-source Open Babel GUI version 3.0.0 (Yoshikawa & Hutchison, , 2019) is used. The generated SMILES notations of all the compounds were then used in an open source and online software molinspiration version 2024 (Suganya et al., 2020) to calculate some of molecular properties like miLogP, Total Polar Surface Area (TPSA), number of hydrogen bond donors and acceptors, molecular weight, Volume, number of atoms, number of rotatable bonds and for the prediction of bioactivity score for drug targets as GPCR ligands, kinase inhibitors, Protease inhibitor, ion channel modulators, enzymes and nuclear receptors.

***In silico* Molecular docking studies:** The binding affinities between the compound (ligand) and the receptor have been studied through docking studies. AutoDock4 tool (Valdés et al., 2020) have been utilized for docking and the analysis of docking results have been carried out with the help of Molegro Molecular Viewer. To examine the interaction of studied compounds to the reported targets or receptors namely IL-6, IL-17, TNF-α, MMP-9, MAPK and IL-1β from the Protein Data Bank (PDB ID: 1ALU, 5APH, 3KMC, 1L6J, 3S4E, 4GAF respectively) (Protein Data Bank), docking simulation were carried by using AutoDock 4.2.6 program of MGL Tool 1.5.7 software (Jafar et al., 2023).

Before proceeding to molecular docking, protein optimization is an important task, in which the inhibitor is removed from the protein and energy is minimized to prepare the protein for running docking simulation. There are mainly four steps for preceding molecular docking studies using AutoDock 4.0 program: Protein preparation, Ligand preparation, Grind formation, docking preparation following running of docking algorithms. In protein preparation the co-crystallized ligand structure and hydrogen atoms were removed with the help of chimera [UCSF Chimera version 1.17.3] (Meng et al., 2023). Then step vice, polar hydrogen atoms, kollman charges were added and AD4 type atoms were assigned to the protein structure. The protein file was saved in the *. pdbqt format. For Ligand preparation, The 2D structure of compound was generated by ChemSketch (Hassan et al., 2022) and converted into the 3D format using Open Babel version 3.0.0 (Yoshikawa & Hutchison, 2019). The ligand was prepared and saved in .pdbqt format after detecting and choosing root of torsion tree. In grid formation, The protein molecule and ligand were chosen and grid box was set in the target protein (eg. 1ALU) which was identified by PUBMED literature of 1ALU (i.e., x-axis = 60, y-axis = 60, z-axis = 60) and the file was saved in the .gpf (grid parameter file) format. Auto grid computes the vander walls energies at each single grid point. For Auto dock calculation, Lamarckian genetic algorithm was used for minimization of all default parameters. After this, The protein molecule and ligand were chosen in .pdbqt file format, and now this file was saved in .dpf (docking parameter file) format with default parameters (Like GA runs = 10; population size = 150 etc.). Finally, to run the docking algorithm Cygwin64 Terminal was used (Hamza et al., 2024). By Cygwin, .glg and .dlg files were created from the grid file .gpf and .dpf file respectively. For running autogrid and autodock, the algorithms **"**./autogrid4.exe –p 1alu.gpf –l 1alu.glg &**"** and **"**./autodock4.exe –p 1alu.dpf –l 1alu.dlg &**"** respectively were used. Now, .dlg file converted into run.pdbqt file following run.pdb by implementing the algorithm "grep '^DOCKED' 1alu.dlg | cut -c9- > 1alu_run.pdbqt" and "cut -c-66 1alu_run.pdbqt > 1alu_run.pdb" respectively. From .dlg file, the best run (minimum run table) with minimum binding energy was selected and the corresponding coordinates were retrieved from run.pdb file. These coordinates were then pasted in the protein optimization file and saved in the .pdb format.

Visualization of docked protein: To visualize the hydrogen bond interaction between protein and ligand molecule, electrostatic interaction, hydrophobicity or hydrophilicity of the molecule, pose organizer view of lead, Chimera1.13.1 (http://www.cgl.ucsf.edu/chimera/) and Molegro Molecular Viewer were used. This view helps us to show that in which conformation the ligand is most stable in protein structure or in secondary structure of protein.

3. RESULTS AND DISCUSSION

The natural leads or molecules (compound 1-4) along with their experimental anti-inflammatory inhibitors activity were sampled from the literature. The quantum chemical calculation for all these compounds to calculate conceptual-DFT based local and global reactivity descriptors have been achieved at highest level of theory that is B3LYP/6-311G(d,p). The *In Silico* ADMET and molecular docking studies of all compounds have also been carried out to get knowledge about the interaction between the anti-inflammatory inhibitors and the protein active site. The results of quantum-chemical calculations, *In Silico* ADMET, and *in Silico* molecular docking are presented in the following sections.

3.1 Quantum Chemical Calculations

Conceptual DFT based ground state geometry optimization and quantum chemical calculations (Gaurav & Krishna, 2021)on compound 1-4 have been successfully achieved in gas phase. In order to search a computationally economic and feasible method for the electronic structure calculations of the compounds, a comparative analysis of the results obtained for various functional and basis sets in gaseous phase have been presented in Supplementary Table S1. There are five basis sets and all of them are as Hartree-Fock (HF) - HF/3-21, DFT - B3LYP/3-21G, B3LYP/6-31G(d,p), B3LYP/6-31++G(d,p) and B3LYP/6-311G(d,p). At the highest level ie., B3LYP/6-311G(d,p) all of these natural molecules (1-4) have minimum optimization energy, low dipole moment, computational cost was high and no. of steps for optimization is decreasing consistently in each group. Table showing the most negative value of ESCF in absolute terms gives the optimized structure of all compounds. The maximum negative value of ESCF energy is obtained in compound-3 whereas minimum negative value of ESCF is found in compound-2. The dipole moment found

in molecule-3 is also highest while the minimum is achieved in compound-4 at B3LYP/6-311G (d,p) level of theory as mentioned in the Supplementary Table S1. An important criterion for the relevancy of a DFT in quantum-chemical calculations is the need of availability or computational time. For optimized compound the CPU time is given in the Supplementary Table S1. Table also gave evidence that with the increase in level of theory with basis set, computational cost increases. The number and nature of atoms present in the molecule also affect computational cost. The maximum and minimum computational cost of Compound-4 and Compound-2 due to presence of maximum and minimum no. of atom and oxygen group respectively (Optimized compound structures as shown in Supplementary Fig. S3).

By using DFT at B3LYP/6-311G(d,p) level of theory, the geometry optimization was achieved. The condition of optimization is said to be fulfilled when the value of four parameters named Maximum Force, Maximum Displacement, RMS Force, and RMS Displacement is greater than their threshold value. The various energetic and thermo-chemical parameters for all Compounds in the gas phase are evaluated at 1atm pressure and 298.15K temperature at HF/3-21G, B3LYP/3-21G, B3LYP/6- 31G(d,p), B3LYP/6-31++G(d,p), B3LYP/6-311G(d,p) level of theory, results are presented in Supplementary Table S2. The difference in the energy of ground state vibration is Zero-Point Vibrational Energy (ZPVE). The ZPVE of Compouns-3 is highest among all studied compounds. Further, after Zero-point correction and thermal correction to energy, enthalpy, Gibbs free energy, and total energy of all studied compounds has also been calculated in gaseous phase. Results in Supplementary Table S2 demonstrate that all these compounds are exothermic in nature.

The calculation of effective atomic charges at the selected atoms of all compounds played an important role in the application of quantum-chemical calculations to molecular systems. The electron density distribution has been known through multiple population analysis named as NPA (Natural Population Analysis), MPA (Mulliken Population Analysis), and HPA (Hirshfeld Population Analysis) is given in Supplementary Table S3, S4 and S5 respectively. A very good correlation is found between these different schemes, and they lead us to acquire better understanding of the charge distribution. The plot of atomic charge calculated based on NPA, MPA and HPA charge schemes are represented in Supplementary Fig. S1**.** The MEP, created in the space around a molecule is related to the electron density of the molecule. The plot of MEP of entire studied compound is given in Supplementary Fig. S2**.** The contour maps along with the ground state optimized geometry of Compound 1-4 in gas phase are presented in Supplementary Fig. S3**.**

Antiradical activity of a compound can be demonstrated from the oxidation and reduction potential that is based on ionization potential **(*I*)** and electron affinity *(A)* of the compound, respectively. A molecule containing low value of ***I*** is easily oxidized, therefore it is a good electron donor. Antiradical capacity of entire studied compounds is represented in Supplementary Table S6. Compound-1 having highest ionization potential acts as an antioxidant whereas compound-4 having high electron affinity showing a good anti-redundant activity. For the Frontier molecular orbital analysis and conceptual DFT based global reactivity descriptors, The Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) with their band gap ($\Delta E = E_{LUMO} - E_{HOMO}$) is showing in Supplementary Fig. S4**.** The calculated frontier molecular orbital energies, energy band gap, energy of neutral, anionic and cationic species on the basis of NPA, electronic chemical potential, dipole moment, global hardness, global softness, electronegativity and electrophilicity index by employing B3LYP/6-311G(d, p) level of theory given in the Supplementary Table S7. Conceptual DFT based local descriptors such as, local softness, local hardness, Fukui function, local electrophilicity, relative electrophilicity, relative nucleophilicity, and dual descriptors are presented in Supplementary Table S8. As per result, evaluated from the Supplementary Table S8, in compound-1 Fukui function in atom no. (C20) has maximum f+ value and (O11) minimum. Local softness of atom (C20) was high and (O11) low. Local electrophilicity of atom (C19) was more and (N37) less. Local hardness at (C19) atom was high, relative nucleophilicity at atom (C31) was high and relative electrophilicity at atom (C31) was high. At atom (C19) dual descriptor was high. Variations of some local descriptors are presented in the Supplementary Fig. S5 to S14 for all studied Compounds.

3.2 *In silico* ADMET Studies

The *In Silico* ADMET studies includes not only physico-chemical property but also bioactivity property of the molecules and these are calculated using molinspiration (Suganya et al., 2020). The results for both physico-chemical property as well as bioactivity property for all the studied compounds are presented in Supplementary Table S9 and Table S10, respectively.

3.3 In silico Molecular Docking Studies

The molecular docking studies have been performed with four different multi-targeting and anti-inflammatory compounds. All the compounds of the data set have been independently docked on the active sites of the target proteins, to examine the safety and activity of newly designed anti-inflammatory drug for the given target. Supplementary Table S11 clearly indicates the results of all studied compounds. All the docked protein structures with different views have been shown in Supplementary Fig. S15.

4. CONCLUSION

The present study successfully carried out the DFT-based electronic structure calculations of compounds (1-4). The calculated geometric parameters, atomic charges and the molecular electrostatic potential maps have identified the regions in the studied lead from where they can have intermolecular interactions with the protein molecule. The frontier molecular orbital's calculated conceptual-DFT based local and global reactivity descriptors of these compounds successfully accounts for the relationship of charge density and electronic distribution within the studied systems with that of experimental anti-inflammatory activity. Further, the *In silico* ADMET and molecular docking studies provided a deeper insight into the behavior in terms of physio-chemical properties and interactions with residues at the active site of the protein. The results successfully confirm the experimental inhibitory activity.

The DFT-based electronic structure calculations coupled with the *in silico* molecular docking analysis have provided a basis to correlate the electronic charge distribution with the biological activity of the molecule. It successfully accounts for the redistribution of electronic energy upon interaction with the residues at active site of the protein. Most significantly, the present study provides a basis to calculate the electronic structure properties of natural leads and to understand their behaviour *In silico* upon interaction with active site residues of the protein. Thus, it provides a benefit to make a change in the skeleton of the structure for in vitro synthesis of this modified molecule, leading to the development of more effected anti-inflammatory drug.

SUPPLEMENTARY MATERIALS

Supplementary materials available in this link: https://journaljsrr.com/index.php/JSRR/libraryFiles/downloadPublic/28

DATA AVAILABILITY

All data generated or analysed during this study are cited in references.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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