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An Introduction to the Exploration of the Electronic Structure Properties of Biologically Active Natural Compounds Using Quantum Chemical Methods

Ashok Kumar Mishra[1]*, Satya Prakash Tewari[1] and Aniket Kumar[2]

[1]Department of Physics, Dr. Shakuntala Misra National Rehabilitation University, Lucknow, India
[2]Shobhit Institute of Engineering & Technology, Meerut, India

Abstract

Various naturally occurring bioactive compounds have already been isolated from plants of different species and characterized for the identification of their molecular structure, but the phenomena correlated with their activity need to be explored for the prediction of their derived structure and related noble applications. The viability of quantum chemical calculation for exploring the electronic properties of such macromolecules has been substantiated through this recent study. The present chapter underlies a brief history of some of such bioactive natural compounds and discusses precisely the quantum chemical approaches feasible for the study of these natural compounds. The *ab-initio* methods and the most recent density functional theory are systematically presented along with the molecular docking approach.

***Keywords*:** Natural compound, molecular mechanics, DFT, molecular docking, QSAR, QSPR

1.1 Natural Compounds: Past, Present, and Future

The study of naturally occurring compounds has been a course for scientists since the ancient period, and its records are available in the *Vedic system*

**Corresponding author*: akmishra2k5@gmail.com

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of medicine, i.e., Ayurveda 1,000 BC. The Ayurvedacharya (medical scientist) like *Charaka* and *Sushruta* described the various types of mineral and natural products having medicinal properties and their applications [1]. In *Sushruta Sanhita* written by *Acharya Sushruta*, 700 types of medicinal plants, 64 types of medicines extracted from minerals, and 57 types of medicines extracted from animal sources have been described wherein the application of herbs like turmeric was mentioned to have begun in 1,900 BC. In the sequence of ancient records, we found the books, namely, De Materia Medica and Theophrastus Historia Plantarum authored in Greece (Europe) during 400 BC. Shanog Benckawo investigated the Maa-Huwang plant supposed to be the source of the modern ephedrine drug. The Canon of Medicine authored by Awsena in 1025 AD described 800 types of natural products and modern herbal medicines. Although the modern system of medicine (allopathy) based on synthetic chemicals and biomolecules has a rapid impact on health but is associated with toxicity issues, i.e., side effects, natural product-based drugs would be more user-friendly with either no or fewer harmful effects.

Commencing from the Vedic period (ancient period) to the recent time, the investigation of naturally occurring biomolecules has succeeded to find about 2,000 natural drugs derived from India's different traditional medicine systems and folklore practices where plants played a major role, included in the Indian Materia Medica. Reports pertaining to the sources of new drugs exhibit that about 50% of the approved drugs are derived from natural products, and the World Health Organization (WHO) has also been engaged in formulating guidelines for herbal medicines. The Council of Scientific and Industrial Research (CSIR), Govt. of India, took an initiative in 1996 to carry out research focusing on new bioactive molecules that are occurring in natural sources like plants, fungi, microbes, insects, etc., and the Central Drugs Research Institute (CDRI), Lucknow, is one of those CSIR laboratories which are part of this initiative, with an objective to standardize the Ayurvedic, Unani, Siddha, and Homeopathy (AUSH) system of medicine along with developing new natural drugs of national and global importance. Plants or plant-derived phytochemicals have been used for the treatment of various chronic diseases like cancer for a long time. Hartwell listed more than 3,000 of such plant species and 60% of the currently used anticancer agents are derived directly or indirectly from plants, marine organisms, and microorganisms, and

plant-derived bioactive natural molecules are beneficial to combat cancer [2] over synthetic drugs associated with harmful side effects. The phytochemicals contained in fruits and vegetables are found to be active as antioxidants scavenging free radicals, modulating enzymes, regulating gene expression, etc. The various bioactive natural biomolecules exhibiting anticancer activity have already been marketized, and semisynthetic derivatives of epipodophyllotoxin isolated from the roots of *Podophyllum* species belonging to the Berberidaceae family are used as an anticancer agent. Many plant-derived bioactive natural molecules have also been reported, possessing anti-inflammatory, antiviral, antimicrobial, and antidepressant activities. Recently, research has been carried out to report the biological activity and characterization of the various naturally occurring bioactive molecules isolated from *Castanopsis indica* and *Anthocephalus cadamba* plants possessing antidiabetic, anticancer, and anti-osteoporosis activities [3, 4].

The future scope for the study on naturally occurring biomolecules is full of probability of developing a low-cost, user-friendly, and multifunctional drug agent with the lowest toxicity for various fatal diseases for which the theoretical study on such biomolecules is needed to be carried out for tracking the pathway of bioactivity at the molecular level.

The theoretical research for establishing the scientific basis of the inherent bioactivity of such naturally occurring biomolecules using existing physical principles at the molecular level can now be carried out in the present century as high-level quantum computational techniques are available [5]. Moreover, the references for exploiting these computational techniques for carrying out such research on biologically active molecules are also available, and the theoretical investigations pertaining to the electronic structure and properties of some of such biomolecules contained in the leaves and fruits of *Anthocephalus chinensis* (Lamk) syn. *Anthocephalus cadamba* (Roxb) Miq. (family Rubiaceae) widely found in India, Nepal, Sri Lanka, Bangladesh, Burma, Thailand, China, and eastward through Malaysia to New Guinea have already been carried out using recent computational techniques [6–8]. These computational approaches are based on electronic structure methods to explore the chemistry of these biologically active molecules by using quantum mechanical theories. The theoretical framework useful for setting up quantum chemical calculations is discussed below.

1.2 Theoretical Framework for Quantum Chemical Calculations

While going through the available literature pertaining to the quantum mechanics calculations on molecules, we are inspired by the opinion of Dirac, which we quote as follows:

> *"The underlying physical law necessary for the mathematical theory of a large part of physical and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much to complicated to be soluble"* (P A M Dirac 1929).

Presently, there are mainly five approaches for carrying out the quantum chemical calculations for the theoretical study of any molecular system at the atomic scale, namely:

1. ***Ab-Initio* Methods**
2. **Semiempirical Methods**
3. **Molecular Mechanics**
4. **Molecular Dynamics**
5. **Density Functional Theory**

1.2.1 *Ab-Initio* Methods

The computation derived directly from the theoretical principles excluding the experimental data is categorized into *ab-initio* methods, and this includes approximate quantum mechanical calculations, namely, the Moller–Plesset (MP) perturbation theory (PT), the Hartree–Fock theory, configuration interaction (CI), coupled cluster method, multiconfigurational self-consistent field theory, and the quantum Monte Carlo method.

1.2.1.1 Hartree–Fock (HF) Theory

This theory includes two approximations [9] wherein the first approximation accounts for the estimation of the central field, which takes into account the coulombic electron–electron repulsion and provides the average effect of repulsion but not the explicit repulsion interaction. The approximate energies calculated are all equal to or greater than the exact

energy in a unit called Hartree (1 Hartree = 27.2116 eV) and tend to a limiting value called the Hartree–Fock limit as the basis set is improved. The many-electron Schrodinger equation is transformed into simpler one-electron equations. Single-electron wave functions, called orbitals, and eigenvalues, called orbital energy, are yielded by solving each one-electron equation. The behavior of an electron in the net field of all the other electrons is described by the orbital. A second approximation is related to the wave function, which is known exactly for only a few one-electron systems. Linear combinations of Gaussian-type orbitals e^{-ar^2} are used most often as functions. The wave function is formed from linear combinations of atomic orbitals or mathematically linear combinations of basis functions.

The wave function of a particle is described by the well-known Schrödinger equation [10], which is the fundamental equation of motion in quantum mechanics.

$$\left\{\frac{-\hbar^2}{2m}\nabla^2 + V\right\}\psi = i\hbar\frac{\partial\Psi}{\partial t} \tag{1.1}$$

The Schrödinger equation for Ψ, subject to the appropriate boundary conditions, can yield the energy and many other properties of the particle. Different stationary states of the system correspond to many different wave functions that could be the solutions.

If the wavefunction is written as the product of a spatial function and a time function:

$$\Psi\ (r,t) = \Psi r\ (r)\,\Psi t(t) \tag{1.2}$$

The two equations will be obtained by Equation (1.1) if these new functions are substituted, one of which depends on the position of the particle independent of time and the other of which is a function of time alone. For the problems in which we are interested, this separation is valid, and the familiar time-independent Schrödinger equation is focused entirely on.

$$H\Psi\ (r) = E\Psi\ (r) \tag{1.3}$$

Where H is the Hamiltonian operator and E is the energy of the particle, given by:

$$H = \frac{-\hbar^2}{2m}\nabla^2 + V \tag{1.4}$$

A multiple of the function itself is produced as the result when a function is acted upon by the operator, having the general form:

$$f\Psi = \lambda\Psi \tag{1.5}$$

In the Schrödinger approach, the energies corresponding to the various stationary states of the molecular structure are the eigenvalues of the Schrödinger equation. The Hamiltonian is composed of kinetic and potential energy terms, where each nucleus is studied as an accumulated entity and each electron is investigated independently:

$$H = T + V \tag{1.6}$$

The K.E. is a summation of ∇^2 over all the particles in the molecule

$$T = -\frac{\hbar^2}{2}\sum_{k}^{\beta}\frac{1}{m_k}\left(\frac{\partial^2}{\partial x_k^2} + \frac{\partial^2}{\partial y_k^2} + \frac{\partial^2}{\partial z_k^2}\right) \tag{1.7}$$

The Coulomb repulsion between each pair of charged entities (treating each atomic nucleus as a single charged mass) is the potential energy component:

$$V = \frac{1}{4\pi\varepsilon_0}\sum_j\sum_{k<j}\frac{e_j e_k}{\Delta r_{jk}} \tag{1.8}$$

Where Δr_{jk} is the distance, and e_j and e_k are the charges on electrons j and k, respectively. The potential energy compound for a molecular structure is as follows:

$$V = \frac{1}{4\pi\varepsilon_0}\left(-\Sigma_i^{electrons\ nuclei}\Sigma_l\left(\frac{Z_l e^2}{\Delta r_{il}}\right) + \Sigma_i^{electrons}\Sigma_{j<i}\left(\frac{e^2}{\Delta r_{ij}}\right) + \Sigma_l^{nuclei}\Sigma_{j<l}\left(\frac{Z_l Z_j e^2}{\Delta R_{ij}}\right)\right) \tag{1.9}$$

Electron–nuclear attraction corresponds to the first term, electron–electron repulsion to the second term, and nuclear–nuclear repulsion to the third term.

The Born–Oppenheimer Approximation

The first approximation used to simplify the solution of the Schrödinger equation is related to the general molecular problem by separating nuclear and electronic motions because the mass of the typical nucleus is a thousand times greater than that of an electron. It assumes that electron distribution within the molecule depends on the positions of the nuclei and not on their velocities, and electronic motion can be supposed to take place in a field of fixed nuclei.

The Hamiltonian can be written as for the molecular system:

$$H = T^{electron}(\vec{r}) + T^{nuclei}\left(\vec{R}\right) + V^{nuclei-electron}\left(\vec{R}\vec{r}\right) + V^{electron}(\vec{r}) + V^{nuclei}\left(\vec{R}\right) \tag{1.10}$$

The K.E. term for the nuclei is neglected by the electronic Hamiltonian:

$$H^{electron} = -\frac{1}{2}\sum_{i}^{electrons}\left(\frac{\partial^2}{\partial x_i^2} + \frac{\partial^2}{\partial y_i^2} + \frac{\partial^2}{\partial z_i^2}\right) - \sum_{i}^{electrons\ nuclei} \Sigma_l \left(\frac{Z_l}{\left|\overrightarrow{R_l} - \vec{r}_i\right|}\right) + \sum_i^{electrons} \Sigma_{j<i}\left(\frac{1}{\left|\vec{r}_i - \vec{r}_i\right|}\right) + \sum_I^{nuclei} \Sigma_{J<I}\left(\frac{Z_l Z_J}{\left|\overrightarrow{R_l} - \overrightarrow{R_J}\right|}\right) \tag{1.11}$$

The motion for Hamiltonian of electrons in the field of fixed nuclei is described by the Schrödinger equation:

$$H^{electron}\Psi^{electron}\left(\vec{r}\vec{R}\right) = E^{eff}\left(\overrightarrow{R_l}\right)\Psi^{electron}\left(\vec{r}\vec{R}\right) \tag{1.12}$$

Condition on the Electronic Wave Function

There are two important restrictions to be imposed on the wave function Ψ: first is that it is normalized to represent the probability which should be the number of particles, i.e.,

$$\int_{-\infty}^{\infty} |d\Psi|^2 \, dv = n_{particles} \tag{1.13}$$

Secondly, for a simple function, the following relation holds: ψ must be antisymmetric.

$$f(i,j) = -f(j,i) \tag{1.14}$$

The following condition must be satisfied by any valid wavefunction: It is essentially a requirement that the results of experimental physics must agree with by ψ.

$$\Psi(\vec{r_1},\vec{r_2},\ldots,\overrightarrow{r_{n-1}},\vec{r_n}) = -\Psi(\vec{r_2},\vec{r_1},\ldots,\overrightarrow{r_{n-1}},\vec{r_n}) \tag{1.15}$$

The molecular orbital theory decomposes ψ into a combination of molecular orbitals: $\phi_1,\phi_2,\phi_3,\ldots\ldots\ldots\ldots$ and we choose the molecular orbitals of a normalized, orthogonal set:

$$\begin{aligned} \iiint \phi_i^* \phi_i dxdydz &= 1 \\ \iiint \phi_i^* \phi_j dxdydz &= 0; i \neq j \end{aligned} \tag{1.16}$$

The Hartree product is formed by the molecular orbitals.

$$\Psi\vec{r} = \phi_1(\vec{r_1})\phi_2(\vec{r_2})\ldots\ldots\ldots\phi_n(\vec{r_n}) \tag{1.17}$$

This Hartree product is an inadequate wave function which improved to an antisymmetric function by introducing the concept of determinant. It is a combination of molecular orbitals in which electrons can have spin up $\left(+\frac{1}{2}\right)$ or down $\left(-\frac{1}{2}\right)$.

We discussed two spin relations, α and β, as follows:

$$\begin{aligned} \alpha(\uparrow) &= 1 \qquad & \alpha(\downarrow) &= 0 \\ \beta(\uparrow) &= 0 \qquad & \beta(\downarrow) &= 1 \end{aligned} \tag{1.18}$$

The value of 1 is assigned to the α function for a spin-up electron, and the value of 1 is assigned to the β function for a spin-down electron. The values of α and β for electron i will be designated as $\alpha(i)$ and $\beta(i)$, respectively.

The electrons to these orbitals in pairs of opposite spin:

$$\Psi(\vec{r}) = \frac{1}{\sqrt{n!}} \begin{vmatrix} \phi_1(\vec{r_1})\alpha(1)\phi_1(\vec{r_1})\beta(1)\phi_2(\vec{r_1})\alpha(1)\phi_2(\vec{r_1})\beta(1)\ldots\phi_{\frac{n}{2}}(\vec{r_1})\alpha(1)\phi_{\frac{n}{2}}(\vec{r_1})\beta(1) \\ \phi_1(\vec{r_2})\alpha(2)\phi_1(\vec{r_2})\beta(2)\phi_2(\vec{r_2})\alpha(2)\phi_2(\vec{r_2})\beta(2)\ldots\phi_{\frac{n}{2}}(\vec{r_2})\alpha(2)\phi_{\frac{n}{2}}(\vec{r_2})\beta(2) \\ \vdots \\ \phi_1(\vec{r_i})\alpha(i)\phi_1(\vec{r_i})\beta(i)\phi_2(\vec{r_i})\alpha(i)\phi_2(\vec{r_i})\beta(i)\ldots\phi_{\frac{n}{2}}(\vec{r_i})\alpha(i)\phi_{\frac{n}{2}}(\vec{r_i})\beta(i) \\ \phi_1(\vec{r_j})\alpha(j)\phi_1(\vec{r_j})\beta(j)\phi_2(\vec{r_j})\alpha(j)\phi_2(\vec{r_j})\beta(j)\ldots\phi_{\frac{n}{2}}(\vec{r_j})\alpha(j)\phi_{\frac{n}{2}}(\vec{r_j})\beta(j) \\ \vdots \\ \phi_1(\vec{r_n})\alpha(n)\phi_1(\vec{r_n})\beta(n)\phi_2(\vec{r_n})\alpha(n)\phi_2(\vec{r_n})\beta(n)\ldots\phi_{\frac{n}{2}}(\vec{r_n})\alpha(n)\phi_{\frac{n}{2}}(\vec{r_n})\beta(n) \end{vmatrix} \tag{1.19}$$

The wave function is formed by mixing all of the possible orbitals of all of the electrons in the molecular system using this determinant.

Basis Sets

The molecular orbitals are expressed as a linear combination of a pre-defined set of one-electron functions known as basis functions in the next approximation. Usually, these basis functions are centered on the atomic nuclei and bear some resemblance to atomic orbitals. However, any set of appropriately defined functions may be used in the actual mathematical treatment, which is more general than this.

An individual molecular orbital is defined as:

$$\phi_l = \sum_{l=1}^{N} c_{nl}\chi_n \tag{1.20}$$

Where the molecular orbital expansion coefficients are known as the coefficients $c_{\mu i}$

$$g(\alpha,\vec{r}) = cx^n y^m z^l e^{-\alpha r^2} \tag{1.21}$$

A constant for normalization, so that:

$$\int g^2 = 1 \tag{1.22}$$

Thus, c depends on $\alpha, l, m,$ and n.

The Gaussian functions are generally known to be represented as suffix s, p_y, and d_{xy} types as written down below

$$g_s(\alpha, \vec{r}) = \left(\frac{2\alpha}{\pi}\right)^{\frac{3}{4}} e^{-ar^2}$$

$$g_y(\alpha, \vec{r}) = \left(\frac{128\alpha^5}{\pi^3}\right)^{\frac{1}{4}} ye^{-ar^2}$$

$$g_{xy}(\alpha, \vec{r}) = \left(\frac{2048\alpha^7}{\pi^3}\right)^{\frac{1}{4}} xye^{-ar^2} \tag{1.23}$$

1.2.1.2 Moller–Plesset (MP) Perturbation Theory

The Moller–Plesset perturbation theory is called an approach to add the electron correlation and extend it with the size of the molecular system under investigation. The HF wave function is mapped onto a perturbation theory formulation in which HF becomes a first-order perturbation. The second-order MP2 method adds a minimal amount of correlation. The third-order (MP3) and fourth-order (MP4) calculations are also common, while MP5 and higher calculations are seldom done due to high computational requirements [11]. The Moller–Plesset calculations are not variational.

Dividing the Hamiltonian into two parts forms the basis of the perturbation theory:

$$H = H_0 + \lambda H' \tag{1.24}$$

Such that H_0 is soluble exactly, and $\lambda H'$ is a perturbation applied to H_0, a correction which is assumed to be small in comparison to it.

The assumption that H' is a small perturbation to H_0 suggests that the perturbed wavefunction and energy can be expressed as a power series in terms of the parameter λ as follows:

$$\Psi = \Psi^{(0)} + \lambda\Psi^{(1)} + \lambda^2\Psi^{(2)} + \lambda^3\Psi^{(3)} + \ldots$$
$$E = E^{(0)} + \lambda E^{(1)} + \lambda^2 E^{(2)} + \lambda^3 E^{(3)} + \ldots \quad (1.25)$$

The Schrödinger equation is where the perturbed wavefunction and energy are substituted back into.

$$(H_0 + \lambda H')(\Psi^{(0)} + \lambda\Psi^{(1)} + \cdots) = E^{(0)} + \lambda E^{(1)} + \cdots)(\Psi^{(0)} + \lambda\Psi^{(1)} + \cdots) \quad (1.26)$$

We equate the coefficients of each power of λ, which gives us a series of relations representing successively higher orders of perturbation. The first three such equations corresponding to powers of 0, 1, and 2 of λ are given by:

$$(H_0 - E^0)\Psi^{(0)} = 0$$
$$(H_0 - E^0)\Psi^{(1)} = (E^{(1)} - H')\Psi^{(0)}$$
$$(H_0 - E^0)\Psi^{(2)} = (E^{(1)} - H')\Psi^{(1)} + E^{(2)}\Psi^{(0)} \quad (1.27)$$

The MP perturbation theory defines H_0 as the sum of the one-electron Fock operation:

$$H_0 = \sum_i F^i \quad (1.28)$$

Where F^i is the Fock operator action on the i^{th} electron.
Thus,

$$H_0\Psi_s = E_s\Psi_s \quad (1.29)$$

for all substituted determinant wavefunctions.

$$E^0 = \langle\Psi^{(0)}|H_0|\Psi^{(0)}\rangle = \sum_i \varepsilon_i \quad (1.30)$$

To obtain the expression for $E^{(1)}$, we can use simple linear algebra. We begin by forming the inner product of both sides of the second relation in Equation (1.28) with a suitable wavefunction:

$$<\Psi^{(0)}:$$

$$\langle\Psi^{(0)}|H_0 - E^{(0)}|\Psi^{(1)} = \langle\Psi^{(0)}|E^{(1)} - H'|\Psi^{(0)}\rangle \Rightarrow$$

$$\langle\Psi^{(0)}|H_0|\Psi^{(1)}\rangle - E^{(0)}\langle\Psi^{(0)}|\Psi^{(1)}\rangle = E^{(1)}\langle\Psi^{(0)}|\Psi^{(1)}\rangle - \langle\Psi^{(0)}|H'|\Psi^{(0)}\rangle \tag{1.31}$$

Leaving this expression for $E^{(1)}$:

$$E^1 = \Psi^{(0)}|H'|\Psi^{(0)} \tag{1.32}$$

Summation $E^{(0)}$ and $E^{(1)}$ yields the HF energy (since $H_0 + V$ is the full Hamiltonian):

$$\begin{aligned} E^0 + E^1 &= \langle\Psi^{(0)}|H_0|\Psi^{(0)}\rangle + \langle\Psi^{(0)}|H'|\Psi^{(0)}\rangle \\ &= \langle\Psi^{(0)}|H_0 + H'|\Psi^{(1)}\rangle = \langle\Psi^{(0)}|H_0|\Psi^{(0)}\rangle = E^{HF} \end{aligned} \tag{1.33}$$

We will begin to examine the third relation in Equation (1.28) in the same way:

$$\langle\Psi^{(0)}|H_0 - E^{(0)}|\Psi^{(2)}\rangle = \langle\Psi^{(0)}|E^{(1)} - H'|\Psi^{(1)}\rangle + E^{(2)}\langle\Psi^{(0)}|\Psi^{(1)}\rangle \Rightarrow$$

$$E^{(2)} = \langle\Psi^{(0)}|V - E^{(1)}|\Psi^{(1)} = \langle\Psi^{(0)}|V|\Psi^{(1)}\rangle \tag{1.34}$$

Before we can calculate $E^{(2)}$, we need to find $\Psi^{(1)}$, and we will form it as a linear combination of substituted wavefunctions and solve for the coefficients.

$$\Psi^{(1)} = \sum_x a_s\Psi_s \ni H_0\Psi_s = E_s\Psi_s \tag{1.35}$$

This time, we will use the second relation in Equation (1.27) to find the coefficients for $\Psi^{(1)}$:

$$(H_0 - E^0)\sum_s a_s \Psi_s = \left(E^{(1)} - H'\right)\Psi^{(0)} \tag{1.36}$$

The inner product of both sides of Equation (1.36) with an arbitrary substituted wavefunction Ψ_t will be formed, and then a_t will be solved for:

$$\begin{gathered}\langle \Psi_t | (H_0 - E^0) | \sum_s a_s \Psi_s \rangle = \langle ¤_t | E^1 - H' | \Psi^{(0)} \rangle \Rightarrow \\ \sum_s a_s \langle \Psi_t | (H_0 - E^0) | \Psi_s \rangle = E^{(1)} \langle \Psi_t | \Psi^{(0)} \rangle - \langle \Psi_t | H' | \Psi^{(0)} \rangle \Rightarrow \\ \sum_s a_s \langle \Psi_t | (H_0) | \Psi_s \rangle \langle \Psi_t | (E^0) | \Psi_s \rangle = E^{(1)} \langle \Psi_t | \Psi^{(0)} \rangle - \langle \Psi_t | H' | \Psi^{(0)} \rangle\end{gathered} \tag{1.37}$$

The left side of the final Equation (1.37) yields a non-zero value only when $s = t$.

$$\begin{gathered}a_t \left(E_t - E^{(0)}\right) = -\langle \Psi_t | H' | \Psi^{(0)} \rangle \Rightarrow \\ a_t = \frac{\langle \Psi_t | H' | \Psi^{(0)} \rangle}{E^{(0)} E_t}\end{gathered} \tag{1.38}$$

It is indicated by the result in Equation (1.38) that larger contributions to the perturbation are made by substitutions close in energy to the ground state.

The following expression for Ψ^1 is obtained from these coefficients:

$$\Psi^{(1)} = \sum_t \left(\frac{\langle \Psi_t | H' | \Psi^{(0)} \rangle}{E^{(0)} E_t} \right) \Psi_t \tag{1.39}$$

The expression for E^2:

$$E^{(2)} = \langle \Psi^{(0)} | H' | \Psi^{(1)} \rangle = \langle \Psi^{(0)} | H' | \sum_t a_t \Psi_l \rangle = \sum_t a_t \langle \Psi^0 | H' | \Psi_t \rangle$$
$$= \sum_t \frac{\langle \Psi^0 | H' | \Psi_t \rangle \langle \Psi_t | H' | \Psi^0 \rangle}{E^0 - E_t}$$
$$= -\sum_t \frac{|\langle \Psi^0 | H' | \Psi_t \rangle|^2}{E_t - E^0} \tag{1.40}$$

It is known that both the numerator and denominator in the final expression are always positive expressions, with the denominator being always positive because E^0 is the lowest energy eigenvalue of the unperturbed system.

1.2.1.3 Configuration Interaction (CI) Method

A multiple-determinant wave function, known as a configuration interaction wave function, is constructed by starting with the HF wave function and making new determinants by promoting electrons from the occupied to unoccupied orbitals. Configuration interaction calculations, which can be very accurate, are classified by the number of excitations used to make each determinant. A configuration interaction single-excitation (CIS) calculation is performed when only one electron has been moved for each determinant. CIS calculations give an approximation to the excited states of the molecule but do not change the ground-state energy. A ground-state energy that has been corrected for correlation can be obtained by performing configuration interaction single- and double-excitation (CISD) calculations. Configuration interaction single-double and triple excitation (CISDT) and configuration interaction single-double-triple-quadruple-excitation (CISDTQ) calculations are done only when very-high-accuracy results are desired. However, the cost in CPU time for these calculations is very high.

The term used for a configuration interaction calculation that involves all possible excitations is full CI. Performing a full CI calculation with an infinitely large basis set yields an exact quantum mechanical result. Nevertheless, due to the immense amount of computer power required,

full CI calculations are rarely carried out. The full CI method involves forming the wavefunction ψ as a linear combination of the Hartree–Fock determinant and all possible substituted determinants:

$$\Psi = a_0\Psi_0 + \sum_{l>0} a_l\Psi_l \tag{1.41}$$

The Hartree–Fock level is represented by the 0-indexed term.

1.2.1.4 Coupled Cluster Method (CCM)

Coupled cluster calculations involve constructing a wave function as a linear combination of many determinants, and they share this aspect with configuration interaction calculations. However, the method used to choose the determinants in a coupled cluster calculation is more complex than in a CI calculation. The orders of the CC expansion, such as CCSD, CCSDT, etc., are similar to those in CI. In a CCSD (T) calculation, the triple excitations are included perturbatively rather than exactly.

1.2.2 Semiempirical Methods

Semiempirical methods do not include the core electrons in the calculation and use only a minimal basis set. The omitted values are obtained by fitting the results to experimental data or *ab-initio* calculations, and often, these parameters replace some of the excluded integrals. Semiempirical calculations have the advantage of being much faster than *ab-initio* calculations. However, the disadvantage is that the results can be erratic and fewer properties can be predicted reliably. If the molecule being computed is similar to the molecules in the database used to parameterize the method, the results may be very good. Conversely, if the molecule being computed is significantly different from anything in the parameterization set, the results may be very poor.

The semiempirical method is a computational approach that starts from the Hückel theory and has been extended to various other methods, including PPP, CNDO, INDO, MINDO, MNDO, SINDO1, PRDO, AM1, PM3, PHM, TNDO, SAM1, and the Gaussian theory. These methods use a minimal basis set and do not include core electrons in the calculations. Instead, they use parameters that are fitted to experimental data or *ab-initio* calculations to replace excluded integrals. Semiempirical calculations are much faster than *ab-initio* calculations but can produce erratic results and predict fewer properties reliably [12].

The Hückel calculation, which is the basis for the semiempirical methods, models only the p valence electrons in a planar conjugated hydrocarbon and uses a parameter to describe the interaction between bonded atoms. However, there are no second atom effects. While Hückel calculations can provide qualitative insights and reflect orbital symmetry and coefficients, they are limited in their ability to deal with large molecular systems and give only crude quantitative information. The PPP method is an extension of the Hückel method that can handle heteroatoms other than hydrogen, and it is still occasionally used when only minimal amounts of electronic effects are required. It is also useful for developing simple parameterized analytic expressions for molecular properties.

The MINDO method has three variations: MINDO/1, MINDO/2, and MINDO/3. However, these have been replaced by more accurate methods such as AM1 and PM3. MINDO/3 is still sometimes used as a starting point for *ab-initio* calculations. The MNDO method is popular for its ability to give reasonable qualitative results for many organic systems and has been incorporated into several semiempirical programs.

An extrapolation method called the G1 method, which uses *ab-initio* calculations, is seldom used due to its lower accuracy compared with the G2 method. G2 is an accurate way to model small organic molecules, but its accuracy decreases when applied to chlorofluorocarbons [13]. The G3 method shows some improvement in accuracy, particularly for chlorofluorocarbons. These extrapolation methods use empirically defined equations parameterized to accurately reproduce results from a test set of molecules [14].

1.2.3 Molecular Mechanics

It has been found possible to model the behavior of a large molecular system avoiding the quantum mechanics treatment pertaining to the *ab-initio* and semiempirical calculations totally by using molecular mechanics. Bypassing these quantum mechanical treatments becomes significant in view of the limitations imposed with *ab-initio* and semiempirical calculations on the large molecular and biomolecular system.

The equations describe various aspects of the molecule, such as bond stretching, bond bending, torsions, electrostatic interactions, van der Waals forces, and hydrogen bonding. We call a set of equations with their associated constants a "force field." Since this method does not explicitly include electrons, it cannot model electronic processes.

The table below presents the mathematical form of energy terms that are frequently used in popular force fields:

Name of force field	Parameter used	Energy term
Harmonic	Bond stretching	$k (l - l_o)^2$
Harmonic	Angle bending	$k (\theta - \theta_o)^2$
Cosine	Torsion	$k [1 + \cos (n \theta)]$
Leonard-Jones 6–12	van der Waals	$4k (A/r)^{12} - (B/r)^6$
Leonard-Jones 10–12	van der Waals	$4k (A/r)^{12} - (B/r)^{10}$
Coulomb	Electrostatic interaction	$\frac{q_1 q_2}{4\pi\varepsilon_0 r}$
Taylor	Stretching–bending	$k (\theta - \theta_o) [(l_1 - l_{10}) (l_2 - l_{20})$
Morse	Bond stretching	$D_e [1 - e^{-a(l-l0)}]^2$

Abbreviations: k, α, A, B: constants particular to the elements in a certain hybridization state; l: bond length; θ: bond angle; n: an integer; q: charge; D_e: dissociation energy.
*Source: Ref. [5].

The constants in these equations must be obtained from experimental data or an *ab-initio* calculation. The success of the method is dependent on the database of compounds used for parameterization. Most force fields simplify the calculations by omitting most of the hydrogen atoms and modifying the parameters describing each backbone atom to account for the behavior of the attached hydrogens. This approach is known as united atom force fields or intrinsic hydrogen methods and is commonly used to describe large biomolecules. Originally developed for proteins and nucleic acids, it is now applied to a range of studies such as molecular dynamics, salvation, crystal packing, vibrational analysis, and QM/MM studies. Five valence terms, including an electrostatic term, are used in CHARMM [15]. DREIDING is another important force field program used for simulating biomolecules.

1.2.4 Molecular Dynamics

The time-dependent behavior of a molecular system, such as vibrational motion or Brownian motion, is simulated in molecular dynamics, which requires a way to compute the energy of the system, most often using a

molecular mechanics calculation. The forces on the atoms for any given geometry are computed using this energy expression. An equilibrium system can be simulated using a well-defined procedure for executing molecular dynamics. If the purpose of the simulation is to search conformation space for geometry optimization, the force field is designed to describe intermolecular forces and vibrations away from equilibrium. Computer programs embedded with force fields like GROMOS or OPLS are available for simulating bulk systems. Several equations of motion such as the Verlet algorithm, velocity, Beeman's algorithm, and Gear predictor-corrector algorithm, to name a few, are used for molecular dynamics simulations. Predictor corrector algorithms give accurate integration but are seldom used due to their large computational needs.

To verify the simulation results obtained for a synthetic system, it is important to execute the aforesaid algorithm for a system with a constant volume, number of particles, and temperature.

1.2.5 Density Functional Theory (DFT)

The popularity of density functional theory (DFT) in recent years is justified by the pragmatic observation that it is less computationally intensive than other methods with similar accuracy. The electronic energy in current DFT methods is partitioned into several terms using an approximate functional:

$$E = E^T + E^V + E^J + E^{XC} \tag{1.42}$$

The electronic energy in current DFT methods is partitioned into several terms as follows: The kinetic energy term, arising from the motion of the electrons, is denoted by E^T. The potential energy of the nuclear–electron attraction and the repulsion between pairs of nuclei are included in E^V. The electron–electron density repulsion term, also known as the Coulomb self-interaction of the electron density, is denoted by E^J, and the exchange-correlation term, which includes the remaining part of the electron–electron interactions, is denoted by E^{XC}.

E^J is given by the following expression.

$$E^J = \frac{1}{2}\int\int \rho(\vec{r_1})(\Delta r_{12})^{-1}\rho(\vec{r_2})d\vec{r_1}\vec{r_2} \tag{1.43}$$

An integral involving only the spin densities and possibly their gradients is usually used to approximate E^{XC} in practice:

$$E^{XC}(\rho) = \int f(\rho_\alpha(\vec{r}), \rho_\beta(\vec{r}).\nabla\rho_\alpha(\vec{r})\nabla\rho_\beta(\vec{r}))d^3\vec{r} \tag{1.44}$$

The α spin density is denoted by ρ_α, the β spin density is denoted by ρ_β, and the total electron density $(\rho_\alpha + \rho_\beta)$ is denoted by ρ. E^{XC} is divided into separate parts, corresponding to same-spin and mixed-spin interactions and referred to as the exchange and correlation parts, respectively:

$$E^{XC}(\rho) = E^X(\rho) + E^C(\rho) \tag{1.45}$$

The electron density determines the nature of all three terms, and the functionals that define the two components on the right side of Equation (1.45) are known as exchange functionals and correlation functionals, respectively. Both components can be of two types: local functionals, which depend only on the electron density, and gradient-corrected functionals, which depend on both ρ and its gradient, ∇_ρ.

In the sample functional, the local exchange functional is virtually always defined as follows:

$$E^X_{\text{LDA}} = -\frac{3}{2}\left(\frac{3}{4\pi}\right)^{\frac{1}{3}} \int \rho^{\frac{4}{3}} d^3\vec{r} \tag{1.46}$$

Of course, ρ is a function of r. The local exchange functional in the form mentioned above was developed to reproduce the exchange energy of a uniform electron gas. However, this functional has weaknesses when it comes to describing molecular systems. Becke formulated the following gradient-corrected exchange functional, which is based on the local density approximation (LDA) exchange functional and is now widely used:

$$E^X_{\text{Becke88}} = E^X_{\text{LDA}} - \gamma \int \frac{\rho^{\frac{4}{3}} x^2}{1 + 6\gamma \sin h^{-1} x} d^3\vec{r} \tag{1.47}$$

Here, $x = \rho^{-\frac{4}{3}} |\nabla_\rho|$. The parameter γ is chosen to fit the known exchange energies of the inert gas atoms, and Becke defines its value as

0.0042 Hartrees. As Equation (1.47) shows, Becke's functional is a correction to the local density exchange functional and successfully remedies many of the deficiencies of the LDA functional.

There are also local and gradient-corrected correlation functionals. For instance, Perdew and Wang formulated the following local part of their 1992 correlation functional [16]:

$$E^C = \int \rho \varepsilon_C \left(r_s \left(\rho(\vec{r}) \right), \zeta \right) d^3\vec{r}$$

$$r_s = \left[\frac{3}{4\pi\rho} \right]^{\frac{1}{3}}$$

$$\zeta = \frac{\rho_\alpha - \rho_\beta}{\rho_\alpha + \rho_\beta}$$

$$\varepsilon_C(r_s,\zeta) = \varepsilon_C(\rho,0) + a_C(r_s)\frac{f(\zeta)}{f''(0)}(1-\zeta^4) + [\varepsilon_C(\rho,1) - \varepsilon_C(\rho,0)] f(\zeta)\zeta^4$$

$$f(\zeta) = \frac{[(1+\zeta)^{4/3} + (1-\zeta)^{4/3} - 2]}{(2^{\frac{4}{3}} - 2)} \tag{1.48}$$

r_s is termed the density parameter. ζ is the relative spin polarization. $\zeta = 0$ corresponds to equal α and β densities, $\zeta = 1$ corresponds to all α density, and $\zeta = -1$ corresponds to all β density. It is noted that $f(0) = 0$ and $f(\pm 1) = 1$.

The general expression for ε_C involves both r_s and ζ its final term performs an interpolation for mixed spin cases. The following function G is used to compute the values of $\varepsilon_C(r_s,0), \varepsilon_C(r_s,1)$, and $-a_C(r_s)$ as:

$$G(r_s, A, \alpha_1, \beta_1, \beta_2, \beta_3, \beta_4, P) = -2A(1+\alpha_1 r_s) in \left(1 + \frac{1}{2A(\beta_1 r_s^{\frac{1}{2}} + \beta_2 r_s + \beta_3 r_s^{\frac{3}{2}} + \beta_4 r_s^{P+1})} \right) \tag{1.49}$$

In Equation (1.47), the parameters for G, except for r_s, were chosen by Perdew and Wang to reproduce accurate calculations on uniform electron gases. When G is used to evaluate each of $\varepsilon_C(r_s,0), \varepsilon_C(r_s,1)$, and $-a_C(r_s)$, the

parameter sets differ. Similar to the exchange functional examined earlier, a gradient correction can improve a local correlation functional.

Pairing an exchange functional with a correlation functional defines pure DFT methods. For instance, the well-known BLYP functional pairs Becke's gradient-corrected exchange functional with the gradient-corrected correlation functional of Lee, Yang, and Parr [17, 18].

1.3 Theoretical Framework for Biological Activity

Great commercial interest exists in predicting the activity of a compound in a biological system, encompassing both desired properties like drug activity and undesired properties like toxicity. The complexity of biological systems makes such predictions very challenging. Molecular simulation techniques can be utilized to predict how a compound will interact with a specific active site of a biological molecule. These techniques are categorized as QSAR, QSPR, and molecular docking, which are discussed below.

1.3.1 Quantitative Structure–Activity Relationship (QSAR)

QSAR is widely used to study the biological activity of a molecular system. It involves creating an equation that predicts biological activity from the properties of the individual molecule only, using a curve fitting technique. To parameterize a QSAR equation, a quantified activity for a set of compounds must be known, typically referred to as lead compounds in the pharmaceutical industry. However, test results are usually available for only a small number of compounds, making it challenging to select a number of descriptors that will provide useful results without fitting to anomalies in the test set. Normally, three to five lead compounds per descriptor in the QSAR equation are considered adequate.

It may be desirable to use parabolic functions instead of linear functions in drug design, as the descriptor for an ideal drug candidate often has an optimum value. In such cases, drug activity will decrease when the value is either larger or smaller than the optimum value, and this functional form can be described by a parabola instead of a linear relationship. QSAR is useful for determining general criteria for activity, but it does not readily yield detailed structural predictions.

1.3.2 Quantitative Structure–Property Relationship (QSPR)

To develop a QSPR equation, one should begin by compiling a list of compounds with known experimentally determined properties. It is ideal to have a large list, often including thousands of compounds. If there are fewer compounds than parameters to be fitted in the equation, the curve fitting will fail. An exact fit obtained by fitting the equation to all the anomalies in the data can be misleading and may not reflect the correct trends needed for a predictive method. To ensure that the method will be predictive, there should be ideally 10 times as many test compounds as the fitted parameters. The choice of compounds is crucial, as fitting the equation with only hydrocarbon data will only be reliable for predicting hydrocarbon properties.

The next step is to obtain geometries for the molecules. While crystal structure geometries can be used, it is better to use theoretically optimized geometries. Theoretical geometries cancel out any systematic errors in computation and enable the method to predict compounds that have not been synthesized yet. Some of the simpler methods require only connectivity.

To compute molecular descriptors, researchers must use any numerical value that describes the molecule. They can obtain many descriptors from molecular mechanics or semiempirical calculations, such as energies, population analysis, and vibrational frequency analysis with associated thermodynamic quantities. After computing the descriptors, researchers must decide which ones to use by computing correlation coefficients. Correlation coefficients measure the linear relationship between the descriptor and the property. A correlation coefficient of 1 indicates an exact description of the property, while a coefficient of zero means the descriptor is irrelevant. Researchers should choose descriptors with the largest correlation coefficients to create a property prediction equation through curve fitting.

Such as

$$\text{Property} = c_0 + c_1 d_1 + c_2 d_2 \ldots\ldots\ldots \tag{1.50}$$

Where c_i are the fitted parameters and d_i the descriptors. The process described in the preceding paragraphs has been automated very well in the more sophisticated QSPR programs.

1.3.3 Molecular Docking

Computational docking methods like DOCK, FLEXL, and GOLD in combination with empirical screening functions are used to predict the

orientation of ligands on protein binding sites and their binding affinity. These methods are used to predict the protein–ligand interaction study, including the binding energy of the complex and the types of signals produced, which have significant applications in medicine.

The docking methods are categorized as lock and key/rigid docking, in which both the internal geometry of the receptor and ligand is kept fixed, and induced fit/flexible docking, in which enumeration on the rotations of one of the molecules (usually the smaller one) is performed, and energy is calculated. Later, the most optimum pose is selected. Several program packages are available for molecule docking, including Sanjeevini, Schrodinger, Dock Autolock Tools [19], Discovery Studio, and iGemDock.

1.4 Future Scope

The future study may be focused to investigate the electronic properties and conformation by using quantum mechanical computation which has not been ever carried out on the biomolecules naturally contained in the leaves and fruits of various natural sources already isolated and characterized in order to explore their novel applications and their derivatives.

Due to the naturally occurring biomolecules' large size, DFT-based quantum chemical calculations have been found to be more dominant than *ab-initio* and semiempirical methods due to their consistency with experimental measurements. Recent reports have shown that the DFT approach is best suited for quantum chemical calculations on biomolecules [20, 21]. Biophysical studies using docking approaches have also been carried out to investigate the molecular forces controlling the biological interactions [22, 23] of these biomolecules with protein receptors and to calculate binding energy and subsequent bioactivity, as this approach has been found to be most appropriate for this purpose [24]. Although these naturally occurring biomolecules have been reported to be biologically active upon isolation from the aforementioned plant, the physical principles behind such bioactivity are yet to be elaborated. Therefore, quantum chemical calculations and molecular docking are carried out to explore the physical principles behind the bioactivity and prediction of novel applications. The development of computational techniques has opened up avenues for such investigations in the light of existing theories of physics.

We intend to utilize DFT-based quantum chemical calculations to determine the optimized geometry, Mulliken atomic charge distribution, HOMO–LUMO energy band gap, global reactivity descriptors, molecular electrostatic potential (MESP) surface, non-linear optical (NLO)

properties, and spectroscopic characteristics (IR, Raman, NMR, and UV–visible spectra) [25, 26]. Additionally, we propose conducting a molecular docking study to investigate protein–ligand interaction and compute the free energy of binding. Furthermore, the natural bond orbital (NBO) analysis and local reactivity descriptors, such as Fukui function ($f_k^{\pm}$), local softness ($s_k^{\pm}$), and local electrophilicity ($\omega_k^{\pm}$), will be computed using DFT-based quantum chemical calculations on biologically active natural compounds. This article offers several research ideas that could help to elucidate the physical principles behind the bioactivity of these natural compounds and to identify potential novel applications.

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