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ORIGINAL ARTICLE

Reactivity and Structure Analysis of Anticancer Properties of Citronellol, Linalool and Geraniol Essential Oils by Using DFT Calculation

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Abstract

Objective: The purpose of this research is to look at the reactivity and structural feature of essential oils that have anti-cancer capabilities. **Method:** Citronellol, linalool, and geranial's molecular structures are retrieved from PubChem (7794, 637566, and 6549). This aids in understanding the reactivity and stability by using a density functional theory (DFT) calculation with the B3LYP functional, that includes Becke's three-parameter exchange function and the Lee-Yang-Parr correlation function, alongside the 6-311++G(d,p) basis set for accurate modelling of the electronic structure. **Finding**: According to the International Organisation for Research on Cancer, there were approximately 19.3 million new instances of cancer globally in 2022, and over ten million individuals suffered from this terrible illness. Cancer is expected to affect almost every organ in the human body, including the liver as well as the stomach, breast, and lungs, and cause a 70% increase in cancer-related fatalities during the next 20 years. Natural products contain a substantial number of anti-cancer agents. Natural products have an important part in cancer therapy. Citronellol, Linalool, and Geraniol are used in the treatment of cancer. Citronellol, Linalool, and geraniol are essential oil that comes from plants. Density functional theory (DFT) is a computer technique that predicts biological molecules' electrical structures, interactions, and reactions. It aids in drug binding, folding, and stability, bridges the gap between quantum chemistry and biology, and aids in drug design and development. It also predicts drug toxicity and metabolism, improving safety. **Novelty:** The difference in energies from HOMO and LUMO states is used to assess stability and reactivity. Local and global characteristic determine hardness and softness as well as nucleophilic and electrophilic nature.

Keywords: Citronellol; Linalool; Geraniol; Descriptors of global and local reactivity; Density of state; Density functional theory

1 Introduction

The International Agency for Cancer estimates that there are 19.3 million newly diagnosed cancer cases globally, with around 10 million of those instances ending in death from the disease's final stages. Cancer is projected to impact almost every organ in the human body, including the lungs, liver, stomach, and breasts, and cause a 70% increase in mortality attributable to the disease during the next two decades. From ancient times natural products are used for preventing and treatment of various diseases.[(1)] Natural product continuously works as therapeutics for healing cancer in between 1950 and 1960. The National cancer institute recognizes the medicinal value of natural products. The two most prosperous examples are camptothecin and taxol. These two compounds are used especially in leukemia (blood cancer). NCI examine many plants in 1970 and found Taxol. The main indications for this medication include the treatment of ovarian and breast malignancies. Many medicinal herbs and spices such as garlic and turmeric seeding in the Indian ancient medicinal system Ayurveda. In vitro (conducted in a lab) and in vivo (conducted on real organisms) research employ some natural substances. Numerous natural components have anticancer properties which come from plants, microbial and marine sources. At present time essential oil which comes from plants is widely employed in the treatment of many diseases. The essential oil also called volatile oils is synthesized by aromatic plants. Commonly essential oils are volatile and have a strong odor. Many studies notify about the various application of essential oil in pharmaceutical, biomedical, cosmetic food, and agriculture areas. Recent studies prove that essential oils have anti-cancer properties, many biological activities, and antimicrobial activity.[(2)] For example, various essential oils are used in different types of cancer. Breast cancer is treated with Boswellia sacra, a plant in the Burseraceae family. Geraniol uses in colon or colorectal cancer. *Cymbopogon citratus* is administrative for the treatment of ovarian cancer. The essential oil which is isolated from the leaf of Neolitsea variabillis used in oral cancer. The leaf of Caesarian sylvestris and Neolitsea variabillis is utilized to manage leukemia cancer. Essential oil gets from thymus citriodorus Artemisia indica and pituranthos tortuous used in liver cancer. Citronella, Geraniol, and Linalool are the essential oil which is used in cancer treatment. Citronellol ($C_{10}H_{20}O$) is a natural cyclic monoterpenoid essential oil that has many medicine pharmacies as well as cosmetic fragrance industries.[(3)] Citronellol and Geraniol are two of them Indonesian natural products. Citronellol and Geraniol are both compounds used as guiding compounds to develop chemoprevention chemotherapeutic agent's compound for cancer, especially for leukemia cancer. Linalool's chemical formula is ($C_{10}H_{18}O$) linalool is unsaturated monoterpene alcohol. Linalool (3,7-dimethyl, 6-octadien 3) exists as a prime component of the essential oil of plants, especially coriander and lavender. Recent vitro and Vivo studies indicate that, linalool possesses pharmaceutical properties that cause its cancerous effect. Linalool may work as a stimulus of immune cells, which is accountable for its cancer effect. Linalool is present in many cosmetics, perfumes, shampoos, and in cleaning products. Linalool is the root of odour and tang. Many studies notify that essential oils have various properties such as anticancer, anti-microbial, and biological activity.[(4)] Essential oils are used for treating many diseases. Current studies on the antioxidant and antibacterial qualities of essential oils, especially citronellol, geraniol, and linalool, demonstrate technical shortcomings. Without having a firm understanding of electrical interactions and structures, these include a lack of computational methods such as density functional theory (DFT), an inability to understand their synergistic effects, and unknown chemical interactions. Moreover, a focus on certain medications and uneven methods weakens the body of knowledge. In this paper we study the reactivity along with the structural characteristics by Gaussian 6-311++G(d,p) basis set and the B3LYP function. The descriptors for global and local responsiveness explain the molecule's stability. This tells about the softness and hardness of the molecule. Density functional theory (DFT) is a computer technique used to predict the electrical structures, interactions, and reactions of biological molecules. In order to assist explain drug binding, folding, and bimolecular stability, it offers accurate predictions for bond lengths, geometries, and non-covalent interactions. Due to its ability to bridge the gap between quantum chemistry and biology, DFT is essential to the development of novel biological materials and the design of drugs. It looks into reaction mechanisms, optimum medicine binding affinity, and non-covalent interactions including hydrogen bonding. DFT also clarifies transition states and spectroscopic features associated with pharmaceutical action. Additionally, it forecasts drug toxicity and metabolism, improving the safety of medications. DFT supports rational drug design and the development of new drugs by offering a cost-effective and practical way to accelerate drug discovery and development. Previous research has focused on empirical or experimental evaluations of the compounds' activities, leaving them unexplored. The DFT approach will concentrate on particular alterations at the atomic level or advancements in the design of molecules using quantum calculations. These are areas that have been previously investigated and continue to have implications for green chemistry and sustainability. Prior research has focused on more general applications without tying these quantum-level electrical features to the underlying electronic structure, hence it has not thoroughly investigated these properties.

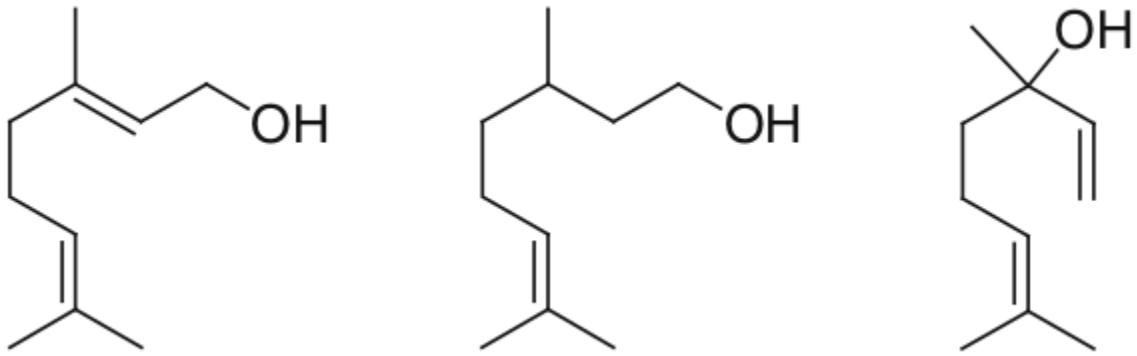

Fig 1. structure of Geraniol, Citronellol and Linalool

2 Methodology

The molecular structure of Citronellol, linalool, and geranial are taken from PubChem (7794, 637566, and 6549). At the B3LYP/6-311++G(d,p) level of theory, density functional theory, also known as DFT, was used in order to optimise the structure to its minimal energy. In Figure 2 the optimized structure is display and their optimized participation coordinates are provided in the supplementary information. "The 6-311++G(d,p) basis set is commonly used in conjunction with B3LYP, a hybrid functional developed by Mori-Sánchez et al., to produce molecular structure predictions that closely resemble experimental findings. Researchers looking into organic molecules made of elements up to the third row of the periodic table frequently use this method. For determining the nature of the stationary point, analytical frequency calculations were performed on the optimized structure. All the frequencies in the optimized structures are positive therefore structure represents true minima. Natural bond orbital (NBO) interpretation was carried out to investigate intra- and intermolecular interactions. Hirshfeld population analysis was subsequently applied to determine the local moreover global reactivity of these molecules. Using the Gaussian perspective, monograms of the molecular geometries and computed data have been produced. The Local and global reactivity of molecules such as hardness, softness, electronegativity (χ) and electrophilic index (ω) was concluded by HOMO energies levels and LUMO energies levels.

3 Results and Discussion

3.1 Structural Properties

The computed optimized by Gaussian 09. The optimized structures of three essential oils, Citronellol, linalool, and geraniol, are shown in Figures 2, 3, and 4. The bond lengths between H-O in citronellol, linalool, and geraniol are 0.9626, 0.9639, and 0.9629. This is about the identical as the average O-H bond length. The molecular weights of Citronellol, Geraniol, and Linalool are 152.233, 154.249, and 154.249.

3.2 Frontier Molecular Orbitals (FMOs)

For describing the chemical reactivity of molecules we use FMO's theory. A molecule's electrical transport characteristics, stability, biological activity, and chemical reactivity are all influenced by the energies of its LUMO and HOMO as well as the gap between them. When the energy difference between HOMO and LUMO is large it describes as a hard molecule and when the distinct between the homo and LUMO is small it describes as a soft molecule. The large and small void between HOMO and LUMO is related to the reactivity of the molecule. If the gap is large it is polarise (reactive) and related to a high chemical reactivity (less stable). It is additionally related to molecular stability, which illustrated the molecule's harness and softness. This indicates the hardness and softness of the molecule. If the stability is lower, it shows a harder molecule, and diminished stability shows entails the molecule has acquired greater chemical reactivity and is softer. When HOMO energies are high it is a very reactive molecule with electrophiles, while it has low energies in LUMO it shows as nucleophiles.[5] Citronellol, linalool, and Geranial's calculated HOMO and LUMO energies illustrate that they are stable because all of the values possess negative magnitudes. These molecules appear to be hard and chemically stable considering the large energy gap between HOMO

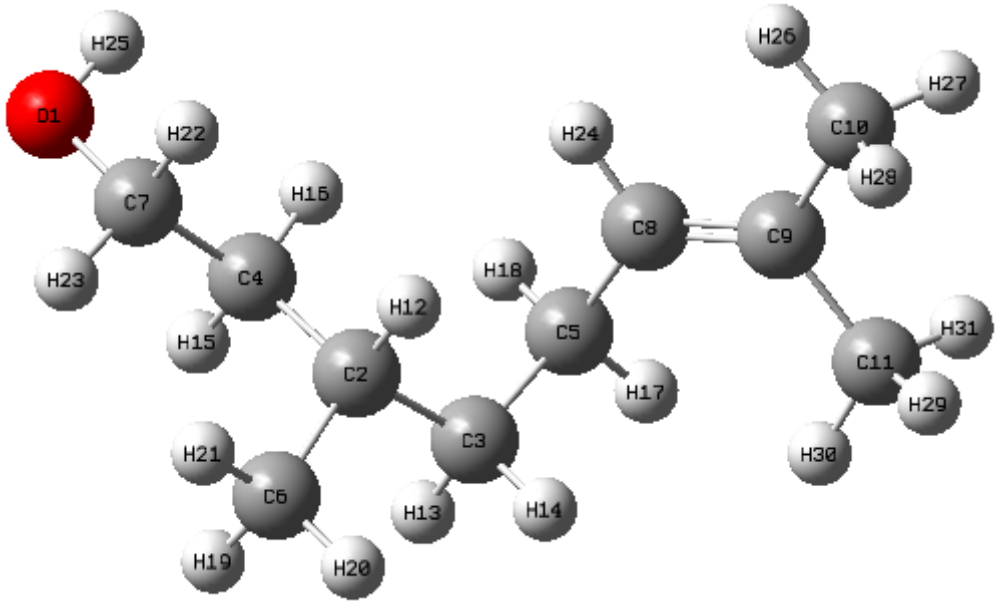

Fig 2. Optimized Structure of Citronellol

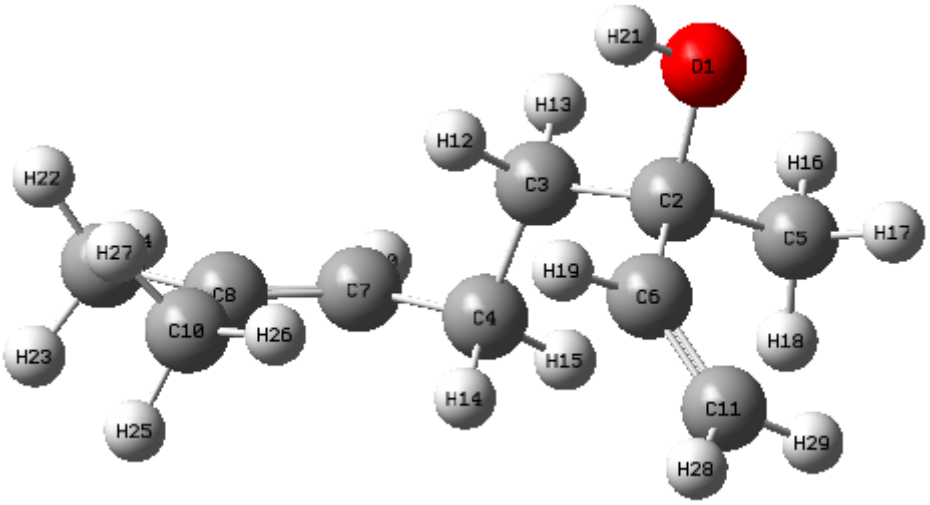

Fig 3. Optimized Structure of Linalool

and LUMO. The determined HOMO energies for citronellol, linalool, and geraniol are -6.5507 eV, -6.435 eV, and -6.4541 eV, respectively. The corresponding LUMO energies are -0.4056 eV, -0.4130 eV, and -0.5471 eV.

3.3 Molecular Electrostatic Potential

Reactivity, hydrogen bonds, and the interaction between a molecule's structure and activity are all emphasized by the molecular electrostatic potential. It also provides illumination on the relationships between these characteristics, biomolecular interactions, and possible medicinal applications.A molecule's or an atom's surrounding electrostatic potential at a position r is

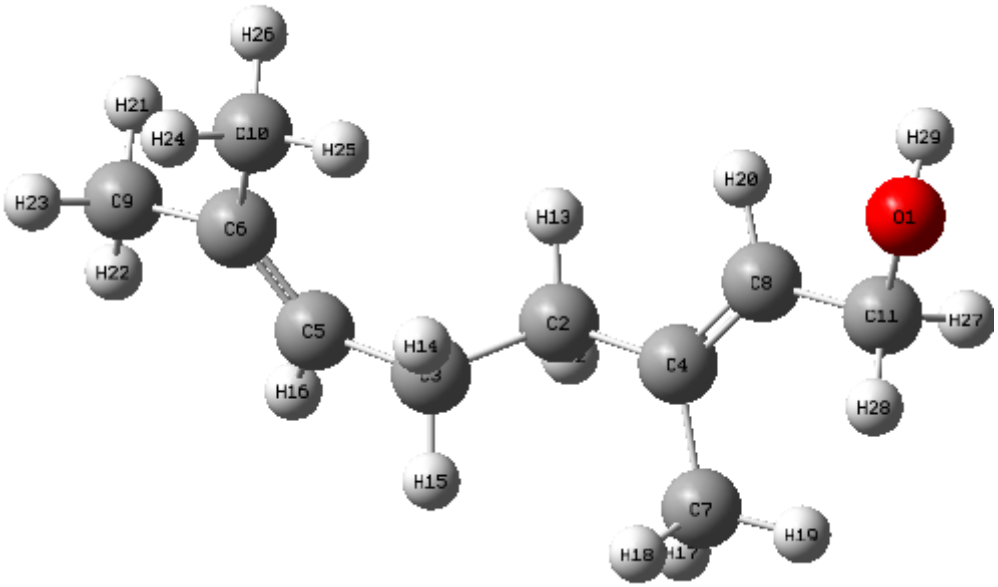

Fig 4. Optimized Structure of Geraniol

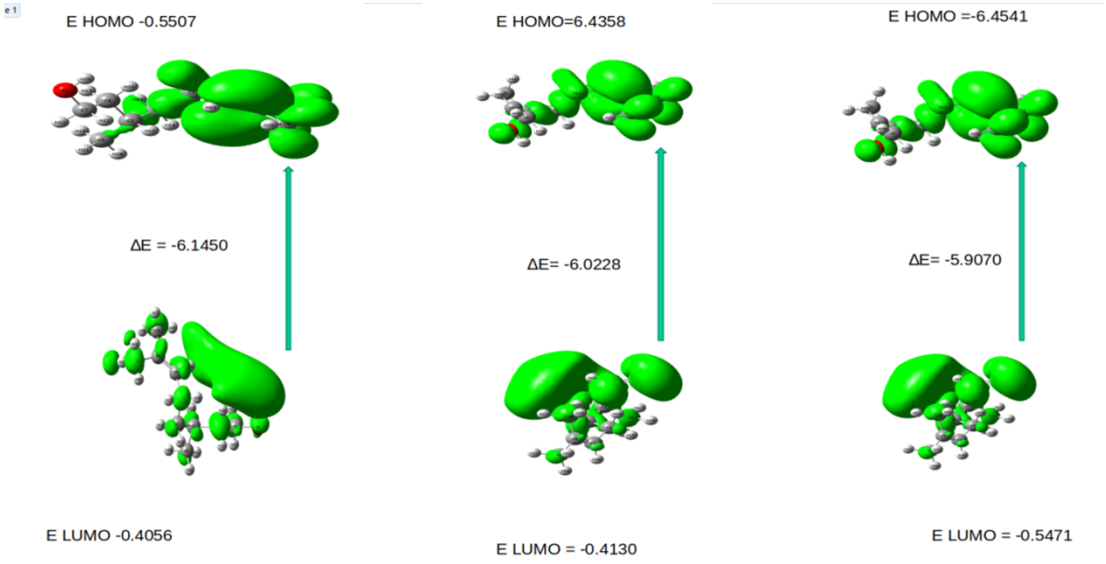

Fig 5. Molecular orbital of Citronellol, geraniol and linalool

expressed in atomic units (au.).

$$V(r) = \sum_{A}^{N} \frac{Z}{\overline{R}} - \int \frac{\rho(r')dr'}{|r' - \vec{r}|}$$

At each location r, V(r) denotes the total electrostatic effect derived by the molecule's electron and nuclei. The function for electronic density is represented by nucleus A at R a charge ZA ρ(r^'). The second term, the electron, and the nuclei can all have an essential part. The reactive region of an electrophilic and nucleophilic attack on a molecular system is described by MEP. To determine the electronic change throughout the entire structure, it is frequently formed by tracing the electrostatic potential on the isoelectronic density surface of the molecule. At the structure, this method is helpful for comprehending the

hydrogen bond interaction, the molecule surroundings and the biological recognition process.[6] Color is used to represent the various electrostatic potential values at the surface. The domain of negative electrostatic potential was indicated by red, the most positive electrostatic potential was indicated by blue, and the zero potential was represented by green. Whereas the red domain denotes an electrophilic nature, the blue domain is an electron-deficient region that indicates nucleophilic character. Nucleophilic attacks are likely to target the species closest to these areas. The hydrogen atoms with the highest specific potential among them are H24, H25, and H27 in citronellol, H29 in geraniol, and H25 in linalool. These atoms are attached to bright blue domains. Conversely oxygen particle across the carbonyl group achieves the electrophilic attack, which has a red zone with the most unpleasant potential. The receptor site that reacts dynamically is a part of the biological acknowledgment system.

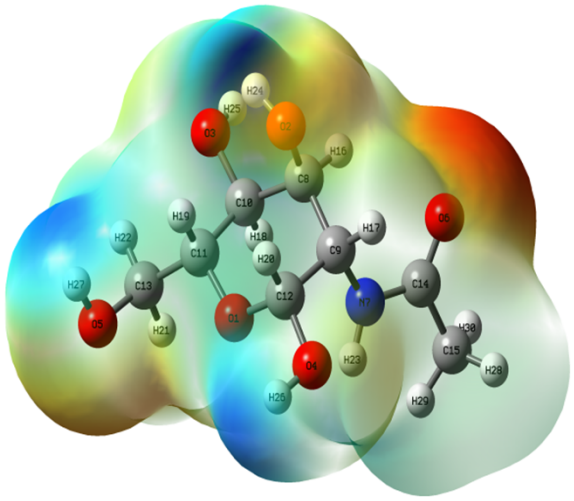

Fig 6. Molecular electrostatic surfaces (MEP) of Citronella **-6.439e-2 6.439e-2**

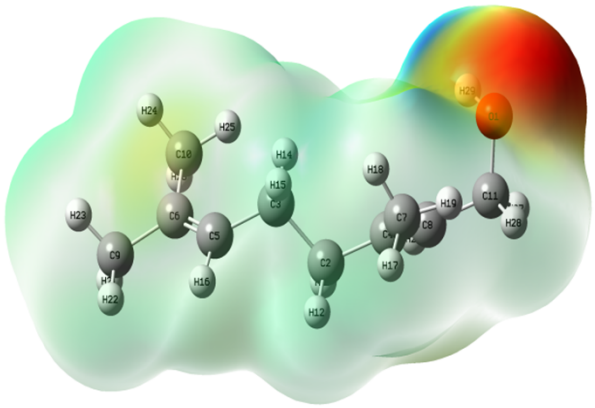

Fig 7. Molecular electrostatic surfaces (MEP) of Geraniol **-4.956e-2 4.956e-2**

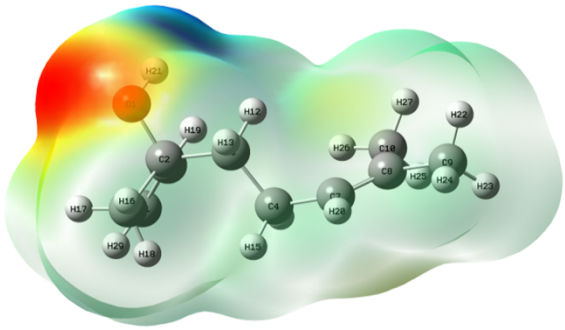

Fig 8. Molecular electrostatic surface (MEP) of Linalool **-4.781e-2 4.781e- 2**

3.4 Global Reactivity Descriptors

We evaluate the global descriptor for the purpose to more fully comprehend the correlation among structure, stability and global chemical reactivity. The global reactivity descriptor chemical potential (μ), electronegativity (χ), global softness (s), global hardness (η) and electrophilicity index (ω) is used to understand the relationship between structure, stability, and global chemical reactivity. Electrophilicity indicates an electrophile's capacity and informs about the stability and the transfer of electron. A molecule's overall reactivity and site selectivity are both determined by its electrophilicity (ω). This calibrates the biological activity. The chemical potential (μ) that is negative is showing that the electron is facile but is very tough to drop an electron.[7] The chemical potential measures the fugacity of an electron. Negative chemical potential indicates that it does not decompose into elements. The level of hardness and softness of the molecule signify the energy variation between HOMO and LUMO. When the gap is large, the molecule is hard and when the gap is small the molecule is soft. Soft molecules are highly polarized, which affects their chemical reactivity, whereas hard molecules usually have smaller and less polarizable. The energies of frontier molecular orbitals, HOMO-LUMO, and given equations were utilized in the descriptor calculation.

1. The electronegativity $(\chi) = 1/2(^{\epsilon}\text{LUMO} + {}^{\epsilon}\text{HOMO})$
2. The chemical potential $(\mu) = -1/2(^{\epsilon}\text{LUMO} + {}^{\epsilon}\text{HOMO})$
3. The global hardness $(^{\eta}) = 1/2(^{\epsilon}\text{LUMO} - {}^{\epsilon}\text{HOMO})$
4. The softness (s) $= 1/2^{\eta}$
5. Global electrophilicity index $(\omega) = \mu^2/2\eta$

The small value of the global electrophilicity index (ω) shows a good nucleophile and the higher value shows a good electrophile. A large value of μ and a small value of ω show nucleophilic actions. The Citronellol, linalool, and geraniol have smaller values of ω (1.9687, 1.9470, 2.0739) and larger values of χ (3.4781, 3.4244, 3.4995), which show a nucleophilic action. Citronellol, linalool and geraniol act as an electron donor.

Table 1. Global Descriptor Reactivity

Molecule	**electronegativity**(χ)	**chemical potential** (μ)	**global hardness**$(^{\eta})$	**softness (s)**	**Global electrophilicity index** (ω)
Citronellol	-3.4781	3.4781	3.0724	0.1627	1.9687
Linalool	-3.4244	3.4244	3.0114	0.16603	1.9470
geraniol	-3.4995	3.4995	2.9523	0.1693	2.0739

3.5 Local Reactivity Descriptor

Site-selectivity and reactivity in chemical reactions are distinguished using local reactivity descriptors, such as the Fukui function, local softness, and local electrophilicity indices. These descriptors aid in describing the reactivity of particular reactive

centers, such as radical, electrophilic, and nucleophilic sites. The local descriptors—Fukui functions ($fk+$, $fk-$, $fk\,0$) (f k +,f k − ,f k 0), local softness ($sk+$, $sk-$, $s\,k\,0$) (s k +, s k −,s k 0), and local electrophilicity indices ($\omega\,k+$, $\omega\,k-$, $\omega\,k\,0$) (ω k +,ω k −,ω k 0)—are all calculated using the B3LYP/6-311++G(d,p) method. These local reactivity parameters are calculated using the following formulas.

1. $f^{+}{}_{k}$ = [q (N+1) – q (N)] nucleophilic attack
2. $f^{-}{}_{k}$ = [q(N)-q (N-1)] electrophilic attack
3. $f^{0}{}_{k}$ = 1/2 [q (N+1) + (N-1)] radical attack

N, N+ 1 and N-1 represent the total electrons in the molecule's neutral, cation, and the anion states, respectively, in the equation above. The following formulae can be used to calculate the local softness and electrophilicity indices.

$S^{+}{}_{k} = S^{f+k}$, $S^{-}{}_{k} = s^{f-k}$, $S^{0}{}_{k} = s^{f0+k}$

$\omega^{+}{}_{k} = \omega^{+}\, f^{+}{}_{k}$, $\omega\,{}_{k}{}^{-} = \omega^{-}\, f^{-}{}_{k}$, $\omega\,{}_{k}{}^{0} = \omega^{0}\, f^{0}{}_{k}$

In the above equation + sing shows a nucleophilic, - sing shows an electrophilic and 0 shows a radical attack. Reactivity of the atom of the molecule described by the local softness and local electrophilicity indices. Fukui function ($f^{+}{}_{k}$, $f_{k}{}^{-}$, $f_{k}{}^{0}$) local softness ($S_{k}{}^{+}$, $S_{k}{}^{-}$, Sk^{0}) and local electrophilicity indices (ω^{+},ω^{-},ω^{0}) are indicate that Citronellol, geraniol, and linalool are more prone to reactant attack.

3.6 Density of State

The forbidden energy gap is a disparity in energy between the HOMO and LUMO states that correspond to the valence and conduction bands. The below-energy state of HOMO is referred to as a valence band, and the above-energy state of LUMO is referred to as conduction band, and at a value of 0 eV, it shows a Fermi level (E_{p}). The resultant DOS spectrum is procured due to SP hybridization. The DOS spectrum is calculated by the Gaussum 3.2 programmer. The Fermi energies of citronellol, geraniol, and linalool are 5.428 eV, 0.8531 eV, and 5.31 eV. The Fermi energy shows that citronellol and linalool have similar properties in nature, i.e., they act as insulators, and geraniol behaves as a conductor in nature.

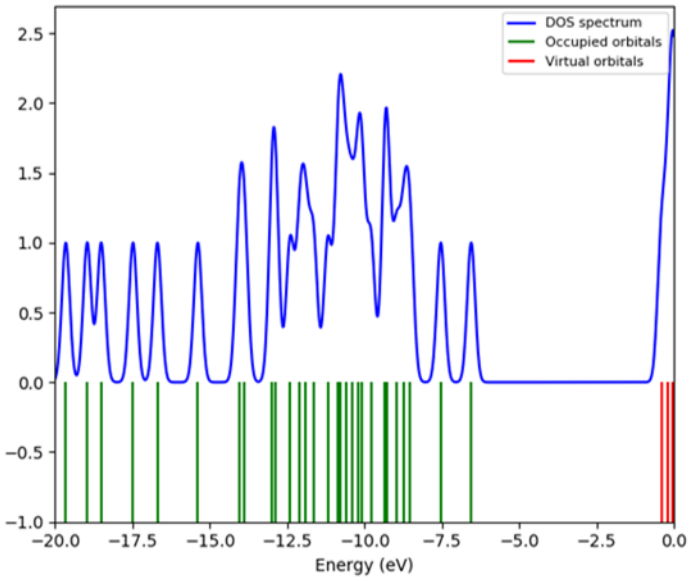

Fig 9. Density of state spectrum of Citronellol

4 Conclusion

The study is focused on the analysis of the structure and reactivity of essential oils, which have anticancer properties. We chose the essential oils citronellol, geraniol and linalool. A detailed DFT study of these monoterpenes gives the article a

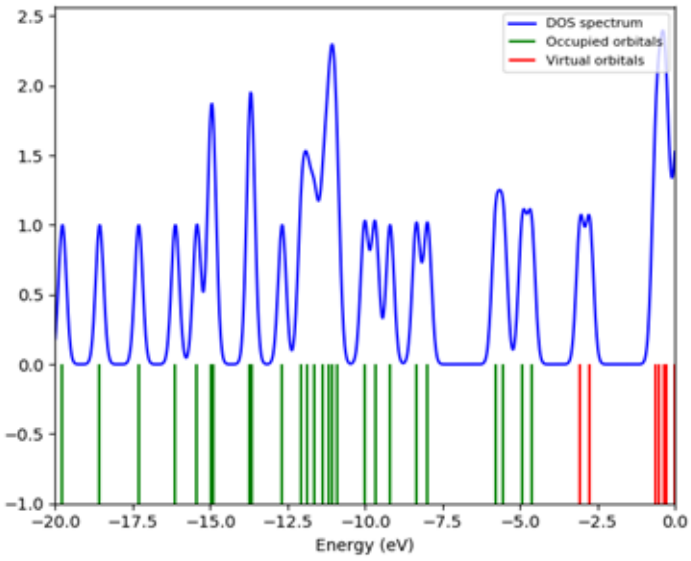

Fig 10. Density of state spectrum of Geraniol

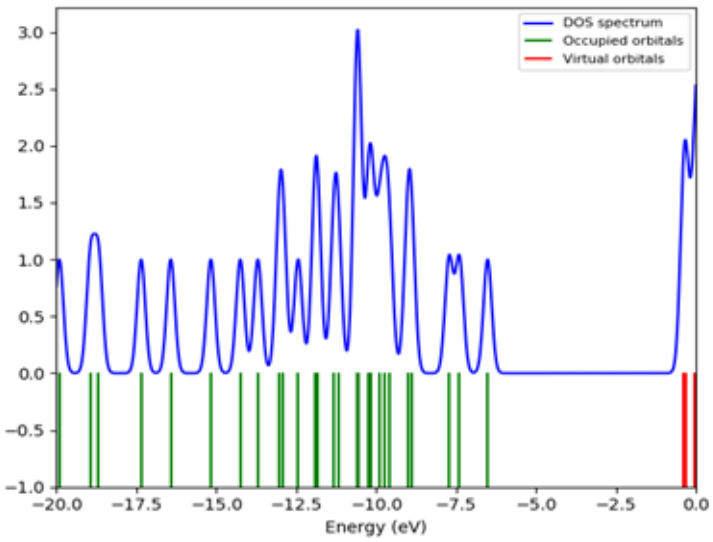

Fig 11. Density of state spectrum of Linalool

comparative understanding of geraniol, linalool, and citronellol. It highlights minor variations in electrical characteristics, potential reactivity, and molecular interactions that haven't been thoroughly examined in earlier research. The study also clarifies the connection between the molecular structures of these chemicals and their chemical behaviours, such as their antibacterial and antioxidant properties. The results could offer a theoretical foundation for upcoming computational and experimental research projects that seek to identify molecules with higher biological activity. The stability, hardness, and softness of the molecule are described by the energy variance between the lowest vacant molecular orbital and the highest occupied molecular orbital. The stability of citronellol, geraniol, and linalool was verified by the frontier molecular orbital theory. The map depicting molecule electrostatic potential, or MEP, is demonstrated by adverse domain which is mainly located around the hydrogen and positive domain is located around the oxygen. Negative and positive domains are shown by red and blue colour. Each molecule's site selectivity is highlighted by the molecular electrostatic potential (MEP) map. Citronellol, geraniol, and linalool have lower values in the analysis of global reactivity descriptors, whereas the electrophilicity index (ω) has higher values, indicating

that these molecules are nucleophilic. Linalool, geraniol, and citronellol are the three essential oils that function as electron donors. Density of state defines an energy state, which describes the conducting band, valence band, and forbidden energy gap. Citronellol and linalool are both insulators and geraniol conductors in nature. In order to validate theoretical predictions about the biological activities of Citronellol, linalool, and geraniol, future research should concentrate on experimental validation of DFT results. It is important to investigate derivatives in order to evaluate possible uses in natural or pharmaceutical goods. Research on intermolecular interactions has to be carried out in order to comprehend their modes of activity. To examine their behaviour in intricate settings, DFT can be used with computer techniques such as molecular dynamics simulations. It is important to investigate the wider uses of these substances in sectors such as agrochemicals, food preservation, and cosmetics, evaluating their safety and effectiveness profiles. This work increases our knowledge of the reactivity and structure of essential oils. This helps in many other studies and increases the properties of essential oils. This work enhances understanding of the structure–reactivity relationship of essential oils. The study establishes a theoretical framework for forthcoming computational and experimental investigations in natural product-oriented drug development.

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