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# Unveiling Nature's Arsenal: Virtual Screening Of Phytoconstituents For Anti-Acne Potentials In Medicinal Plants

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This study utilizes in-silico screening techniques to identify potential anti-acne phytoconstituents from six medicinal plants. Through comprehensive virtual screening against acne-related protein targets, ten promising compounds were prioritized based on their favorable biological activity, drug likeliness, bioavailability, and non-toxic profiles. These findings highlight the potential of these phytoconstituents for developing safe and effective anti-acne formulations, although further validation through clinical studies is warranted. Overall, this in-silico screening approach offers valuable insights for efficiently identifying potential anti-acne compounds and accelerating the drug discovery process.

**Keywords:** In-silico screening, Phytoconstituents, Anti-acne activity, Medicinal plants, Drug discovery.

## 1 Introduction:

Acne is a common skin condition that affects millions of people worldwide, leading to significant physical and psychological distress [1], [2]. Despite various treatment options available, including topical creams, antibiotics, and oral medications, the increasing prevalence of antibiotic resistance and adverse effects has sparked interest in natural alternatives [3], [4]. Medicinal plants have long been recognized for their therapeutic potential due to the presence of diverse bioactive compounds [5] known as phytoconstituents [6], [7], [8].

In recent years, in-silico screening techniques have emerged as powerful tools in drug discovery, enabling the identification of potential lead compounds in a cost-effective and time-efficient manner [6], [9], [10]. Virtual screening allows researchers to computationally evaluate large datasets of phytoconstituents and predict their interactions with specific protein targets related to acne pathogenesis [7], [8].

In this context, we aimed to exploit the vast potential of in-silico screening to identify novel phytoconstituents from commonly used medicinal plants with promising anti-acne activity [1], [2], [11], [12], [13]. We focused on six medicinal plants, including orange peel, lemon peel, green tea, turmeric, neem, and pomegranate peel, known for their therapeutic properties against various skin ailments [14], [15]. TNF-alpha (Tumor Necrosis Factor-alpha) and GehA (Glycerol-ester hydrolase A) are two potential anti-acne targets that have been studied for their roles in the pathogenesis of acne and as potential points of intervention for acne treatment [16].

### TNF-alpha as an anti-acne target:

TNF-alpha is a pro-inflammatory cytokine that plays a crucial role in the inflammatory response, including skin inflammation. In the context of acne, increased levels of TNF-alpha have been observed in acne lesions, indicating its involvement in the inflammatory process associated with acne development. Elevated levels of TNF-alpha contribute to the recruitment of immune cells, formation of inflammatory lesions, and exacerbation of acne symptoms [17]. Targeting TNF-alpha as an anti-acne strategy involves inhibiting its activity or blocking its receptor. Drugs that can neutralize or reduce TNF-alpha activity have been used in various inflammatory conditions and may have potential for treating acne by reducing inflammation and suppressing the inflammatory response in the skin [7], [12], [18].

### GehA as an anti-acne target:

GehA, also known as lipase or glycerol-ester hydrolase A, is an enzyme produced by certain bacteria, including Propionibacterium acnes, which is a key bacterium involved in the development of acne. GehA is responsible for breaking down triglycerides in sebum into free fatty acids, contributing to the formation of comedones and inflammation in acne lesions [19]. Inhibiting the activity of GehA could be a promising approach for acne treatment, as it may reduce the release of pro-inflammatory free fatty acids and mitigate the inflammatory response associated with acne. By targeting GehA, the overproduction of free fatty acids can be controlled, potentially leading to a decrease in the severity of acne lesions.

Both TNF-alpha and GehA represent potential targets for the development of novel anti-acne treatments. Targeting these molecules could help modulate the inflammatory response and lipase activity, respectively, contributing to the management of acne symptoms.

In this study, we conducted a comprehensive analysis of 50 phytoconstituents [6], [7] sourced from the IMPPAT database, which is a curated repository of phytochemicals from Indian medicinal plants. Our primary objective was to identify potential lead compounds with favorable drug-like properties that could be utilized for anti-acne applications. To ensure that the selected phytoconstituents had a higher likelihood of being orally bioavailable and drug-like, we applied Lipinski's rule of five. This well-established rule helps filter out compounds with poor pharmacokinetic properties, such as high molecular weight, excessive hydrogen bond donors, hydrogen bond acceptors, and lipophilicity. By adhering to Lipinski's rule, we narrowed down the candidate pool to compounds with improved prospects for further development[7], [8].

Subsequently, we performed molecular docking studies to predict the binding affinity of the selected phytoconstituents with specific target proteins (GehA and TNF-alpha), involved in acne pathogenesis [6]. This process allowed us to identify compounds that potentially interacted favorably with the target proteins, suggesting their potential efficacy against acne. To further assess the safety and pharmacokinetic characteristics of the shortlisted compounds, we employed ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) property analysis. This step is crucial in evaluating the compounds' potential for absorption, distribution within the body, metabolism, excretion, and potential toxicity risks. By considering these ADME and toxicity parameters, we aimed to identify compounds that have a higher likelihood of successful development as anti-acne agents.nMoreover, we also conducted PASS (Prediction of Activity Spectra for Substances) evaluation, which is a computational tool used to predict the probability of biological activity for the compounds [20], [21], [22]. This analysis enabled us to identify compounds with potential anti-acne activity based on their structural similarity to known active compounds in the PASS database. Overall, the combined use of Lipinski's rule of five, molecular docking, ADMET properties, and PASS evaluation allowed us to prioritize and identify promising phytoconstituents with optimal drug-like properties and potential biological activity against acne [6], [7], [23], [24], [25]. The compounds selected through this rigorous in-silico screening process hold great promise for further investigation and development as potential components in safe and effective anti-acne formulations [26]. However, it is important to note that further experimental validation, such as in vitro and in vivo studies, and potentially clinical trials, will be necessary to confirm their actual anti-acne efficacy and safety before practical application [10].

## 2 Methodology:

### 2.1 Selection of Phytoconstituents:

A total of 50 phytoconstituents were chosen from the IMPPAT database, a curated repository of phytochemicals derived from Indian medicinal plants, based on their reported anti-acne potential in the existing literature. These compounds were derived from six different medicinal plants, including orange peel, lemon peel, green tea, turmeric, neem, and pomegranate peel [27], [28], [29], [30], [31], [32], [33], [34].

**2.2 Lipinski's Rule of Five Screening:**

The selected 50 phytoconstituents were subjected to Lipinski's Rule of Five analysis to assess their drug-like properties. Parameters such as molecular weight (MW), lipophilicity (LogP), hydrogen bond donors (HBD), and hydrogen bond acceptors (HBA) were evaluated. Compounds that satisfied all of Lipinski's criteria (MW ≤ 500, LogP ≤ 5, HBD ≤ 5, HBA ≤ 10) were retained for further analysis, as they are more likely to have favorable pharmacokinetic properties [35], [36].

**2.3 Protein Targets Selection:**

Two potential protein targets, GehA (Glycerol-ester hydrolase A) and TNF-alpha (Tumor Necrosis Factor-alpha), were chosen based on their known involvement in acne pathogenesis. GehA is associated with the hydrolysis of lipids, while TNF-alpha is a pro-inflammatory cytokine [8], [37], [38], [39], [40], [41].

**2.4 Homology Modeling (GehA):**

The amino acid sequence of GehA was retrieved from the UniProtKB database (UniProt ID: Q6A601) for homology modeling. A suitable template with a known three-dimensional structure and high sequence similarity to GehA was identified from the Protein Data Bank (PDB) using the Swiss Model automated homology modeling server. The homology model of GehA was generated using the target sequence and the chosen template through alignment-based comparative modeling [8], [41].

**2.5 Receptor Preparation (TNF-alpha):**

The X-ray crystal structure of TNF-alpha (PDB ID: 2AZ5, resolution: 2.10Å) was downloaded from the RCSB-PDB database in PDB format. The protein structure was prepared by removing water molecules, heteroatoms, and co-crystallized ligands using BIOVIA Visualizer software, leaving only the TNF-alpha protein for further analysis [42], [43].

**2.6 Molecular Docking-Based Virtual Screening:**

The homology model of GehA and the prepared structure of TNF-alpha were used as receptors in molecular docking simulations. The library of the 50 selected phytoconstituents was prepared by converting their chemical structures into 3D molecular structures. Molecular docking simulations were performed using specialized docking software (PyRx) to predict the binding interactions between the phytoconstituents and the GehA and TNF-alpha proteins. Discovery Studio Visualizer. Docking scores, as well as binding modes and interactions, were analyzed to identify phytoconstituents with potential high affinity to the target proteins [7], [15], [26].

**2.7 ADMET Property Analysis:**

The phytoconstituents with high docking scores were subjected to ADMET property prediction and evaluation using two computational tools, pkCSM and SwissADME. The ADMET prediction aimed to assess the compounds' drug-like physicochemical and pharmacokinetic properties, such as solubility, absorption, metabolism, distribution, and potential toxicity. ADMET analysis assessed the compounds' pharmacokinetic properties, including solubility, permeability, metabolism, and potential toxicity, to ensure their suitability for further development as drug candidates [7], [8].

### 2.8 PASS Evaluation:

The selected phytoconstituents were evaluated using the PASS (Prediction of Activity Spectra for Substances) online tool. PASS predicts the probability of biological activity for the compounds based on their structural similarity to known active compounds in the PASS database. Compounds with high PASS prediction scores for anti-acne activity were prioritized as potential lead candidates[6].

### 2.9 Interaction Analysis

The interaction analysis aimed to investigate the binding interactions between the docked protein-ligand complexes. Using Discovery Studio Visualizer, the binding poses and all possible interactions were explored. Discovery Studio Visualizer was used to explore the type of interactions, residual participation, and atomic coordinates. Compounds with specific interactions towards critical residues of GehA and TNFα, including the active site and binding site, were chosen for further analysis. This analysis identified lead compounds with potential anti-acne activity and provided valuable insights for further investigation and formulation development [16], [44], [45], [46], [47].

### 2.10 Data Analysis and Lead Molecule Selection:

The data obtained from molecular docking, ADMET analysis, and PASS evaluation were collectively analyzed to identify the most promising phytoconstituents with high binding affinity, favorable drug-like properties, and potential anti-acne activity. Based on the comprehensive analysis, a set of lead molecules that exhibited the most desirable characteristics were selected as potential candidates for anti-acne drug development [48], [49], [50], [51], [52], [53], [54], [55].

## 3 Results and Discussion

### 3.1 Molecular Docking-Based Virtual Screening

A virtual screening process was conducted using molecular docking to identify phytoconstituents from the IMPPAT database that could strongly bind to GehA and TNFα, two target proteins. The output provided the affinities and docked poses for each compound. Based on their binding affinity towards GehA and TNFα, the compounds were filtered, and the top 10 hits out of 50 were selected. [Table 1] These chosen compounds demonstrated significant binding affinity with the binding pocket of GehA and TNFα, suggesting their potential as high-affinity partners. This outcome highlights the promising therapeutic potential of these selected phytoconstituents in the drug development process.

#### 3.1.1 Table 1

**The top 10 hits and their binding affinities**

| Sr. | Compound ID | Phytochemical Name | Source | Target | Binding | Interacting | Distance | Interactions |
|---|---|---|---|---|---|---|---|---|

| **No.** | | | | | **Affinity** | **Residue** | | |
|---|---|---|---|---|---|---|---|---|
| **1.** | 1794427 | o-Caffeoylquinic acid | ***Camellia sinensis*** | GehA | -7.8 | HIS A:168 | 3.00 | Conventional H-bond |
| | | | | | | THR A:103 | 3.15 | |
| | | | | | | GLY A:97 | 2.83 | |
| | | | | | | SER A:58 | 3.14 | |
| | | | | | | ARG A:62 | 2.90 | |
| | | | | | | | 3.73 | C-H bond |
| | | | | | | LEU A:331 | 5.00 | Pi-alkyl |
| | | | | | | VAL A:330 | 3.74 | Pi-Sigma |
| | | | | 2AZ5 | -8 | ARG B:82 | 3.00 | Conventional H-bond |
| | | | | | | ASN D:92 | 2.92, 1.94, 2.50 | |
| | | | | | | LEU D:93 | 5.10 | Pi-alkyl |
| **2.** | 65064 | Epigallocatechin gallate | ***Camellia sinensis*** | GehA | -8.4 | SER A:169 | 2.35 | Conventional H-bond |
| | | | | | | GLN A:237 | 3.09 | |
| | | | | | | THR A:96 | 3.07 | |
| | | | | | | GLY A:298 | 3.20 | |
| | | | | | | THR A:103 | 3.12 | |
| | | | | | | SER A:58 | 2.48, 1.99, 2.89 | |
| | | | | | | SER A:59 | 2.71 | |
| | | | | | | ALA A:102 | 2.51 | |
| | | | | | | ARG A:62 | 2.89 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | HIS A:297 | 3.62 | C-H bond |
| | | | | | | | 4.76 | Pi-Pi T-shaped |
| | | | | | | THR A:269 | 3.79 | Pi-Sigma |
| | | | | | | VAL A:3330 | 4.26 | Pi-alkyl |
| | | | | 2AZ5 | -9 | GLN B:125 | 3.26 | Conventional H-bond |
| | | | | | | GLY C:121 | 2.45, 1.97 | |
| | | | | | | LEU C:120 | 2.06 | |
| | | | | | | SER C:60 | 2.99 | |
| | | | | | | TYR C:151 | 2.97 | |
| | | | | | | LEU B:55 | 5.34 | Pi-alkyl |
| | | | | | | TYR C:119 | 4.95 | Pi-Pi stacked |
| **3.** | 73330 | strictinin | *Punica granatum* | GehA | -9.5 | THR A:103 | 1.71 | Conventional H-bond |
| | | | | | | THR A:269 | 3.04 | |
| | | | | | | THR A:103 | 2.81 | |
| | | | | | | THR A:269 | 2.82 | |
| | | | | | | HIS A:297 | 3.05 | |
| | | | | | | HIS A:297 | 3.19 | |
| | | | | | | SER A:58 | 3.22 | |
| | | | | | | ARG A:62 | 2.97 | |
| | | | | | | VAL A:330 | 5.37 | Pi-alkyl |
| | | | | | | ALA A:102 | 5.10 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ARG A:62 | 3.31 | C-H bond |
| | | | | | | GLY A:98 | 3.61 | |
| | | | | | | GLY A:298 | 3.11 | |
| | | | | 2AZ5 | -10 | LYS B90 | 2.79 | Conventional H-bond |
| | | | | | | ARG B:82 | 3.07 | |
| | | | | | | GLN B:125 | 2.64 | |
| | | | | | | ARG D:82 | 2.94 | |
| | | | | | | ASN B:92 | 3.18 | |
| | | | | | | ASN B:92 | 3.39 | C-H bond |
| **4.** | 10151874 | Valoneic_acid_bilactone | *Punica granatum* | GehA | -8 | HIS A:297 | 2.96 | Conventional H-bond |
| | | | | | | GLY A:298 | 3.12 | |
| | | | | | | ARG A:62 | 3.33 | |
| | | | | | | SER A:58 | 2.95 | |
| | | | | | | ASN A:99 | 3.27 | |
| | | | | | | | 3.05 | |
| | | | | | | | 3.27 | |
| | | | | | | THR A:103 | 2.16 | |
| | | | | | | VAL A:330 | 5.33 | Pi-alkyl |
| | | | | | | LEU A:331 | 5.33 | |
| | | | | | | ARG A:62 | 5.33 | |
| | | | | | | ALA A:102 | 4.85 | |
| | | | | 2AZ5 | -9.2 | GLY C:121 | 2.90 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | TYR D:151 | 2.21 | Conventional H-bond |
| | | | | | | TYR C:151 | 3.04 | |
| | | | | | | TYR C:59 | 4.40 | Pi-Pi stacked |
| | | | | | | | 4.70 | |
| | | | | | | | 3.70 | |
| | | | | | | LEU C:120 | 4.67 | Amide-Pi-Stacked |
| **5.** | 9064 | Catechin | ***Camellia sinensis & Punica granatum*** | Geh A | -7 | ALA A:102 | 2.04 | Conventional H-bond |
| | | | | | | THR A:103 | 2.06 | |
| | | | | | | THR A:96 | 3.97 | Pi-Sigma |
| | | | | 2AZ5 | -8.6 | LEU D:93 | 2.42 | Conventional H-bond |
| | | | | | | LEU B:93 | 2.56 | |
| **6.** | 72276 | Epicatechin | ***Camellia sinensis & Punica granatum*** | Geh A | -6.7 | THR A:103 | 2.10 | Conventional H-bond |
| | | | | | | THR A:269 | 2.85 | |
| | | | | | | SER A:58 | 2.87 | |
| | | | | | | ALA A:102 | 5.10 | Pi-alkyl |
| | | | | | | VAL A:330 | 4.50 | |
| | | | | | | ARG A:62 | 5.42 | |
| | | | | 2AZ5 | -8.4 | GLN D:125 | 2.06 | Conventional H-bond |
| | | | | | | ARG D:82 | 2.95 | |
| | | | | | | ASN B:92 | 2.97 | |
| | | | | | | GLN B:125 | 2.18 | |
| | | | | | | | 2.38 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **7.** | 12313376 | Nimbolide | ***Azadirachta indica*** | GehA | -8.4 | TYR A:234 | 3.12 | Conventional H-bond |
| | | | | | | TYR A:234 | 3.14 | |
| | | | | | | TYR A:234 | 3.11 | |
| | | | | | | THR A:103 | 2.98 | |
| | | | | | | TYR A:234 | 3.76 | Pi-donor H bond |
| | | | | | | GLU A:132 | 3.68 | C-H bond |
| | | | | 2AZ5 | -9.2 | GLY C:121 | 3.27 | Conventional H-bond |
| | | | | | | TYR D:151 | 2.75 | |
| | | | | | | TYR C:59 | 3.71 | Pi-Pi stacked |
| | | | | | | GLY C:121 | 3.62 | C-H bond |
| **8.** | 11119228 | Nimbiol | **Azadirachta indica** | GehA | -7.3 | ALA A:204 | 4.39 | Pi-alkyl |
| | | | | | | ALA A:204 | 4.64 | |
| | | | | | | LEU A:207 | 5.09 | |
| | | | | | | PRO A:215 | 4.45 | |
| | | | | | | TYR A:234 | 4.59 | Pi-Pi stacked |
| | | | | 2AZ5 | -8.2 | TYR C:59 | 4.46 | Pi-alkyl |
| | | | | | | LEU C:57 | 3.71 | |
| | | | | | | GLY C:121 | 5.51 | Amide-Pi stacked |
| **9.** | 52951893 | 7-desacetyl-7-benzoylazadiradione | **Azadirachta indica** | GehA | -9.7 | SER A:58 | 3.00 | Conventional H-bond |
| | | | | | | HIS A:297 | 3.30 | |
| | | | | | | GLY A:298 | 2.80 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | LEU A:31 | 5.15 | Pi-alkyl |
| | | | | | | ARG A:329 | 4.54 | |
| | | | | | | MET A:268 | 5.54 | Pi-sulfur |
| | | | | 2AZ5 | -11 | VAL B:123 | 5.11 | Pi-alkyl |
| | | | | | | LEU D:57 | 4.54 | |
| | | | | | | TYR C:119 | 4.09 | Pi-donor H bond |
| | | | | | | TYR C:119 | 4.60 | C-H bond |
| **10.** | 52951892 | 17-hydroxyazadiradione | **Azadirachta indica** | GehA | -8.1 | GLY A:298 | 2.96 | Conventional H-bond |
| | | | | | | HIS A:297 | 3.16 | |
| | | | | | | SER A:58 | 3.03 | |
| | | | | 2AZ5 | -9.1 | - | - | - |

### 3.2 Drug likeliness

The pharmacokinetic properties (Absorption, Distribution, Metabolism, Excretion; ADME), drug-likeness, and toxicity profiles of selected ligands were evaluated using computational tools, namely SwissADME, Pro Tox II, and pkCSM. This investigation aimed to assess the suitability of these bioactive phytochemicals as potential drug candidates. Through in-silico methodologies, essential physicochemical characteristics governing the efficacy, safety, and metabolic fate of the molecules within the biological system were predicted. Notably, Lipinski's rule of five was employed as a pivotal criterion in rational drug design, facilitating the identification of compounds with drug-like properties. As per Lipinski's rule, optimal drug candidates typically possess molecular weights below 500 Daltons, LogP values less than 3, and fewer than 10 hydrogen bond acceptors, indicative of favorable oral absorption and permeability. The application of computational tools enabled the expedited assessment of prospective drug candidates, streamlining the process of drug discovery and development.

#### 3.2.1 Table 2

Drug likeliness of the top 10 compounds.

| Sr. No. | Ligand | MF | Molecule PubChem CID | Lipinski's Rule of 5 | | | | | Lipinski's Viol. | Lipinski's Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | MW (g/mol) | Log P | HBA | HBD | MR | | |
| **1** | Epicatechin | C15H14O6 | 72276 | 290.27 | 1.5461 | 6 | 5 | 74.33 | 0 | Yes |
| **2** | O-Caffeoylquinic acid | C16H18O9 | 1794427 | 354.31 | -0.6459 | 9 | 6 | 83.50 | 1 | Yes |
| **3** | Strictinin | C27H22O18 | 73330 | 634.45 | -0.2965 | 18 | 11 | 141.85 | 3 | No |
| **4** | Valoneic acid dilactone | C21H10O13 | 10151874 | 470.30 | 2.2145 | 13 | 7 | 112.83 | 2 | No |
| **5** | catechin | C15H14O6 | 9064 | 290.27 | 1.5461 | 6 | 5 | 74.33 | 0 | Yes |
| **6** | Epigallocatechin Gallate | C22H18O11 | 65064 | 458.37 | 2.2332 | 11 | 8 | 112.06 | 2 | No |
| **7** | Nimbiol | C18H24O2 | 11119228 | 272.38 | 4.37102 | 2 | 1 | 82.44 | 0 | Yes |
| **8** | Nimbolide | C27H30O7 | 12313376 | 466.52 | 3.7431 | 7 | 0 | 120.99 | 0 | Yes |
| **9** | 7-Deacetyl-7-benzoylepoxyazadiradione | C33H36O6 | 52951893 | 528.64 | 5.923 | 6 | 0 | 144.86 | 1 | Yes |
| **10** | 17-Hydroxyazadiradione | C28H34O6 | 52951892 | 466.57 | 4.5219 | 6 | 1 | 126.52 | 0 | Yes |

### 3.3 ADMET features of selected ligands

pharmacokinetic properties of chemical compounds. The compounds selected as hits from the molecular docking study were subjected to an additional screening process to predict their respective ADMET properties, as shown in Table 3. Nine compounds out of the initial ten were chosen for further analysis as they exhibited toxicity levels falling within the acceptable range for drug candidacy. These selected compounds demonstrated predicted LD50 values and toxicity class that met the required criteria, making them suitable for advancing to the next stage of evaluation.

#### 3.3.1 Table 3

ADMET properties of the top 10 compounds.

| Ligand | In-silico ADMET | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Absorption | | Distribution | Metabolism | | | | | Toxicity |
| | Water Solubility | Skin Permeability | BBB permeability | 2D6 | 3A4 | 1A2 | 2C19 | 2C9 | Predicted LD50 & Toxicity Class: |
| **Epicatechin** | -3.117 | -2.735 | -1.054 | No | No | No | No | No | **10000 mg/kg (Class:6)** |
| **O-Caffeoylquinic acid** | -2.449 | -2.735 | -1.407 | No | No | No | No | No | **5000 mg/kg (Class: 5)** |
| **Strictinin** | -2.892 | -2.735 | -2.612 | No | No | No | No | No | **2260 mg/kg (Class: 5)** |
| **Valoneic acid** | -2.892 | -2.735 | -2.735 | No | No | No | No | No | **1000 mg/kg** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **dilactone** | | | | | | | | | **(Class: 4)** |
| **catechin** | -3.117 | -2.735 | -1.054 | No | No | No | No | No | **10000 mg/kg (Class:6)** |
| **Epigallocatechin Gallate** | -2.894 | -2.735 | -2.184 | No | No | No | No | No | **1000 mg/kg (Class: 4)** |
| **Nimbiol** | -4.077 | -2.69 | 0.106 | Yes | No | No | Yes | Yes | **5000 mg/kg (Class: 5)** |
| **Nimbolide** | -5.166 | -3.599 | -0.675 | No | No | No | No | No | **1000 mg/kg (Class: 4)** |
| **7-Deacetyl-7-benzoylepoxyazadiradione** | -4.798 | -2.809 | -0.472 | No | No | No | No | Yes | **274 mg/kg (Class: 3)** |
| **17-Hydroxyazadiradione** | **-4.186** | **-3.149** | **-0.302** | **No** | **Yes** | **No** | **No** | **No** | **555 mg/kg (Class: 4)** |

### 3.4 PASS Evaluation:

#### 3.4.1

Natural compounds often exhibit diverse chemico-biological properties, potentially leading to synergistic or antagonistic effects. To discern compounds that manifest both safety and efficacy with desirable attributes, it is imperative to scrutinize the biological properties of identified hit molecules. In this study, the biological properties of hit molecules were investigated utilizing Prediction of Activity Spectra for Substances (PASS) analysis. This analysis furnished insights into the potential properties of the compounds, with summarized results, including confidence levels, presented in Table 4. The findings revealed that the four selected compounds—Valoneic acid dilactone, Strictinin, Epigallocatechin Gallate, and Nimbiol—possess substantial potential for acne treatment, offering antioxidant, anti-inflammatory, astringent, dermatologic, and antiseborrheic benefits. PASS analysis corroborated these observations, affirming the considerable promise of these compounds for utilization in anti-acne therapeutic interventions.

#### 3.4.2 Table 4

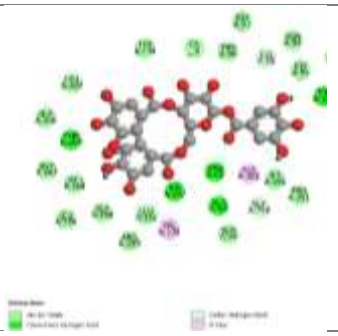
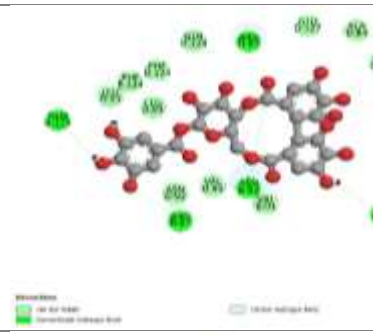
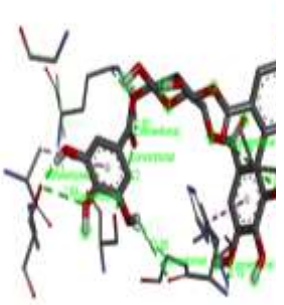
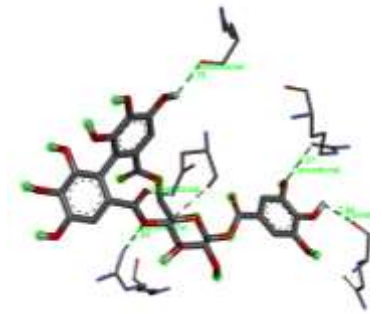
Biological properties of the elucidated phytoconstituents predicted through the PASS webserver.

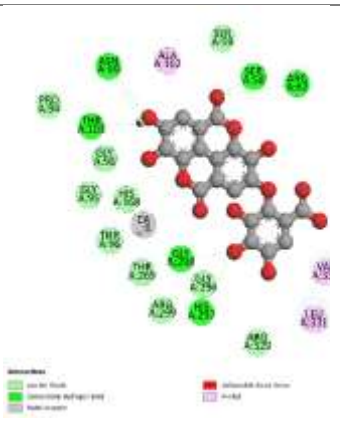
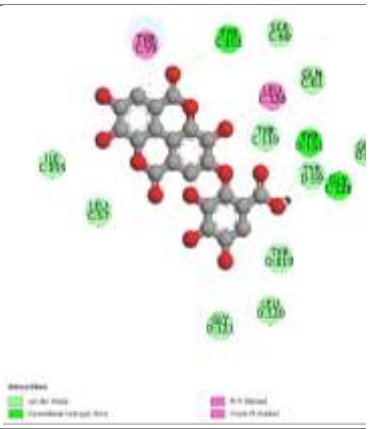
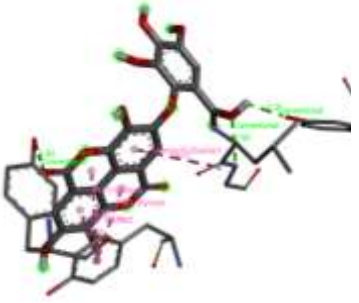
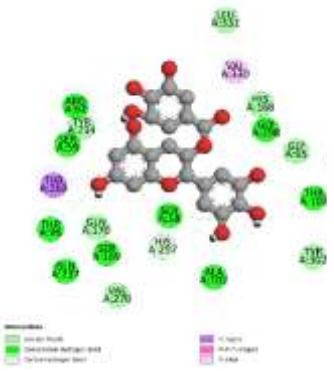
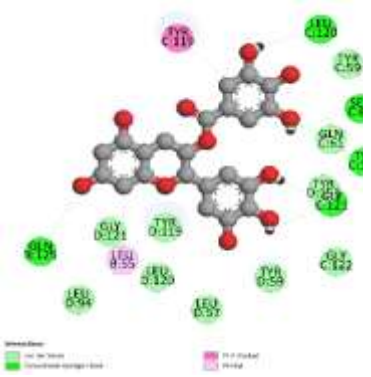
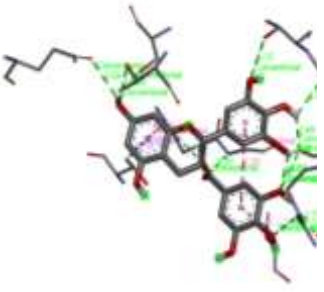
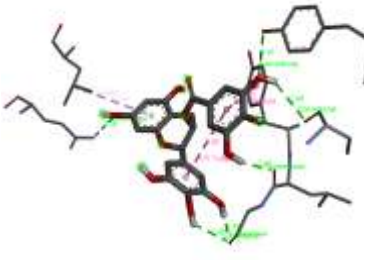
| Compound | Pa | Pi | Biological Activity |
|---|---|---|---|
| **Epicatechin** | 0,737 | 0,031 | Antiseborrheic |
| | 0,548 | 0,044 | Antiinflammatory |
| | 0,810 | 0,003 | Antioxidant |
| **O-Caffeoylquinic acid** | 0,785 | 0,004 | Antioxidant |
| | 0,598 | 0,032 | Antiinflammatory |
| | 0,537 | 0,013 | Antibacterial |
| | 0,123 | 0,042 | Antiacne |
| | 0,479 | 0,036 | Dermatologic |
| **Strictinin** | 0,840 | 0,003 | Antioxidant |
| | 0,809 | 0,006 | Antiinflammatory |
| | 0,591 | 0,009 | Antibacterial |
| | 0,434 | 0,045 | Dermatologic |
| **Valoneic acid dilactone** | 0,935 | 0,001 | Astringent |
| | 0,809 | 0,006 | Antiinflammatory |
| | 0,707 | 0,004 | Antioxidant |
| | 0,449 | 0,022 | Antibacterial |
| | 0,426 | 0,087 | Antiseborrheic |
| **catechin** | 0,548 | 0,044 | Antiinflammatory |
| | 0,810 | 0,003 | Antioxidant |
| | 0,737 | 0,031 | Antiseborrheic |
| **Epigallocatechin Gallate** | 0,623 | 0,027 | Antiinflammatory |
| | 0,814 | 0,003 | Antioxidant |
| | 0,505 | 0,072 | Antiseborrheic |

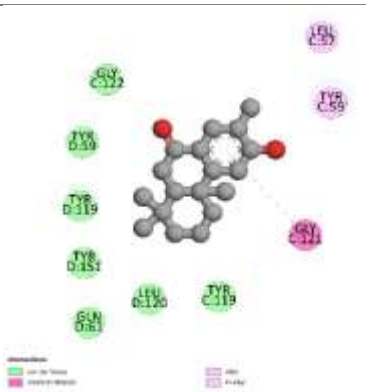
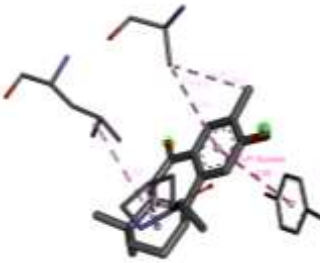
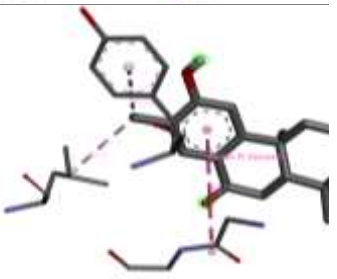
| | | | |
|---|---|---|---|
| **Nimbiol** | 0,814 | 0,017 | Antiseborrheic |
| | 0,373 | 0,012 | Antiacne |
| | 0,644 | 0,024 | Antiinflammatory |
| | 0,636 | 0,012 | Dermatologic |
| **Nimbolide** | 0,371 | 0,111 | Antiinflammatory |
| **17-Hydroxyazadiradione** | 0,118 | 0,044 | Antiacne |
| | 0,532 | 0,048 | Antiinflammatory |
| | 0,417 | 0,089 | Antiseborrheic |
| | 0,575 | 0,019 | Dermatologic |

### 3.5 Interaction Analysis of Selected Compounds

The compounds' interactions with GehA and TNFα were analyzed using PyRx and Discovery Studio visualizer. The focus was on understanding how the compounds bind to the target proteins and identifying the specific residues they interact with. Through this analysis, hydrogen bonding and other types of interactions between the compounds and the proteins were visualized and studied. Discovery Studio and PyRx were utilized for this purpose, helping to gain insights into the binding modes and interaction patterns of the selected compounds with GehA and TNFα based on the interacting residues. [Table 5]

| **Ligand** | **Structure** | **Docked with** | |
|---|---|---|---|
| | | **Geh-A** | **2AZ5** |
| **Strictinin** | 2D |  |  |
| | 3D |  |  |

| | | | |
|---|---|---|---|
| **Valoneic acid dilactone** | 2D |  |  |
| | 3D |  |  |
| **Epigallocatechin Gallate** | 2D |  |  |
| | 3D |  |  |

| | | | |
|---|---|---|---|
| **Nimbiol** | 2D |  |  |
| | 3D |  |  |

## 4. Conclusion

This research highlights the promising potential of natural compounds derived from medicinal plants as therapeutic agents for acne management. By targeting key proteins GehA and TNF-alpha implicated in acne pathogenesis, our computational approach identified ten phytoconstituents with notable anti-acne activity. Among these, Valoneic acid dilactone, Strictinin, Epigallocatechin Gallate, and Nimbiol demonstrated significant biological activities encompassing anti-inflammatory, antioxidant, antimicrobial, and dermatological properties, making them attractive candidates for further development as anti-acne therapeutics. The systematic virtual screening approach employed in this study underscores the utility of computational methods in accelerating the discovery and development of novel acne treatments from natural sources. These findings pave the way for future investigations and potential translation of these natural compounds into effective clinical interventions for acne and related dermatological conditions.

## CRediT authorship contribution statement

- Credit authorship contribution statement Pranali R. Pangam: Investigation, Conceptualization, Methodology, Visualization, Writing – original draft.
- Shubhangi B. Sutar: Conceptualization, Methodology, Writing – review & editing.
- Sachinkumar V. Patil: Supervision, Writing – review & editing.
- Sachin S. Mali: Supervision, Writing – review & editing.

## Data availability

Data will be made available on request.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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