2024 SICASH
SLIIT INTERNATIONAL CONFERENCE ON ADVANCEMENTS IN SCIENCES & HUMANITIES

# *In silico* Toxicity Analysis of Potential Wound Healing Drug Candidates to Assess Drug Suitability

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**Abstract**

Drug development typically takes several years, but *in-silico* techniques, computational biology and chemical solutions can expedite toxicity analysis and other sections of the drug development process. Therefore, screening of potential drug candidates has become efficient. These techniques provide results quickly, cost-effectively, and without harming animals or humans. This research leverages bioinformatics to analyse the toxicity of chemical compounds in a potential wound-healing drug, specifically Bilirubin, Pinocembrin, and Resveratrol. Software such as Discovery Studios, Chem3D Pro, OpenBabel, Osiris Explorer, and EpiWeb 4.1 were used for visualization, energy minimization, SMILES string generation, and toxicity analysis. A one-way ANOVA test was performed on drug scores obtained from Osiris Explorer using PRISM version 10.2.1. The statistical analysis of these scores facilitated alternative hypothesis selection of validating drug suitability using *in-silico* toxicity studies. Despite challenges, this research provides valuable insights into performing toxicity analysis on ligands.

***Keywords:*** bioinformatics; drug development; toxicity; computational biology; statistics

## Introduction

Bioinformatics is used to analyse the toxicity of Bilirubin, Pinocembrin, and Resveratrol in a wound-healing drug using *in-silico* methods. Bioinformatics combines computer science, applied math, and statistics to organize biological data at the molecular level (Luscombe *et al*., 2000). Traditional toxicology involves lengthy, costly procedures with ethical concerns regarding animal testing (Gilbert and Eaton, 2009). In contrast, *in-silico* methods offer rapid, cost-effective alternatives for predicting chemical toxicity using computational models like QSARs (Rim, 2020). During drug development, pre-clinical trials that use in-vitro and in-vivo testing methods to ensure that the drug is not toxic to humans take about 4-7 years (Amoranitis, 2023). *In-silico* toxicity analysis methods do not harm animals or humans as the research is conducted through software, reduces the cost, and improves the efficiency of drug development. In addition to this, potential harms can be detected at a very early stage with the help of machine learning strategies and chemical data to detect carcinogenicity, mutagenic levels, and biodegradability. This helps the research team remove any negative candidates in their research and implement a different approach by quickening the approach (Brunner, 2023).

Bilirubin is the primary byproduct of the liver's breakdown of heme, which is the bile pigment. It is eliminated by urine and bile. The porphyrin ring is the main component of heme (American Chemical Society, 2017). Bilirubin has antioxidant, anti-inflammatory, and immunomodulatory properties. (Adin, 2021) When an injury occurs, the activation



https://doi.org/10.54389/SSEG9731

of platelets and macrophages causes the release of large amounts of Reactive oxygen species (André-Lévigne et al., 2017), and administration of Bilirubin at low concentrations can identify and destroy ROS molecules (Singla et al., 2023).

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a naturally occurring polyphenol that has been identified in over 70 plant species, primarily in the skin and seeds of grapes (Salehi, 2018). Resveratrol's antioxidative properties help stabilize cell proliferation, improve migration quality, and maintain ultrastructure. Resveratrol also has anti-fungal and antibacterial properties that show immune-stimulating effects (Hecker et al., 2021).

Pinocembrin is a naturally occurring compound in fruits, vegetables, and leaves. It is identified that pinocembrin influences keratinocyte build-up, and it is considered a wound closure-promoting agent. It also modulates the enzyme that is needed for the wound-healing process (Ruttanapattanakul et al., 2022).

Oral Administration is preferred in this research because it is accepted by patients, safe, convenient for intake, and pain prevention, and is adaptable to different varieties of medications (Zhang et al., 2017).

The research contributes to academic understanding and has practical implications for developing safer, more effective wound-healing treatments, as seen with products like RestoDerma (University of Colombo, 2023). This study underscores and aims to understand the efficiency and ethical benefits of the use of *in-silico* methods in toxicity analysis, a crucial step in the drug development process.

In this *In silico* toxicity study, the software that was used are Chem3D Pro, Osiris Property Explorer, RasWin, OpenBabel, and EpiWeb 4.1.

A molecular graphics application called RasMol was created to operate on X-Windows, VAX, VMS, and Unix platforms. Since this software is free and open-source, developers are welcome to submit their source codes to help make it better. Molecular biology and structural biology are the two main fields in which the program is used, along with teaching. Proteins, nucleic acids, and macromolecular structures may all be analysed with RasWin (the Windows format of RasMol). The user is presented with a color-coded visual depiction of the molecules. In the event of launching RasWin, two windows will open: the Viewing window, in which the molecules are observed, and the Command Window, where the user can enter specific commands to display the molecules in a form the user specifies (File.org, 2023.c).

A browser extension may view and manipulate embedded 3D molecular models with the help of the Chem3D plug-in software. Together with ChemDraw and ChemFinder, it completes the ChemOffice package. Chem 3D was developed by the cheminformatics company CambridgeSoft(File.org, 2013). Chem 3D can be used to create vibrant three-dimensional chemical structures for use on webpages, posters, and presentations. 2D chemical structures from ChemDraw can then be converted to 3D by importing CIF or PDB files to modify and visualise the structure and determine bond lengths and angles. Chem 3D can do molecular modelling computations using MMFF94 and MM2, and carry out computations for molecular dynamics. (Françoise,2023).

An open-source chemical toolkit called Open Babel can communicate with chemical data in a variety of languages. Version 2.3 of Open Babel supports over 110 format conversions. A library that implements a broad range of cheminformatics algorithms is necessary to describe the vast array of chemical and molecular data, ranging from partial charge assignment and aromaticity detection to bond order perception and canonicalization. One way to address the growth of chemical file formats is using Open Babel. It also offers a wide range of practical utilities, such as batch conversion, substructure and similarity searching, filtering, and 2D visualisation in addition to conformer searching. It may be utilized

by programmers as a programming library to manage chemical data in fields including computational chemistry, materials science, organic chemistry, and drug design. (O'Boyle et al, 2011).

When a structure is valid, the OSIRIS Property Explorer allows you to sketch chemical structures and instantly calculates a variety of drug-relevant characteristics (cLogP, solubility, Molecular Weight, Toxicity Risk Assessment, Overall Drug-Score, etc.). Value and colour coding are used to predict findings. Red indicates properties that have a high potential for negative consequences, such as mutagenicity or poor intestine absorption. Green, on the other hand, denotes drug-conformant conduct (R&D Chemicals, 2023.c).

The United States Environmental Protection Agency (EPA) administered and developed the EPIWEB 4.1 software. It presents both qualitative and quantitative methods for estimating a chemical's environmental performance when its chemical structure is the only information that may be available. Henry's law constants, water solubility, soil absorption coefficients, concentration factors, and octanol-water partition coefficient are examples of molecular characteristics that are commonly employed in environmental performance assessments. The techniques covered in the curriculum are commonly referred to as quantitative structure-activity relationships (QSARs), structure-activity relationships (SARs), or group contribution techniques. (Montes-Alba et al, 2019) In EpiWeb 4.1, the SMILES (Simplified Molecular Input Line Entry Specification) notation of the chemical structure may be used to determine Koc (organic carbon sorption constant), MW (molecular weight), VP (vapor pressure), and SOL (solubility). Using the CAS numbers that the applicant provides, this tool may be used to determine the SMILES notation. The Koc value that is recommended by the EPIWEB tool is obtained from the first-order molecular connectivity index (European Food Safety Authority, 2014).

**Materials and Methods**

The research follows Saunders' Research Onion model, which helps researchers develop a study plan. The research design, detailed within this model, guides the philosophy, strategy, method, and other necessary elements to ensure the research meets scientific standards and avoids drawing incorrect conclusions (Mardiana, 2020).

This research aims to use computational tools and analyse the different chemicals and drug candidate compounds' suitability to be used as a wound-healing active pharmaceutical ingredient. The main objective of this research is to ensure that the drug that is being developed is non-toxic to the patients who will be using it.

**Null hypothesis:** There is no significant difference between the findings of the computational assays and the toxicity levels of the chosen drug candidates.

**Alternative Hypothesis:** There is a significant difference between the findings of the computational assays and the toxicity levels of the drug candidates.

**1. Chemical Structure Retrieval and Energy Minimization**

The chemical structures of the three selected ligands were downloaded in SDF format from the PubChem server and later stored in .PDB format (Selvaraj et al., 2017). These structures were visualized using Discovery Studios (Rao, 2023) and Chem3D Pro. Chem3D Pro renders the chemical structure in 3D for preliminary analysis (Ok et al., 2013). The structure was then visualized using Discovery Studios (Rao, 2023) and subjected to energy minimization using Chem3D Pro (Padmi et al., 2023). The energy-minimized structure was saved in .PDB format for subsequent toxicity and solubility assessment studies. A canonical SMILES string for the structure was generated using OpenBabel software (Noel M. O'Boyle et al., 2011; Quirós et al, 2018).

**2. Predicting toxicity and aqueous solubility.**

Operating on the Java platform, OSIRIS Property Explorer (Sander, 1999) was used to predict in-silico toxicity and aqueous solubility values. Java was installed prior to analysis. The software assessed any associated toxicity risks based on provided descriptors and predicted the solubility parameter, defined as the logS value. Compounds with a logS value greater than -4 align with approximately 80% of drugs on the market, while lower values indicate lower solubility. The predicted logP value of the compound, indicating hydrophilicity, was -8.91. Ideally, compounds should have logP values around 5 or less for high absorption, as higher logP values can lead to poor absorption or permeation. The primary results from this analysis were documented (Kumar, Kabilan, & Parthasarathy, 2016).

**3. Chemical property prediction from EPIweb server** (US EPA, 2023)

The EPIweb server was employed in this step to predict properties such as half-life, AMES toxicity, and degradation patterns for the compound (EFSA Journal, 2016).

**4. Statistical analysis**

The drug score obtained from the Osiris Explorer software of the three ligands was statistically by one-way ANOVA using the Prism (Version 10.2.1) software program. The significance level was set at P values less than 0.05 at a confidence interval of 95% (Kharchoufa *et al*, 2020).

**Results and Discussion**

**3.1 Visualizations obtained from Discovery Studio**

In Discovery Studios, the structure of the ligands can be viewed in multiple ways by altering the bonds of the ligands into stick form, wire formation, ball and stick, cylindrical bonds, and space-filling formation, to visualize the bond angles and the atoms' placement. The structure of the three ligands below has been displayed in ball and stick mode as shown below:

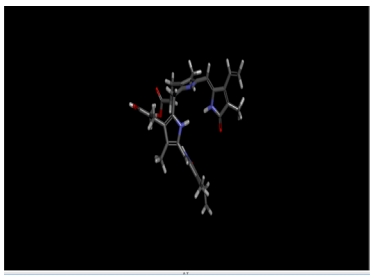

**Figure 1.** Bilirubin structure

**Figure 2.** Pinocembrin structure

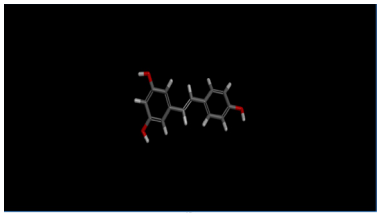

**Figure 3.** Resveratrol structure

**3.2 Energy Minimization through Chem 3D Pro.**

In Chem 3D pro, the ligands were energy-minimized. Energy minimization is crucial to figuring out the right molecule arrangement in space. A molecule's potential energy is made up of several energy components, such as stretching, bending, and torsion. For this reason, when an energy minimization algorithm is executed, the molecule will instantly approach a minimal local energy value (Roy, Kar and Das, 2015). Energy-minimized structures are as follows:

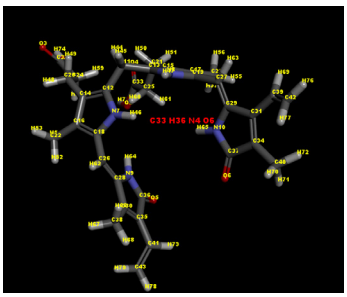

**Figure 4.** Bilirubin structure

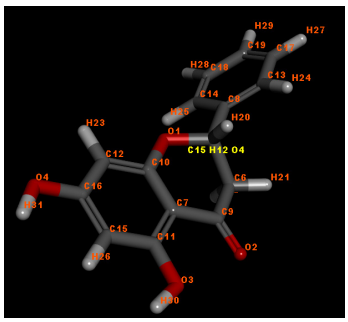


**Figure 5.** Pinocembrin structure

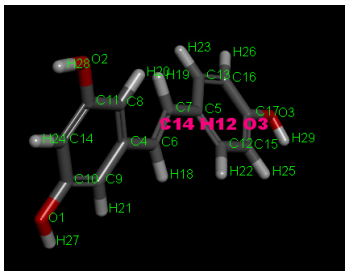


**Figure 6.** Resveratrol structure

### 3.3 SMILES strings obtained from OpenBabel.

SMILES (Simplified Molecular Input Line Entry System) enable a user to represent a chemical structure in a format that the computer can understand (Environmental Protection Agency, 2016). The SMILES strings obtained for the ligands are as follows:

- Bilirubin:OC(=O)CCc1c([nH]c(c1C)CC1=C([C@H](C(=O)N1)C=C)C)Cc1[nH]c(c(c1CCC(=O)O)C)CC1=C([C@H](C(=O)N1)C)C=C
- Resveratrol : Oc1cc(/C=C/c2ccc(O)cc2)cc(O)c1
- Pinocembrin : O1[C@@H](CC(=O)c2c1cc(O)cc20)c1ccccc1

### 3.4 Toxicity predicted by OSIRIS

The OSIRIS Property Explorer is a tool that allows users to instantly calculate diverse drug-related properties such as cLogP, solubility, Molecular Weight, Toxicity Risk Assessment, and Overall Drug-Score (R&D Chemicals, 2024).

***Table 1.*** Osiris Explorer Results Analysis

| | Bilirubin | Pinocembrin | Resveratrol |
|---|---|---|---|
| **cLogP** | 3.696 | 2.501 | 2.829 |
| **logS** | -5.313 | -2.935 | -2.863 |
| **Molecular weight** | 588.0 | 256.0 | 228.0 |
| **Drug-likeness** | 0.81 | 1.952 | -3.246 |
| **Mutagenicity** | 1.0 | 1.0 | 0.6 |
| **Tumour genericity** | 1.0 | 1.0 | 1.0 |
| **Irritating effects** | 1.0 | 1.0 | 1.0 |
| **Reproductive effects** | 1.0 | 1.0 | 0.6 |
| **Drug score** | 0.338 | 0.829 | 0.164 |

### 3.5 Chemical Property Prediction of the Ligands through EpiWeb 4.1

EpiWeb 4.1 serves multiple purposes in environmental assessments. This tool aids in calculating the organic carbon sorption constant (Koc), molecular weight, vapor pressure, and solubility, all of which are substance-dependent parameters crucial for estimating the PECporewater (European Food Security Authority, (EFSA), 2016).

***Table 2.*** EpiWeb 4.1 Results Analysis

| | Bilirubin | Pinocembrin | Resveratrol |
|---|---|---|---|
| **LogKow** | 5.21 | 3.09 | 3.084 |
| **Water solubility** | 0.006751mg/L | 189.5 mg/L | 275mg/L |
| **Molecular weight** | 588.71 | 256.26 | 228.25 |
| **Probability of Rapid Biodegradation** | 1.4156 | 0.9863 | 1.1240 |
| **Half-life of Bioaccumulation** | 0.04695 days | 0.01254 days | 0.04112 days |
| **Removal in water** | 83.33% | 6.53% | 6.43% |

### 3.6 Statistical Analysis

The drug scores of the three ligands are as follows:

***Table 3.*** Drug scores of Ligands

| | Drug Score 1 |
|---|---|
| Bilirubin | 0.338 |
| Resveratrol | 0.164 |
| Pinocembrin | 0.829 |

A one-way ANOVA test was performed to analyse the drug scores using the results above and the software PRISM version 10.2.1. The results were found to be extremely significant, with a P value less than 0.001.

***Table 4.*** One-way ANOVA test results

| | Ordinary one-way ANOVA | | | | | |
|---|---|---|---|---|---|---|
| 1 | Table Analyzed | Data 1 | | | | |
| 2 | Data sets analyzed | A-C | | | | |
| 3 | | | | | | |
| 4 | **ANOVA summary** | | | | | |
| 5 | F | 89618 | | | | |
| 6 | P value | <0.0001 | | | | |
| 7 | P value summary | **** | | | | |
| 8 | Significant diff. among means (P < 0.05)? | Yes | | | | |
| 9 | R squared | 1.000 | | | | |
| 10 | | | | | | |
| 11 | **Brown-Forsythe test** | | | | | |
| 12 | F (DFn, DFd) | +infinity (2, 3) | | | | |
| 13 | P value | <0.0001 | | | | |
| 14 | P value summary | **** | | | | |
| 15 | Are SDs significantly different (P < 0.05)? | Yes | | | | |
| 16 | | | | | | |
| 17 | **Bartlett's test** | | | | | |
| 18 | Bartlett's statistic (corrected) | | | | | |
| 19 | P value | | | | | |
| 20 | P value summary | | | | | |
| 21 | Are SDs significantly different (P < 0.05)? | | | | | |
| 22 | | | | | | |
| 23 | **ANOVA table** | **SS** | **DF** | **MS** | **F (DFn, DFd)** | **P value** |
| 24 | Treatment (between columns) | 0.4780 | 2 | 0.2390 | F (2, 3) = 89618 | P<0.0001 |
| 25 | Residual (within columns) | 8.000e-006 | 3 | 2.667e-006 | | |
| 26 | Total | 0.4780 | 5 | | | |
| 27 | | | | | | |
| 28 | **Data summary** | | | | | |
| 29 | Number of treatments (columns) | 3 | | | | |
| 30 | Number of values (total) | 6 | | | | |

### Discussion

The wound-healing drug will be administered orally, requiring a risk analysis specific to oral medication.

### 4.1 OSIRIS Explorer Results Analysis:

Resveratrol, and Pinocembrin. All three compounds exhibit suitable logP values, indicating high hydrophilicity. Pinocembrin and Resveratrol show appropriate solubility values, while Bilirubin exceeds the standard value (-4), indicating lower solubility. Pinocembrin and Resveratrol possess low molecular weights, whereas Bilirubin has a higher molecular weight. The results reveal that Bilirubin and Pinocembrin are commonly found in commercial drugs, but Resveratrol has limited commercial usage. Regarding toxicity, Bilirubin and Pinocembrin exhibit no mutagenic effects, while Resveratrol presents high-risk fragments associated with reproductive effects. None of the compounds display tumorigenicity or irritating effects. Finally, the drug score analysis indicates that Pinocembrin has the highest drug score, suggesting its potential for drug development, while Resveratrol has the lowest, rendering it unsuitable for further development.

### 4.2 EpiWeb 4.1 Results Analysis:

Bilirubin, Resveratrol, and Pinocembrin. Pinocembrin and Resveratrol have suitable log KoW values,

being less than 5, whereas Bilirubin exceeds this threshold, indicating higher lipophilicity. Bilirubin also shows the lowest water solubility, while Pinocembrin and Resveratrol exhibit suitable water solubilities, each above 100 mg/L. The molecular weight analysis reveals that Bilirubin exceeds the threshold of 500, while Pinocembrin and Resveratrol are within acceptable limits. All three compounds demonstrate rapid degradation, with values greater than 0.5. Pinocembrin has the shortest half-life for bioaccumulation at 18 minutes, followed by Resveratrol at 49 minutes, and Bilirubin with the longest half-life at 66 minutes. Lastly, Bilirubin shows the highest percentage of water removal, while Resveratrol and Pinocembrin exhibit very low water removal percentages. These findings suggest that Pinocembrin and Resveratrol have more favourable properties for drug development compared to Bilirubin.

**4.3 Statistical Analysis:**

An analysis of variance (ANOVA) tests if the means of three or more groups differ significantly, linking univariate and multivariate statistics and examining correlations between variables (Mahbobi & Tiemann, 2015). A One-Way ANOVA evaluates the means of two or more independent groups to determine if there is statistical support for a significant difference in population means, serving as a parametric test (Kent State University, 2023). The P value, ranging from 0 to 1, indicates the likelihood that an observed difference is due to chance, with values less than 0.05 suggesting rejection of the null hypothesis (Dahiru, 2011).

**Conclusion**

From the results obtained from Osiris Explorer and EpiWeb 4.1, Bilirubin was observed to be the most toxic compared to Pinocembrin and Resveratrol. Bilirubin has the highest molecular weight, lowest water solubility, and highest lipophilicity, contributing to its bioaccumulation in the body and potential complications (Agostinho *et al*., 2021). Additionally, Resveratrol showed risk factors for mutagenicity and reproductive effects. Despite all three ligands degrading rapidly (Çeçen and Gül, 2020), their high lipophilicity indicates good absorption, although Bilirubin's low solubility could affect drug functionality. Bilirubin's high molecular weight and lipophilicity facilitate its removal from wastewater (Ksibi, 2021). None of the compounds showed tumorigenicity or irritating effects. Osiris Explorer and EpiWeb 4.1 provided similar results regarding water solubility and molecular weight but differed in the octanol-water partition coefficient (KOW) for Bilirubin. Osiris Explorer indicated a suitable range, while EpiWeb 4.1 showed it exceeded the threshold (Cumming and Rücker, 2017). Statistical analysis using a one-way ANOVA test yielded a p-value of 0.0001, leading to the rejection of the null hypothesis. From the compounds evaluated using this study, Pinocembrin was shown to have better indicators of drug suitability exhibiting low toxicity in the study parameters. Also, the study conducted the possibility of utilizing computational tools to assess preliminary toxicity analysis in screening a library of drug candidate compounds. In the future, this research can be improved and further developed by predicting additional toxicity endpoints (hepatotoxicity, high nephrotoxicity, cardiotoxicity) using QSAR (Quantitative structure-activity relationship) to provide a complete safety spectrum. To assess the efficacy of the drug candidates molecular docking studies can be performed to predict the binding affinity, and binding energy of the three ligands to the chosen receptors (Skariyachan & Garka, 2018).

**Acknowledgment**

I would like to extend my deepest gratitude to my research supervisor, Ms. Upeka Bandaranayake, whose unwavering support, patience, guidance, and expertise have been invaluable throughout this journey.

I would like to also thank my colleagues for being there through the highs and lows, cheering me on every step of the way.

Last but certainly not least, I want to express my heartfelt appreciation to my family. The boundless love, sacrifices, and belief in my abilities have been the driving force behind my accomplishments.

This endeavour would not have been possible without the collective support of these incredible individuals.

**References**

Adin, C. A. (2021). Bilirubin as a therapeutic molecule: challenges and opportunities. Antioxidants, 10(10), 1536. https://doi org/10.3390/antiox10101536

Agostinho, D. A., Santos, F., Esperança, J. M., Duarte, A. R., & Reis, P. M. (2021). New non-toxic biocompatible dianionic ionic liquids that enhance the solubility of oral drugs from BCS class II. Journal of Ionic Liquids, 1(1), 100003. https://doi.org/10.1016/j.jil.2021.100003

Amercian Chemical Society. (2017, March 17). Bilirubin. American Chemical Society. https://www.acs.org/molecule-of-the-week/archive/b/bilirubin.html

Amoranitis, F. (2023, January 18). Drug development – The four phases. BioStock. https://www.biostock.se/en/2023/01/drug-development-the-four-phases/

André-Lévigne, D., Modarressi, A., Pepper, M., & Pittet-Cuénod, B. (2017). Reactive oxygen species and NOX enzymes are emerging as key players in cutaneous wound repair. International Journal of Molecular Sciences, 18(10), 2149. https://doi.org/10.3390/ijms18102149

Brunner, K. (2023). Three benefits of using in silico technologies for drug discovery. https://www.pharmasalmanac.com/articles/three-benefits-of-using-in-silico-technologies-for-drug-discovery

Çeçen, F. and Gül, G. (2020) 'Biodegradation of five pharmaceuticals: estimation by predictive models and comparison with activated sludge data,' International Journal of Environmental Science and Technology, 18(2), pp. 327–340. https://doi.org/10.1007/s13762-020-02820-y

Cumming, H. and Rücker, C. (2017) 'Octanol–Water partition coefficient measurement by a simple 1H NMR method,' ACS Omega, 2(9), pp. 6244–6249. https://doi.org/10.1021/acsomega.7b01102

Dahiru, T. (2011) 'P-Value, a true test of statistical significance? a cautionary note,' Annals of Ibadan Postgraduate Medicine, 6(1). https://doi.org/10.4314/aipm.v6i1.64038

Eurpean Food Security Authority (EFSA) (2016) 'Safety and efficacy of thiazoles, thiophene and thiazoline belonging to chemical group 29 when used as flavourings for all animal species,' EFSA Journal, 14(6). https://doi.org/10.2903/j.efsa.2016.4441

File.org. (2013, October 21). File.org. File.org; File.org. https://file.org/free-download/chem3d

Françoise, M. (2023). Library: Chemistry Software: Chem3D. Library.bath.ac.uk. https://library.bath.ac.uk/chemistry-software/chem3d

Gilbert, S. G., & Eaton, D. L. (2009). Ethical, legal, social and professional issues in toxicology. General, Applied and Systems Toxicology. https://doi.org/10.1002/9780470744307.gat128

Hecker, A., Schellnegger, M., Hofmann, E., Luze, H., Nischwitz, S. P., Kamolz, L., & Kotzbeck, P. (2021). The impact of resveratrol on skin wound healing, scarring, and aging. International Wound Journal, 19(1), 9–28. https://doi.org/10.1111/iwj.13601

Ken State University (2023) LibGuides: SPSS Tutorials: One-Way ANOVA. https://libguides.library.kent.edu/SPSS/OneWayANOVA (Accessed: March 18, 2024).

Kharchoufa, L. et al. (2020) 'Acute and Subacute Toxicity Studies of the Aqueous Extract from Haloxylon scoparium Pomel (Hammada scoparia (Pomel)) by Oral

Administration in Rodents,' BioMed Research International, 2020, pp. 1–11. https://doi.org/10.1155/2020/4020647

Ksibi, M. (2021) Removal of Pharmaceuticals from Water. https://encyclopedia.pub/entry/12654

Kumar, A., Kabilan, S., & Parthasarathy, V. (2016). Comparison of molecular docking and molecular dynamics simulations of 1H-benzo[d]imidazole with TGF-β type. . . ResearchGate. https://www.researchgate.net/publication/316588775_Comparison_of_molecular_docking_and_molecular_dynamics_simulations_of_1H-benzodimidazole_with_TGF-b_type_I_protein

Levine, J. M. (2017). The effect of oral medication on wound healing. Advances in Skin & Wound Care, 30(3), 137–142. https://doi.org/10.1097/01.asw.0000512112.60254.28

Luscombe, N. M., Greenbaum, D., & Gerstein, M. (2001). What is Bioinformatics? A Proposed Definition and Overview of the Field. Methods of Information in Medicine, 40(04), 346–358. https://doi.org/10.1055/s-0038-1634431

Mahbobi, M. and Tiemann, T.K. (2015) Chapter 6. F-Test and One-Way ANOVA. https://opentextbc.ca/introductorybusinessstatistics/chapter/f-test-and-one-way-anova-2/

Mardiana, S. (2020). Modifying research onion for information systems research. ResearchGate. https://www.researchgate.net/publication/359542575_Modifying_Research_Onion_for_Information_Systems_Research

Mazzotta, S., Governa, P., Borgonetti, V., Marcolongo, P., Nanni, C., Gamberucci, A., Manetti, F., Pessina, F., Carullo, G., Brizzi, A., & Aiello, F. (2021). Pinocembrin and its linolenoyl ester derivative induce wound healing activity in HaCaT cell line potentially involving a GPR120/FFA4 mediated pathway. Bioorganic Chemistry, 108, 104657. https://doi.org/10.1016/j.bioorg.2021.104657

Montes-Alba, E. J., De Jesús Camargo-Vargas, G., Agudelo-Valencia, R. N., & Dévora-Isiordia, G. E. (2019). Adsorption study of acid red 114 and basic blue 3 on sunflower stalk. Journal of Water Resource and Protection, 11(01), 68–81. https://doi.org/10.4236/jwarp.2019.111005

Ok, K., Jung, Y. W., Jee, J., & Byun, Y. (2013). Facile Docking and Scoring Studies of Carborane Ligands with Estrogen Receptor. Bulletin of the Korean Chemical Society, 34(4), 1051–1054. https://doi.org/10.5012/bkcs.2013.34.4.1051

O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. R. (2011). Open Babel: An open chemical toolbox. Journal of Cheminformatics, 3(1). https://doi.org/10.1186/1758-2946-3-33

Padmi, H., Fitriani, N., Saraswati, P. B. A., Nurhidayati, S. Z., Ilhami, B. T. K., Sunarwidhi, A. L., Widyastuti, S., & Prasedya, E. S. (2023). Anti-melanoma potential of fucoxanthin by inhibition MC1R receptor: In Silico study. AIP Conference Proceedings. https://doi.org/10.1063/5.0174957

Quirós, M., Gražulis, S., Girdzijauskaitė, S., Merkys, A., & Vaitkus, A. (2018). Using SMILES strings for the description of chemical connectivity in the Crystallography Open Database. https://d-nb.info/1163463418/34

R&D Chemicals (2024) OSIRIS Property Explorer - Calculation of Molecular Properties and Drug-Likeness. https://www.rdchemicals.com/drug-relevant-properties.html (Accessed: February 4, 2024)

Rao, C.M.P. (2023) 'Insights from the molecular docking and simulation analysis of P38 MAPK phytochemical inhibitor complexes,' Bioinformation, 19(3), pp. 323–330. https://doi.org/10.6026/97320630019323

Rao, C.M.P. (2023) 'Insights from the molecular docking and simulation analysis of P38 MAPK phytochemical inhibitor complexes,' Bioinformation, 19(3), pp. 323–330. https://doi.org/10.6026/97320630019323

Rim, K.-T. (2020) 'In silico prediction of toxicity and its applications for chemicals at work,' Toxicology and Environmental Health Sciences, 12(3), pp. 191–202. https://doi.org/10.1007/s13530-020-00056-4

Roy, K., Kar, S. and Das, R.N. (2015) 'Computational chemistry,' in Elsevier eBooks, pp. 151–189. https://doi.org/10.1016/b978-0-12-801505-6.00005-3

Ruttanapattanakul, J., Wikan, N., Potikanond, S., & Nimlamool, W. (2022). Molecular targets of pinocembrin underlying its regenerative activities in human keratinocytes. Pharmaceuticals, 15(8), 954. https://doi.org/10.3390/ph15080954

Singla, K., P, S. K. M., Bhattacharjya, A., Saxena, R., Choudhary, N., & Goyal, B. (2023). Bilirubin in wound healing: A double-edged sword. Cell Biochemistry and Function, 41(8), 953–958. https://doi.org/10.1002/cbf.3849

Skariyachan, S., & Garka, S. (2018). Exploring the binding potential of carbon nanotubes and fullerene towards major drug targets of multidrug resistant bacterial pathogens and their utility as novel therapeutic agents. In Elsevier eBooks (pp. 1–29). https://doi.org/10.1016/b978-0-12-813691-1.00001-4

University of Colombo. (2023, February 27). Launch of "Restoderma", a Poly-herbal Miracle Wound Healer Cream. University of Colombo, Sri Lanka. https://cmb.ac.lk/restoderma-product-launch

Zhang, J., Xie, Z., Zhang, N., & Zhong, J. (2017). Nanosuspension drug delivery system: preparation, characterization, postproduction processing, dosage form, and application. In Elsevier eBooks (pp. 413–443). https://doi.org/10.1016/b978-0-323-46143-6.00013-0