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# Pharmacokinetics and Toxicity Prediction of *Lansium domesticum* Corr.

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***ABSTRACT:*** *A wide range of compounds has been isolated from Lansium domesticum Corr. Secondary metabolites are commonly utilised as valuable resources for potential drug for research and development. An exemplary drug candidate must possess efficacy against the therapeutic target, safety, and favourable pharmacokinetic characteristics. The objective of this study was to determine the pharmacokinetic characteristics and toxicity potentials of 23 compounds derived from Lansium domesticum Corr. utilising the pKCSM online tool and the drug-likeness using swissADME online tool. Based on pKCSM prediction, compounds 14 (methyl angolensate) and 22 (7,14(27)-Onoceradiene-3,21-dione) from Lansium domesticum Corr. are identified as having favourable pharmacokinetic properties and are not expected to exhibit mutagenic or hepatotoxic effects. The $LD_{50}$ values for compounds 14 and 22 were 2.983 and 1.813 (mol/kg), respectively, indicating their lethal dosages. In conclusion, only compound 14 that also met all the Lipinski's Rule of Five.*

***Keywords:*** *ADMET; knapsack; Lansium domesticum; pkcsm; swissadme*

## 1. Introduction

*Lansium domesticum* Corr., a member of the Meliaceae family, is widely available in the Southeast region and has been documented for its use in traditional medicine [1]. *L. domesticum* Corr. shows good potential as an antioxidant, antibacterial and cytotoxic activity [2–15].

Plants produce secondary metabolites to serve as a form of defense including polyphenols, terpenoids, and alkaloids, have been scientifically demonstrated to contain various therapeutic properties such as antioxidant, anti-allergic, anti-inflammatory, anticancer, antihypertensive, and antibacterial activity [16]. The compounds of interest are frequently utilized as a foundation or source of inspiration for developing semisynthetic medicines with enhanced pharmacokinetic and pharmacodynamic characteristics [17]. Nevertheless, although several compounds have demonstrated specific bioactivities, their development has been hindered, and they have yet to be successful in clinical trials due to pharmacokinetic challenges. Therefore, it is necessary to conduct pharmacokinetic screening [18,19]. Both in vitro and in vivo techniques can be used to assess the pharmacokinetic properties of compounds, such as their toxicity potencies (T) and absorption, distribution, metabolism, and excretion (ADME). Nevertheless, these studies can be costly, mainly when testing many compounds. A wide range of in silico models are being developed for predicting a compound's ADMET characteristics. This strategy has improved success rates and reduced experimental medication trials, making it a helpful tactic [20].

The work involved the collection of compounds from *Lansium domesticum* Corr. using the Knapsack database, which was a comprehensive resource for plant metabolites [21]. The pharmacokinetic characteristics and toxicity potentials of compounds from *Lansium domesticum* Corr. were assessed using the pKCSM and Lipinski Rules of Five were asessed using the swissadme. pKCSM was a costless online service which employs graph-based signatures to generate ADMET characteristics prediction and a web application known as SwissADME provided unrestricted access to a repository of robust and speedy predictive models pertaining to physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry compatibility [22,23]. Further research is needed to confirm the results due to the computational limitations of this work. This study contributed in proposing the potential compound for the further research of *Lansium domesticum* Corr. plant by in vitro and in vivo evaluation.

## 2. Methods

The *Lansium domesticum* Corr. compounds were obtained using Knapsack database [20]. The SMILES sequences of every molecule were inputted to pKCSM for assess the pharmacokinetic, and toxicological potentials and *swissADME* for assess the Lipinski Rules of Five of these compounds of *Lansium domesticum* Corr.

## 3. Results and discussions

### *3.1. Results*

Twenty-three *LansiIum domesticum* Corr. compounds were obtained from the Knapsack database and listed in Table 1. Then, to predict the compounds', pharmacokinetic properties, and toxicological potentials, the pKCSM online program was utilized and listed in Table 2 [22]. The prediction of drug-likeness of *Lansium domesticum* Corr. compound using swissADME online program was utilized and listed in Table 3 [23].

### *3.2. Discussions*

Table 1 showed KNApSAcK as a comprehensive source for identifying plant metabolites including compound ID, metabolite name and Molecular formula which could be used to determine pharmacokinetics, toxicity and drug-likeness of *Lansium domesticum* Corr. compounds [21].

Table 2 showed pharmacokinetics characteristics and toxicity potensies of *Lansium domesticum* Corr. [22]. Compound including % absorbed compounds in human intestinal (A1), Caco-2 permeability (A2), $VD_{ss}$ (D1), BBB permeability (D2), CNS permeability (D3), CYP1A2 inhibitor (M1), CYP2C19 inhibitor (M2), CYP2C9 inhibitor (M3), CYP2D6 inhibitor (M4), CYP3A4 inhibitor (M5), renal OCT2 substrate (E1), AMES toxicity or mutagenicity (T1), hepatotoxicity (T2) and $LD_{50}$ (T3).

Most drugs are generally absorbed from the upper part of the small intestine [24]. pKCSM determined the percentage of human intestinal absorption (% HIA) and the permeability of intestinal mucosa (Caco-2 permeability) to assess drug absorption. A compound was considered well-

**Table 1.** Identified compounds of *Lansium domesticum* Corr. by Knapsack

| Compound | Compound ID | Metabolite name | Molecular formula |
|---|---|---|---|
| **1** | C00035024 | 6-Acetoxymexicanolide | C29H34O9 |
| **2** | C00035026 | 6-Hydroxymexicanolide | C27H32O8 |
| **3** | C00035054 | Azadiradione | C28H34O5 |
| **4** | C00035079 | Domesticulide A | C27H34O8 |
| **5** | C00035080 | Domesticulide B | C29H36O9 |
| **6** | C00035081 | Domesticulide C | C29H36O11 |
| **7** | C00035082 | Domesticulide D | C29H36O11 |
| **8** | C00035083 | Domesticulide E | C27H32O10 |
| **9** | C00035088 | Dukunolide B | C26H26O10 |
| **10** | C00035089 | Dukunolide C | C28H28O11 |
| **11** | C00035090 | Dukunolide D | C26H28O8 |
| **12** | C00035124 | Lansiolic acid | C30H48O3 |
| **13** | C00035125 | Lansioside B | C36H58O8 |
| **14** | C00035129 | Methyl angolensate | C27H34O7 |
| **15** | C00045537 | 21alpha-Hydroxyonocera-8(26), 14-dien-3-one | C30H48O2 |
| **16** | C00045558 | 3beta-Hydroxyonocera-8(26), 14-dien-21-one | C30H48O2 |
| **17** | C00046072 | Lansic acid | C30H46O4 |
| **18** | C00046073 | Lansionic acid | C30H46O3 |
| **19** | C00056344 | Dukunolide E | C26H28O9 |
| **20** | C00056491 | Dukunolide F | C26H28O9 |
| **21** | C00056734 | 3-Hydroxycycloart-24-en-21-oic acid | C30H48O3 |
| **22** | C00057217 | 7,14(27)-Onoceradiene-3,21-dione | C30H46O2 |
| **23** | C00057658 | Secodukunolide F | C27H32O9 |

**Table 2.** Pharmacokinetics characteristics and toxicity potencies of *Lansium domesticum* Corr. compounds

| No. | Compound | % absorbed compound in HIA (A1) | Caco-2 permeability (A2) | $VD_{ss}$ (D1) | BBB permeability (D2) | CNS permeability (D3) | CYP1A2 inhibitor (M1) | CYP2C19 inhibitor M2) | CYP2C9 inhibitor (M3) | CYP2D6 inhibitor (M4) | CYP3A4 inhibitor (M5) | Renal OCT2 substrate (E1) | AMES toxicity or mutagenicity (T1) | Hepatotoxicity (T2) | $LD_{50}$ (T3) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 6-Acetoxymexicanolide | 100 | 0.952 | -0.218 | -1.098 | -3.057 | - | - | - | - | + | - | - | + | 3.082 |
| 2 | 6-Hydroxymexicanolide | 100 | 0.874 | -0.258 | -0.727 | -3.073 | - | - | - | - | + | - | - | + | 3.01 |
| 3 | Azadiradione | 98.484 | 0.749 | 0.134 | -0.197 | -1.561 | - | - | - | - | + | - | - | - | 2.724 |
| 4 | Domesticulide A | 76.982 | 0.621 | -0.054 | -0.761 | -3.022 | - | - | - | - | - | - | - | + | 3.326 |
| 5 | Domesticulide B | 80.743 | 0.707 | 0.036 | -0.991 | -2.981 | - | - | - | - | + | - | - | - | 3.487 |
| 6 | Domesticulide C | 86.209 | 0.526 | 0.333 | -1.359 | -3.032 | - | - | - | - | - | - | - | - | 2.774 |
| 7 | Domesticulide D | 83.305 | 0.481 | 0.366 | -1.36 | -3.028 | - | - | - | - | - | - | - | - | 2.857 |
| 8 | Domesticulide E | 90.213 | 0.375 | -0.169 | -0.641 | -3.473 | - | - | - | - | - | - | + | - | 2.481 |
| 9 | Dukunolide B | 73.5 | 0.826 | 0.636 | -0.439 | -3.082 | - | - | - | - | - | - | - | - | 4.559 |
| 10 | Dukunolide C | 80.119 | 0.812 | 0.558 | -0.513 | -3.068 | - | - | - | - | - | - | - | - | 4.513 |
| 11 | Dukunolide D | 84.067 | 0.734 | 0.196 | -0.189 | -3.044 | - | - | - | - | - | - | - | - | 3.28 |
| 12 | Lansiolic acid | 92.278 | 1.244 | -0.622 | -0.103 | -1.552 | - | - | - | - | - | - | - | + | 2.051 |
| 13 | Lansioside B | 40.256 | -0.236 | -1.269 | -1.187 | -3.235 | - | - | - | - | - | - | - | - | 2.348 |
| 14 | Methyl angolensate | 100 | 0.994 | 0.119 | -0.706 | -2.881 | - | - | - | - | + | - | - | - | 2.983 |
| 15 | 21alpha-Hydroxyonocera-8(26),14-dien-3-one | 93.323 | 1.19 | 0.46 | 0.073 | -2.398 | - | - | - | - | - | - | - | + | 1.925 |
| 16 | 3beta-Hydroxyonocera-8(26),14-dien-21-one | 94.604 | 1.414 | 0.326 | 0.047 | -2.443 | - | - | - | - | - | - | - | + | 2.054 |
| 17 | Lansic acid | 95.222 | 0.522 | -1.512 | 0.158 | -1.808 | - | - | - | - | - | - | - | - | 2.265 |
| 18 | Lansionic acid | 94.803 | 1.265 | -0.686 | -0.042 | -1.459 | - | - | - | - | - | - | - | - | 1.973 |
| 19 | Dukunolide E | 79.161 | 0.75 | 0.038 | -0.534 | -3.467 | - | - | - | - | - | - | - | + | 4.031 |
| 20 | Dukunolide F | 79.161 | 0.718 | 0.014 | -0.917 | -3.467 | - | - | - | - | - | - | - | + | 3.998 |
| 21 | 3-Hydroxycycloart-24-en-21-oic acid | 100 | 1.369 | -1.302 | -0.398 | -1.268 | - | - | - | - | - | - | - | + | 3.717 |
| 22 | 7,14(27)-Onoceradiene-3,21-dione | 97.826 | 1.244 | 0.443 | 0.004 | -2.261 | - | - | - | - | - | - | - | - | 1.813 |
| 23 | Secodukunolide F | 75.994 | 0.923 | 0.752 | -0.226 | -3.243 | - | - | - | - | + | - | - | - | 3.686 |

**Table 3.** Lipinski's rules of five of *Lansium domesticum* Corr. compounds

| No. | Metabolite | Molecular weight | Log P | H-bond donor | H-acceptor | Molar refractivity |
|---|---|---|---|---|---|---|
| **1** | 6-Acetoxymexicanolide | 526.57 | 3.58 | 0 | 9 | 133.59 |
| **2** | 6-Hydroxymexicanolide | 484.54 | 3.01 | 1 | 8 | 123.85 |
| **3** | Azadiradione | 450.57 | 5.42 | 0 | 5 | 125.48 |
| **4** | Domesticulide A | 486.55 | 1.49 | 2 | 8 | 126.49 |
| **5** | Domesticulide B | 528.59 | 3.54 | 1 | 9 | 136.23 |
| **6** | Domesticulide C | 560.59 | 1.94 | 1 | 11 | 136.84 |
| **7** | Domesticulide D | 560.59 | 1.94 | 1 | 11 | 136.84 |
| **8** | Domesticulide E | 516.54 | 1.17 | 2 | 10 | 126.18 |
| **9** | Dukunolide B | 498.48 | 0.72 | 2 | 10 | 116.28 |
| **10** | Dukunolide C | 540.52 | 1.05 | 2 | 11 | 127.70 |
| **11** | Dukunolide D | 468.50 | 2.37 | 2 | 8 | 117.79 |
| **12** | Lansiolic acid | 456.70 | 7.57 | 2 | 3 | 140.71 |
| **13** | Lansioside B | 618.84 | 5.39 | 5 | 10 | 173.10 |
| **14** | Methyl angolensate | 470.55 | 4.24 | 0 | 7 | 123.61 |
| **15** | 21alpha-Hydroxyonocera-8(26), 14-dien-3-one | 440.70 | 7.51 | 1 | 2 | 137.24 |
| **16** | 3beta-Hydroxyonocera-8(26), 14-dien-21-one | 440.70 | 7.51 | 1 | 2 | 137.24 |
| **17** | Lansic acid | 470.68 | 7.83 | 2 | 4 | 143.22 |
| **18** | Lansionic acid | 454.68 | 7.77 | 1 | 7 | 139.75 |
| **19** | Dukunolide E | 484.50 | 1.58 | 2 | 9 | 117.27 |
| **20** | Dukunolide F | 484.50 | 1.58 | 2 | 9 | 117.27 |
| **21** | 3-Hydroxycycloart-24-en-21-oic acid | 456.70 | 7.23 | 2 | 5 | 136.91 |
| **22** | 7,14(27)-Onoceradiene-3,21-dione | 438.69 | 7.72 | 0 | 2 | 136.28 |
| **23** | Secodukunolide F | 484.54 | 2.49 | 2 | 8 | 123.07 |

absorbed in the pKCSM prediction model if its absorption value was greater than 80% and poorly absorbed if it was less than 30%. Furthermore, if a molecule was expected to have high intestinal mucosa permeability if its Caco-2 permeability values was greater than 0.90 [22]. In absorption features, compounds **1-3**, **5-8**, **10-12**, **14-18**, and **21-22** exhibited absorption values (A1) >80%, according to pKCSM predictive models. The Caco-2 permeability values (A2) of compounds **1**, **12**, **14-16**, **18**, and **21-23** were more significant than 0.90. It indicated that these compounds had a high intestinal mucosa permeability and were well-absorbed.

The volume of distribution (VD) is a crucial pharmacokinetic measurement that quantifies the relationship between the drug concentration in the body and its concentration in the plasma [25]. pKCSM created a predictive model for human $VD_{ss}$. If the logarithm of $VD_{ss}$ was less than -0.15, it was considered a low $VD_{ss}$. Conversely, if the logarithm of $VD_{ss}$ was more significant than 0.45, it was considered a high $VD_{ss}$, drugs might additionaly be transported to brain [22]. Never-

theless, the blood-brain barrier (BBB) served as a barrier that inhibits the passage of medicines into the brain. pKCSM offers predictions on the permeability of a drug via the blood-brain barrier (BBB) and its potential effects on the central nervous system (CNS). A drug with a logarithm of the blood-brain barrier (logBB) more than 0.3 was considered to have easy penetration into the blood-brain barrier (BBB), while a compound with a logBB less than -1 was considered to have poor distribution to the brain. In addition, a compound with a logPS value of more than -2 could enter the central nervous system (CNS). In contrast, compounds with a logPS value lower than -3 could not enter the CNS [22]. Based on the pKCSM prediction, compounds **3-7**, **9-11**, **14-16**, **19-20** and **22-23** had log VDss (D1) ≥-0.15, but only **9-10**, 15, and **23** had a log VDss (D1) value more than or equal to -0.15. However, only compounds 9-10, 15, and 23 had a log VDss value greater than 0.45, indicating that they could be substantially distributed, resulting in more significant tissue concentrations than plasma. Compounds **2-5**, **8-12**, and **14-23** exhibited a logBBB value (D2) greater than or equal to -1, indicating that these compounds could easily traverse the blood-brain barrier. Compounds **3**, **5**, **12**, **14-18**, and **21-22** had a logPS value (D3) greater than -3, indicating their ability to permeate the central nervous system (CNS). Safety issues have arisen throughout the development of medications that possess the ability to readily traverse the blood-brain barrier (BBB) and enter the central nervous system (CNS) due to unanticipated neurotoxic effects [26].

Cytochrome P450 (CYP) inactivates certain medications and can activate many drugs in the liver [27]. The molecule's inhibiting activity of the cytochrome P450 enzyme (CYP) is likely the cause of several interactions with medications. Hence, evaluating the cytochrome P450 substrates and inhibitors of potential pharmaceutical compounds is crucial. pKCSM offers prognostic models for five CYP isoforms, namely CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, which play a crucial role in drug metabolism [22]. None of the 23 compounds exhibited inhibitory effects on CYP1A2 (M1), CYP2C19 (M2), CYP2C9 (M3), and CYP2D6 (M4) enzymes in metabolic studies. But, compounds **3-5**, **14**, and **23** were identified as inhibitors of the CYP3A4 enzyme (M5).

Organic cation transporter 2 (OCT2) is a renal transporter responsible for regulating the reabsorption of drugs from the bloodstream. It has a crucial function in distributing and eliminating medicines through the kidneys [28]. Therefore, evaluating a prospective compounds that could be taken up again by OCT2 (OCT2 substrates) offers valuable insights into its elimination (excretion) and possible contraindications [22]. Based on the pKCSM results for elimination features (E), none of the compounds were supposed to be taken up again with renal OCT2 (OCT2 substrates).

Assessing toxicity is crucial to ensure potential safety of drug candidates. pKCSM also forecasted the possible mutagenicity and hepatotoxicity of compounds derived from *Lansium domesticum* Corr. The $LD_{50}$ is the lethal dose of a compound administered in a single instance that results in the death of 50% of a cohort of experimental animals [22]. Compound 8 was anticipated to have mutagenic potential (T1). Compounds **1-2**, **4**, **12**, **15-16**, and **19-21** were identified as potentially hepatotoxic compounds (T2). The $LD_{50}$ values of 23 *Lansium domesticum* Corr. compounds range from 1.831 to 4.559 (mol/kg), indicating their expected lethal dosage.

According to the findings, compounds **14**, **15**, **16** and **22** were determined to exhibit favourable absorption and distribution characteristics. Compounds **14**, **16** and **22** were determined to have no inhibitory effects on CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, or OCT2. Compounds **14** and **22** were determined to lack the potential to induce mutagenicity or hepatotoxicity in toxicity assessment. The compounds were expected to have $LD_{50}$ values of 2.983, 1.925, 2.054, and 1.813 (mol/kg), respectively.

Table 3 shows Lipinski first of five rules that classify small molecules according to their drug-likeness: Molecular weight <500 dalton, log P <5, H-bond donor <5, H-acceptor <10 and molar refractivity 40-130 [29].

Molecular weight is related to the compounds ability to diffuse and penetrate cell membranes [30]. Molecular weight of **2-4**, **6-7**, **9**, **11-13**, and **14-23** compounds were less than 500 Da. Log P is related to the compounds ability to penetrate in an immiscible biphasic system of lipids (fats, oils, organic solvents) [29]. Log P of **1-12**, **14-16**, **19-20**, and **23** compounds were less than 5. It can be concluded that these compounds were hydrophobic and could penetrate the immiscible biphasic system of lipids. The minimum number of H-bond donors is 5, while the minimum number of H-bond acceptors is 10. All compounds met the requirement excluding compound **13** for H-bond donors and compounds **8-10**, and **13** for H-bond acceptor did not meet the requirement. H-bond donors and H-bond acceptors demonstrated that the energy required for the absorption process increased with the number of H-bonds [29]. Molar refractivity shows that the polarity of a compound must be in the range of 40-130 and the molar refraction of compounds **2-4**, **6-12**, **14-17**, **19-20**, and **23** were in that range. Compounds **2-4**, 6-7, **11-12**, **14-16**, **19-20**, and **23** met all the requirements of the Rule of Five, meaning they were well absorbed and potentially effective for oral human consumption [29].

Admet and Lipinski rule of five (RO5) prediction result by computation could be use to analyze the potential compund effectively and efficienty. This result representative for further in vitro and in vivo evaluation. Figure 1 showed the compounds structures of compound **14** (methyl angolensate).

## 4. Conclusion

Based on the pharmacokinetics prediction, compounds **14** (methyl angolensate) and **22** (7,14(27)-Onoceradiene-3,21-dione) had favourable pharmacokinetic characteristics and were non-toxic. In addition **14** (methyl angolensate) was the only compound that met Lipinski's Rule of Five. Therefore, this compound has great potential for further research as a potential drug candidate. This computational method is beneficial for evaluating a substantial quantity of compounds. Nevertheless, additional research is required to validate these predictions.

The results of this research were only computationally predictive, so further research is needed to prove it using in vitro and in vivo models. However, this prediction can save time and costs com-

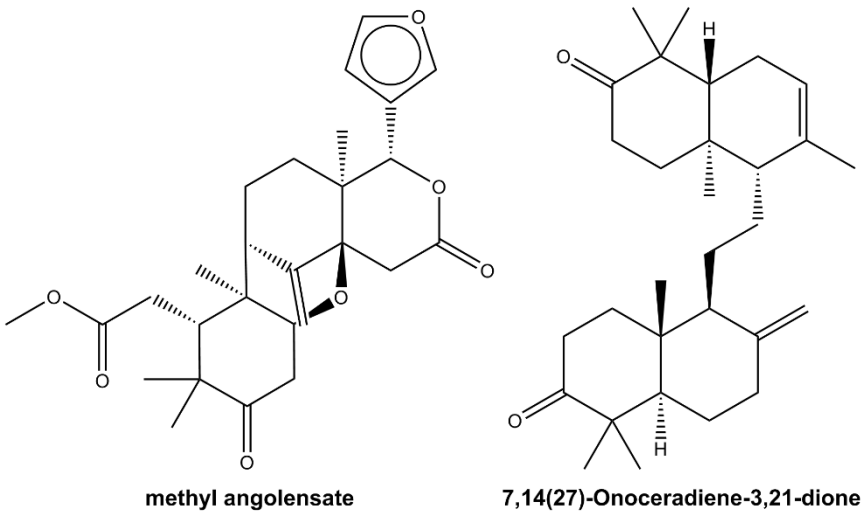


**Figure 1.** Structures of compounds **14** (methyl angolensate) and **22** (7,14(27)-Onoceradiene-3,21-dione)

pared to in vitro and in vivo models so that this research can be used for further development.

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