In Silico ADMET and Toxicity of *Hibiscus sabdariffa* L. Metabolites

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Abstract. Hibiscus sabdariffa L. has been widely utilized in traditional medicine and is known to contain various bioactive compounds. However, comprehensive information regarding the pharmacokinetic properties, drug-likeness, and toxicity profiles of its metabolites remains limited. This study aimed to evaluate the potential of metabolites from Hibiscus sabdariffa L. using an in silico approach. Compound identification was conducted using the KNApSAcK database, followed by pharmacokinetic and drug-likeness analysis employing SwissADME. Acute toxicity prediction and organ-specific toxicity assessment were performed using ProTox-3.0. A total of 13 metabolites were identified, consisting of flavonoids, phenolic compounds, organic acids, sugars, alkaloids, terpenoids, and sterols. Several compounds demonstrated favorable gastrointestinal absorption and complied with Lipinski's Rule of Five, with bioavailability scores ranging from 0.55 to 0.56, indicating a moderate probability of oral bioavailability. Toxicity prediction results showed that most compounds belonged to toxicity classes 4–6, suggesting low to moderate acute toxicity, while a few compounds exhibited moderate to higher toxicity levels. This in silico evaluation provides preliminary insights into the pharmacokinetic behavior and safety profiles of Hibiscus sabdariffa L. metabolites, supporting their potential for further investigation as drug candidates.

Keywords: *Hibiscus sabdariffa L, In Silico, SwissADME.*

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A. Introduction

Hibiscus sabdariffa L. is a medicinal plant widely used in traditional medicine and as a functional food ingredient due to its diverse pharmacological activities [1]. Various studies have reported its antioxidant, anti-inflammatory, antidiabetic, and cardioprotective effects, which are largely attributed to its rich content of bioactive secondary metabolite [1]. Despite its extensive utilization, detailed evaluations of the pharmacokinetic characteristics and safety profiles of individual compounds derived from Hibiscus sabdariffa L. remain limited.

In drug discovery and development, early evaluation of pharmacokinetic properties and toxicity is essential to reduce failure rates in later experimental stages [2]. In silico approaches have emerged as effective tools to predict absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles, allowing rapid screening of potential drug candidates prior to in vitro and in vivo studies [2]. Databases such as KNApSAcK facilitate the identification of plant metabolites, while computational platforms such as SwissADME and ProTox enable systematic prediction of drug-likeness and toxicity parameters.

This study aimed to identify metabolites present in Hibiscus sabdariffa L. and to evaluate their pharmacokinetic properties, drug-likeness, and toxicity profiles using an in silico approach. The findings of this study are expected to provide preliminary scientific evidence regarding the potential and safety of Hibiscus sabdariffa L. metabolites, thereby supporting their further development as prospective therapeutic agents.

B. Method

This study was conducted following the workflow illustrated in Figure 1. The research began with the identification of chemical constituents of Hibiscus sabdariffa L. using the KNApSAcK database. The identified compounds were subsequently analyzed for their pharmacokinetic profiles and drug-likeness parameters using the SwissADME platform. Furthermore, each compound was evaluated for its toxicity potential through in silico analysis using ProTox-3.0. The toxicity parameters assessed included LD_{50} values, toxicity class, and predictions of organ-specific toxicities, namely hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, and cardiotoxicity.

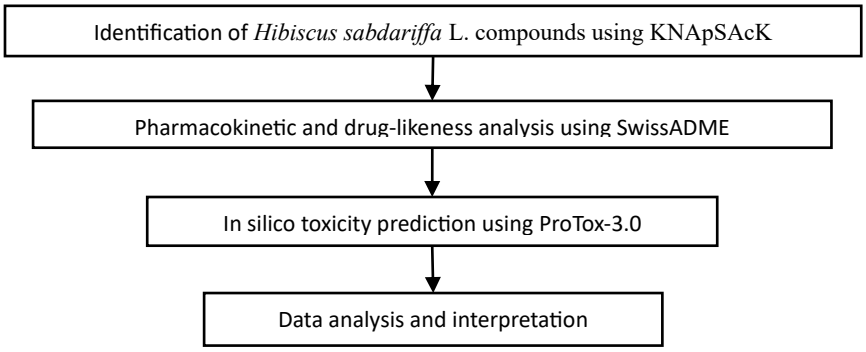

Figure 1. Stages of the research

C. Result and Discussion

The present study employed an in silico strategy to systematically evaluate the chemical composition, pharmacokinetic properties, drug-likeness, and toxicity profiles of metabolites derived from Hibiscus sabdariffa L. This approach allows an integrated assessment of both efficacy-related parameters and safety considerations at an early stage of drug discovery [3]. By combining metabolite identification with computational prediction tools, this study provides a comprehensive overview of the potential suitability of Hibiscus sabdariffa L. metabolites as drug candidates.

The analysis focused on small-molecule characteristics, oral absorption potential, blood brain barrier permeability, and acute toxicity classification. Such parameters are critical in determining whether a compound may proceed to further experimental evaluation. The following subsections

discuss the identification of metabolites, their pharmacokinetic and drug-likeness profiles, and the predicted toxicity outcomes based on computational models.

Metabolite Profiling Based on the KNApSAcK Database

Table 1. Identified metabolites of Hibiscus sabdariffa L. retrieved from the KNApSAcK database

No	Compound	Formula	Molecular weight
1	Eugenol	C10H12O2	164,0837
2	Myricetin	C15H10O8	318,0376
3	Trigonelline	C7H7NO2	137,0477
4	3,4-Dihydroxybenzoic acid	C7H6O4	154,0266
5	Cholesterol	C27H46O	386,3549
6	Ergosterol	C28H44O	396,3392
7	Spinasterol	C29H48O	412,3705
8	Quercetin	C15H10O7	302,0427
9	Gossypetin	C15H10O8	318,0376
10	Citric acid	C6H8O7	192,0270
11	D-Galactose	C6H12O6	180,0634
12	alpha-Terpineol	C10H18O	154,1358
13	Malic acid	C4H6O5	134,0215

Based on the search conducted using the KNApSAcK database, 13 compounds were identified as constituents of Hibiscus sabdariffa L., as presented in Table 1. These compounds exhibit considerable diversity in chemical structure and molecular weight and belong to various classes, including phenolics, flavonoids, organic acids, sugars, alkaloids, terpenoids, and sterols. This diversity indicates that Hibiscus sabdariffa L. contains both primary and secondary metabolites. The chemical structures of the identified compounds are shown in Figure 2, illustrating the molecular frameworks of each metabolite. The presence of compound groups such as flavonoids, phenolics, and organic acids is consistent with previous phytochemical reports indicating that Hibiscus sabdariffa L. is rich in polyphenolic compounds and other bioactive constituents that contribute to its various biological activities [4].

The flavonoid group was identified as relatively dominant, particularly myricetin, quercetin, and gossypetin. Flavonoids are recognized as polyphenolic compounds that act as potent antioxidants through their ability to donate electrons and stabilize free radicals [5]. The presence of multiple flavonoids suggests potential pharmacological activities, including anti-inflammatory, cardioprotective, and antidiabetic effects, which have been widely reported for various flavonoid compounds [6]. In addition to flavonoids, simple phenolic compounds such as eugenol and 3,4-dihydroxybenzoic acid were also identified. Phenolic compounds generally contribute to antioxidant and antimicrobial activities due to the presence of aromatic hydroxyl groups that are reactive toward reactive oxygen species [7]. The presence of eugenol is particularly noteworthy, as this compound is known to exhibit analgesic and anti-inflammatory effects [7]. Organic acids such as citric acid and malic acid are primary metabolites involved in plant cellular metabolic cycles and may also contribute to biological properties through their roles in redox processes and cellular homeostasis [8]. The identification of D-galactose as a simple sugar indicates the presence of carbohydrate components commonly found in plant tissues [8].

The alkaloid compound identified was trigonelline. Trigonelline has been reported to possess various biological activities, including potential antidiabetic, neuroprotective, and antioxidant effects, thereby contributing to the bioactivity profile of Hibiscus sabdariffa L [9]. Terpenoid and sterol groups were also detected, including α-terpineol, cholesterol, ergosterol, and spinasterol. Terpenoid compounds such as α-terpineol are known for their antimicrobial and anti-inflammatory activities [9]. Meanwhile, plant sterols such as spinasterol and other sterol derivatives have been reported to exhibit potential as anti-inflammatory and immunomodulatory agents [9].

In terms of molecular weight, most of the identified compounds fall within the range of <400 Da, which is consistent with the characteristics of small molecules and is generally associated with favorable oral bioavailability [10]. This parameter provides a useful basis for subsequent analysis of pharmacokinetic profiles and drug-likeness in the next stage of this study. The identification results obtained from the KNApSAcK database indicate that Hibiscus sabdariffa L. possesses a complex chemical composition dominated by bioactive metabolites, particularly flavonoids and phenolic compounds, which have been scientifically associated with various previously reported pharmacological activities.

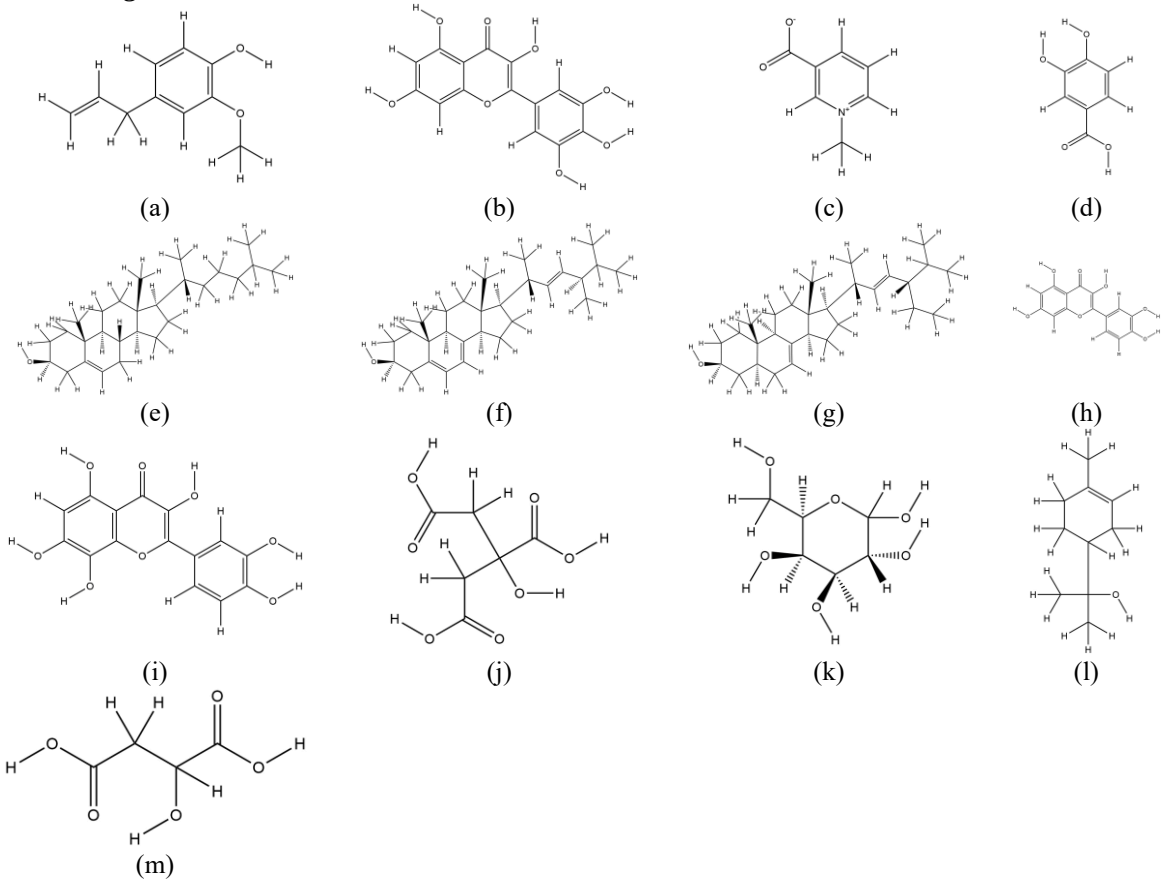

Figure 2. Chemical structures of metabolites identified from Hibiscus sabdariffa L. (a) Eugenol, (b) Myricetin, (c) Trigonelline, (d) 3,4-Dihydroxybenzoic acid, (e) Cholesterol, (f) Ergosterol, (g) Spinasterol, (h) Quercetin, (i) Gossypetin, (j) Citric acid, (k) D-Galactose, (l) alpha-Terpineol, and (m) Malic acid.

Drug-Likeness and Pharmacokinetic Prediction Using SwissADME

Table 2. Predicted pharmacokinetic properties of Hibiscus sabdariffa L. metabolites using SwissADME

No	Compound	Log Kp (cm/s)	GI absorption	BBB permeant
1	Eugenol	-5,69	High	Yes
2	Myricetin	-7,4	Low	No
3	Trigonelline	-6,77	High	No
4	3,4-Dihydroxybenzoic acid	-6,42	High	No
5	Cholesterol	-2,47	Low	No
6	Ergosterol	3,44	Low	No
7	Spinasterol	-2,92	Low	No

8	Quercetin	-7,05	High	No
9	Gossypetin	-6,96	Low	No
10	Citric acid	-8,69	Low	No
11	D-Galactose	-9,7	Low	No
12	alpha-Terpineol	-4,83	High	Yes
13	Malic acid	-8,01	High	No

The predicted pharmacokinetic properties of the compounds identified from Hibiscus sabdariffa L. using SwissADME are presented in Table 2. The analyzed parameters included skin permeability (Log Kp), gastrointestinal absorption (GI absorption), and blood brain barrier permeability (BBB permeant). The data indicate variations in absorption and permeability characteristics among the analyzed compounds. Based on the data presented in Table 2, several compounds exhibited good potential for oral absorption, as indicated by the high GI absorption category, including eugenol, trigonelline, 3,4-dihydroxybenzoic acid, quercetin, alpha-terpineol, and malic acid. High gastrointestinal absorption is generally associated with relatively small molecular size and a favorable balance between lipophilicity and polarity, which support passive diffusion across the intestinal membrane [11]. These findings suggest that several metabolites of Hibiscus sabdariffa L. may possess favorable oral bioavailability.

Conversely, as presented in Table 2, myricetin, gossypetin, citric acid, D-galactose, cholesterol, ergosterol, and spinasterol were predicted to exhibit low gastrointestinal absorption. This limited absorption may be attributed to their high polarity, larger molecular size, or excessively lipophilic structures, which can restrict solubility and passive diffusion across biological membranes [11]. Flavonoids bearing multiple hydroxyl groups, such as myricetin and gossypetin, are often associated with limited membrane permeability due to their high polarity, despite exhibiting strong biological activities [6].

Based on the BBB permeability parameter shown in Table 2, only eugenol and alpha-terpineol were predicted to be capable of crossing the blood brain barrier. Compounds that can penetrate the BBB generally possess small molecular size and sufficient lipophilicity to support passive diffusion through the endothelial membranes of brain capillaries [12]. This potential BBB permeability suggests the possibility of pharmacological effects on the central nervous system. In contrast, most of the other compounds were predicted not to cross the BBB, which may reduce the risk of side effects on the central nervous system and indicate that their activity is more likely to be directed toward peripheral tissues [12]. The Log Kp parameter presented in Table 2 indicates variations in skin penetration ability among the analyzed compounds. Higher Log Kp values, meaning less negative values, are associated with better skin permeability [13]. In this study, alpha-terpineol and eugenol exhibited relatively higher Log Kp values compared to the other compounds, suggesting greater potential for skin penetration. In contrast, compounds with very low Log Kp values, such as D-galactose, citric acid, and malic acid, showed limited skin permeability, which is consistent with their highly polar nature.

The SwissADME analysis indicates that not all compounds from Hibiscus sabdariffa L. possess pharmacokinetic profiles that are ideal for oral administration. However, certain compounds, such as eugenol and alpha-terpineol, demonstrated a more favorable combination of absorption and permeability characteristics. These variations highlight the importance of early stage in silico evaluation to screen for compounds with better pharmacokinetic potential prior to further studies.

Table 3. Drug-likeness evaluation of identified metabolites using SwissADME

No	Metabolite	Lipinski	Bioavailability Score
1	Eugenol	Yes; 0 violation	0.55
2	Myricetin	Yes; 1 violation: NHorOH>5	0.55
3	Trigonelline	Yes; 0 violation	0.55
4	3,4-Dihydroxybenzoic acid	Yes; 0 violation	0.56
5	Cholesterol	Yes; 1 violation: MLOGP>4.15	0.55
6	Ergosterol	Yes; 1 violation: MLOGP>4.15	0.55

7	Spinasterol	Yes; 1 violation: MLOGP>4.15	0.55
8	Quercetin	Yes; 0 violation	0.55
9	Gossypetin	Yes; 1 violation: NHorOH>5	0.55
10	Citric acid	Yes; 0 violation	0.56
11	D-Galactose	Yes; 0 violation	0.55
12	alpha-Terpineol	Yes; 0 violation	0.55
13	Malic acid	Yes; 0 violation	0.56

The evaluation of drug-likeness using SwissADME, as shown in Table 3, indicated that all compounds identified from Hibiscus sabdariffa L. generally satisfied the basic criteria of Lipinski's Rule of Five, which is commonly used to predict the potential oral bioavailability of a compound [10]. However, several compounds exhibited a single parameter that slightly deviated from these criteria, which may influence their pharmacokinetic characteristics. Compounds such as eugenol, trigonelline, 3,4-dihydroxybenzoic acid, quercetin, citric acid, D-galactose, α-terpineol, and malic acid fully complied with Lipinski's criteria. This indicates that their molecular weight, lipophilicity, and numbers of hydrogen bond donors and acceptors fall within ranges that are generally supportive of good oral absorption [10]. These compounds theoretically possess characteristics consistent with small molecule drug candidates.

Conversely, several compounds showed a single deviation from Lipinski's criteria. Myricetin and gossypetin exceeded the recommended limit for the number of hydrogen bond donors (NH or OH > 5). A high number of hydroxyl groups can increase molecular polarity, thereby reducing membrane permeability and potentially limiting oral absorption [10]. Nevertheless, the presence of one deviation from Lipinski's criteria is often considered acceptable in drug development, particularly for natural compounds with strong biological activities [10]. Within the sterol group, including cholesterol, ergosterol, and spinasterol, a deviation was observed in the lipophilicity parameter (MLOGP > 4.15). Excessively high lipophilicity may enhance affinity for lipid membranes while reducing solubility in aqueous environments, which can potentially limit absorption and systemic distribution [10]. This is consistent with the inherently hydrophobic nature of sterol compounds. In addition, the bioavailability scores for most compounds ranged from 0.55 to 0.56, which, according to the Abbott bioavailability score model implemented in SwissADME, indicate a moderate probability that a compound possesses oral bioavailability of at least 10%. Although this value does not guarantee actual in vivo bioavailability, it can serve as an initial indicator in the screening and development of potential drug candidates [14].

The drug-likeness analysis indicates that most metabolites of Hibiscus sabdariffa L. possess characteristics that are reasonably consistent with the criteria for orally active drug molecules, although some compounds exhibit limitations due to high polarity or excessive lipophilicity. This drug-likeness evaluation represents an important step in the early screening of compounds prior to more detailed pharmacokinetic and biological studies.

In Silico Toxicity Prediction Using ProTox-3.0

Table 4. Predicted toxicity profiles of Hibiscus sabdariffa L. metabolites based on ProTox 3.0 analysis

No	Compound	LD_{50} (mg/kg)	Toxicity Class	Organ Toxicity	Prediction	Probability
1	Eugenol	1930	4	Hepatotoxicity	Inactive	0,67
				Neurotoxicity	Active	0,51
				Nephrotoxicity	Inactive	0,63
				Respiratory toxicity	Inactive	0,98
				Cardiotoxicity	Inactive	0,89
2	Myricetin	159	3	Hepatotoxicity	Inactive	0,69

3	Trigonelline	3720	5	Neurotoxicity	Inactive	0,89
				Nephrotoxicity	Active	0,62
				Respiratory toxicity	Active	0,83
				Cardiotoxicity	Inactive	0,99
				Hepatotoxicity	Inactive	0,6
4	3,4-Dihydroxybenzoic acid	2000	4	Neurotoxicity	Active	0,76
				Nephrotoxicity	Inactive	0,59
				Respiratory toxicity	Active	0,69
				Cardiotoxicity	Inactive	0,75
				Hepatotoxicity	Inactive	0,59
5	Cholesterol	890	4	Neurotoxicity	Inactive	0,86
				Nephrotoxicity	Active	0,61
				Respiratory toxicity	Inactive	0,58
				Cardiotoxicity	Inactive	0,9
				Hepatotoxicity	Inactive	0,85
6	Ergosterol	10	2	Neurotoxicity	Active	0,51
				Nephrotoxicity	Inactive	0,92
				Respiratory toxicity	Active	0,82
				Cardiotoxicity	Inactive	0,81
				Hepatotoxicity	Inactive	0,8
7	Spinasterol	2000	4	Neurotoxicity	Active	0,53
				Nephrotoxicity	Inactive	0,95
				Respiratory toxicity	Active	0,82
				Cardiotoxicity	Inactive	0,89
				Hepatotoxicity	Inactive	0,85
8	Quercetin	159	3	Neurotoxicity	Active	0,57
				Nephrotoxicity	Inactive	0,89
				Respiratory toxicity	Active	0,9
				Cardiotoxicity	Inactive	0,82
				Hepatotoxicity	Inactive	0,69
9	Gossypetin	159	3	Neurotoxicity	Inactive	0,89
				Nephrotoxicity	Active	0,62
				Respiratory toxicity	Active	0,83
				Cardiotoxicity	Inactive	0,99
10	Citric acid	80	3	Hepatotoxicity	Inactive	0,89

				Neurotoxicity	Inactive	0,99
				Nephrotoxicity	Inactive	0,55
				Respiratory toxicity	Active	0,72
				Cardiotoxicity	Inactive	0,91
				Hepatotoxicity	Inactive	0,98
				Neurotoxicity	Inactive	0,95
11	D-Galactose	23000	6	Nephrotoxicity	Active	0,7
				Respiratory toxicity	Inactive	0,99
				Cardiotoxicity	Active	0,92
				Hepatotoxicity	Inactive	0,72
				Neurotoxicity	Inactive	0,58
12	alpha-Terpineol	2830	5	Nephrotoxicity	Inactive	0,89
				Respiratory toxicity	Inactive	0,88
				Cardiotoxicity	Inactive	0,95
				Hepatotoxicity	Inactive	0,9
				Neurotoxicity	Inactive	0,98
13	Malic acid	2497	5	Nephrotoxicity	Active	0,55
				Respiratory toxicity	Inactive	0,64
				Cardiotoxicity	Inactive	0,86

The in silico toxicity prediction using ProTox, as presented in Table 4, revealed variations in acute toxicity levels based on LD_{50} values and their corresponding toxicity classifications. According to the LD_{50} classification, as shown in Table 5, most compounds fall into the slightly toxic to relatively harmless categories, indicating relatively low acute toxicity [15]. Compounds such as trigonelline, alpha-terpineol, malic acid, 3,4-dihydroxybenzoic acid, eugenol, and spinasterol exhibited LD_{50} values above 500 mg/kg, which are generally associated with lower acute toxicity. In contrast, several compounds, including myricetin, quercetin, gossypetin, and citric acid, were categorized as moderately toxic, with LD_{50} values ranging from 50 to 500 mg/kg. Meanwhile, ergosterol showed a very low LD_{50} value and was classified as highly toxic, indicating a greater potential for acute toxicity compared to the other compounds [15]. These findings emphasize that not all natural metabolites are inherently safe, and toxicity evaluation remains essential in the screening of drug candidates.

Based on organ-specific toxicity predictions, most compounds were estimated to be non-hepatotoxic and non-cardiotoxic, which are important parameters in safety evaluation. However, several compounds demonstrated potential toxicity toward specific organs, particularly nephrotoxicity and respiratory toxicity, as predicted for myricetin, quercetin, gossypetin, and certain organic acids. In addition, compounds such as eugenol, trigonelline, cholesterol, ergosterol, and spinasterol showed a moderate probability of neurotoxic effects. The ProTox prediction results suggest that the majority of metabolites from Hibiscus sabdariffa L. exhibit relatively low to moderate acute toxicity profiles, although some compounds warrant further attention due to their potential organ-specific toxicities. These findings highlight the importance of subsequent toxicological evaluations to ensure safety prior to further development as drug candidates.

Table 5. LD_{50} Toxicity Classification

LD_{50} (mg/kg)	**Toxicity Category**
< 5	Extremely toxic
5 – 50	Highly toxic

50 – 500	Moderately toxic
500 – 5,000	Slightly toxic
5,000 – 15,000	Practically non-toxic
> 15,000	Relatively harmless

Source: **[15]**

D. Conclusion

This study successfully identified thirteen metabolites from Hibiscus sabdariffa L. using the KNApSAcK database and evaluated their pharmacokinetic properties, drug-likeness, and toxicity profiles through in silico analysis. Most identified compounds demonstrated molecular characteristics consistent with small-molecule drug candidates and generally complied with Lipinski's Rule of Five, with bioavailability scores indicating a moderate probability of oral bioavailability. Toxicity prediction results revealed that the majority of metabolites exhibited low to moderate acute toxicity, although several compounds showed potential organ-specific toxicities that warrant further attention. These findings suggest that Hibiscus sabdariffa L. contains metabolites with promising pharmacokinetic and safety profiles. Nevertheless, further in vitro and in vivo studies are required to validate these computational predictions and to confirm their therapeutic potential and safety.

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