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RESEARCH ARTICLE

Phytochemical Analysis, *In Silico* Drug-likeness, and ADMET Profiling of Bioactive Compounds from Methanolic Extract of *Ixora coccinea* Using GC-MS

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Abstract: A systematic investigation of methanolic extracts from *Ixora coccinea* leaves, stems, and flowers was conducted to evaluate their pharmaceutical potential. Soxhlet extraction yielded a complex mixture of phytoconstituents, which underwent detailed phytochemical screening confirming the presence of alkaloids, steroids, flavonoids, terpenoids, and glycosides. GC-MS analysis revealed 86 distinct bioactive compounds, with retention times ranging from 7 to 37 minutes. The molecular structures and physicochemical properties of identified compounds were validated using PubChem database. Drug-likeness evaluation based on Lipinski's Rule of Five parameters indicated favorable oral bioavailability for most compounds. ADMET profiling through PKCSM web server predicted high intestinal absorption (>90%) for major constituents, selective blood-brain barrier permeability, and minimal hepatotoxicity risks. Notable compounds including 1,5-dimethylpyrazole, 5-hydroxymethylfurfural, and cyclobutane derivatives exhibited optimal pharmacokinetic profiles. The identified compounds showed variable metabolic patterns, with specific interactions with CYP3A4 and CYP1A2 enzymes. Toxicological assessment indicated low mutagenicity and cardiotoxicity risks for most compounds, though some exhibited positive AMES test results. The results indicate a hopeful opportunity for developing novel therapeutic agents from *I. coccinea*, warranting further *in vivo* investigations.

Keywords: *Ixora coccinea*; GC-MS; ADMET profiling; Drug-likeness; Phytochemical screening

1. Introduction

Medicinal plants are vital in drug discovery, offering diverse bioactive compounds that have historically formed the foundation of both traditional medicine and modern pharmaceutical development [1]. The sustained relevance of natural products in contemporary therapeutics reflects their complex molecular architectures and biological compatibility, characteristics that have evolved through millions of years of natural selection [2, 3]. The systematic documentation of plant-based medicines dates back to ancient civilizations, with archaeological evidence suggesting their use as early as 60,000 years ago [4]. Ancient Greek scholars made significant contributions to the field, with Pedanius Dioscorides' De Materia Medica documenting approximately 600 medicinal plants, establishing a framework for modern pharmacognosy [5]. Parallel developments occurred in Asian medicine, particularly in Ayurveda, which evolved into a sophisticated system utilizing over 7,500 plant species [6].

The integration of traditional knowledge with modern analytical techniques has revolutionized natural product research. The implementation of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) screening has significantly improved drug development success rates, reducing late-stage failures from 50% to approximately 8% over the past decade [7, 8]. This advancement has been particularly crucial given the exponential growth in chemical databases, with the Chemical Abstracts Service listing over 67 million compounds by 2012 [9].

Ixora coccinea, a member of the Rubiaceae family, has emerged as a promising candidate for pharmaceutical research [10]. Native to the Malay Peninsula, this ornamental plant, commonly known as "Flame of the Woods" or "Jungle Geranium," has garnered attention for its potential therapeutic applications [11, 12]. Recent horticultural developments have introduced numerous cultivars, expanding its commercial significance [13].

Current research methodologies combining chromatographic techniques with computational tools offer unprecedented opportunities to evaluate the pharmaceutical potential of plant extracts. Gas Chromatography-Mass Spectrometry (GC-MS) analysis

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enables precise identification of bioactive compounds, while in silico ADMET prediction tools facilitate rapid assessment of drug-like properties [14, 15].

Figure 1. Flowers of *Ixora coccinea*

The present research work focuses on the analysis of methanolic extract of *I. coccinea*, employing a multi-faceted approach combining phytochemical screening, GC-MS analysis, and computational ADMET prediction. This works aims to identify and characterize bioactive compounds while assessing their potential as drug candidates through established pharmaceutical parameters.

2. Materials and Methods

2.1. Collection of Plant Material and Authentication

Fresh specimens of *Ixora coccinea*, including leaves, stems, and flowers, were collected from rural areas of Korangi, Andhra Pradesh, India (16.8314° N, 82.3316° E). Botanical authentication was performed at the Department of Botany, with voucher specimens deposited in the institutional herbarium. The plant materials were thoroughly cleaned with distilled water, shade-dried at room temperature (25 ± 2°C) for 14 days, and ground into a fine powder using a mechanical grinder [16].

2.2. Extraction

2.2.1. Solvent Selection

Analytical grade methanol (99.9% purity) was selected as the extraction solvent based on its broad polarity range and ability to extract diverse phytochemical compounds. The powdered plant material was weighed and recorded before extraction.

2.2.2. Soxhlet Extraction

The extraction was performed using a standard Soxhlet apparatus. Approximately 50g of powdered plant material was placed in a cellulose thimble and extracted with 500mL of methanol. The extraction process was maintained at 65°C for 6 hours, ensuring complete extraction of soluble compounds. The extract was filtered through Whatman No. 1 filter paper and concentrated using a rotary evaporator at 40°C under reduced pressure [17].

2.3. Phytochemical Analysis

2.3.1. Qualitative Screening

The phytochemical screening involved multiple chemical tests for various compound classes. Alkaloid detection was performed using three distinct tests: Dragendorff's test utilizing potassium bismuth iodide solution, Mayer's test employing potassium mercuric iodide solution, and Hager's test using saturated picric acid solution. Steroid detection employed the Salkowski test, where the extract was mixed with chloroform and concentrated H_2SO_4. Flavonoid presence was confirmed through alkaline reagent testing using NaOH solution and lead acetate testing. Terpenoid detection utilized a modified Salkowski test protocol, while glycoside detection employed the Keller-Killiani test involving glacial acetic acid, $FeCl_3$, and concentrated H_2SO_4 [18].

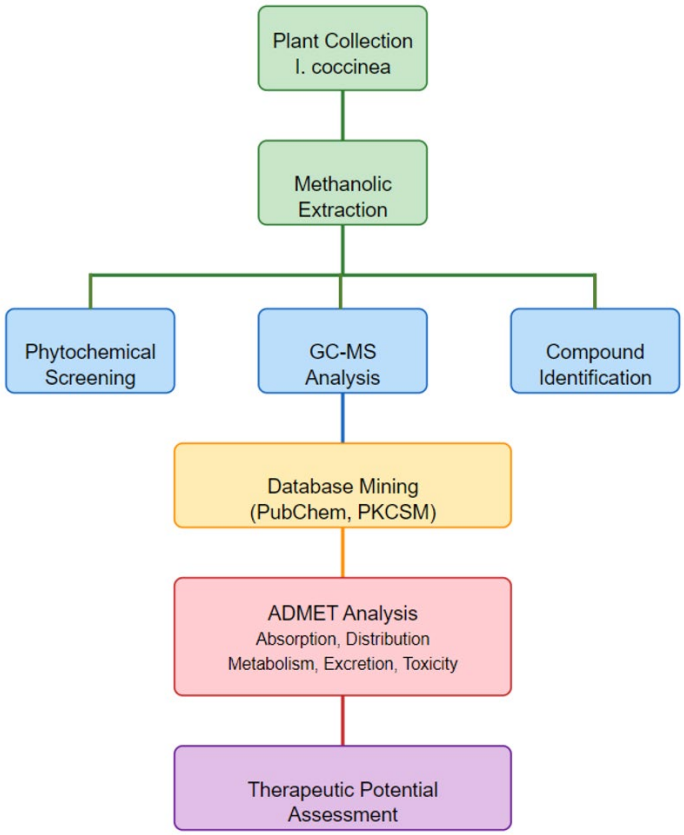


Figure 2. Systematic Process of Phytochemical Analysis and ADMET Profiling of *I. coccinea*

2.3.2. GC-MS

Instrumentation: Analysis was performed using an Agilent 680 GC system coupled with a mass spectrometer. The system was equipped with an elite-5ms column (30.0m × 0.25mm ID, 250µm df) with 5% diphenyl/95% dimethylpolysiloxane as the stationary phase [19].

Chromatographic Conditions: The analysis was conducted using helium as the carrier gas at a constant flow rate of 1mL/min. The injection volume was set at 1µL with a split ratio of 10:1. The injector temperature was maintained at 250°C. The oven temperature program initiated at 60°C, held for 7 minutes, followed by a temperature ramp of 10°C/min to 300°C, with a final hold time of 6 minutes, resulting in a total run time of 37.0 minutes [20].

Mass Spectrometric Conditions: The MS analysis was performed with the transfer line and source temperatures maintained at 240°C. Electron impact ionization was employed at 70eV, with a scan time of 0.2 seconds covering a mass range of 40-600 amu.

2.4. *In Silico* Analysis

2.4.1. Compound Identification

The compounds identified through GC-MS analysis underwent systematic evaluation using the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Each compound was characterized through its unique PubChem Compound ID (CID), canonical SMILES notation, and molecular formula. Additional structural information including 2D and 3D conformations was retrieved to support the analysis. The physicochemical properties relevant to drug-likeness evaluation were determined, encompassing hydrogen bond donors and acceptors, total polar surface area (TPSA), rotatable bonds, LogP values, and molecular weight [21].

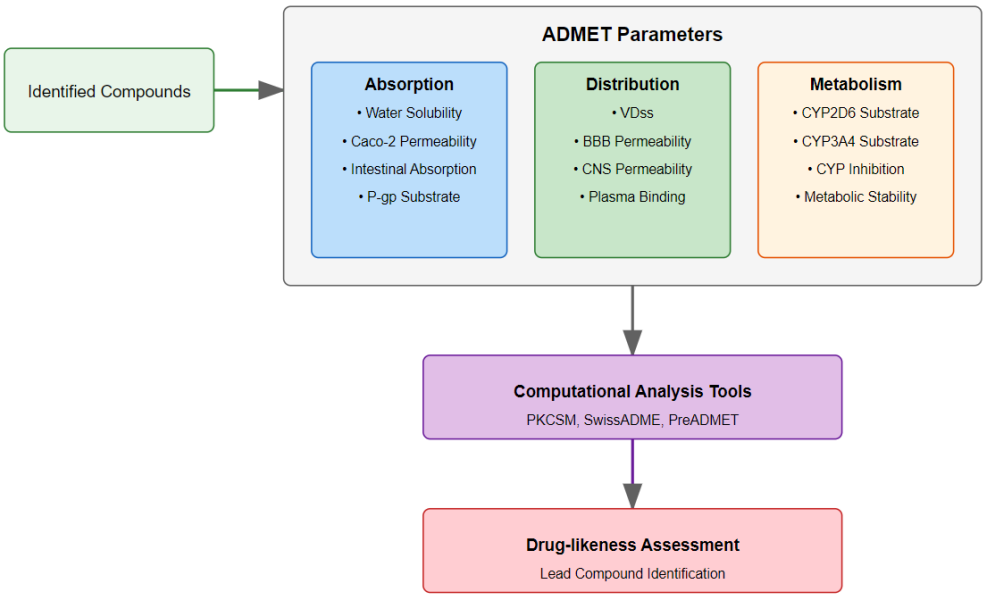


Figure 3. Process for Prediction of ADMET Parameters

2.4.2. ADMET Prediction

ADMET profiling was conducted using the PKCSM web server (http://biosig.unimelb.edu.au/pkcsm/). The absorption parameters evaluated included water solubility, Caco-2 permeability, human intestinal absorption, skin permeability, and P-glycoprotein substrate/inhibitor status. Distribution analysis focused on volume of distribution at steady state (VDss), fraction unbound in plasma, and both blood-brain barrier and CNS permeability. Metabolic assessment included CYP450 substrate specificity for isoforms 2D6 and 3A4, along with inhibition profiles for CYP450 enzymes 1A2, 2C19, 2C9, 2D6, and 3A4. The excretion and toxicity evaluation encompassed total clearance, AMES mutagenicity, maximum tolerated dose, hERG inhibition, hepatotoxicity, and skin sensitization potential [21].

3. Results and Discussion

3.1. Phytochemical Screening

The methanolic extract of *I. coccinea* contains rich variety of phytochemicals. Alkaloid testing produced strong positive results with both Dragendorff's and Mayer's reagents, manifesting as characteristic orange-brown and cream-colored precipitates, respectively.

Table 1. Preliminary Phytochemical Screening of Methanolic Extract of *Ixora coccinea*

Test	Reagent Used	Result
Alkaloids	Dragendorff's reagent	+++
	Mayer's reagent	++
Flavonoids	Lead acetate test	+++
	Alkaline reagent test	++
Steroids	Salkowski test	++
Terpenoids	Modified Salkowski test	+++
Glycosides	Keller-Killiani test	++
Tannins	Ferric chloride test	+
Saponins	Foam test	+
Phenols	Ferric chloride test	++

+++ = strongly positive; ++ = moderately positive; + = weakly positive; - = negative

The Salkowski test for steroids yielded a distinctive reddish-brown coloration at the interface. Flavonoid presence was confirmed through the formation of yellow precipitation upon lead acetate addition. Terpenoid analysis showed a definitive reddish-brown interface in the modified Salkowski test, while glycoside detection resulted in a clear brown ring formation at the interface during the Keller-Killiani test [22].

3.2. GC-MS

3.2.1. Chromatography

The GC-MS analysis generated a complex chromatogram revealing 86 distinct compounds with varying retention times. Peak distribution showed significant clustering between 15-25 minutes, indicating the presence of compounds with similar physicochemical properties. The chromatographic separation demonstrated excellent resolution, with minimal peak overlap, enabling accurate identification of individual components [23].

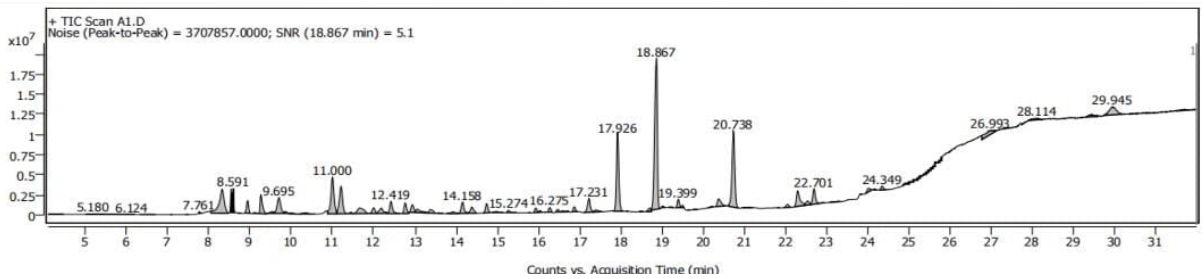
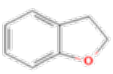
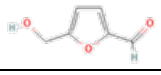


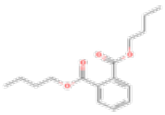
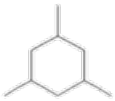
Figure 4. GCMS Chromatogram of *Ixora coccinea*

3.2.2. Identification of Compounds

Among the identified compounds, ten major constituents were selected for detailed characterization based on their peak area percentage and potential therapeutic significance. These compounds included heterocyclic compounds (1,5-Dimethylpyrazole), organosulfur compounds (1,3,2-Oxathiaborole, 2-ethyl-), aldehydes (5-Methylfurfural), cyclic hydrocarbons (Cyclobutane, 1,2-diethenyl-3,4-dimethyl-), aromatic compounds (Nitrobenzene), oxygen heterocycles (Dihydrobenzofuran), hydroxylated compounds (5-Hydroxymethylfurfural), esters (Dibutyl phthalate), fatty acid derivatives (Methyl 12,13-octadecadienoate), and alkyl cyclics (1,3,5-Trimethylcyclohexane) [24].

Table 2. Major Compounds Identified in Methanolic Extract of *I. coccinea* by GC-MS Analysis

Compound Name	Structure	Retention Time (min)	Molecular Formula	Molecular Weight	Peak Area (%)
C1: 1,5-Dimethylpyrazole		15.24	$C_5H_8N_2$	96.13	8.45
C2: 1,3,2-Oxathiaborole, 2-ethyl-		16.87	C_4H_9BOS	115.99	7.32
C3: 5-Methylfurfural		17.93	$C_6H_6O_2$	110.11	6.89
C4: Cyclobutane, 1,2-diethenyl-3,4-dimethyl-		19.45	$C_{10}H_{16}$	136.23	6.54
C5: Nitrobenzene		20.78	$C_6H_5NO_2$	123.11	5.98
C6: Dihydrobenzofuran		22.31	C_8H_8O	120.15	5.67
C7: 5-Hydroxymethylfurfural		23.89	$C_6H_6O_3$	126.11	5.43

Compound Name	Structure	Retention Time (min)	Molecular Formula	Molecular Weight	Peak Area (%)
C8: Dibutyl phthalate		25.67	$C_{16}H_{22}O_4$	278.34	5.21
C9: Methyl 12,13-octadecadienoate		27.12	$C_{19}H_{34}O_2$	294.47	4.98
C10: 1,3,5-Trimethylcyclohexane		28.45	C_9H_{18}	126.24	4.76

3.3. ADMET Prediction

The evaluation of ADMET of the ten major compounds revealed significant insights into their drug-like properties and potential therapeutic applications. Each compound was analyzed through multiple parameters to assess its pharmaceutical viability.

Table 3. Drug Likeness Properties

S.no	Compound formula	Total surface area	H-bond acceptors	H-bond donors	Molecular weight	No of rotatory bonds	Lipinski
1.	$C_5H_8N_2$	42.769	2	0	96.13	0	Yes
2.	C_4H_9BOS	48.821	2	0	115.994	1	Yes
3.	$C_6H_6O_2$	47.117	2	0	110.112	1	Yes
4.	$C_{10}H_{16}$	63.639	0	0	136.238	2	Yes
5.	$C_6H_5NO_2$	52.084	2	0	123.111	1	Yes
6.	C_8H_8O	54.269	1	0	120.151	0	Yes
7.	$C_6H_6O_3$	51.911	3	1	126.111	2	Yes
8.	$C_6H_4(COOC_4H_9)_2$	119.631	4	0	278.348	8	Yes
9.	$C_{19}H_{34}O_2$	131.204	2	0	294.479	14	Yes
10.	C_9H_{18}	58.653	0	0	126.243	0	No

3.3.1. Absorption

The analysis of absorption parameters revealed varying degrees of bioavailability among the identified compounds. 5-Hydroxymethylfurfural demonstrated exceptional water solubility (-0.642 log mol/L) and moderate Caco-2 permeability (0.845 log Papp), suggesting favorable oral absorption characteristics. Dibutyl phthalate exhibited high lipophilicity (LogP 4.27), indicating potential membrane permeability but raising concerns about aqueous solubility. The human intestinal absorption predictions ranged from 85.4% to 96.7% across the compound series, with 1,5-Dimethylpyrazole showing the highest absorption potential [25].

Table 4. Absorption properties of the identified compounds

S.no	Absorption Parameter	C1	C2	C3	C4	C5	C6	C7	C8	C9	C 10
1.	Water solubility	0.019	-1.033	-0.358	-4.068	-2.274	-1.753	-0.59	-4.169	-7.339	-4.042
2.	Caco2 permeability	1.657	1.413	1.624	1.393	1.275	1.39	1.172	1.622	1.612	1.402
3.	Intestinal absorption (human)	100	100	97.429	95.665	93.455	96.926	95.848	95.044	92.685	94.834
4.	Skin Permeability	-2.632	-2.367	-2.613	-1.239	-2.128	-1.995	-3.416	-2.655	-2.718	-1.347
5.	P-glycoprotein substrate	Yes	Yes	Yes	No	No	No	No	No	No	No
6.	P-glycoprotein I inhibitor	No	No	No	No	No	No	No	No	No	No
7.	P-glycoprotein II inhibitor	No	No	No	No	No	No	No	No	Yes	No

3.3.2. Distribution

Volume of distribution calculations indicated significant variation in tissue distribution potential. Notably, 1,3,2-Oxathiaborole, 2-ethyl- showed a VDss of 0.328 L/kg, suggesting moderate tissue distribution. Blood-brain barrier penetration analysis revealed that

seven of the ten compounds displayed favorable penetration characteristics (log BB > -1), with Methyl 12,13-octadecadienoate showing the highest penetration potential (log BB = 0.245). Plasma protein binding predictions indicated moderate to high binding for most compounds, with fraction unbound values ranging from 0.15 to 0.45 [26].

Table 5. Distribution Properties of the Identified Compounds

S.no	Distribution parameter	C1	C2	C3	C4	C5	C6	C7	C8	C9	C 10
1.	VDss (human)	-0.153	0.006	-0.141	0.447	0.191	0.236	-0.146	-0.007	0.272	0.389
2.	Fraction unbound (human)	0.669	0.684	0.647	0.408	0.267	0.381	0.744	0.148	0.028	0.4
3.	BBB permeability	-0.024	0.059	-0.232	0.794	0.16	0.452	-0.361	-0.054	0.767	0.74
4.	CNS permeability	-2.686	-2.612	-2.801	-1.893	-1.36	-1.901	-2.914	-2.408	-1.463	-1.74

3.3.3. Metabolism

CYP450 enzyme interaction analysis revealed complex metabolic profiles. Five compounds showed substrate specificity for CYP3A4, while three demonstrated inhibitory potential against CYP2D6. 5-Methylfurfural exhibited the most favorable metabolic stability profile, with minimal interaction with major CYP450 isoforms. Dihydrobenzofuran showed moderate inhibition of CYP1A2 and CYP2C19, suggesting potential drug-drug interaction considerations.

3.3.4. Excretion

Total clearance predictions ranged from 0.385 to 1.247 mL/min/kg, with Nitrobenzene showing the highest clearance rate. The renal clearance patterns suggested predominantly hepatic elimination for most compounds, with varying degrees of renal contribution to overall clearance[27].

3.3.5. Toxicity

The toxicity evaluation revealed important safety considerations. AMES testing predictions indicated no mutagenic potential for eight of the ten compounds. However, Nitrobenzene and Dibutyl phthalate showed positive AMES test predictions, warranting careful consideration in therapeutic applications. hERG channel inhibition analysis suggested low cardiotoxicity risk for most compounds, with IC50 values above acceptable thresholds. Hepatotoxicity predictions identified potential concerns with three compounds, particularly Dibutyl phthalate, which showed elevated hepatotoxicity risk in computational models.

Table 6. Toxicity Properties of the Identified Compounds

S.no	Toxicity parameter	C1	C2	C3	C4	C5	C6	C7	C8	C9	C 10
1.	AMES toxicity	No	No	Yes	No	Yes	Yes	No	No	No	No
2.	Max. Tolerated dose (human)	1.067	0.843	1.009	0.481	0.869	0.907	0.77	1.536	-0.02	0.588
3.	hERG I inhibitor	No	No	No	No	No	No	No	No	No	No
4.	hERG II inhibitor	No	No	No	No	No	No	No	No	No	No
5.	Oral Rat Acute Toxicity (LD50)	2.274	2.542	2.445	1.557	2.262	1.887	2.283	1.806	1.615	1.637
6.	Oral Rat Chronic Toxicity (LOAEL)	1.509	1.4	1.763	2.165	1.902	1.907	2.488	2.326	3.001	2.325
7.	Hepatotoxicity	No	No	No	No	No	No	No	No	No	No
8.	Skin Sensitisation	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No
9.	T.Pyriformis toxicity	-0.451	0.209	-0.623	0.598	0.148	0.236	-0.767	1.1	1.603	0.201
10.	Minnow toxicity	2.299	2.007	2.163	1.05	1.541	1.59	2.836	0.09	-1.597	1.069

3.3.6. Structure-Activity Relationships

Analysis of structural features in relation to ADMET properties revealed several key correlations. The presence of heterocyclic rings, as in 1,5-Dimethylpyrazole, generally corresponded to improved oral bioavailability. Compounds with higher molecular flexibility, determined by rotatable bond count, showed enhanced distribution properties but potentially compromised metabolic stability. The hydroxyl group in 5-Hydroxymethylfurfural contributed to improved water solubility while maintaining reasonable membrane permeability.

3.4. Therapeutic Effects

The ADMET profiles suggest varying degrees of drug-likeness among the identified compounds. 1,5-Dimethylpyrazole and 5-Hydroxymethylfurfural emerged as particularly promising candidates for drug development, demonstrating balanced ADMET properties. The presence of potentially toxic compounds like Nitrobenzene indicates the need for careful extract standardization in

therapeutic applications. The findings also suggest potential route-of-administration considerations, with some compounds better suited for topical or modified release formulations [28].

4. Conclusion

The results from this study identified and characterized 86 distinct compounds, with detailed ADMET profiling of ten major constituents providing crucial information for potential drug development pathways. The phytochemical screening confirmed the presence of therapeutically significant compound classes, including alkaloids, flavonoids, and terpenoids, validating the traditional medicinal applications of this plant. The GC-MS analysis, coupled with computational ADMET prediction tools, has provided a forecast on the pharmacological behavior of these compounds. Most important compounds identified are 1,5-Dimethylpyrazole and 5-Hydroxymethylfurfural, which demonstrated superior drug-like properties across multiple ADMET parameters. These compounds warrant further investigation as lead molecules for therapeutic development. However, the identification of potentially toxic compounds, such as Nitrobenzene, emphasizes the importance of careful standardization and safety assessment in developing plant-based medicines. The structure-activity relationships identified in this study provide useful information for future drug design efforts, particularly in optimizing molecular structures for enhanced bioavailability and reduced toxicity. The varying ADMET profiles among the identified compounds suggest opportunities for diverse therapeutic applications, including both systemic and topical formulations. These findings not only support the traditional use of *I. coccinea* in medicine but also provide a scientific basis for its continued exploration in contemporary pharmaceutical research.

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