

# Supplementary Materials

**Table S1.** Multivariate tests of significance, effect sizes, and powers. Sigma-restricted Parameterization Effective Hypothesis Decomposition

Effect of group									
Effect	Test	Value	F	Effect df	Error df	p-value	Partial eta-squared	Non-centrality	Observed power ( $\alpha=0.05$ )
Intercept	Wilks	0.000843	197.6399	6	1	0.054395	0.999157	1185.840	0.642775
Groups	Wilks	0.280371	0.1481	12	2	0.989152	0.470499	1.777	0.057159
Effect of tissue									
Intercept	Wilks	0.003610	261.5143	19	18	0.000000	0.996390	4968.772	1.000000
Tissue	Wilks	0.001315	25.1791	38	36	0.000000	0.963739	956.806	1.000000

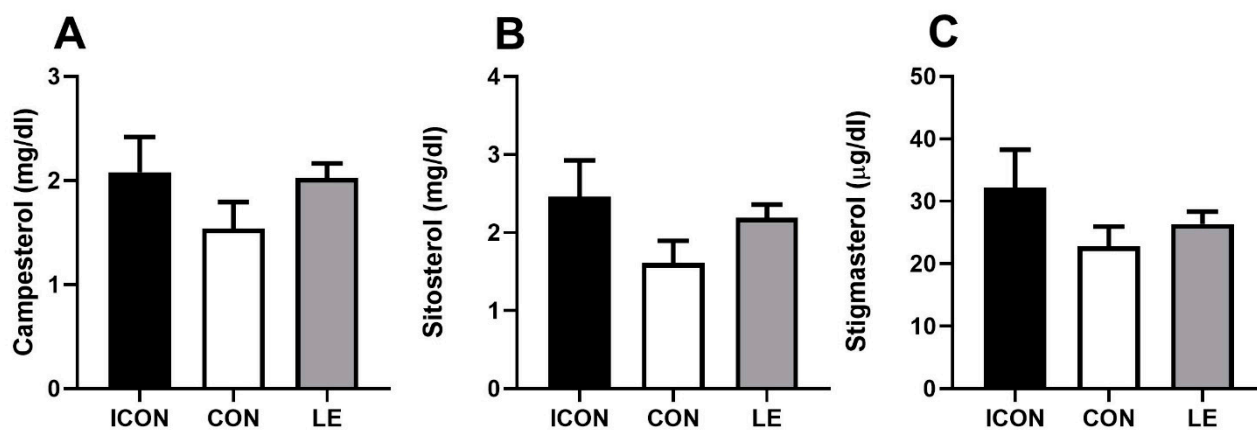
**Table S2.** Results of One-way ANOVA of the comparison between groups for the investigated parameters.

<b>LIVER</b>				
<b>Variable</b>	<b>MS</b>	<b>F</b>	<b>p-value</b>	<b>SEM</b>
SOD	79641	0.4028	0.677940	197738
CAT	1.193864E+08	0.5867	0.572646	2.034806E+08
GSH-Px	8.822080E+08	0.6635	0.534505	1.329668E+09
GR	7109209	1.21233	0.334343	5864090
GST	2.305335E+07	0.0177	0.982476	1.301846E+09
GSH	4924593	10.3319	0.002982 *	476640
SH	4.190	0.8682	0.001419 *	4.826
LPO	2228435	12.620	0.141900	176579
PCO	745045	1.5974	0.246010	466415
TOS	742.19	95.556	0.000000 *	7.77
TAS	121976	5.7426	0.019598 *	21.240
OSI	5.3364	13.1717	0.001204 *	0.4051
Total Cholesterol	1.802	2.105	0.149379	0.856
Lanosterol	7.9465	1.65852	0.216827	4.7913
Lathosterol	0.33890	3.6585	0.045280 *	0.09263
Desmosterol	0.000070	17.7191	0.000045 *	0.000004
7 $\alpha$ -hydroxycholesterol	12.4056	13.2166	0.000253 *	0.9386
27-hydroxycholesterol	0.48105	1.06702	0.363768	0.45083
24-hydroxycholesterol	0.000929	4.9881	0.018145 *	0.000186
Cyp7a1 gene expression	0.9163	0.38038	0.693084	2.4089
OD CYP7A1	0.000139	0.0749	0.928350	0.001858
<b>SERUM</b>				
Total Cholesterol	1.802	2.105	0.149379	0.856
Lanosterol	0.33890	3.6585	0.045280 *	0.09263
Lathosterol	0.000070	17.7191	0.000045 *	0.000004
Desmosterol	7.9465	1.65852	0.216827	4.7913
7 $\alpha$ -hydroxycholesterol	0.000929	4.9881	0.018145 *	0.000186
27-hydroxycholesterol	0.48105	1.06702	0.363768	0.45083
24-hydroxycholesterol	0.020205	2.7824	0.109280	0.340904
<b>JEJUNUM</b>				
SOD	637296	3.0393	0.085528	209688
CAT	2796	0.10824	0.89828	25828
GSH-Px	2852901	2.0605	0.170117	1384592
GR	392919	0.3472	0.713548	1131749
GST	3.754228E+07	1.6140	0.239450	2.325975E+07
GSH	64879	3.9503	0.048071 *	16424
SH	78581	0.40006	0.678896	196422
LPO	79.0952	13.39477	0.000877 *	5.9049
PCO	968495	0.80114	0.471428 *	1208891
TOS	350.64	23.0321	0.000078 *	15.22
TAS	612745	13.7760	0.000780 *	44479
OSI	6.51393	9.88888	0.002900 *	0.65871
Total Cholesterol	1.8769	0.5211	0.606710	3.6018
Lanosterol	2.26315	2.11206	0.163727	1.07154
Lathosterol	0.003279	1.58265	0.245459	0.002072
Desmosterol	14378.1	1.258062	0.319142	11428.7
7 $\alpha$ -hydroxycholesterol	1.45518	0.77205	0.483710	1.88482
27-hydroxycholesterol	0.000750	0.1960	0.824606	0.003828
24-hydroxycholesterol	0.000520	2.0283	0.174250	0.000256
<b>ILEUM</b>				
SOD	39500	3.0548	0.088071	12930
CAT	2844.4	0.69528	0.519589	4091.0
GSH-Px	146533	0.7327	0.502640	199977
GR	385768	0.2933	0.751434	1315151

<b>GST</b>	3763426	2.3901	0.137417	1574588
<b>GSH</b>	44784	3.8247	0.045828 *	11709
<b>SH</b>	20152	0.5177	0.609718	38927
<b>LPO</b>	3.1074	1.1571	0.349892	2.6855
<b>PCO</b>	128310	0.25854	0.776739	496279
<b>TOS</b>	91.28	3.8314	0.045612 *	23.82
<b>TAS</b>	965308	37.073	0.000013 *	26038
<b>OSI</b>	780.018	33.6690	0.000020 *	23.16
<b>Total Cholesterol</b>	5.455	2.0678	0.157100	2.638
<b>Lanosterol</b>	0.2456	0.17221	0.843250	1.4263
<b>Lathosterol</b>	0.002207	0.862337	0.439840	0.002559
<b>Desmosterol</b>	27106	0.48513	0.623886	55875
<b>7<math>\alpha</math>-hydroxycholesterol</b>	14.5237	6.19055	0.009555 *	2.3461
<b>27-hydroxycholesterol</b>	0.003650	2.2053	0.140753	0.001655
<b>24-hydroxycholesterol</b>	0.000831	9.3917	0.001789 *	0.000089

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Significantly differences between groups after One-way ANOVA: \*p<0.05.



**Figure S1.** Effects of lemon flavonoid extract Eriomin (LE) on the concentration of plant sterols campesterol (A), sitosterol (B), and stigmasterol (C) in serum in old-aged male rats. The groups are abbreviated as follows: intact control (ICON), sunflower oil-treated control (CON), and lemon extract-treated group (LE). Data are expressed as mean  $\pm$  SEM ( $n=7/\text{group}$ ); comparisons between the CON and the study groups were not statistically significant (one-way ANOVA followed by Dunnet's post hoc).

Table S3. Listing results of in silico analysis using ADMETlab 3.0 for eriocitrin

Additionally, the corresponding relationships of the three labels are as follows: ● excellent; ● medium; ● poor;

Metabolism		ERIOCITRIN	
Property	Value	Decision	Comment
CYP1A2 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.001	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.001	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2B6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2B6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C8 inhibitor	0.081	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
HLM Stability	0.005	●	■ human liver microsomal (HLM) stability ■ Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM ≤ 30 min). The output value is the probability of human liver microsomal instability, where a value closer to 1 indicates a higher likelihood of instability. The range is between 0 and 1.

## Toxicity

## ERIOCITRIN

Property	Value	Decision	Comment
hERG Blockers	0.062	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10μM or ≥50% inhibition at 10 μM were classified as hERG+ (Category 1),</li> <li>■ while molecules with IC50 &gt;10μM or &lt; 50% inhibition at 10μM were classified as hERG - (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
hERG Blockers (10um)	0.677	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10 μM are classified as hERG+ (Category 1),</li> <li>■ and molecules with IC50 &gt; 10μM are classified as hERG- (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
DILI	0.864	●	<ul style="list-style-type: none"> <li>■ Drug Induced Liver Injury.</li> <li>■ Category 1: drugs with a high risk of DILI;</li> <li>■ Category 0: drugs with no risk of DILI.</li> <li>■ The output value is the probability of being toxic.</li> </ul>
AMES Muta genicity	0.872	●	<ul style="list-style-type: none"> <li>■ AMES Toxicity</li> <li>■ Category 1: Ames positive(+);</li> <li>■ Category 0: Ames negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Rat Oral Acute Toxicity	0.518	●	<ul style="list-style-type: none"> <li>■ Rat Oral Acute Toxicity.</li> <li>■ Category 0: low-toxicity, &gt; 500 mg/kg;</li> <li>■ Category 1: high-toxicity, &lt; 500 mg/kg.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
FDAMDD	0.402	●	<ul style="list-style-type: none"> <li>■ FDA Maximum (Recommended) Daily Dose.</li> <li>■ Category 1: FDAMDD (+);</li> <li>■ Category 0: FDAMDD (-);</li> <li>■ The output value is the probability of being positive.</li> </ul>
Skin Sensi zation	0.386	●	<ul style="list-style-type: none"> <li>■ Category 1: Sensitizer;</li> <li>■ Category 0: Non-sensitizer.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Carcinogeni city	0.111	●	<ul style="list-style-type: none"> <li>■ Category 1: carcinogens;</li> <li>■ Category 0: non-carcinogens;</li> <li>■ The output value is the probability of being toxic.</li> </ul>

Eye Corrosion	0.0	●	<ul style="list-style-type: none"> <li>■ Eye Corrosion</li> <li>■ Category 1: corrosives;</li> <li>■ Category 0: noncorrosives;</li> <li>■ The output value is the probability of being corrosives.</li> </ul>
Eye Irritation	0.024	●	<ul style="list-style-type: none"> <li>■ Eye Irritation</li> <li>■ Category 1: irritants;</li> <li>■ Category 0: nonirritants;</li> <li>■ The output value is the probability of being irritants.</li> </ul>
Respiratory	0.024	●	<ul style="list-style-type: none"> <li>■ Category 1: respiratory toxicants;</li> <li>■ Category 0: non-respiratory toxicants.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Human Hep atotoxicity	0.475	●	<ul style="list-style-type: none"> <li>■ Human Hepatotoxicity</li> <li>■ Category 1: H-HT positive(+);</li> <li>■ Category 0: H-HT negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Drug-induce d Nephrotox icity	0.08	●	<ul style="list-style-type: none"> <li>■ Category 0: non-nephrotoxic (-);</li> <li>■ Category 1: nephrotoxic (+).</li> <li>■ The output value is the probability of being nephrotoxic (+), within the range of 0 to 1.</li> </ul>
Ototoxicity	0.994	●	<ul style="list-style-type: none"> <li>■ Category 0: non-ototoxicity (-);</li> <li>■ Category 1: ototoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hematotoxic ity	0.024	●	<ul style="list-style-type: none"> <li>■ Category 0: non-hematotoxicity (-);</li> <li>■ Category 1: hematotoxicity (+).</li> <li>■ The output value is the probability of being hematotoxicity (+), within the range of 0 to 1.</li> </ul>
Genotoxicity	0.823	●	<ul style="list-style-type: none"> <li>■ Category 0: non-Genotoxicity (-);</li> <li>■ Category 1: Genotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
RPMI-8226 Immunotoxici ty	0.062	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
A549 Cytotoxicity	0.665	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hek293 Cytotoxicity	0.848	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Drug-induce d Neurotox icity	0.084	●	<ul style="list-style-type: none"> <li>■ Category 0: non-neurotoxic (-);</li> <li>■ Category 1: neurotoxic (+).</li> <li>■ The output value is the probability of being neurotoxic (+), within the range of 0 to 1.</li> </ul>

Table S4. Listing results of in silico analysis using ADMETlab 3.0 for naringin

Metabolism		NARINGIN	
Property	Value	Decision	Comment
CYP1A2 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.105	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.001	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2B6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2B6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C8 inhibitor	0.037	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
HLM Stability	0.0	●	■ human liver microsomal (HLM) stability ■ Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM ≤ 30 min). The output value is the probability of human liver microsomal instability, where a value closer to 1 indicates a higher likelihood of instability. The range is between 0 and 1.

## Toxicity

NARINGIN

Property	Value	Decision	Comment
hERG Blockers	0.067	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10μM or ≥50% inhibition at 10 μM were classified as hERG+ (Category 1),</li> <li>■ while molecules with IC50 &gt;10μM or &lt; 50% inhibition at 10μM were classified as hERG - (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
hERG Blockers (10um)	0.446	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10 μM are classified as hERG+ (Category 1),</li> <li>■ and molecules with IC50 &gt; 10μM are classified as hERG- (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
DILI	0.736	●	<ul style="list-style-type: none"> <li>■ Drug Induced Liver Injury.</li> <li>■ Category 1: drugs with a high risk of DILI;</li> <li>■ Category 0: drugs with no risk of DILI.</li> <li>■ The output value is the probability of being toxic.</li> </ul>
AMES Muta genicity	0.774	●	<ul style="list-style-type: none"> <li>■ AMES Toxicity</li> <li>■ Category 1: Ames positive(+);</li> <li>■ Category 0: Ames negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Rat Oral Acute Toxicity	0.426	●	<ul style="list-style-type: none"> <li>■ Rat Oral Acute Toxicity.</li> <li>■ Category 0: low-toxicity, &gt; 500 mg/kg;</li> <li>■ Category 1: high-toxicity; &lt; 500 mg/kg.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
FDAMDD	0.32	●	<ul style="list-style-type: none"> <li>■ FDA Maximum (Recommended) Daily Dose.</li> <li>■ Category 1: FDAMDD (+);</li> <li>■ Category 0: FDAMDD (-);</li> <li>■ The output value is the probability of being positive.</li> </ul>
Skin Sensiti zation	0.189	●	<ul style="list-style-type: none"> <li>■ Category 1: Sensitizer;</li> <li>■ Category 0: Non-sensitizer.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Carcinogeni city	0.187	●	<ul style="list-style-type: none"> <li>■ Category 1: carcinogens;</li> <li>■ Category 0: non-carcinogens;</li> <li>■ The output value is the probability of being toxic.</li> </ul>

Eye Corrosion	0.0	●	<ul style="list-style-type: none"> <li>■ Eye Corrosion</li> <li>■ Category 1: corrosives;</li> <li>■ Category 0: noncorrosives;</li> <li>■ The output value is the probability of being corrosives.</li> </ul>
Eye Irritation	0.059	●	<ul style="list-style-type: none"> <li>■ Eye Irritation</li> <li>■ Category 1: irritants;</li> <li>■ Category 0: nonirritants;</li> <li>■ The output value is the probability of being irritants.</li> </ul>
Respiratory	0.038	●	<ul style="list-style-type: none"> <li>■ Category 1: respiratory toxicants;</li> <li>■ Category 0: non-respiratory toxicants.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Human Hep atotoxicity	0.689	●	<ul style="list-style-type: none"> <li>■ Human Hepatotoxicity</li> <li>■ Category 1: H-HT positive(+);</li> <li>■ Category 0: H-HT negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Drug-induce d Nephrotox icity	0.287	●	<ul style="list-style-type: none"> <li>■ Category 0: non-nephrotoxic (-);</li> <li>■ Category 1: nephrotoxic (+).</li> <li>■ The output value is the probability of being nephrotoxic (+), within the range of 0 to 1.</li> </ul>
Ototoxicity	0.987	●	<ul style="list-style-type: none"> <li>■ Category 0: non-ototoxicity (-);</li> <li>■ Category 1: ototoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hematotoxic ity	0.061	●	<ul style="list-style-type: none"> <li>■ Category 0: non-hematotoxicity (-);</li> <li>■ Category 1: hematotoxicity (+).</li> <li>■ The output value is the probability of being hematotoxicity (+), within the range of 0 to 1.</li> </ul>
Genotoxicity	0.561	●	<ul style="list-style-type: none"> <li>■ Category 0: non-Genotoxicity (-);</li> <li>■ Category 1: Genotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
RPMI-8226 Immunotoxici ty	0.123	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
A549 Cytotoxicity	0.223	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hek293 Cytotoxicity	0.883	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Drug-induce d Neurotoxi city	0.321	●	<ul style="list-style-type: none"> <li>■ Category 0: non-neurotoxic (-);</li> <li>■ Category 1: neurotoxic (+).</li> <li>■ The output value is the probability of being neurotoxic (+), within the range of 0 to 1.</li> </ul>



Table S5. Listing results of in silico analysis using ADMETlab 3.0 for hesperidin

Metabolism		HESPERIDIN	
Property	Value	Decision	Comment
CYP1A2 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.161	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.049	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2B6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2B6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C8 inhibitor	0.069	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
HLM Stability	0.003	●	■ human liver microsomal (HLM) stability ■ Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM ≤ 30 min). The output value is the probability of human liver microsomal instability, where a value closer to 1 indicates a higher likelihood of instability. The range is between 0 and 1.

## Toxicity

## HESPERIDIN

Property	Value	Decision	Comment
hERG Blockers	0.066	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10μM or ≥50% inhibition at 10 μM were classified as hERG+ (Category 1),</li> <li>■ while molecules with IC50 &gt;10μM or &lt; 50% inhibition at 10μM were classified as hERG - (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
hERG Blockers (10um)	0.565	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10 μM are classified as hERG+ (Category 1),</li> <li>■ and molecules with IC50 &gt; 10μM are classified as hERG- (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
DILI	0.907	●	<ul style="list-style-type: none"> <li>■ Drug Induced Liver Injury.</li> <li>■ Category 1: drugs with a high risk of DILI;</li> <li>■ Category 0: drugs with no risk of DILI.</li> <li>■ The output value is the probability of being toxic.</li> </ul>
AMES Muta genicity	0.86	●	<ul style="list-style-type: none"> <li>■ AMES Toxicity</li> <li>■ Category 1: Ames positive(+);</li> <li>■ Category 0: Ames negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Rat Oral Acute Toxicity	0.501	●	<ul style="list-style-type: none"> <li>■ Rat Oral Acute Toxicity.</li> <li>■ Category 0: low-toxicity, &gt; 500 mg/kg;</li> <li>■ Category 1: high-toxicity; &lt; 500 mg/kg.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
FDAMDD	0.365	●	<ul style="list-style-type: none"> <li>■ FDA Maximum (Recommended) Daily Dose.</li> <li>■ Category 1: FDAMDD (+);</li> <li>■ Category 0: FDAMDD (-);</li> <li>■ The output value is the probability of being positive.</li> </ul>
Skin Sensiti zation	0.055	●	<ul style="list-style-type: none"> <li>■ Category 1: Sensitizer;</li> <li>■ Category 0: Non-sensitizer.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Carcinogeni city	0.186	●	<ul style="list-style-type: none"> <li>■ Category 1: carcinogens;</li> <li>■ Category 0: non-carcinogens;</li> <li>■ The output value is the probability of being toxic.</li> </ul>

Eye Corrosion	0.0	●	<ul style="list-style-type: none"> <li>■ Eye Corrosion</li> <li>■ Category 1: corrosives;</li> <li>■ Category 0: noncorrosives;</li> <li>■ The output value is the probability of being corrosives.</li> </ul>
Eye Irritation	0.012	●	<ul style="list-style-type: none"> <li>■ Eye Irritation</li> <li>■ Category 1: irritants;</li> <li>■ Category 0: nonirritants;</li> <li>■ The output value is the probability of being irritants.</li> </ul>
Respiratory	0.062	●	<ul style="list-style-type: none"> <li>■ Category 1: respiratory toxicants;</li> <li>■ Category 0: non-respiratory toxicants.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Human Hep atotoxicity	0.49	●	<ul style="list-style-type: none"> <li>■ Human Hepatotoxicity</li> <li>■ Category 1: H-HT positive(+);</li> <li>■ Category 0: H-HT negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Drug-induce d Nephrotox icity	0.206	●	<ul style="list-style-type: none"> <li>■ Category 0: non-nephrotoxic (-);</li> <li>■ Category 1: nephrotoxic (+).</li> <li>■ The output value is the probability of being nephrotoxic (+), within the range of 0 to 1.</li> </ul>
Ototoxicity	0.983	●	<ul style="list-style-type: none"> <li>■ Category 0: non-ototoxicity (-);</li> <li>■ Category 1: ototoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hematotoxic ity	0.05	●	<ul style="list-style-type: none"> <li>■ Category 0: non-hematotoxicity (-);</li> <li>■ Category 1: hematotoxicity (+).</li> <li>■ The output value is the probability of being hematotoxicity (+), within the range of 0 to 1.</li> </ul>
Genotoxicity	0.593	●	<ul style="list-style-type: none"> <li>■ Category 0: non-Genotoxicity (-);</li> <li>■ Category 1: Genotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
RPMI-8226 Immunotoxici ty	0.211	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
A549 Cytotoxicity	0.296	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hek293 Cytotoxicity	0.891	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Drug-induce d Neurotox icity	0.318	●	<ul style="list-style-type: none"> <li>■ Category 0: non-neurotoxic (-);</li> <li>■ Category 1: neurotoxic (+).</li> <li>■ The output value is the probability of being neurotoxic (+), within the range of 0 to 1.</li> </ul>

Table S6. Listing results of in silico analysis using ADMETlab 3.0 for didymin

Metabolism		DIDYMIN	
Property	Value	Decision	Comment
CYP1A2 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP1A2 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C19 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C19 substrate	0.001	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C9 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2C9 substrate	0.056	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2D6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2D6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP3A4 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP3A4 substrate	0.001	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2B6 inhibitor	0.0	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
CYP2B6 substrate	0.0	●	■ Category 1: Substrate; Category 0: Non-substrate; ■ The output value is the probability of being substrate.
CYP2C8 inhibitor	0.039	●	■ Category 1: Inhibitor; Category 0: Non-inhibitor; ■ The output value is the probability of being inhibitor.
HLM Stability	0.002	●	■ human liver microsomal (HLM) stability ■ Category 0: stable+ (HLM > 30 min); Category 1: unstable- (HLM ≤ 30 min). The output value is the probability of human liver microsomal instability, where a value closer to 1 indicates a higher likelihood of instability. The range is between 0 and 1.

## Toxicity

DIDYMIN

Property	Value	Decision	Comment
hERG Blockers	0.124	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10 μM or ≥50% inhibition at 10 μM were classified as hERG+ (Category 1),</li> <li>■ while molecules with IC50 &gt;10 μM or &lt; 50% inhibition at 10 μM were classified as hERG- (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
hERG Blockers (10um)	0.578	●	<ul style="list-style-type: none"> <li>■ Molecules with IC50 ≤10 μM are classified as hERG+ (Category 1),</li> <li>■ and molecules with IC50 &gt; 10 μM are classified as hERG- (Category 0).</li> <li>■ The output value is the probability of being hERG+, within the range of 0 to 1.</li> </ul>
DILI	0.921	●	<ul style="list-style-type: none"> <li>■ Drug Induced Liver Injury.</li> <li>■ Category 1: drugs with a high risk of DILI;</li> <li>■ Category 0: drugs with no risk of DILI.</li> <li>■ The output value is the probability of being toxic.</li> </ul>
AMES Mutagenicity	0.889	●	<ul style="list-style-type: none"> <li>■ AMES Toxicity</li> <li>■ Category 1: Ames positive(+);</li> <li>■ Category 0: Ames negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Rat Oral Acute Toxicity	0.479	●	<ul style="list-style-type: none"> <li>■ Rat Oral Acute Toxicity.</li> <li>■ Category 0: low-toxicity, &gt; 500 mg/kg;</li> <li>■ Category 1: high-toxicity, &lt; 500 mg/kg.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
FDAMDD	0.324	●	<ul style="list-style-type: none"> <li>■ FDA Maximum (Recommended) Daily Dose.</li> <li>■ Category 1: FDAMDD (+);</li> <li>■ Category 0: FDAMDD (-);</li> <li>■ The output value is the probability of being positive.</li> </ul>
Skin Sensitization	0.03	●	<ul style="list-style-type: none"> <li>■ Category 1: Sensitizer;</li> <li>■ Category 0: Non-sensitizer.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Carcinogenicity	0.194	●	<ul style="list-style-type: none"> <li>■ Category 1: carcinogens;</li> <li>■ Category 0: non-carcinogens;</li> <li>■ The output value is the probability of being toxic.</li> </ul>

Eye Corrosion	0.0	●	<ul style="list-style-type: none"> <li>■ Eye Corrosion</li> <li>■ Category 1: corrosives;</li> <li>■ Category 0: noncorrosives;</li> <li>■ The output value is the probability of being corrosives.</li> </ul>
Eye Irritation	0.009	●	<ul style="list-style-type: none"> <li>■ Eye Irritation</li> <li>■ Category 1: irritants;</li> <li>■ Category 0: nonirritants;</li> <li>■ The output value is the probability of being irritants.</li> </ul>
Respiratory	0.049	●	<ul style="list-style-type: none"> <li>■ Category 1: respiratory toxicants;</li> <li>■ Category 0: non-respiratory toxicants.</li> <li>■ The output value is the probability of being toxic, within the range of 0 to 1.</li> </ul>
Human Hepatotoxicity	0.544	●	<ul style="list-style-type: none"> <li>■ Human Hepatotoxicity</li> <li>■ Category 1: H-HT positive(+);</li> <li>■ Category 0: H-HT negative(-);</li> <li>■ The output value is the probability of being toxic.</li> </ul>
Drug-induced Nephrotoxicity	0.403	●	<ul style="list-style-type: none"> <li>■ Category 0: non-nephrotoxic (-);</li> <li>■ Category 1: nephrotoxic (+).</li> <li>■ The output value is the probability of being nephrotoxic (+), within the range of 0 to 1.</li> </ul>
Ototoxicity	0.986	●	<ul style="list-style-type: none"> <li>■ Category 0: non-ototoxicity (-);</li> <li>■ Category 1: ototoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hematotoxicity	0.086	●	<ul style="list-style-type: none"> <li>■ Category 0: non-hematotoxicity (-);</li> <li>■ Category 1: hematotoxicity (+).</li> <li>■ The output value is the probability of being hematotoxicity (+), within the range of 0 to 1.</li> </ul>
Genotoxicity	0.413	●	<ul style="list-style-type: none"> <li>■ Category 0: non-Genotoxicity (-);</li> <li>■ Category 1: Genotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
RPMI-8226 Immunotoxicity	0.185	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
A549 Cytotoxicity	0.225	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Hek293 Cytotoxicity	0.876	●	<ul style="list-style-type: none"> <li>■ Category 0: non-cytotoxicity (-);</li> <li>■ Category 1: cytotoxicity (+).</li> <li>■ The output value is the probability of being ototoxicity (+), within the range of 0 to 1.</li> </ul>
Drug-induced Neurotoxicity	0.472	●	<ul style="list-style-type: none"> <li>■ Category 0: non-neurotoxic (-);</li> <li>■ Category 1: neurotoxic (+).</li> <li>■ The output value is the probability of being neurotoxic (+), within the range of 0 to 1.</li> </ul>