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Exploration of Moringa Oleifera and Curcuma Longa Compounds as Multi-Target Agents for Alzheimer's Disease Through Bioinformatics Analysis

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ABSTRACT
Background: Alzheimer's disease is a multifactorial neurodegenerative disorder. Current synthetic inhibitors often fail to address its complexity. Natural multitarget agents like Moringa oleifera and Curcuma longa may offer safer alternatives. **Objective**: This study aims to systematically evaluate the bioactive compounds of *Moringa oleifera* and *Curcuma longa* as potential multi-target agents against AD using molecular docking, ADME profiling, and toxicity prediction. **Methods**: This in silico study targeted five Alzheimer-related proteins (BACE1, GSK-3β, AChE, Tau, PKR) retrieved from the PDB and prepared using AutoDock Tools. LC-MS compounds were modeled with Biovia Discovery Studio and docked via PyRx. Toxicity was evaluated using ProTox-3.0. **Results**: The top 10 compounds showed binding affinities from –7.3 to –10.2 kcal/mol and were "inactive" for hepatotoxicity, neurotoxicity, and cytotoxicity. Turmeric compounds were also non-mutagenic and non-carcinogenic. **Conclusion**: Moringa oleifera and Curcuma longa demonstrate promising multitarget activity with a favorable safety profile. Bioinformatics enables efficient early screening.
Keyword: Alzheimer's disease, Curcuma longa, Moringa oleifera, multitarget, molecular docking.

ABSTRAK
Latar Belakang: Alzheimer merupakan gangguan neurodegeneratif multifaktorial. Inhibitor sintetik saat ini dinilai belum mampu mengatasi kompleksitasnya. Senyawa multitarget alami seperti Moringa oleifera dan Curcuma longa berpotensi lebih aman. **Tujuan**: Penelitian ini bertujuan untuk mengevaluasi secara sistematis senyawa bioaktif Moringa oleifera dan Curcuma longa sebagai agen multi-target potensial terhadap AD menggunakan docking molekuler, profil ADME, dan prediksi toksisitas. **Metode**: Studi in silico ini menargetkan lima protein Alzheimer (BACE1, GSK-3β, AChE, Tau, PKR) dari PDB yang diproses di AutoDock Tools. Senyawa LC-MS dimodelkan di Biovia Studio dan didocking menggunakan PyRx. Toksisitas dievaluasi via ProTox-3.0. **Hasil**: Sepuluh senyawa teratas menunjukkan afinitas –7,3 s.d. –10,2 kcal/mol dan "inactive" terhadap hepatotoksisitas, neurotoksisitas, serta sitotoksisitas. Senyawa kunyit juga tidak mutagenik dan tidak karsinogenik. **Kesimpulan**: Moringa oleifera dan Curcuma longa berpotensi sebagai terapi multitarget Alzheimer yang aman. Bioinformatika mendukung skrining awal yang efisien
Kata Kunci: Curcuma longa, Moringa oleifera, multitarget, molecular docking, Penyakit Alzheimer

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and accounts for 60–70% of dementia cases globally, making it the seventh leading cause of death worldwide according to WHO data.[1] The prevalence of AD continues to increase in line with global aging trends reaching 57 million in 2021 and projected to surpass 150 million by 2050.[2][3] Indonesia, facing a similar demographic shift, is expected to see

cases rise to over 4 million by 2050, yet clinical diagnosis remains alarmingly low at under 1% of cases.[4][5] Beyond its medical burden, AD imposes significant social and economic challenges, with global costs reaching USD 1.3 trillion in 2019.[4]

Neuropathologically, AD involves a complex interplay of mechanisms including β-amyloid (Aβ) accumulation, tau hyperphosphorylation, cholinergic deficit, and neuroinflammation.[6] Current approved therapies such as donepezil primarily target the cholinergic pathway and offer only transient symptomatic relief without halting disease progression.[7][8] Disease-modifying agents targeting β-secretase 1 (BACE1) like verubecestat and anti-tau strategies such as methylene blue have failed in clinical trials despite initial preclinical promise, highlighting the multifactorial nature of AD and the need for multi-targeted interventions.[9][10]. In this context, the involvement of protein kinase R (PKR) as a master regulator of multiple AD pathways including Aβ formation, tau phosphorylation via GSK-3β, apoptosis, and inflammation underscores the complexity of potential therapeutic targets.[6]

Natural products with multitarget potential are increasingly explored as safer alternatives. *Moringa oleifera* and *Curcuma longa* are two medicinal plants with a wide range of neuroprotective properties, supported by their historical use and emerging scientific validation.[11][12][13] Curcumin, demethoxycurcumin, and bisdemethoxycurcumin from *Curcuma longa*, as well as quercetin and glucomoringin from *Moringa oleifera*, have demonstrated activity against Alzheimer's disease-related mechanisms, including acetylcholinesterase inhibition, antioxidative effects, and anti-inflammatory properties.[12][13][14] However, the multi-target pharmacological potential of these compounds, especially toward crucial AD-related proteins such as BACE1, GSK-3β, AChE, tau, and PKR, remains underexplored in silico.

Therefore, this study aims to systematically evaluate the bioactive compounds of *Moringa oleifera* and *Curcuma longa* as potential multi-target agents against AD using molecular docking, ADME profiling, and toxicity prediction. LC-MS-based phytochemical screening was conducted to identify key constituents, followed by docking against five major AD protein targets and computational pharmacokinetics and toxicology analyses. This comprehensive in silico strategy is expected to identify safe, brain-penetrant, and bioactive natural compounds that warrant further validation in experimental models.

2. Method

The identification of bioactive compounds was based on untargeted metabolomics data from two peer-reviewed studies. Compounds from *Moringa oleifera* were obtained through UPLC-Q-Exactive Orbitrap-MS analysis,[14] while those from *Curcuma longa* were identified via LC-HRMS profiling of ethyl acetate and hexane fractions.[13] A total of 73 metabolites were initially identified 43 from *Moringa oleifera* and 30 from *Curcuma longa*. However, not all compounds proceeded to the in silico phase.

Only compounds with valid 3D structures and CID entries in the PubChem database were advanced for molecular docking and pharmacoinformatics. Some compounds within the original LC-MS dataset were excluded due to lack of valid structures or conversion errors. In total, 63 compounds (38 from *Moringa* and 25 from *Curcuma*) were deemed suitable for further computational analysis. *A comprehensive table of LC-MS-identified compounds is presented in Appendix 1.*

To ensure neutrality and avoid bias toward known compound identities, all included ligands were renamed as Compound 1 through Compound 63. This standardization was maintained throughout the manuscript. Each compound was mapped to its original name and source plant. *The complete compound-to-identity mapping table is available in Appendix 2.*

Five major protein targets involved in Alzheimer's disease (AD) pathology were selected for molecular docking:

- Acetylcholinesterase (AChE, PDB ID: 4EY7) – degrades acetylcholine and contributes to cognitive decline.
- β-secretase 1 (BACE1, PDB ID: 5HU1) – catalyzes the formation of neurotoxic β-amyloid.
- Glycogen Synthase Kinase-3β (GSK-3β, PDB ID: 1Q3W) – mediates tau hyperphosphorylation.

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- Tau protein (PDB ID: 1J1B) – forms neurofibrillary tangles upon phosphorylation.
- Protein Kinase R (PKR, PDB ID: 2A19) – promotes cellular stress and neuroinflammation.

Each target was paired with a well-established reference inhibitor validated in experimental studies: Donepezil for AchE[15], Verubecestat for BACE1[8], Alsterpaullone for GSK-3β[16], Methylene Blue for tau[10], and C16 for PKR.[17]

Molecular docking was performed using PyRx 0.8 with the AutoDock Vina engine. Ligand and protein target structures were converted to .pdbqt format and prepared using BIOVIA Discovery Studio Visualizer. Grid box coordinates were centered around the native ligand binding sites, as identified through 3D structural visualization.

The resulting binding affinity values (in kcal/mol) were used to assess ligand–protein interactions. Each ligand's performance was compared against the respective control inhibitor for each target.

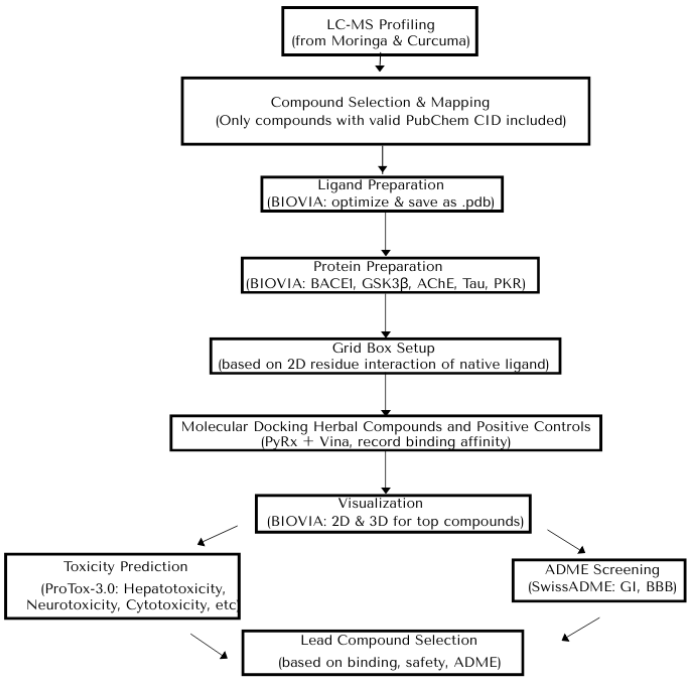

Figure 1. The docking workflow and grid box configuration

To assess the safety and drug-likeness of each compound, toxicity profiles were predicted using ProTox 3.0, while pharmacokinetic properties were assessed using SwissADME. Only compounds with valid docking results and PubChem structures were included in this step.

From the ProTox 3.0 platform, we evaluated the following toxicity endpoints:

- Hepatotoxicity
- Neurotoxicity
- Cytotoxicity

Meanwhile, key pharmacokinetic indicators were analyzed using SwissADME:

- Gastrointestinal (GI) absorption
- Blood–brain barrier (BBB) permeant status
- Lipinski's rule of five compliance

All toxicity outputs were reported as "active" or "inactive", while pharmacokinetic parameters were presented as binary or categorical outputs (e.g., "High" vs. "Low" GI absorption; "Yes" vs. "No" for BBB permeant). *The combined summary of all parameters is presented in Appendix 3.*

From the total of 63 compounds docked, ten were shortlisted based on optimal performance in binding affinity, pharmacokinetics, and safety. Five top-ranking compounds were derived from *Moringa oleifera* and five from *Curcuma longa*.

A summary of binding affinity comparisons versus reference inhibitors is available in table 4. Two-dimensional and three-dimensional interaction visualizations of the top compounds are provided in Figure 2.

3. Result

3.1 Binding Affinity of Top Compounds

Ten bioactive compounds derived from *Moringa oleifera* and *Curcuma longa* were selected based on LC-MS profiling and subjected to molecular docking against five major Alzheimer's disease (AD) protein targets: AChE, BACE1, GSK-3β, tau, and PKR. The binding affinity values (in kcal/mol) for each compound are presented in Table 4.

Table 4. Top 10 of binding affinity comparisons versus reference inhibitors

Compound (neutral)	Protein target	Binding Affinity per Protein	Total	Average	Positive control	Binding *Moringa oleifera*	Binding *Curcuma longa*
compound 36	AChE (4EY7)	-10,2	-10,2	-10,2	Donepezil	–12.1	–12.2
Compound 18	BACE1 (5HU1), AChE (4EY7)	-19,1	-19,1	-9,5	Verubecestat	–10.3	–10.3
Compound 33	BACE1 (5HU1)	-9,3	-9,3	-9,3	Methylene Blue	–6.9	–7.6
compound 30	TAU (1J1B), GSK-3β (1Q3W), PKR (2A19), AChE (4EY7), BACE1 (5HU1)	-44,8	-44,8	-8,9	Alsterpaullone	–9	–9.0
Compound 26	TAU (1J1B), GSK-3β (1Q3W), PKR (2A19), BACE1 (5HU1)	-34,7	-34,7	-8,6	C16	–7.6	–5.7
Compound 54	AChE (4EY7), BACE1 (5HU1)	-19,7	-19,7	-9,85			
Compound 52	PKR (2A19), AChE (4EY7)	-18,7	-18,7	-9,35			
Compound 56	BACE1 (5HU1), AChE (4EY7), TAU (1J1B), PKR (2A19)	-36,4	-36,4	-9,1			
Compound 50	BACE1 (5HU1), GSK-3β (1Q3W), AChE (4EY7), TAU (1J1B)	-35,5	-35,5	-8,8			
Compound 55	BACE1 (5HU1)	-8,9	-8,9	-8,9			

Notably, Compound 36 (quercetin) demonstrated the strongest affinity for AChE (−10.2 kcal/mol), while Compound 54 (demethoxycurcumin) and Compound 52 (bisdemethoxycurcumin) showed superior dual-target affinities for both BACE1 and AChE. Compound 30 (kaempferol-3-O-rutinoside) and Compound 26 (rutin) exhibited broad interaction across four to five targets, with consistently low binding energy.

To better illustrate the interaction profiles, Figure 2 display representative 3D and 2D binding visualizations for selected compound protein complexes.

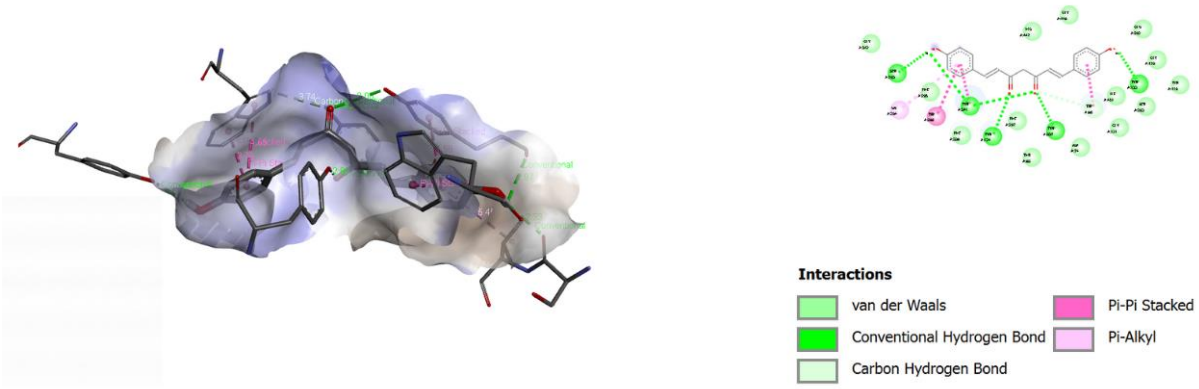

Figure 2. Two-dimensional and three-dimensional interaction visualizations of Bisdemethoxycurcumin

3.2 Toxicity Prediction

All ten compounds were evaluated using ProTox-3.0 for toxicity profiling. As summarized in *Appendix 3*, none of the compounds showed predicted hepatotoxicity, neurotoxicity, or cytotoxicity. All parameters returned "inactive" status, indicating a high safety margin for potential therapeutic use.

3.3 ADME Profiling and Drug-Likeness

Pharmacokinetic properties were assessed via SwissADME. Most compounds showed high gastrointestinal (GI) absorption and favorable blood–brain barrier (BBB) permeability (presented in *Appendix 3*). While some compounds partially violated Lipinski's Rule of Five due to molecular weight or hydrogen bonding, they remained promising based on CNS drug-likeness profiles. Together, the results support the potential of selected phytocompounds from *Moringa oleifera* and *Curcuma longa* as safe, multi-target neuroprotective agents, particularly those demonstrating dual-target binding and CNS accessibility.

4. Discussion

The Given the multifactorial pathophysiology of Alzheimer's disease (AD), an ideal therapeutic approach should be capable of modulating several molecular targets involved in its progression ranging from cholinergic dysfunction to β-amyloid accumulation, tau hyperphosphorylation, and neuroinflammatory processes.[9][18] Due to this complexity, multitarget-directed ligands (MTDLs) are increasingly considered a promising therapeutic strategy to address multiple pathological hallmarks of AD simultaneously.[18]

In this study, ten selected compounds from Moringa oleifera and Curcuma longa exhibited strong binding affinities against five AD-related protein targets: acetylcholinesterase (AChE), beta-secretase 1 (BACE1), glycogen synthase kinase-3β (GSK-3β), tau, and PKR. These findings demonstrate the multitarget potential of plant-derived molecules in modulating neurodegenerative pathways.

Among the Moringa group, Compound 36 (quercetin) showed the highest affinity toward AChE (−10.2 kcal/mol), suggesting a strong potential for cholinergic pathway modulation. This aligns with previous findings showing quercetin's neuroprotective, antioxidant, and acetylcholinesterase-inhibiting effects [2]. Similarly, Compound 30 (kaempferol-3-O-rutinoside) and Compound 26 (rutin) displayed broad interaction with four to five protein targets, maintaining average affinities between −8.6 and −8.9 kcal/mol, which supports their candidacy as multitarget modulators.

For the Curcuma group, Compound 54 (demethoxycurcumin) and Compound 52 (bisdemethoxycurcumin) demonstrated high selectivity for BACE1 and AChE, even surpassing the docking scores of donepezil and verubecestat. This dual-targeting capability suggests their ability to modulate both amyloidogenic and cholinergic pathways effectively. Previous docking studies have similarly reported favorable interaction of curcumin derivatives with BACE1 and AChE.[9][12]

Interestingly, the number of protein targets bound was not directly proportional to the average binding affinity. Compound 30, for example, interacted with all five targets, yet showed slightly lower affinity compared to

Compound 54, which only targeted two proteins. This suggests that specificity and binding strength may be more important than mere target quantity in predicting therapeutic relevance.

Toxicity prediction using ProTox-3.0 revealed that all ten top compounds were non-toxic in terms of hepatotoxicity, neurotoxicity, and cytotoxicity. These results correspond with existing reports on the low systemic toxicity of dietary polyphenols and phytochemicals.[19] In addition, SwissADME analysis indicated favorable gastrointestinal absorption and blood–brain barrier (BBB) permeability for several compounds, particularly quercetin and demethoxycurcumin, further supporting their suitability as CNS-active agents.[19]

5. Conclusion

This in silico study successfully identified ten promising bioactive compounds from *Moringa oleifera* and *Curcuma longa* with high binding affinities toward multiple molecular targets implicated in Alzheimer's disease pathogenesis. These compounds also demonstrated favorable predicted safety and pharmacokinetic profiles, supporting their potential as multitarget therapeutic candidates for AD.

However, as this study was limited to computational simulation, further validation through in vitro and in vivo experiments is necessary. Future researchers and clinicians are encouraged to investigate these compounds as alternative, plant-based therapeutic options for Alzheimer's disease, especially considering their accessibility and multitarget capabilities. This approach may contribute to the development of more holistic, affordable interventions for neurodegenerative disorders.

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Appendix

Appendix 1

*Table SEQ Table * ARABIC 1 LC-MS Compounds and CID from Moringa*

No.	Compound	Formula	Ion	tR (min)	Measured m/z	Cal. m/z	ppm	CID
1	Malic acid	C4H6O5	[M-H]	0.8	133.0142	133.0131	8.3	CID 525
2	Trigonelline	C7H7NO2	[M+H]+	0.87	138.0551	138.055	0.7	CID 5570
3	5-Hydroxymethylfurfural	C6H6O3	[M+H]+	0.95	127.0392	127.039	1.6	CID 237332
4	L-Valine	C5H11NO2	[M+H]+	1.06	118.0863	118.0863	0	CID 6287
5	Cytosine	C4H5N3O	[M+H]+	1.26	112.0506	112.0505	0.9	CID 597
6	Benzaldehyde	C7H6O	[M+H]+	1.43	107.0491	107.0491	0	CID 240
7	Cinnamic acid	C9H8O2	[M+H]+	1.45	149.0598	149.0597	0.7	CID 444359
8	p-Coumaric acid	C9H8O3	[M+H]+	1.51	165.0545	165.0546	0.6	CID 637542
9	Citric Acid	C6H8O7	[M-H]	1.63	191.0197	191.0186	5.8	CID 311
10	Cinnamaldehyde	C9H8O	[M+H]+	1.67	133.0649	133.0648	0.8	CID 637511
11	L-Leucine	C6H13NO2	[M+H]+	1.72	132.102	132.1019	0.8	CID 6106
12	Protocatechuic acid-4-O-glucoside	C13H16O9	[M-H]	2.31	315.0724	315.0711	4.1	CID 91309592
13	Salicylic acid	C7H6O3	[M-H]	2.49	137.0244	137.0233	8	CID 338
14	Nicotinamide	C6H6N2O	[M+H]+	2.57	123.0554	123.0553	0.8	CID 936
15	Guanosine	C10H13N5O5	[M+H]+	2.96	284.0981	284.0989	2.8	CID 135398635
16	L-Phenylalanine	C9H11NO2	[M+H]+	3.31	166.0863	166.0863	0	CID 6140
17	Gallic acid 4-O-glucoside	C13H16O10	[M-H]	3.34	331.0671	331.066	3.3	CID 10088114
18	Glucomoringin	C20H29NO14S2	[M-H]	3.34	570.0956	570.0946	1.8	CID 162639104
19	Adenosine	C10H13N5O4	[M+H]+	3.34	268.1042	268.104	0.7	CID 60961
20	Gallic acid	C7H6O5	[M-H]	3.36	169.0143	169.0131	7.1	CID 370
21	Neochlorogenic acid	C16H18O9	[M-H]	3.38	353.0897	353.0867	8.5	CID 5280633
22	Protocatechuic acid	C7H6O4	[M-H]	3.4	153.0194	153.0182	7.8	
23	Chlorogenic acid	C16H18O9	[M-H]	3.53	353.088	353.0867	3.7	CID 1794427
24	Vicenin-2	C27H30O15	[M-H]	3.61	593.1511	593.1501	1.7	
25	7-Hydroxycoumarin	C9H6O3	[M+H]+	3.62	163.0392	163.039	1.2	CID 57369215
26	p-Coumaroylquinic acid	C16H18O8	[M-H]	3.63	337.0934	337.0918	4.7	CID 5281766
27	Cryptochlorogenic acid	C16H18O9	[M-H]	3.64	353.0891	353.0867	6.8	CID 9798666
28	Rutin	C27H30O16	[M-H]	3.78	609.1464	609.145	2.3	CID 5280805
29	Protocatechualdehyde	C7H6O3	[M-H]	3.79	137.0244	137.0233	8	CID 8768
30	3-O-Feruloylquinic acid	C17H20O9	[M-H]	3.81	367.1024	367.1024	0	CID 6451331
31	Vitexin	C21H20O10	[M-H]	3.83	431.0982	431.0973	2.1	CID 5280441
32	Kaempferol-3-O-rutinoside	C27H30O15	[M-H]	3.83	593.1514	593.1501	2.2	CID 5318767
33	Isoquercitrin	C21H20O12	[M-H]	3.9	463.0883	463.0871	2.6	CID 5484006
34	Astragalin	C21H20O11	[M-H]	3.91	447.0931	447.0922	2	
35	Quercetin-acetyl-glycoside	C23H22O13	[M-H]	3.93	505.0989	505.0977	2.4	CID 44259187
36	Isorhamnetin-3-O-glucoside	C22H22O12	[M-H]	3.93	477.104	477.1028	2.5	CID 5318645
37	Kaempferol	C15H10O6	[M+H]+	3.93	287.0555	287.055	1.7	CID 5280863
38	Quinic acid	C7H12O6	[M-H]	3.94	191.0553	191.055	1.6	CID 37439
39	Kaempferol-acetyl-glycoside	C23H22O12	[M-H]	3.95	489.1039	489.1028	2.2	
40	Quercetin	C15H10O7	[M+H]+	3.99	303.0501	303.0499	0.7	CID 5280343
41	Ferulic acid	C10H10O4	[M-H]	4.38	193.0506	193.0495	5.7	CID 445858
42	Isorhamnetin	C16H12O7	[M-H]	4.51	315.0511	315.0499	3.8	CID 5281654
43	α-Linolenic acid	C18H30O2	[M+H]+	5.2	279.2317	279.2319	0.7	
44	1,7-Bis(3,4-dihydroxyphenyl)-6-hydroxyheptan-3-one	C19H22O6	[M−H]−	14.7	345.134	345.1344	0.9	CID 45783138
45	4-hydroxycinnamic acid	C9H8O3	[M+H]+	15.3	165.0551	165.0546	2.8	CID 322
46	Ferulic acid	C10H10O4	[M+H]+	15.7	195.0657	195.0652	2.7	CID 445858
47	3,5-dihydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane	C19H24O5	[M+H]+	15.8	333.1705	333.1697	2.6	CID 636849
48	7-(3,4-Dihydroxyphenyl)-5-hydroxy-1-(4-hydroxyphenyl)heptan-3-one	C19H22O5	[M−H]−	16.4	329.1394	329.1394	0	CID 13347314
49	1,7-Bis(3,4-dihydroxyphenyl)heptan-3-one	C19H22O5	[M+H]+	17.1	329.1392	329.1384	2.6	CID 11573476
50	(3R,5R)-1,7-bis(4-hydroxyphenyl)-3,5-heptanediol	C19H24O4	[M−H]−	17.4	315.1602	315.1602	0	CID 11034432
51	3-Hydroxy-1,7-bis-(4-hydroxyphenyl)-6-heptene-1,5-dione	C19H18O5	[M−H]−	17.7	325.1082	325.1081	0	CID 91307775
52	1-(4-hydroxyphenyl)-7-(3,4-dihydroxyphenyl)-1,6-heptadiene-3,5-dione	C19H16O5	[M+H]+	18.3	325.108	325.1071	3	
53	1,7-bis(3,4-dihydroxyphenyl)hepta-4,6-dien-3-one	C19H18O5	[M+H]+	18.6	327.1233	327.1227	1.9	
54	1,7-Bis(4-hydroxyphenyl)-5-hydroxy-1-heptene-3-one	C19H20O4	[M+H]+	18.7	313.1441	313.1441	2.2	CID 102176225
55	1,5-bis(4-hydroxyphenyl)-1,4-pentadien-3-one	C17H14O3	[M+H]+	20.6	267.1021	267.1016	2.1	CID 107441
56	1,7-Bis (4-hydroxyphenyl)-1,4,6-heptatrien-3-one	C19H16O3	[M+H]+	22.2	293.1178	293.1172	2.1	CID 71346280
57	(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione	C19H16O5	[M−H]−	22.4	323.0928	323.0925	1.2	CID 25055438
58	Monodemethylcurcumin	C20H18O6	[M+H]+	22.8	355.1185	355.1176	2.5	CID 5469426
59	Bisdemethoxycurcumin	C19H16O4	[M+H]+	23.9	309.1127	309.1121	1.7	CID 5315472
60	1,7-Bis(4-Hydroxyphenyl)-1-Heptene-3,5-Dione	C19H18O4	[M+H]+	24.2	311.128	311.1278	0.8	CID 9796708
61	Demethoxycurcumin	C20H18O5	[M+H]+	24.8	339.1229	339.1227	0.6	CID 5469424
62	Curcumin	C21H20O6	[M+H]+	25.3	369.1337	369.1333	1.2	CID 969516
63	Didemethoxybisabolocurcumin ether	C34H38O6	[M+H]+	27	543.2747	543.2741	1.2	
64	Demethoxybisabolocurcumin ether	C35H40O7	[M+Na]+	30.1	595.2675			CID 71459740
65	Bisabolocurcumin Ether	C36H42O8	[M+Na]+	30.7	625.2786			
66	Vanillin	C8H8O3	[M+H]+	16	153.0547	153.0546	0.7	CID 1183
67	Vanillylidene acetone	C11H12O3	[M−H]−	18.2	191.0712	191.0714	0.7	CID 5354238
68	Dehydrocurdione	C15H22O2	[M+H]+	24.5	235.1688	235.1693	1.8	CID 14191392
69	(6s)-6-methyl-5-(3-oxobutyl)-2-(propan-2-ylidene)cyclohept-4-en-1-one	C15H22O2	[M+H]+	26.4	235.1697	235.1693	2	
70	9-hydroxy-10,12,15-octadecatrienoic acid	C18H30O3	[M−H]−	28	293.2125	293.2122	1	CID 6439873
71	8-Hydroxy-ar-turmerone	C15H20O2	[M+H]+	28.5	233.1534	233.1536	0.7	CID 102079805
72	Coriolic acid	C18H32O3	[M−H]−	29.6	295.2282	295.2279	1.3	CID 5282947
73	Ar-Tumerone	C15H20O	[M+H]+	31.2	217.1588	217.1587	0.3	CID 160512

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Appendix 2

Table 2 Compound Mapping

Compound (neutral)	GI absorption	BBB permeant	Hepatotoxicity	Cytotoxicity	Neurotoxicity
Compound 1	High	No	Inactive	Inactive	Inactive
Compound 2	High	Yes	Active	Inactive	Inactive
Compound 3	High	No	Inactive	Inactive	Inactive
Compound 4	High	Yes	Inactive	Inactive	Inactive
Compound 5	High	No	Active	Inactive	Inactive
Compound 6	High	Yes	Inactive	Inactive	Inactive
Compound 7	High	Yes	Active	Inactive	Inactive
Compound 8	High	Yes	Inactive	Inactive	Inactive
Compound 9	High	No	Inactive	Inactive	Inactive
Compound 10	High	Yes	Inactive	Inactive	Inactive
Compound 11	High	Yes	Inactive	Inactive	Inactive
Compound 12	Low	No	Inactive	Inactive	Inactive
Compound 13	High	Yes	Active	Inactive	Inactive
Compound 14	High	No	Active	Inactive	Inactive
Compound 15	Low	No	Inactive	Inactive	Inactive
Compound 16	High	Yes	Inactive	Inactive	Inactive
Compound 17	Low	No	Inactive	Inactive	Inactive
Compound 18	Low	No	Inactive	Inactive	Inactive
Compound 19	Low	No	Inactive	Active	Inactive
Compound 20	High	No	Inactive	Inactive	Inactive
Compound 21	Low	No	Inactive	Inactive	Inactive
Compound 22	Low	No	Inactive	Inactive	Inactive
Compound 23	High	Yes	Inactive	Inactive	Inactive
Compound 24	Low	No	Inactive	Inactive	Inactive
Compound 25	Low	No	Inactive	Inactive	Inactive
Compound 26	Low	No	Inactive	Inactive	Inactive
Compound 27	High	No	Inactive	Inactive	Inactive
Compound 28	Low	No	Inactive	Inactive	Inactive
Compound 29	Low	No	Inactive	Inactive	Inactive
Compound 30	Low	No	Inactive	Inactive	Inactive
Compound 31	Low	No	Inactive	Inactive	Inactive
Compound 32	Low	No	Inactive	Inactive	Inactive
Compound 33	Low	No	Inactive	Inactive	Inactive
Compound 34	High	No	Inactive	Inactive	Inactive
Compound 35	High	No	Inactive	Inactive	Inactive
Compound 36	High	No	Inactive	Inactive	Inactive
Compound 37	High	Yes	Inactive	Inactive	Inactive
Compound 38	High	No	Inactive	Inactive	Inactive
Compound 39	High	No	Inactive	Inactive	Inactive
Compound 40	High	Yes	Inactive	Inactive	Inactive
Compound 41	High	Yes	Inactive	Inactive	Inactive
Compound 42	High	Yes	Inactive	Inactive	Inactive
Compound 43	High	No	Inactive	Inactive	Inactive
Compound 44	High	No	Inactive	Inactive	Inactive
Compound 45	High	No	Inactive	Inactive	Inactive
Compound 46	High	No	Inactive	Inactive	Inactive
Compound 47	High	Yes	Inactive	Inactive	Inactive
Compound 48	High	Yes	Inactive	Inactive	Inactive
Compound 49	High	Yes	Inactive	Inactive	Inactive
Compound 50	High	No	Inactive	Inactive	Inactive
Compound 51	High	No	Inactive	Inactive	Inactive
Compound 52	High	Yes	Inactive	Inactive	Inactive
Compound 53	High	Yes	Inactive	Inactive	Inactive
Compound 54	High	No	Inactive	Inactive	Inactive
Compound 55	High	No	Inactive	Inactive	Inactive
Compound 56	low	No	Inactive	Inactive	Inactive
Compound 57	High	Yes	Inactive	Inactive	Inactive
Compound 58	High	Yes	Inactive	Inactive	Inactive
Compound 59	High	Yes	Inactive	Inactive	Inactive
Compound 60	low	No	Inactive	Inactive	Inactive
Compound 61	High	Yes	Inactive	Inactive	Inactive
Compound 62	High	Yes	Inactive	Inactive	Inactive
Compound 63	High	Yes	Inactive	Inactive	Inactive

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Appendix 3

Table 3 Toxicity and Pharmacokinetic Profiles of All 63 Compounds

No.	Compound	Compound (neutral)	Plant Source
1	Malic acid	Compound 1	*Moringa oleifera*
2	Trigonelline	Compound 2	*Moringa oleifera*
3	5-Hydroxymethylfurfural	Compound 3	*Moringa oleifera*
4	L-Valine	Compound 4	*Moringa oleifera*
5	Cytosine	Compound 5	*Moringa oleifera*
6	Benzaldehyde	Compound 6	*Moringa oleifera*
7	Cinnamic acid	Compound 7	*Moringa oleifera*
8	p-Coumaric acid	Compound 8	*Moringa oleifera*
9	Citric Acid	Compound 9	*Moringa oleifera*
10	Cinnamaldehyde	Compound 10	*Moringa oleifera*
11	L-Leucine	Compound 11	*Moringa oleifera*
12	Protocatechuic acid-4-O-glucoside	Compound 12	*Moringa oleifera*
13	Salicylic acid	Compound 13	*Moringa oleifera*
14	Nicotinamide	Compound 14	*Moringa oleifera*
15	Guanosine	Compound 15	*Moringa oleifera*
16	L-Phenylalanine	Compound 16	*Moringa oleifera*
17	Gallic acid 4-O-glucoside	Compound 17	*Moringa oleifera*
18	Glucomoringin	Compound 18	*Moringa oleifera*
19	Adenosine	Compound 19	*Moringa oleifera*
20	Gallic acid	Compound 20	*Moringa oleifera*
21	Neochlorogenic acid	Compound 21	*Moringa oleifera*
22	Chlorogenic acid	Compound 22	*Moringa oleifera*
23	7-Hydroxycoumarin	Compound 23	*Moringa oleifera*
24	p-Coumaroylquinic acid	Compound 24	*Moringa oleifera*
25	Cryptochlorogenic acid	Compound 25	*Moringa oleifera*
26	Rutin	Compound 26	*Moringa oleifera*
27	Protocatechualdehyde	Compound 27	*Moringa oleifera*
28	3-O-Feruloylquinic acid	Compound 28	*Moringa oleifera*
29	Vitexin	Compound 29	*Moringa oleifera*
30	Kaempferol-3-O-rutinoside	Compound 30	*Moringa oleifera*
31	Isoquercitrin	Compound 31	*Moringa oleifera*
32	Quercetin-acetyl-glycoside	Compound 32	*Moringa oleifera*
33	Isorhamnetin-3-O-glucoside	Compound 33	*Moringa oleifera*
34	Kaempferol	Compound 34	*Moringa oleifera*
35	Quinic acid	Compound 35	*Moringa oleifera*
36	Quercetin	Compound 36	*Moringa oleifera*
37	Ferulic acid	Compound 37	*Moringa oleifera*
38	Isorhamnetin	Compound 38	*Moringa oleifera*
39	1,7-Bis(3,4-dihydroxyphenyl)-6-hydroxyheptan-3-one	Compound 39	*Curcuma longa*
40	4-hydroxycinnamic acid	Compound 40	*Curcuma longa*
41	Ferulic acid	Compound 41	*Curcuma longa*
42	3,5-dihydroxy-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptane	Compound 42	*Curcuma longa*
43	7-(3,4-Dihydroxyphenyl)-5-hydroxy-1-(4-hydroxyphenyl)heptan-3-one	Compound 43	*Curcuma longa*
44	1,7-Bis(3,4-dihydroxyphenyl)heptan-3-one	Compound 44	*Curcuma longa*
45	(3R,5R)-1,7-bis(4-hydroxyphenyl)-3,5-heptanediol	Compound 45	*Curcuma longa*
46	3-Hydroxy-1,7-bis-(4-hydroxyphenyl)-6-heptene-1,5-dione	Compound 46	*Curcuma longa*
47	1,7-Bis(4-hydroxyphenyl)-5-hydroxy-1-heptene-3-one	Compound 47	*Curcuma longa*
48	1,5-bis(4-hydroxyphenyl)-1,4-pentadien-3-one	Compound 48	*Curcuma longa*
49	1,7-Bis (4-hydroxyphenyl)-1,4,6-heptatrien-3-one	Compound 49	*Curcuma longa*
50	(1E,6E)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione	Compound 50	*Curcuma longa*
51	Monodemethylcurcumin	Compound 51	*Curcuma longa*
52	Bisdemethoxycurcumin	Compound 52	*Curcuma longa*
53	1,7-Bis(4-Hydroxyphenyl)-1-Heptene-3,5-Dione	Compound 53	*Curcuma longa*
54	Demethoxycurcumin	Compound 54	*Curcuma longa*
55	Curcumin	Compound 55	*Curcuma longa*
56	Demethoxybisabolocurcumin ether	Compound 56	*Curcuma longa*
57	Vanillin	Compound 57	*Curcuma longa*
58	Vanillylidene acetone	Compound 58	*Curcuma longa*
59	Dehydrocurdione	Compound 59	*Curcuma longa*
60	9-hydroxy-10,12,15-octadecatrienoic acid	Compound 60	*Curcuma longa*
61	8-Hydroxy-ar-turmerone	Compound 61	*Curcuma longa*
62	Coriolic acid	Compound 62	*Curcuma longa*
63	Ar-Tumerone	Compound 63	*Curcuma longa*