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Potential drugs for asthma allergy: *In Silico* study and ADMET prediction of secondary metabolites derived from *Curcuma longa* Linn. rhizome

Yusuf Alif Pratama[1], Honey Dzikri Marhaeny[1], Mahardian Rahmadi[2], Kevser Özdemir[3], Hilal Bardakcı[4], Ahmed Abdallah Hasan[5], Burkhard Kleuser[5], Muhammad Taher[6], Junaidi Khotib[2*]

[1]Doctoral Degree in Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
[2]Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya 60115, Indonesia
[3]Department of Pharmacognosy, Faculty of Pharmacy, Fırat University, Elazığ, 23200, Turkiye
[4]Department of Pharmacognosy, Faculty of Pharmacy, İstinye University, İstanbul, 34010, Turkiye
[5]Department of Pharmacology and Toxicology, Institute of Pharmacy, Freie Universität Berlin, Berlin 14195, Germany
[6]Department of Pharmaceutical Technology, Kulliyyah of Pharmacy, International Islamic University Malaysia, Pahang 25200, Malaysia

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ABSTRACT

Introduction: An allergy is a hypersensitivity reaction generally mediated by the immune system, which is usually followed by an increase in IgE levels. The early phase of the molecular pathogenesis of allergies begins with the binding activation of the allergen and protease-activated receptor, followed by the phosphorylation of the three protein kinases. The role of p38 MAPK, ERK1/2, and JNK are integral to the pathophysiology of allergic asthma. *Curcuma longa* has been known as an anti-inflammatory herbal medicine that has a potential to be an asthma allergy drug. The *in silico* and absorption, distribution, metabolism, excretion, and toxicology (ADMET) prediction studies were conducted to identify the *C. longa* secondary metabolites as a potential asthma allergy drug. Those compounds suggest the molecular activity inhibition in the inflammatory pathways underlying allergic manifestations.
Methods: Candidate compounds that fulfilled Lipinski's theoretical requirements were docked to three protein kinases using Molegro Virtual Docker Version 5.5. The rerank score of each compound was compared with those of the standard ligand and existing drug.
Results: At least two compounds with rerank scores consistently lower or comparable to the existing ligands and drugs, namely compound A (1,5-dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one) and compound B (Bisdesmethoxycurcumin), were identified. The ADMET profile gave an outstanding result to be developed as a drug candidate.
Conclusion: The secondary metabolites derived from *C. longa* exhibit potent inhibitory effects on those three kinases. This strategy seems to hold a significant potential for developing novel therapeutics targeting inhalant-induced allergies.

Implication for health policy/practice/research/medical education:
The *in silico* study comes as an initial study for drug development. This study relies on predicting a drug candidate's affinity with its receptor. It will be helpful in drug development to eliminate inactive drugs using the affinity binding value compared with the native ligand.
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Introduction

Asthma is one of the most prevalent chronic respiratory diseases affecting children and adults and has a high mortality rate (1,2). Approximately 250,000 people die each year from asthma, which is equivalent to one in every 250 deaths worldwide. Globally, more than 300 million people are affected by asthma, leading to a significant healthcare and economic burden (3). Asthma

***Corresponding author**: Junaidi Khotib,
Email: junaidi-k@ff.unair.ac.id

is a multifactorial disease characterized by limited airflow, airway hypersensitivity, and increased mucus production, resulting in coughing, wheezing, shortness of breath, and chest tightness (4). Airway obstruction and bronchial hypersensitivity to stimuli are associated with abnormal airway inflammation. Symptoms of asthma result from an inflammatory reaction in the airways, which provokes plasma extravasation and accumulation of inflammatory cells, such as eosinophils, neutrophils, lymphocytes, macrophages, and mast cells (5).

Allergic pathogenesis generally begins after the passage of the allergen through nasal mucosal epithelial cells. When activated, cells release the cytokines interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin, which promote dendritic cells (DCs) (6,7). The release of these cytokines is induced by protein 38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) protein activation (8). The allergen is recognized, taken up, and processed by the DCs, which subsequently activate immune responses that trigger allergies. The DCs then transport allergen proteins to the lymph nodes and induce naïve T helper (Th) cell differentiation into allergen-specific Th2 cells via IL-4 cytokines (9).

The roles of p38 MAPK, ERK1/2, and JNK are integral to the pathophysiology of allergic asthma (6,8). These kinases mediate many cellular responses that underpin the chronic inflammation, airway remodelling, and corticosteroid insensitivity characteristic of the disease. p38 MAPK facilitates the differentiation and activation of T helper 2 (Th2) cells and group 2 innate lymphoid cells, promoting the release of cytokines such as IL-4, IL-5, and IL-13. ERK1/2 signalling is activated by various stimuli, including IL-13, a key cytokine in allergic inflammation (10,11). JNK signalling plays a significant role in T cell-mediated immune responses. Inhibition of JNK signalling has been demonstrated to reduce eosinophil influx and cytokine production in asthma models. The MAPK family, encompassing p38 MAPK, ERK, and JNK, orchestrates critical pathways in the pathogenesis of allergic asthma (12,13).

Most therapeutic management of allergic asthma focuses on administering drugs based on symptom control, such as beta-adrenergic agonists, muscarinic antagonists, leukotriene receptor antagonists, and corticosteroids (14). These drugs also act downstream of the pathological mechanism of asthma; therefore, they are often administered after asthma development (4,15). Consequently, drugs aimed at the upstream phase (early response) of asthma pathogenesis should be developed to implement asthma preventive processes (5,6,16). Targeting these kinases offers a promising avenue for the development of novel therapeutic strategies aimed at modulating the inflammatory and immune responses underlying the disease.

Curcuma longa Linn. rhizome is one of the original spices found in Indonesia, which contains curcuminoids (curcumin and its derivatives, such as demethoxycurcumin, bisdemethoxycurcumin, 5-methoxycurcumin, dihydrocurcumin, and cyclocurcumin), sesquiterpenes (gemacrone, ar-turmerone, turmerones, bisabolene, curcumene, zingiberenecurene, sesquiphone, prohydrone, bisacumol, curcumenol, isoprocurcumenol, epiprocurcumenol, zedoaronediol, curlone, turmeronol A and B), steroids (stigmasterol, sitosterol, cholesterol), anthraquinone, 2-hydroxymethyl anthraquinone, and essential oils (phellandrene, sabinene, cineol, borneol) (17,18).

Curcuma longa has been used empirically by Indonesians for several diseases, such as hemorrhoids, asthma, inflammation, and leprosy (19). Several studies have investigated the anti-inflammatory effects of *C. longa* rhizome (17,18). The curcuminoid-type compound content in *C. longa* rhizome is related to the anti-inflammatory activity against the inhibition of pro-inflammatory cytokine gene expression (TNF-α and IL-β) and the cyclooxygenase (COX)-2 pathway (17,19). Another study also stated that curcumin-rich extracts from *C. longa* rhizome alleviate and inhibit COX-2, lipooxygenase, and nitric oxide synthase enzyme activity and inhibit tumour necrosis factor-α (TNF-α), IL-1, -2, -6, -8, and -12 production (20,21).

Thus, this study developed a drug based on the virtual screening of secondary metabolites from *C. longa* rhizome that inhibit upstream processes (initial response), namely p38 MAPK, ERK2, and JNK, using an *in silico* approach with its absorption, distribution, metabolism, excretion, and toxicity prediction.

Materials and Methods

Materials

The materials used in this study were a set of computers (Lenovo Ideapad Slim 3, Intel Core i3 10th Generation, 12 GB RAM), ChemOffice 2015 software application (*Chem3D* 15.0 and ChemDraw 15.0), Molegro Virtual Docker (Version 5.5) (Molexus, Denmark), SwissADME accessed via http://www.swissadme.ch/ (Swiss Institute of Bioinformatics, Switzerland) (22), KNApSAcK Family accessed through https://www.knapsackfamily.com/KNApSAcK_Family/ (Nara Institute of Science and Technology, Japan), Protein Data Bank accessed through http://www.rcsb.org/ (Piscataway, NJ, USA) (23), and pkCSM accessed through http://www.biosig.unimelb.edu.au/pkcsm/ (Melbourne, Vic, Australia) (24).

Compound retrieval

The candidate compounds were searched using the KNApSAcK Family, which was accessed through http://www.knapsackfamily.com/KNApSAcK_Family/.

Drug-likeness screening

The candidate compounds were selected via SwissADME,

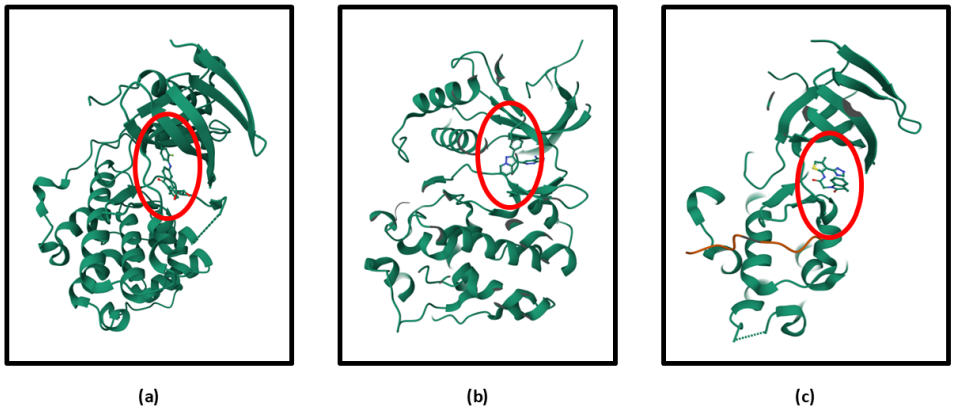


Figure 1. Cartoon representation of p38 MAPK (a), ERK2 (b), and JNK (c) accessed through https://www.rcsb.org/. The red circle shows the native ligand in the active site.

which was accessed at http://www.swissadme.ch. This selection was carried out with the consideration of "Drug-likeness" as the basis for considering these compounds as medicinal compounds. "Drug-likeness" is considered in Lipinski's theory, with the fulfillment of the compounds according to Lipinski's theory.

Molecular docking

The candidate compounds were docked using the Molegro Virtual Docker. The docking process began with a search for protein targets using the Protein Data Bank (PDB) accessed through http://www.rcsb.org. The protein targets, p38 MAPK (ID: 3que), ERK2 (ID: 1tvo), and JNK (ID: 3 ptg) (Figure 1), were prepared by repairing missing amino acid residues and removing water molecules and validated by comparing the standard ligand that formed a complex with the target proteins (Table 1).

ADMET prediction

The candidate compounds with a rerank score lower than standard ligands and existing drugs were analyzed for Adsorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) profiles by pkCSM through http://www.biosig.unimelb.edu.au/pkcsm/.

Results

Molecular docking

Ninety-one compounds were identified as secondary metabolites of *C. longa* Linn. rhizome. Sixty-five compounds were selected according to the "drug-likeness" requirements and docked. Then, the rank scores were sorted and compared with those of the standard ligand and existing drugs. The docking process with p38 MAPK revealed 11 compounds with a lower rank score than the existing ligands and drugs, namely SB202190 (Table 2).

Linear to the second protein target, the docking process with ERK2 revealed six compounds with a lower rank score than existing ligands and drugs, namely, ulixertinib (Table 3).

For the third protein target, the docking process with JNK revealed 12 compounds with a lower rank score than the existing ligands and drugs, namely SP600125 (Table 4).

As a conclusion of the docking process, at least two compounds whose rank scores were consistently better than or almost the same as those of the existing ligands and drugs, namely compound A (1,5-dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one) and compound B (bisdesmethoxycurcumin), were identified (Table 5).

ADMET prediction

The results of physical properties are shown in Table 6, while the ADMET analysis process performed using the pkCSM is shown in Table 7.

Discussion

The molecular docking study conducted to investigate the compounds inhibiting p38 MAPK (ID: 3que), ERK2 (ID: 1tvo), and JNK (ID: 3ptg) protein targets identified at least two compounds, compound A (1,5-Dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one) and compound B

Table 1. The position of the native ligand with the radius of the docking analysis

Protein ID	X position	Y position	Z position	Radius (Å)	Standard drug
3que	3.01	1.64	23.66	14	SB202190
1tvo	6.67	−4.16	16.66	13	Ulixertinib
3ptg	1.04	0.37	31.04	15	SP600125

Table 2. List of candidate compound binding scores from *Curcuma longa* with p38 MAPK (ID: 3que)

No.	C_ID	Compound	Rerank score (kcal/mol)	Moldock score (kcal/mol)	HBond (kcal/mol)
1.	C00056587	1,5-Dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one	−123.839	−144.584	−7.799
2.	C00055176	1,5-Dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	−121.188	−144.149	−6.320
3.	C00056182	1,5-Dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadien-3-one	−116.635	−139.132	−5.785
4.	C00056588	3-Hydroxy-1,7-bis(4-hydroxyphenyl)-6-heptene-1,5-dione	−115.928	−132.259	−3.066
5.	C00042286	Bisdemethoxycurcumin	−113.195	−132.963	−2.500
6.	C00000164	beta-Eudesmol	−112.130	−128.25	−6.476
7.	C00044864	Letestuianin B	−111.938	−136.240	−3.555
8.	C00055412	1,5-Dihydroxy-1,7-bis(4-hydroxyphenyl)-4,6-heptadien-3-one	−108.813	−130.100	−9.878
9.	C00052870	1,7-Bis(4-hydroxyphenyl)-1-heptene-3,5-dione	−108.717	−129.262	−4.261
10.	C00054295	Cyclocurcumin	−107.739	−124.531	−2.312
11.	C00002731	Curcumin	−107.509	−138.425	−4.199
12.	–	Standard ligand	−106.359	−139.592	−5.993
13.	–	SB202190	−99.384	−145.799	−0.203

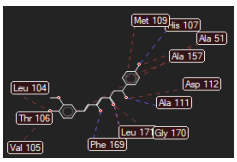
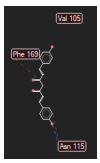
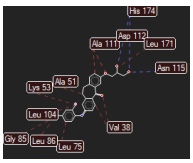
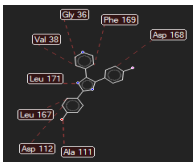
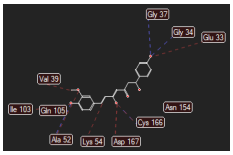
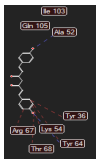
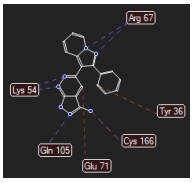
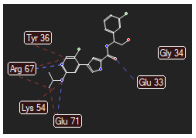
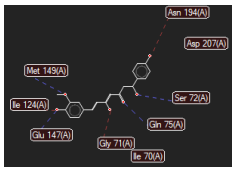
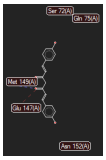
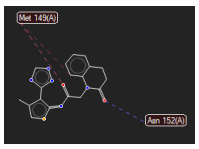
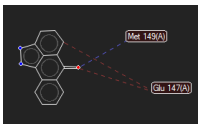
Table 3. List of candidate compounds binding scores from *Curcuma longa* with ERK (ID: 1tvo)

No.	C_ID	Compound	Rerank score (kcal/mol)	Moldock score (kcal/mol)	HBond (kcal/mol)
1.	C00030410	Glycholate Acid	−110.424	−135.668	−10.073
2.	C00052870	1,7-Bis(4-hydroxyphenyl)-1-heptene-3,5-dione	−109.968	−137.860	−3.603
3.	C00055964	Tauroursodeoxycholate Acid	−107.313	−132.604	−7.153
4.	C00045250	Calebin A	−105.636	−122.652	−7.292
5.	C00042286	Bisdemethoxycurcumin	−104.295	−128.006	−4.205
6.	–	Standard Ligand	−103.551	−132.077	−4.544
7.	C00056587	1,5-Dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one	−101.568	−131.928	−6.269
8.	–	Ulixertinib	−97.027	−124.434	−5.338

Table 4. List of candidate compounds binding scores from *Curcuma longa* with JNK (ID: 3ptg)

No.	C_ID	Compound	Rerank score (kcal/mol)	Moldock score (kcal/mol)	HBond (kcal/mol)
1.	C00044864	Letestuianin B	-101.907	-123.070	−7.916
2.	C00054879	Tetrahydrocurcumin	-100.857	-121.718	−4.263
3.	C00056589	1-(4-Hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-1-heptene-3,5-dione	−96.579	−117.019	−6.214
4.	C00002731	Curcumin	−96.406	−121.682	−2.682
5.	C00056587	1,5-Dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one	−96.150	−113.098	−9.459
6.	C00055964	Tauroursodeoxycholate Acid	−95.814	−119.070	−4.313
7.	C00056182	1,5-Dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)-4,6-heptadien-3-one	−95.524	−110.940	−11.417
8.	C00045250	Calebin A	−95.522	−125.541	-2.573
9.	C00030410	Glycholate acid	−94.346	−117.066	−1.266
10.	C00054295	Cyclocurcumin	−93.093	−105.567	−3.306
11.	C00042286	Bisdemethoxycurcumin	−92.451	−113.232	−1.316
12.	C00055176	1,5-Dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-4,6-heptadien-3-one	−92.373	−112.512	−9.216
13.	–	Standard ligand	−90.612	−120.543	−1.854
14.	–	Chemical Standard - Drug	−69.402	−80.831	−0.843

Table 5. Protein interaction between candidate compounds and the protein target

Protein target	Compound A	Compound B	Standard ligand	Chemical standard - drug
p38 MAPK				 SB202190
ERK2				 Ulixertinib
JNK				 SP600125

*Ala: Alanine; Arg: Arginine; Asn: Asparagine; Asp: Aspartic acid; Cys: Cysteine; Glu: Glutamic acid; Gln: Glutamine: Gly: Glycine; His: Histidine; Ile: Isoleucine; Leu: Leucine; Lys: Lysine; Met: Methionine; Phe: Phenylalanine; Ser: Serine; Thr: Threonine; Tyr: Tyrosine; Val: Valine.

(Bisdesmethoxycurcumin) that might be assumed to be active. These two compounds had a lower rerank score than the three ligands and existing drugs. They formed hydrogen and hydrophobic bonds, significantly affecting bond energy and interaction strength.

The activity prediction should not be considered only by the binding score between the compounds and the protein. The type of bond and sequence of amino acids will directly affect the activity (25-27). Hydrogen and hydrophobic bonds will play a vital role in the binding structure between certain functional groups in the candidate compounds with the amino acid in the protein enzyme (28,29). Hydrogen bonds occur in distances lower than 5 Å, while the hydrophobic or Van der Waals bond occurs in distances lower than 2.5 Å (30). The native ligand binds to p38 MAPK through multiple interactions, including hydrogen bonds, electrostatic forces, and steric contacts. Similarly, the antagonist SB202190 interacts with p38 MAPK by forming hydrogen bonds with Asp112 and engaging in hydrophobic interactions with Ala111 and Leu171. Meanwhile, the same interaction between native ligand and candidate compounds forms as hydrogen and sterical bonds in Asn115 for compound B, and Asp112 as a hydrogen bond and Ala51, Leu104, Ala111, and Leu171 as sterical bonds in compound A. Similarly, ERK2 is bound by several bonds with its native ligand. Ulixertinib, as its inhibitor, bound with Arg67 and Glu71 as hydrogen bonds and Tyr36 and Lys54 as steric bonds. Meanwhile, compound B bound with Arg67 as a hydrogen bond, Tyr36, Lys54, and Gln105 as sterical bonds, and compound A bound with Cys166 as a hydrogen bond, and Lys54 and Gln105 as sterical bonds. For the JNK enzyme, SP600125, as the inhibitor, binds with Met149 through a hydrogen bond. Meanwhile, compound B bound with Met149 and Asn152 as hydrogen bonds, and compound A bound with Met194 as a hydrogen bond. Both compounds not only have a lower rerank score than the native ligands and their inhibitors, but also have the same amino acid bound with a specific functional group presented in their structures.

Physicochemical parameters such as molecular weight, lipophilicity (LogP), hydrogen bond donors and acceptors,

Table 6. Physicochemical properties of candidate compounds

Parameter	Compound A	Compound B
Molecular weight, g/mol	356.374	308.333
LogP	3.2543	3.3527
Torsion	7	6
Hydrogen bond acceptors	6	4
Hydrogen bond donors	4	2
Polar surface activity, A^2	150.481	133.575
Water solubility	−3.551	−3.382

Table 7. Pharmacokinetic parameter prediction of candidate compounds

Parameter	Compound A	Compound B
Intestinal absorption, %	72.911	91.081
Skin permeability, log	−2.753	−2.803
Caco-2 permeability, log cm/s	0.923	0.957
Distribution volume, L	0.143	0.140
CYP2D6 inhibitor	No	No
CYP3A4 inhibitor	No	Yes
Total clearance, mL/min/kg BW	0.264	−0.008
Ames toxicity	No	No
Hepatotoxicity	No	No
BBB Permeability, log PS	−1.083	−0.089

and topological polar surface area significantly influence a drug candidate's bioavailability and target site accessibility (21). Moreover, *in silico* ADMET predictions serve as powerful tools for early identification of compounds with favourable pharmacokinetic behaviour and minimal toxicity, thereby reducing the attrition rate during clinical development. Integrating these approaches into the drug discovery pipeline enhances the efficiency of lead optimization. It contributes to developing safer and more effective treatments for allergic asthma (24).

Although bonding with this compound has promising results, it would be ineffective if it has poor ADME characteristics and high toxicity. An investigation of more than 2000 drugs obtained from the World Drug Index (WDI) explains that compounds that have good absorption or permeability must adhere to at least several parameters, such as molecular weight ≤500, partition coefficient ≤5, hydrogen bond donor ≤5, and acceptor, hydrogen bonds ≤10. This standard is the Rule of Five of Lipinski's Theory (31,32). After testing 91 candidate compounds, 66 met the parameters of the Rule of Five of Lipinski's theory. Thereafter, they were docked to obtain two potential compounds with convenient absorption and permeability.

Caco-2 monolayer cells are often used to assay oral drug absorption as an *in vitro* human intestinal mucosal model. Good drug permeability is indicated by a log Papp value > 0.90 cm/s (24,33). The Papp values of both compounds were higher than 0.90 cm/s in this study. Suppose the intestinal absorption value (human) of a compound that can be absorbed is lower than 30%. In that case, it will not be easy to be absorbed (24). In this study, we found that both compounds had intestinal absorption values (humans) above 30%, which supports the idea that these two compounds are easily absorbed (34,35).

In the distribution profile, a high predicted volume of distribution (VDss) implies high VD and drug concentration in the tissue compared to that in the plasma. Previous studies have reported that a drug has a high VDss if > 2.81 L/kg (0.45) and a low VDss if <0.71 L/kg (−0.15) (36,37). The compounds in this study displayed VDss 0.143 and 0.14, which were neither too high nor too low. A compound is considered capable of crossing the blood-brain barrier (BBB) if it has a logBB value greater than 0.3, while a logBB value below −1 indicates limited brain distribution (38,39). Compound A exhibited low BBB permeability, suggesting it probably had no impact on the central nervous system.

Cytochrome P450 plays an essential role in drug metabolism, particularly if a compound can change the metabolic profiles of other drugs that require attention. The inhibition of an enzyme isoform increases the free level of other drugs that are substrates of the enzyme in the blood, the most significant of which is the emergence of toxicity (40,41). In this study, these two candidate compounds were not CYP2D6 inhibitors. However, compound B inhibited the CYP3A4 isoform.

In the excretory profile, total clearance is measured through several excretion processes carried out by eliminating organs, such as the liver and kidneys. High total clearance indicates rapid drug removal from the body (24,42). This study reported that the log total clearance of compound A and compound B were 0.264 and −0.008, respectively. Another advantage of using these two compounds as drug candidates was the absence of mutagenic and hepatic toxic effects.

Conclusion

Secondary metabolites that inhibited the upstream process (initial response) at the p38 MAPK, ERK2, and JNK in *C. longa* based on virtual screening in the *in silico* approach for asthma allergy were compound A (1,5-dihydroxy-7-(4-hydroxy-3-methoxyphenyl)-1-(4-hydroxyphenyl)-4,6-heptadien-3-one) and compound B (Bisdesmethoxycurcumin). Both metabolites can be regarded as new drug leads owing to their good absorption, distribution, metabolism, excretion, and toxicity profiles. This study was still in preliminary experiments. Further research regarding the activity and effectiveness of the candidate compound needs to be done to confirm the potential drug for asthma allergy derived from *C. longa*.

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Authors' contribution

Conceptualization: Yusuf Alif Pratama, Muhammad Taher, Junaidi Khotib.
Data curation: Yusuf Alif Pratama, Mahardian Rahmadi.
Formal analysis: Yusuf Alif Pratama, Kevser Özdemir.
Funding acquisition: Junaidi Khotib.
Investigation: Yusuf Alif Pratama, Honey Dzikri Marhaeny.
Methodology: Yusuf Alif Pratama, Honey Dzikri Marhaeny, Kevser Özdemir, Hilal Bardakci.
Project administration: Junaidi Khotib.
Resources: Honey Dzikri Marhaeny, Mahardian Rahmadi.
Supervision: Mahardian Rahmadi, Ahmed Abdallah Hasan, Burkhard Kleuser.
Validation: Yusuf Alif Pratama, Muhammad Taher.
Visualization: Yusuf Alif Pratama, Honey Dzikri Marhaeny.
Writing–original draft: Yusuf Alif Pratama, Honey Dzikri Marhaeny, Kevser Özdemir.
Writing–review & editing: Yusuf Alif Pratama, Mahardian Rahmadi, Hilal Bardakci, Ahmed Abdallah Hasan, Burkhard Kleuser, Muhammad Taher, Junaidi Khotib.

Conflict of interests

The authors declare that they hold no competing interests.

Ethical considerations

Not applicable.

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