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RESEARCH ARTICLE

In silico approach of *Garcinia mangostana* and *Ortosiphon stamineus* to restore adipokines level as drug candidate for metabolic syndrome

Danti Nur Indiastuti[1], Nada Salsabila[2], Bellinda Zalzabillah Tazkira[2], Arifa Mustika[3], Suharjono[4], Sukardiman[5]

[1] Doctoral programme, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2] Medical Study programme, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[3] Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[4] Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia
[5] Department of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia

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Correspondence
Sukardiman
Department of Pharmaceutical Sciences
Faculty of Pharmacy
Universitas Airlangga
Surabaya
Indonesia
sukardiman@ff.unair.ac.id

Abstract

Background: Metabolic syndrome is a group of metabolic disorders due to dysfunctional adipose tissue. Adipose tissue is an endocrine organ that secretes many pro-inflammatory and anti-inflammatory adipokines. *Garcinia mangostana* and *Orthosiphon stamineus* have demonstrated various pharmacological effects, including antidiabetic, anti-dyslipidemia, antiobesity, antioxidant, and anti-inflammatory properties. **Objective:** This study aimed to analyse the interaction of phytochemical compounds from *Garcinia mangostana* and *Orthosiphon stamineus* in decreasing levels of pro-inflammatory adipokines while increasing levels of anti-inflammatory adipokines. **Method:** This research is an in silico study of phytochemical compounds from *Garcinia mangostana*, and Orthosiphon stamineus retrieved from PubChem and HMDB. Adipokines as target proteins were obtained from RCSB and UniProt. **Result:** Mangostanin, mangostanol, and mangostinone from *Garcinia mangostana*, as well as ladanein, salveginin, sinensetin, and rosmarinic acid from Orthosiphon stamineus, exhibited stable molecular complexes compared to other compounds. **Conclusion:** Phytochemical compounds from *Garcinia mangostana* and *Orthosiphon stamineus* show potential as candidates for metabolic syndrome drugs by restoring adipokine levels. However, further research is still needed.

Introduction

Metabolic syndrome is a group of metabolic disorders that increase the risk of heart disease and type 2 diabetes (NIH, 2022). Its incidence is three times more common than diabetes, which has a global prevalence of 10.5 percent (IDF, 2021). Adipose tissue is an endocrine organ that secretes many pro-inflammatory and anti-inflammatory adipokines. The role of adipokines dysregulation in the development of metabolic diseases. Several previous studies have shown that metabolic syndrome is characterised by increased leptin in parallel to decreased adiponectin concentrations. Therefore, understanding the balance mechanism between pro-inflammatory and anti-inflammatory adipokines is a strategy for preventing metabolic diseases. (Oh *et al*., 2017; Ebert *et al*., 2018). This study implicates adipokines in developing metabolic diseases with herbal treatment as a potential new therapeutic strategy.

Garcinia mangostana contains various bioactive compounds, with α, β, and γ-mangostin being the most abundant, alongside other xanthones are represented by mangostanin, mangostanol, mangostenol, mangostinone (Ansori *et al*., 2020; Rohman *et al*., 2020; Rizaldy *et al*., 2021). The most prominent flavonoids, isolated from hydroalcohols *Orthosiphon stamineus*

extract, mostly represented by 3'-H-TMF, eupatorine, ladanein, salvegenin, sinensetin, caffeic acid and rosmarinic acid (Ameer *et al*., 2012; Li *et al*., 2021a). They have demonstrated various pharmacological effects, including antidiabetic, antidyslipidemia, antiobesity, antioxidant, and anti-inflammatory properties (Ameer *et al*., 2012; Ansori *et al*., 2020). α-mangostin has been reported to improve glucose tolerance, insulin sensitivity, and adiponectin levels (John *et al*., 2022). *Orthosiphon stamineus* has been found to reduce appetite through the leptin signalling pathway (Son, 2011).

Methods

Ligand retrieval and Protein preparation

These ligand compounds were retrieved from the PubChem dataset (https://pubchem.ncbi.nlm.nih.gov/) and HMDB (https://hmdb.ca) (Kim *et al*., 2015). The ligand molecules, comprising phytochemical compounds from *Garcinia mangostana* (α-mangostin (CID=HMDB0035796), β-mangostin (CID=HMDB0036596), γ-mangostin (CID= HMDB0035795), mangostanin (CID=5495929), mangostanol (CID=10048103), mangostenol (CID=5495927), and mangostinone (CID= HMDB0041292)) and *Orthosiphon stamineus* (3'-H-TMF (CID=7020615), eupatorine (CID=97214), ladanein (CID=3084066), sinensetin (CID=145659), salveginin (CID=HMDB0128577), caffeic acid (CID=689043), and rosmarinic acid (CID=5281792)). Adipokines as target proteins were obtained from the UniProtKB database (https://www.uniprot.org/) and PDB RCSB (https://rcsb.org/). Water molecules and native ligands in the target proteins were removed using BIOVIA Discovery Studio software version 2020 (Yang *et al*., 2022).

Molecular docking

Molecular docking was performed using PyRx software version 0.9.9. $Id: LICENSE.txt 112 2012-02-13 22:33:36Z sarkiss $. Copyright (c) [2008-Forever], Sargis Dallakyan and individual contributors. the BIOVIA Discovery Studio 2020 software (Dassault Systems France) was employed to identify chemical interactions visualised using ligand-target proteins' 3D and 2D structure complexes (Yang *et al*., 2022).

Result

Molecular docking, a virtual simulation of ligand and target protein interactions. The stable molecular complexes show the most negative binding affinity values (Mohanty & Mohanty, 2023). Docking analysis of ligand compounds from *Garcinia mangostana* and *Orthosiphon stamineus* are described in Table I.

Table I: Docking analysis of phytochemical compounds from *Garcinia mangostana* and *Orthosiphon stamineus.*

Source	Ligand compound	Target protein Binding affinity (kcal/mol)								
		A	B	C	D	E	F	G	H	I
Garcinia mangostana	1	-8.0	-6.7	-8.1	-7.1	-8.1	-6.1	-7.1	-7.6	-8.1
	2	-7.5	-6.9	-8.1	-6.6	-8.2	-5.9	-7.1	-7.4	-8.3
	3	-8.0	-6.8	-7.8	-7.2	-8.6	-7.2	-7.2	-8.2	-8.7
	4	-8.4	**-7.4**	-8.0	-7.4	**-9.3**	-6.3	**-8.1**	**-8.7**	**-10.4**
	5	**-8.6**	-6.9	-8.0	**-7.7**	-8.4	-6.6	-7.9	-8.4	-9.1
	6	-7.8	-6.4	-8.2	-7.0	-8.2	-7.0	-7.4	-7.5	-8.5
	7	-8.0	-6.9	**-9.5**	-6.8	-8.7	**-9.2**	-6.8	-8.0	-9.9
Orthosiphon stamineus	8	-6.8	-6.9	-7.5	-6.8	-8.0	-6.5	-6.8	-7.1	-8.9
	9	-6.8	-6.9	-8.8	-6.8	-7.9	-5.9	-7.0	-7.4	-8.9
	10	-7.3	**-7.3**	-6.2	**-7.0**	**-8.1**	-7.8	**-7.1**	-7.3	-9.2
	11	-6.8	-7.0	-7.6	-6.9	-7.7	-5.8	-7.0	-7.1	**-9.7**
	12	-6.6	-6.9	**-9.1**	-6.7	-7.7	-5.9	-6.7	-7.0	-8.4
	13	-6.4	-5.5	-6.5	-5.5	-6.0	-6.2	-5.6	-5.8	-8.5
	14	**-8.6**	-6.8	-7.8	-6.2	-7.5	**-8.4**	-6.7	**-7.6**	-8.8

Ligand compounds list: 1 = α-mangostin, 2 = β-mangostin, 3 = γ-mangostin, 4 = mangostanin, 5 = mangostanol, 6 = mangostenol, 7 = mangostinone; 8 = 3'-H-TMF (3'-hydroxy-5,6,7,4'-tetramethoxyflavone), 9 = eupatorine, 10 = ladanein, 11 = salveginin, 12 = sinensetin, 13 = caffeic acid, 14 = rosmarinic acid.
Target proteins list: A = adiponectin, B = omentin1, C = SFRP5 (secreted frizzled-related protein); D = ASP (acylation-stimulating protein), E = chemerin, F = FABP4 (fatty acid binding protein), G = leptin, H = vaspin, I = visfatin.

Mangostanol(5) and rosmarinic acid(14) both show the most negative binding affinity values for adiponectin (-8.6 kcal/mol). Omentin-1 showed a stable interaction with mangostanin(4) and ladanein(10) (-7.4 and -7.3 kcal/mol). Mangostinone(7) and sinensetin(12) exhibited the most negative binding affinity values (-9.5 and -9.1 kcal/mol), suggesting their potential to increase SFRP5 levels. The most negative binding affinity values for ASP are mangostanol(5) and ladanein(10) (-7.7 and -7.0 kcal/ mol). Chemerin showed a stable interaction with mangostanin(4) and ladanein(10) (-9.3 and -8.1 kcal/mol). Mangostinone(7) and rosmarinic acid(14) have the most negative binding affinity values for FABP4 (-9.2 and -8.4 kcal/mol). The most negative binding affinity values for leptin were mangostanin(4) and ladanein(10) (-8.1 and -7.1 kcal/mol). Vaspin showed a stable interaction with mangostanin(4) and rosmarinic acid(14) (-8.7 and -7.6 kcal/mol). Visfatin is predicted to decrease in levels if it binds to mangostanin(4) and salveginin(11), which have the most negative binding affinity values (-10.4 and -9,7 kcal/mol).

The chemical interaction of selected ligand compounds and target proteins based on the most negative binding affinity values (from Table I) are described in Table II and Figure 1. The research results show that mangostanin, mangostanol, and mangostinone from *Garcinia mangostana* as well rosmarinic acid, ladanein, salveginin, and sinensetin from *Orthosiphon stamineus*.

Table II: Chemical interaction of selected ligand compounds and target proteins

Target protein	Ligand compound	Chemical interaction
(A)	Mangostanol	(1): A:Tyr109, B:Leu239 (conventional); A:Leu239 (carbon-hydogen). (2): B:Val110 (alkyl); A:His241, A:His241, **A:Tyr111**, **A:Val110**, **A:Val110**, C:Tyr109, **C:Tyr111** (pi-alkyl); **C:His241** (pi-pi T- shaped).
	Rosmarinic acid	(1): B:His241, B:Tyr111, B:Tyr111, **C:His241**, **C:His241**, **C:His241**, C:Leu239, **C:Tyr111** (conventional). (2): **A:Val110**, C:Val110 (pi-alkyl); C:Tyr240 (pi-pi T-stacked). (4): **A:Tyr111** (donor-donor).
(B)	Mangostanin	(1): B:Gln67, B:Tyr134 (conventional); B:Gln67 (carbon-hydrogen). (2): B:Pro137, B:Pro137, B:Val64, B:Val64 (alkyl); B:Phe57, B:Pro137 (pi-alkyl).
	Ladanein	(1): B:Glu87, B:Met90 (conventional); A:Thr257 (carbon-hydrogen). (2): A:Cys199, A:Cys259 (alkyl); B:Arg91, A:Trp200, (pi-alkyl); A:Trp200 (pi-pi stacked). (3): B:Asp89 (pi-anion).
(C)	Mangostinone	(1): A:Glu187, **A:Tyr307** (conventional). (2): **A:Met139**, **A:Pro94**, **A:Pro94** (alkyl); **A:Phe144**, **A:Phe144, A:Phe144**, **A:Tyr307** (pi-alkyl); **A:Phe144**, **A:Phe310**, **A:Trp 92** (pi-sigma); **A:Tyr142** (pi-pi T-staped). (4): **A:Tyr307** (donor-donor).
	Sinensetin	(1): A:Gln196, A:Gln196 (conventional). (2): A:Ala280, A:Leu95, **A:Met139**, A:Met279 (alkyl); **A:Phe144**, **A:Pro94**, **A:Pro94**, **A:Trp92**, **A:Tyr142**, **A:Tyr307** (pi-alkyl); **A:Phe310** (pi-sigma); **A:Phe144**, **A:Phe144**, **A:Tyr142** (pi-pi stacked).
(D)	Mangostanol	(1): A:Arg704, **A:Arg710** (conventional). (2): A:Cys707 (alkyl); A:Asn701 (pi-sigma). (3): **A:Arg736**, **A:Arg736** (pi-cation). (4): A:Asn701 (donor-donor).
	Ladanein	(1): **A:Arg710** (conventional). (2): A:Arg735, A:Ala739 (alkyl); A:Ala739, A:Arg735, **A:Arg736** (pi-alkyl); A:Thr732 (pi-sigma). (3): **A:Arg736**, **A:Arg736** (pi-cation). (4): A:Phe705 (acceptor-acceptor).
(E)	Mangostanin	(1): A:His95, A:Thr302 (conventional). (2): A:Ala305, A:Ile120, A:Leu119, A:Leu119, A:Leu298, A:Met123, A:Met123, A:Pro299 (alkyl); A:Leu298, A:Phe88, A:Tyr103, A:Tyr276 (pi-alkyl); A:Tyr276 (pi-pi T-stacked). (3): A:Arg178 (pi-cation).
	Ladanein	(1): A:Ser194, A:Tyr214 (conventional); A:Leu284 (carbon-hydrogen). (2): A:His286, A:Phe190, A:Tyr214 (pi-alkyl); A:His217 (pi-pi T- shaped). (4): A:Asp 210 (acceptor-acceptor).
(F)	Mangostinone	(1): **A:Ala76**, **A:Arg107** (conventional).

Target protein	Ligand compound	Chemical interaction
		(2): **A:Ala34**, **A:Ala34**, **A:Ala76**, **A:Met21**, **A:Met21**, A:Val24, A:Val26 (alkyl); A:Ile63, **A:Phe17**, **A:Phe17**, **A:Tyr20** (pi-alkyl).
	Rosmarinic acid	(1): A:Arg79, A:Arg79, **A:Arg107**, A:Arg127 (conventional). (2): **A:Ala34**, **A:Met21** (pi-alkyl); **A:Ala76**, A:Ile105 (pi-sigma); **A:Phe17** (pi-pi stacked). (4): **A:Tyr20** (donor-donor). (5): A:Cys118 (pi-sulfur).
(G)	Mangostanin	(1): A:Lys115, A:Thr71 (conventional); A:Ala112, A:Ser164 (carbon-hydrogen). (2): A:Leu72, A:Leu161, A:Met75, C:Ile24, C:Val110, C:Val110 (alkyl); A:Ala112, A:Ala112, A:Ala112, A:Leu72, A:Leu72, A:Lys115, C:Phe113 (pi-alkyl); A:Leu72 (pi-sigma). (3): A:Lys115, A:Lys115 (pi-cation).
	Ladanein	(1): A:Arg149, E:Gln84 (conventional); E:Gln84, E:Val81 (carbon-hydrogen). (2): A:Ile85, A:Val81, E:Ile85 (alkyl); A:Arg149, A:Arg149, A:Ile85 (pi-alkyl); A:Tyr82 (pi-pi stacked).
(H)	Mangostanin	(1): A:Gly413 (conventional); A:His312 (carbon-hydrogen). (2): B:Lys175, B:Lys175 (alkyl); A:Lys414, A:Lys414 (pi-alkyl). (3): A:Lys355 (pi-cation).
	Rosmarinic acid	(1): A:Leu230, A:Lys232, A:Lys279, A:Lys388 (conventional); A:Pro389 (carbon-hydrogen). (2): A:Leu280, A:Lys232, A:Lys388, A:Pro389 (pi-alkyl); A:Phe229 (pi-pi T- shaped). (4): A:Leu280 (donor-donor); A:Asp276 (acceptor-acceptor).
(I)	Mangostanin	(1): A:Asp219, A:Ser241, A:Ser275 (conventional). (2): **A:Ala244**, **A:Ala244**, A:Pro273, A:Val242 (alkyl); **A:Ala244**, A:Ala379, **A:His191**, A:Ile309, A:Ile309, A:Ile351, A:Ile351, **A:Phe193**, **B:Tyr18**, **B:Tyr18**, **B:Tyr18,** A:Tyr188, A:Val242, A:Val242 (pi-alkyl); **A:Phe193** (pi-sigma).
	Salveginin	(1): A:Arg311, A:His247, B:Arg392 (conventional). (2): **A:Ala244** (alkyl); **A:Ala244**, **A:His191**, A:His247, **A:Phe193**, (pi-alkyl); **A:Phe193**, **B:Tyr18** (pi-pi stacked). (3): A:Asp313 (pi-anion); A:Arg196, A:Arg196, A:Arg311 (pi-cation).

Some ligand compounds have the same interactions with several residues, as indicated by the amino acid residues written in bold. The active site is shown with an underlined amino acid residue. Target proteins list: (A) = adiponectin, (B) = omentin1, (C) = SFRP5; (D) = ASP, (E) = chemerin, (F) = FABP4, (G) = leptin, (H) = vaspin, (I) = visfatin. Types of interactions list: (1) = hydrogen bond, (2) = hydrophobic interaction, (3) = electrostatic interaction, (4) = undesired bond, (5) = other interaction. Ala: Alanine; Asn: Asparagine; Asp: Aspartate; Arg: Arginine; Cys: Cystein; Gln: Glutamine; Glu: Glutamate; Gly: Glycine; His: histidine; Ile: Isoleucine; Leu: Leucine; Lys: Lysine; Met: Methionine; Phe: Phenylalanine; Pro: Proline; Ser: Serine; Thr: Threonine; Trp: Tryptophan; Tyr: Tyrosine; Val: Valine.

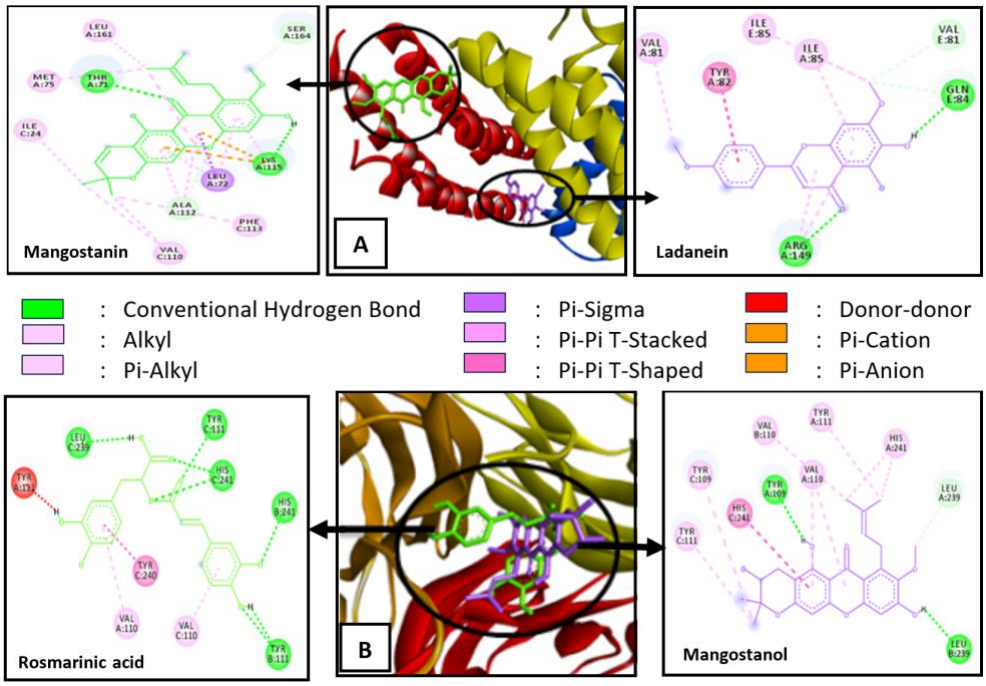

Figure 1: 3D, 2D, and chemical interaction visualisation of selected ligand compounds and target proteins: Leptin (pro-inflammatory adipokines), B. Adiponectin (anti-inflammatory adipokines).

Discussion

Molecular docking was employed to identify the binding affinity and chemical interactions of amino acids between the ligands and the target proteins (Mohanty & Mohanty, 2023). Weak bonds in these interactions, such as hydrogen bonds and hydrophobic and electrostatic interactions, aid in activating and stabilising specific biological responses (Ertan-Bolelli & Bolelli, 2021). Previous studies have indicated a preference for hydrophobic interactions in ligand-protein binding due to their greater strength (Li *et al*., 2021b). The presence of additional hydrogen bonds contributes to the stability and turnover of cellular activity (Meyer *et al*., 2017). Additional electrostatic interaction induces conformational changes in the protein surface, leading to alterations in its structure and conformational stability (Roach *et al*., 2005). Notably, pi-cation interactions are pivotal in protein conformation in hydrophilic and hydrophobic environments (Infield *et al*., 2021). Additionally, the similarity in some ligand binding to several residues and active sites holds potential for development in subsequent tests (Detmar *et al*., 2018).

Metabolic syndrome, due to dysfunctional adipose tissue, is characterised by an increase in leptin in parallel to a decrease in adiponectin concentrations (Oh *et al*., 2017). Figure 1 visualises the chemical interactions of selected ligand compounds and target proteins (represented by leptin and adiponectin). The chemical interactions of the leptin(G)-mangostanin complex featured additional electrostatic interactions, and hydrophobic interactions dominate in this complex, primarily occurring in the A and C chains. Conversely, the leptin(G)-ladanein complex displays a similar bonding pattern but exhibits fewer hydrophobic interactions and additional residues from the E chain. Notably, leptin's A, C, and E chains are essential subunits that bind to leptin receptors and play pivotal roles in regulating body weight (Tsirigotaki *et al*., 2023). Based on research, leptin enhances metabolism and reduces appetite (Oh *et al*., 2017). The adiponectin(A)-mangostanol complex exhibits numerous hydrophobic interactions and absent undesired bonds. The adiponectin(A)-mangostanol and adiponectin(A)-rosmarinic acid complexes exhibit similar bonding patterns with several residues such as A:Tyr111, A:Val110, C:Tyr111, and C:His241. Additionally, residues A:Val110 and C:His241 emerged as prominent binding targets with triple hydrogen bonds (Meyer *et al*., 2017).

Anti-inflammatory adipokines (i.e. adiponectin(A), omentin1(B), and SFRP5(C)) mitigate impaired lipid and glucose metabolism, leading to improved whole-body insulin sensitivity levels (Table II) (Oh *et al*., 2017). The omentin1(B)-mangostanin and omentin1(B)-ladanein complexes were reinforced by hydrogen bonds and hydrophobic interactions. The omentin1(B)-ladanein complex exhibits electrostatic interaction. The SFRP5(C)-mangostinone and SFRP5(C)-sinensetin complexes exhibit similar bonding patterns with several residues such as A:Met139, A:Phe144, A:Phe310, A:Pro94, A:Trp92, A:Tyr142, and A:Tyr307. The SFRP5(C)-mangostinone complex exhibits the presence of undesired binding.

Pro-inflammatory adipokines (i.e. ASP(D), chemerin(E), FABP4(F), leptin(G), vaspin(H), and visfatin(I)) are associated with the development of insulin resistance and metabolic abnormalities (Table II) (Oh *et al*., 2017). The active sites of the ASP(D)-ladanein complex are represented by A:Thr732 and A:Arg735. The ASP(D)-mangostanol and ASP(D)-ladanein complexes form similar bonds at two residues, A:Arg710 and A:Arg736. The ASP(D)-mangostanol and ASP(D)-ladanein complexes exhibit electrostatic interactions and undesired bonds. The chemerin(E)-mangostanin complex involves hydrogen bonds, numerous hydrophobic interactions and electrostatic bonds. The presence of undesired bonds in the chemerin(E)-ladanein complex. The active sites of FABP4(F)-mangostinone and FABP4(F)-rosmarinic acid complexes are represented by A:Ala34, A:Arg107. Additionally, A:Cys118, is only present in FABP4(F)-rosmarinic acid complex. The FABP4(F)-mangostinone and FABP4(F)-rosmarinic acid complexes exhibit similar bonding patterns with several residues, such as A:Arg107, A:Ala34, A:Met21, A:Ala76, A:Phe17, A:Tyr20. The FABP4(F)-mangostinone complex showed a stable interaction due to the distance of chemical interactions and the absence of an undesired bond. The greater the distance between atomic interactions in ligand-protein interactions, the less stable the conformation of the complex (Wang *et al*., 2021). The pi-sulfur bond in the FABP4(F)-rosmarinic acid complex plays a role in stabilising the protein alpha helix, which is preferable to the bond with heteroarene (Arthur & Uzairu, 2019). The vaspin(H)-mangostanin complex exhibits electrostatic interaction and the absence of an undesired bond. Vaspin(H)-mangostanin exhibits fewer chemical interactions in the complex. The visfatin(I)-salvigenin and visfatin(I)-mangostanin complexes exhibit similar bonding patterns with several residues, such as A:Ala244, A:His191, A:Phe193, and B:Tyr18. The hydrophobic interactions with these residues influence target protein turnover (Detmar *et al.*, 2018). The visfatin(I)-salveginin complex featured an electrostatic interaction. The visfatin(I)-mangostanin complex exhibits numerous hydrophobic interactions (Li *et al.*, 2021b).

Conclusion

In silico approach of phytochemical compounds from *Garcinia mangostana* and *Orthosiphon stamineus* show potential as candidates for metabolic syndrome drugs by restoring adipokine levels. These compounds have demonstrated the ability to reduce levels of pro-inflammatory adipokines while increasing anti-inflammatory adipokines. However, further research is still needed.

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Disclosure statement

The authors declare no conflict of interest.

Author Contributions

D.N.I., N.S., and B.Z.T. performed the research and wrote the manuscript. D.N.I., A.M., Shj., and Skd. revised it. All authors have approved the final article.

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