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Original Article

Garcinoxanthones from *Garcinia mangostana* L. against SARS-CoV-2 infection and cytokine storm pathway inhibition: A viroinformatics study

[Garcinoxantonas de *Garcinia mangostana* L. contra la infección por SARS-CoV-2 y la inhibición de la tormenta de citocinas: Un estudio de viroinformático]

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Abstract

Context: Mangosteen (*Garcinia mangostana* L.) is used in traditional medicine as an antibacterial, antioxidant, and anti-inflammatory.

Aims: To determine the molecular mechanism and potential of garciniaxanthone derivate compounds from *G. mangostana* as SARS-CoV-2 antiviral and prevent cytokine storm through *in silico* approach.

Methods: Ligand and protein samples were obtained from databases such as PubChem and Protein Databank, then drug-likeness analysis using Lipinski, Ghose, Veber, Egan, and Muege rules on SwissADME server, prediction of antiviral probability through PASSOnline server. Furthermore, molecular docking simulation with PyRx v1.0 software (Scripps Research, USA) with an academic license, identification of interactions and chemical bond positions of ligands on the target by PoseView server, 3D visualization of PyMOLv.2.5.2 software (Schrödinger, Inc., USA) with an academic license, molecular dynamics simulation for molecular stability prediction by CABS-flex v2.0 server, target prediction of antiviral candidate compounds by SwissTargetPrediction server, pathway analysis through STRING v11.5 database, and toxicity by ProTox-II server were used.

Results: Garciniaxanthone C from *G. mangostana* was found to be a drug-like molecule with low toxicity. This can be a candidate for SARS-Cov-2 antiviral through inhibitor activity on two viral enzymes consisting of M^{pro} and replicase with a binding affinity value that is more negative than other garciniaxanthone derivates and is stable. Garciniaxanthone C is predicted to bind and inhibit pro-inflammatory proteins that trigger cytokine storms, such as NFKB1 and PTGS2.

Conclusions: Garciniaxanthone derivative compounds from *G. mangostana* may be candidates for SARS-CoV-2 antiviral and preventing cytokine storm through garciniaxanthone C activity.

Keywords: *Garcinia mangostana*; SARS-CoV-2; viroinformatics.

Resumen

Contexto: El mangostán (*Garcinia mangostana* L.) se utiliza en la medicina tradicional como antibacteriano, antioxidante y antiinflamatorio.

Objetivos: Determinar el mecanismo molecular y el potencial de los compuestos derivados de garciniaxantona de *G. mangostana* como antivirales contra el SARS-CoV-2 y prevenir la tormenta de citocinas mediante un enfoque *in silico*.

Métodos: Las muestras de ligandos y proteínas se obtuvieron de bases de datos como PubChem y Protein Databank, luego se realizó un análisis de similitud de drogas utilizando las reglas de Lipinski, Ghose, Veber, Egan y Muege en el servidor SwissADME, predicción de probabilidad antiviral a través del servidor PASSOnline. Además, fueron utilizados simulación de acoplamiento molecular con el software PyRx v1.0 (Scripps Research, EE. UU.) con licencia académica, identificación de interacciones y posiciones de enlaces químicos de ligandos en el objetivo mediante el servidor PoseView, visualización 3D del software PyMOLv.2.5.2 (Schrödinger, Inc., EE. UU.) con licencia académica, simulación de dinámica molecular para predicción de estabilidad molecular por el servidor CABS-flex v2.0, predicción de objetivos de compuestos antivirales candidatos por el servidor SwissTargetPrediction, análisis de vías a través de la base de datos STRING v11.5 y toxicidad por ProTox- II servidor.

Resultados: Se encontró que la garciniaxantona C de *G. mangostana* es una molécula similar a un fármaco con baja toxicidad. Este puede ser un candidato antiviral para el SARS-Cov-2 a través de la actividad inhibidora de dos enzimas virales que consisten en M^{pro} y replicasa con un valor de afinidad de unión que es más negativo que otros derivados de garciniaxantona y es estable. Se predice que la garciniaxantona C se une e inhibe las proteínas proinflamatorias que desencadenan tormentas de citocinas, como NFKB1 y PTGS2.

Conclusiones: Los compuestos derivados de garciniaxantona de *G. mangostana* pueden ser candidatos antivirales para el SARS-CoV-2 y prevenir la tormenta de citocinas a través de la actividad de la garciniaxantona C.

Palabras Clave: antiviral; *Garcinia mangostana*; SARS-CoV-2; viroinformática.

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INTRODUCTION

Coronavirus (CoV) from *Nidovirales* with positive-sense single-stranded RNA as genetic material and has an envelope (Hanardi and Rochmawati, 2022; Harisuddin et al., 2023; Mardiawan and Prawitasari, 2023; Minanti et al., 2023; Negoro et al., 2023). The hosts of CoV consist of birds, mammals, and human species that are influential in the world of health, economics, and veterinary (Gulyaeva and Gorbalenya, 2021). Human CoVs such as severe acute respiratory syndrome coronavirus (SARS-CoV), specifically SARS-CoV-2, have been identified during the pandemic and found the virus is highly pathogenic. The virus infects bronchial epithelial cells, pneumocytes, and triggers lung damage if not treated properly. In late 2019, the SARS-CoV-2 pandemic occurred in Wuhan, China, spreading throughout Indonesia (Antonius et al., 2023; Stenmark et al., 2021). SARS-CoV-2 infects host cells through spike interaction with angiotensin-converting enzyme 2 (ACE2) receptors, triggering the virus replication process. SARS-CoV-2 infection triggers a condition where the body's immune system fails to work, such as a cytokine storm following an inflammatory response (V'kovski et al., 2021). Cytokine storm is a phenomenon of immune cells releasing excess pro-inflammatory cytokines when SARS-CoV-2 infection occurs, triggering widespread cellular damage and patient death (Soy et al., 2020; Tungary et al., 2022). The replication mechanism of SARS-CoV-2 and cytokine storm are important objects to study in designing antiviral candidates (Ansori et al., 2022).

SARS-CoV-2 virions have structural proteins consisting of envelope E, spike (S), nucleocapsid (N), membrane (M), and genetic material [RNA (+ssRNA)]. The S on the virion will bind to host cell surface receptors, namely angiotensin-converting enzyme 2 (ACE2) and surface serine protease (TMPRSS2), to trigger viral internalization through fusion (Murgolo et al., 2021). Viral RNA is released during the uncoating process, and the region in the viral genetic material consists of ORF1a and ORF1b for the early translation process to activate non-structural proteins (nsps) such as M^{pro} through the cleavage of pp1a and pp1ab (Harrison et al. 2020). Nsps can trigger viral replication through viral helicase activation and transcription complex formation. M^{pro} or also called 3-chymotrypsin-like proteases ($3CL^{pro}$) has an important role required in SARS-CoV-2 infection for the virus assembly process and can be used as a key target in the design of antiviral COVID-19 treatments (Hu et al., 2022). The helicase enzyme in SARS-CoV-2, also called nsp13, plays a role in viral replication when the release of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) of the virus during the replication. Helicase is a potential target for inhibitors because it prevents the replication process of SARS-CoV-2.

Cytokine storm or hypercytokinemia is a condition of excessive inflammatory reaction by the immune response in host cells. This condition can occur with the invasion of pathogens such as SARS-CoV-2 (Awwaliyah et al., 2022; Hadning et al., 2022; Sari et al., 2022). Cytokine storms involve immune cell types, including alveolar macrophages, dendritic, epithelial cells, B and T cells (Chen et al., 2021). In COVID-19 patients, there is an increased expression of pro-inflammatory cytokines such as TNF-α, IL-2, IL-6, and IL-17 in the pathogenesis of SARS-CoV-2 (Rahman and Haris, 2022; Shahnaz et al., 2023; Utami and Budiarti, 2022). The production of pro-inflammatory cytokines is also influenced by the activation of transcription factors such as the nuclear factor *kappa* B subunit 1 (NFKB1) (Hariharan et al., 2021; Kovalchuk et al., 2021). Activation of NFKB1 signaling is influenced by conditions such as increased oxidative stress, pathogen infection, and injury (Aprianingsih et al., 2023; Pranata et al., 2023). NFKB1 can modulate gene activation during inflammation, such as genes for the release of pro-inflammatory cytokines, immune receptors, chemokines, and acute phase proteins (Muhammad et al., 2022; Reviono et al., 2022; Wulandari et al., 2022). The important role of NFKB1 in the pathogenesis of SARS-CoV-2 can be used as an ideal target for the prediction of NFKB1 blocker pathways (Dharmasamitha et al., 2023; Radityastuti et al., 2022), which can be done through computational screening in SARS-CoV-2 cytokine storm management strategies.

Queen of the fruit as mangosteen (*Garcinia mangostana* L., family *Clusiaceae*) is widely found in Southeast Asia and is used by most communities for alternative medicine (Ansori et al., 2022; Husen et al., 2019; Winarni et al., 2022). Several studies have reported the health benefits of mangosteen such as anticancer, anti-inflammatory, antiobesity, and antioxidant (Arnawati and Sudiana, 2022; Husen et al., 2020; Indharty et al., 2019; Ovalle-Magallanes et al., 2017; Pramana et al., 2021). Many previous studies have also reported the potential of mangosteen as an antiviral, inhibiting viral activity, such as chikungunya virus (CHIKV), through *in vivo* and *in vitro* assays (Patil et al., 2021). α-Mangostin from *G. mangostana* was identified to inhibit the dengue virus (DENV) activity by *in vitro* cell line-based assay. The compound is suspected to interact with NS2B-NS3 protease and glycoprotein E (Panda et al., 2021). The potential of *Garcinia mangostana* L. is reported to trigger apoptosis in cells infected with high-risk HPV-10 and HPV 16 through the TNF-alpha-induced apoptosis pathway (Kharaeva et al., 2022).

However, previous research did not reveal many potential derivative compounds from *G. mangostana,* such as garciniaxanthones, for COVID-19 antiviral and cytokine storm treatment. In brief, *G. mangostana* has a variety of chemical compounds, such as garciniaxanthones with derivatives consisting of garciniaxanthone A, B, C, D, E, F, and G with unknown medicine potential (Espirito Santo et al., 2020). The use of *G. mangostana* by the wider community makes it easy to obtain natural ingredient-based treatments with abundant stock availability. The use of natural ingredients as alternative medicines, such as antivirals, is claimed to have fewer side effects than synthetic drugs, but many alternative natural-based treatments lack scientific evidence (Abate et al., 2022). This study aimed to determine the molecular mechanism and potential of garciniaxanthone compound derivatives from *G. mangostana* as SARS-CoV-2 inhibitors as antivirals to prevent the cytokine storm through an *in silico* approach.

MATERIAL AND METHODS

Ligand preparation

Garciniaxanthones derived from *G. mangostana* consist of garciniaxanthone A, garciniaxanthone B, garciniaxanthone C, garciniaxanthone D, garciniaxanthone E, garciniaxanthone F, and garciniaxanthone G (Espirito Santo et al., 2020). The 3D structure with structure data format (sdf), CID, formula, molecular weight, and SMILE files obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) were used. The sdf file was then converted into a protein databank file (pdb) via ligand minimize with OpenBabel v2.3.1 (Wahyuni et al., 2022). The control drug or reference compound used in this study was remdesivir (GS-5734), with protease and helicase inhibitor characteristics in SARS-CoV-2. Remdesivir was obtained from the database with CID 121304016 (Chen et al., 2021; Huff et al., 2022; Naik et al., 2021).

Protein retrieval

SARS-CoV-2 protease enzyme (M^{pro}) and helicase were used as targets in this study. Samples were obtained from Protein Data Bank (RCSB PDB) (https://www.rcsb.org/) with PDB ID: 7ALH and PDB ID: 6ZSL. Removal of water molecules and native ligands from targets was performed by using PyMOL v.2.5.2 (Schrödinger, Inc., USA) with an academic license (Costanzi et al., 2021; Newman et al., 2021).

Drug-likeness analysis

Drug-likeness is used to characterize a ligand query with drug molecules through various rules. The rules for drug-likeness consist of Lipinski, Ghose, Veber, Egan, and Muege rules. The ability of a drug molecule in a certain amount to circulate through the blood vessels was analyzed as bioavailability. The drug-likeness and bioavailability rules are the main factors for determining the nature of drug-like molecules (Ansori et al., 2022; Dibha et al., 2022). SwissADME (http://www.swissadme.ch/) was used in this study to analyze the drug-likeness of garciniaxanthone derivatives from *G. mangostana*. Previous research showed that remdesivir (reference compound) can act as a drug-like molecule or standard drug molecule for COVID-19 treatment (Shyr et al., 2020).

Antiviral probability

Generic potential as antivirals in garciniaxanthone compound derivatives from *G. mangostana* and remdesivir (reference compound) was assessed through PASS Online (http://way2drug.com/PassOnline/index.php). The activation probability value (Pa) was chosen as 0.3 or medium confidence for proof through computational studies. PASS Online tools are used to predict the activity of query compounds, such as side effects, mechanism of action, gene expression, and pharmacological effects (Kharisma et al., 2020; Listiyani et al., 2022).

Molecular docking and structural visualization

The 3D interactions of garciniaxanthone derivatives from *G. mangostana*, remdesivir, with targets were identified through molecular docking. The activity of the dual inhibitors was determined by compar-

ing the binding affinity values. Molecular docking was performed through PyRx v1.0 (Scripps Research, USA) with an academic license, and compounds with more negative binding affinity were used for further analysis. 3D visualization of the docking results was performed using the 3D software PyMOLv.2.5.2 (Schrödinger, Inc., USA) with an academic license (Proboningrat et al., 2022; Wicaksono et al., 2023).

Chemical interaction

Positions and types of chemical bonds in the molecular complex (ligand-protein) from garciniaxanthone and remdesivir with targets were identified via PoseView (https://proteins.plus/). Types of chemical bonds such as hydrogen, hydrophobic, and pi/alkyl were identified through this server. Molecular interaction analysis produced 2D images of chemical interaction hot spots in the target binding domain (Aini et al., 2022).

Molecular dynamic simulation

The molecular stability of the ligand-protein complex was identified through molecular dynamic simulations with CABS-flex v2.0 (http://biocomp.chem.uw.edu.pl/CABSflex2/submit) for root-mean-square fluctuation (RMSF) calculation. The molecular dynamic simulation was used to show parameters consisting of rigidity, restraints, global C-alpha restraints weight, global side-chain restraints weight, number of cycles, cycles between trajectory, temperature, and RNG seed (Kuriata et al., 2018).

Target prediction

Remdesivir, as a reference compound, has shown target proteins consisting of SARS-CoV-2 helicase and M^{pro} with a mechanism of action through inhibitory activity (Chen et al., 2021; Huff et al., 2022; Naik et al., 2021). Identification of targets of anti-inflammatory pathways in *Homo sapiens* for compounds from *G. mangostana* with binding affinity values was made through SwissTargetPrediction (http://www.swisstargetprediction.ch/). The tool was used to determine the probability of targets based on the similarity of the 2D/3D structure of a query compound in the body of a specific organism (Daina et al., 2019)—documentation of plants and other organisms or starting materials.

Pathway analysis

Activity of remdesivir as SARS-CoV-2 antiviral via direct inhibitory pathway mechanism was tested on viral proteins and indirectly for cytokine storm prevention (Vulturar et al., 2022). Identification of protein biological pathways involved in the inflammatory response in the case of COVID-19 cytokine storm in *Homo sapiens* was established through STRING v11.5 (https://string-db.org/). Pathway visualization was displayed through interaction nodes with supporting data such as gene neighborhood, gene fusions, gene co-occurrence, textmining, co-expression, and protein homology (Szklarczyk et al., 2019).

Toxicity evaluation

Previous studies describing the toxicity levels of remdesivir are known to have several possible hepatotoxicity properties (Aleem et al., 2021; Lin et al., 2022). Antiviral and anti-inflammatory candidate compounds from *G. mangostana* toxicity doses were predicted through ProTox-II (https://tox-new.charite.de/protox_II/). The toxicity of the query compounds referred to LD_{50} values with various classes consisting of Class I, II, III, IV, V, and VI (Banerjee et al., 2018).

Data analysis

The database was used to obtain query compounds and reference compounds. Bioactive compounds from *G. mangostana* were identified as drug-like molecules referring to the rules of Lipinski, Ghose, Veber, Egan, and Muege. The probability value of the query compound and reference compound as antiviral was also identified in this study (Ansori et al., 2022; Dibha et al., 2022). Docking simulation was performed on the query compound with positive prediction results with reference compound to identify the most negative binding affinity value (Proboningrat et al., 2022). Molecular dynamics, toxicity, and biological pathway simulation analysis were performed on the compounds with the most negative binding affinity values (Banerjee et al., 2018; Daina et al., 2019; Szklarczyk et al., 2019).

RESULTS

Drug-like molecule and antiviral candidate from garcinoxanthones

G. mangostana has chemical compounds of garciniaxanthone derivatives such as garciniaxanthones A, B, C, D, E, F, and G in the pericarp (Espirito Santo et al., 2020). The control drug or reference compound used in this study was remdesivir (GS-5734), with protease and helicase inhibitor characteristics in SARS-CoV-2. (Huff et al., 2022). The seven query compounds and remdesivir act as ligands, information consisting of compound name, CID, formula, molecular weight, SMILE, and structure data format (SDF) file obtained from PubChem (Table 1). The target in this study was the SARS-CoV-2 viral enzyme consisting of M^{pro} and helicase with a 3D structure obtained from RCSB PDB. Visualization of the 3D

structure of ligands (Fig. 1) and targets (Fig. 2) was done through PyMOLv.2.5.2 (Schrödinger, Inc., USA) with an academic license through the structure of sticks, cartoons, and transparent surfaces.

Table 1. Ligand informations from PubChem database.

Compound	CID	Formula	Molecular weight (g/mol)	SMILE
Garciniaxanthone A	15293708	$C_{23}H_{24}O_5$	380.4	CC(=CCC1=C(C2=C(C=C1)C(=O)C3=C(C(=CC(=C3O2)O)C(C)(C)C=C)O)O)C
Garciniaxanthone B	10407298	$C_{23}H_{22}O_5$	378.4	CC1(C=CC2=C(O1)C3=C(C=C2)C(=O)C4=C(C(=CC(=C4O3)O)C(C)(C)C=C)O)C
Garciniaxanthone C	9842847	$C_{23}H_{24}O_5$	380.4	CC(=CCC1=C(C2=C(C=C1)C(=O)C3=C(C=C(C(=C3O2)O)CC=C(C)C)O)O)C
Garciniaxanthone D	10454340	$C_{23}H_{24}O_7$	412.4	CC(C)(C=C)C1=CC(=C2C(=C1O)C(=O)C3=C(O2)C4=C(C=C3)C(C(O4)C(C)(C)O)O)O
Garciniaxanthone E	10457167	$C_{28}H_{32}O_6$	464.5	CC(=CCCC(=CCC1=C(C2=C(C(=C1O)O)OC3=CC(=CC(=C3C2=O)O)O)O)CC=C(C)C)C
Garciniaxanthone F	10047025	$C_{24}H_{24}O_6$	408.4	CC(C)(C=C)C1=CC(=C2C(=C1O)C(=O)C3=C(O2)C4=C(C=C3)C=C(O4)C(C)(C)OC)O
Garciniaxanthone G	10404741	$C_{20}H_{16}O_5$	336.3	CC(C)(C=C)C1=CC(=C2C(=C1O)C(=O)C3=C(O2)C4=C(C=C3)C=CO4)O
Remdesivir (Ref. compound)	121304016	$C_{27}H_{35}N_6O_8P$	602.6	CCC(CC)COC(=O)C(C)NP(=O)(OCC1C(C(C(O1)(C#N)C2=CC=C3N2N=CN=C3N)O)O)OC4=CC=CC=C4

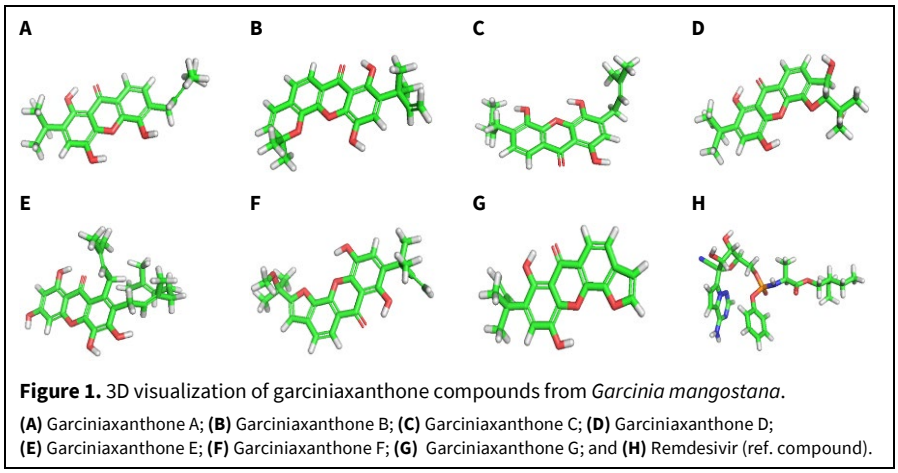

Figure 1. 3D visualization of garciniaxanthone compounds from *Garcinia mangostana*.
(A) Garciniaxanthone A; **(B)** Garciniaxanthone B; **(C)** Garciniaxanthone C; **(D)** Garciniaxanthone D; **(E)** Garciniaxanthone E; **(F)** Garciniaxanthone F; **(G)** Garciniaxanthone G; and **(H)** Remdesivir (ref. compound).

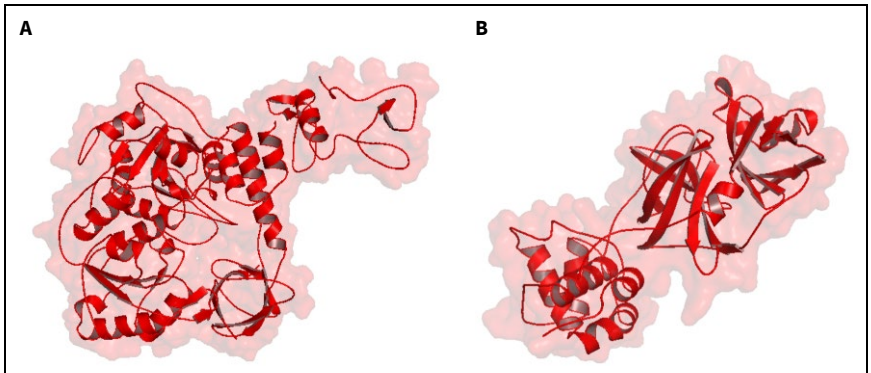

Figure 2. Structural visualization of SARS-CoV-2 target proteins.
(A) Helicase; **(B)** M^{pro}.

Table 2. The results of drug-likeness analysis and antiviral prediction.

Compound	Lipinski	Ghose	Veber	Egan	Muege	Bioavailability score	Probable	Antiviral prediction	
								Pa	Pi
Garciniaxanthone A	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule	0.360	0.055
Garciniaxanthone B	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule	0.359	0.055
Garciniaxanthone C	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule	0.435	0.022
Garciniaxanthone D	Yes	Yes	Yes	Yes	Yes	0.55	Drug-like molecule	0.378	0.045
Garciniaxanthone E	Yes	No	Yes	No	No	0.55	Drug-like molecule	0.644	0.004
Garciniaxanthone F	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule	0.323	0.076
Garciniaxanthone G	Yes	Yes	Yes	Yes	No	0.55	Drug-like molecule	0.360	0.055
Remdesivir (Ref. compound)	-	-	-	-	-	-	-	0.344	0.024

Drug-likeness analysis aims to assess the advisability of the query compounds based on the drug molecule that could be distributed through the human body. The drug-likeness analysis in this study was performed through SwissADME by referring to the five rules, including Lipinski, Ghose, Veber, Egan, and Muege, then the bioavailability score was also considered in determining the drug-like molecule. Moreover, the bioavailability score indicates the ability of a drug-candidate compound to circulate in the body to reach the target organ (Dibha et al., 2022). Garciniaxanthone derivative compounds from *G. mangostana* consisting of garciniaxanthones A, B, C, D, E, F, and G act as drug-like molecules with an average bioavailability score of 0.55. This study used the PASS Online server to identify general antiviral probability score prediction (Listiyani et al., 2022). Antiviral prediction through PASS Online showed that all garciniaxanthone derivative compounds have the potential as antiviral candidates in general because they showed a higher Pa score than Pi (Table 2). Prediction of antiviral probability refers to the Pa score that allows the potential to be activated in the body, and the Pa score must be greater than Pi. In this analysis, the antiviral properties of garciniaxanthone derivate compounds from *G. mangostana* were classified as general or theoretical predictions.

Revealing of garcinoxanthone derivates compounds activity as dual inhibitors

Molecular docking simulation aims to identify ligand activity on the target with respect to the binding affinity score. Binding affinity is the energy of the binding formed when the ligand interacts on the specific domain of a target. The most negative value indicates the strongest ligand interaction on the target and triggers specific activities such as inhibitors (Bansal et al., 2021; Proboningrat et al., 2022). The ligands in this study consisted of garciniaxanthone derivatives A, B, C, D, E, F, and G from *G. mangostana* and the targets were two SARS-CoV-2 proteins, namely helicase and M^{pro}. Autogrid plays a role to direct the ligand at the target binding domain (Mun et al., 2022). This study used docking screening through PyRx v1.0 (Scripps Research, USA) with autogrid on SARS-CoV-2 helicase Center (Å) X:-19.697 Y:23.855 Z:-68.952 Dimensions (Å) X:43.447 Y: 41.905 Z: 46.360 and M^{pro} Center (Å) X: -22.853 Y: 15.193 Z: 61.454 Dimensions (Å) X: 31.882 Y: 36.706 Z: 46.477.

Garciniaxanthone C binds to helicase, and M^{pro} with binding affinities score -8.9 kcal/mol and -7.5 kcal/mol, which was more negative than other compounds (Table 3). Visualization of ligand-protein complexes on garciniaxanthone C with helicase and M^{pro} was performed through PyMOLv.2.5.2 (Schrödinger, Inc., USA) with the structure of transparent surfaces, cartoons, sticks, and color selection (Fig. 3). Drug candidate compounds with dual inhibitor activity can inhibit the activity of two targets with the strongest binding energy. The dual inhibitor activity of antiviral candidates allows for effective inhibition of multiple phases of viral replication, allowing for failure in the formation of new viruses (Mitra et al., 2021). Remdesivir showed a more positive binding affinity value to helicase and M^{pro} than garciniaxanthone C. More negative binding affinity values on both targets were produced by garciniaxanthone C indicating good dual inhibitor properties.

Ligand-protein interactions are weak bonds such as hydrogen and hydrophobic identified through the PoseView server (Ben Hlima et al., 2022). The molecular interaction identification results from PoseView showed **g**arciniaxanthone C interacted at the helicase domain through residues Leu176A, Asn177A, Asn516A with hydrogen bonds and hydrophobic interactions formed at residues Pro175A, Leu176A, Val484A, Ser486A. Garciniaxanthone C interact**ed** on the M^{pro} domain through residues Gln189A and

Table 3. Binding affinity from the ligand-protein complexes**.**

Compound	CID	Minimize energy (kcal/mol)	Binding affinity (kcal/mol)	
			Helicase	M^{pro}
Garciniaxanthone A	15293708	+338.71	-8.2	-7.4
Garciniaxanthone B	10407298	+326.74	-8.6	-7.1
Garciniaxanthone C	9842847	+316.56	**-8.9**	**-7.5**
Garciniaxanthone D	10454340	+498.95	-8.3	-7.2
Garciniaxanthone E	10457167	+445.18	-8.0	-6.5
Garciniaxanthone F	10047025	+523.09	-8.4	-6.7
Garciniaxanthone G	10404741	+426.90	-8.6	-7.1
Remdesivir (ref. compound)			**-8.7**	**-6.9**

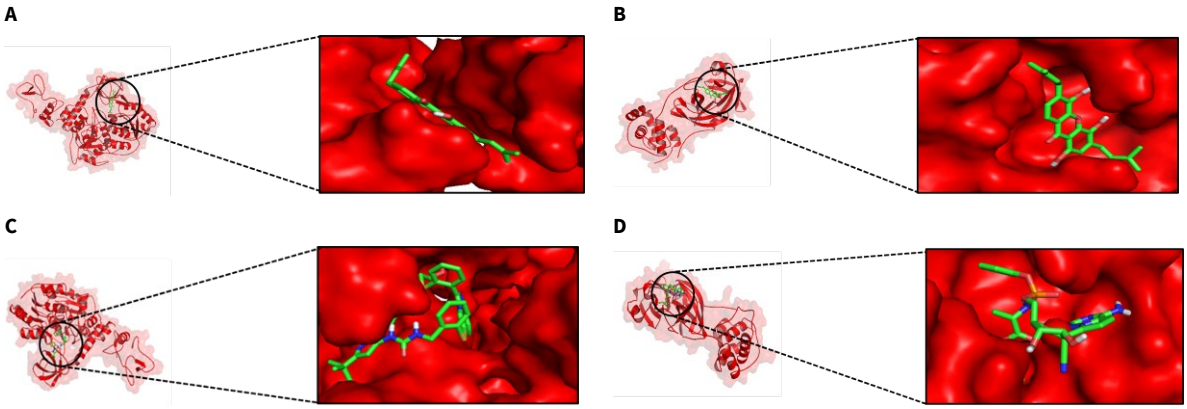

Figure 3. Molecular visualization of ligand-protein from the docking results.
(A) Garciniaxanthone C-Helicase; (**B)** Garciniaxanthone C-M^{pro}; **(C)** Remdesivir-Helicase; and **(D)** Remdesivir-M^{pro}.

His41A with hydrogen bonds, and hydrophobic interactions were formed on residues Cys145A and Met165A. Remdesivir interacted through amino acid residues Asn177A, Asp483A, and Ser486A via hydrogen bonding and hydrophobic interactions at positions Ser486A, Ser485A, and Pro175A on SARS-CoV-2 helicase. Remdesivir interacted through Glu166A, Gly143A, and Gln189A residues by hydrogen bonding, and hydrophobic interactions were formed at Arg188A, Met165A, Met149A, Gln189A, His41A, and Glu166A on SARS-CoV-2 M^{pro} domains. The similarity of the position of the garciniaxanthone-remdesivir interaction on helicase was found at residues Asn177A, Pro175A, and Ser486, while on M^{pro} through residues Gln189A, His41A, Met165A. The similarity in position between the query and reference compounds indicated a similarity in activity (Proboningrat et al., 2022) (Fig. 4).

The molecular interaction stability obtained in the pocket binding domain by garciniaxanthone C on helicase and M^{pro} was identified through molecular dynamics simulations on the CABS-flex v2.0 server. The level of chemical bond stability was determined by the root-mean-square fluctuation (RMSF) score calculated on the ligand-protein complex. RMSF shows the structural conformational fluctuations when a protein has activity (Kuriata et al., 2018; Wijaya et al., 2021). The results of molecular dynamic analysis on the pocket binding domain of the ligand-protein complex, namely **g**arciniaxanthone C-helicase, showed an RMSF score <3 (Å) and garciniaxanthone C-M^{pro} as well. The structural fluctuations of both targets are shown in cartoons with rainbow colors. (Fig. 5). The following is a link to the results of molecular dynamic analysis in this study garciniaxanthone C-helicase (http://biocomp.chem.uw.edu.pl/CABSflex2/job/d11cdb657480b61/), garciniaxanthone C-M^{pro} (http://biocomp.chem.uw.edu.pl/CABSflex2/job/68b6fe7936c3246/), remdesivir-helicase (http://biocomp.chem.uw.edu.pl/CABSflex2/job/26d46c8365dedeb/) and remdesivir-M^{pro} (http://biocomp.chem.uw.edu.pl/CABSflex2/job/5b4f1d4723f22ff/). Garciniaxanthone C interaction with both targets is more stable than remdesivir (Fig. 5).

The molecular interactions generated by garciniaxanthone C on the target domain are stable enough to trigger the inhibitory response activity of both targets.

Garcinoxanthone C toxicity and pathway in COVID-19 cytokine storm

Toxicity prediction of garciniaxanthone C from ProTox-II server showed an LD_{50} score of 3200 mg/kg, a predicted toxicity class of 5, and a prediction accuracy of 67.38%. Garciniaxanthone C did not include fatal toxicity properties, and its use was free but limited according to the recommended dose (Banerjee et al. 2018). Previous studies describing the toxicity levels of remdesivir were known to have several possible hepatotoxicity properties (Aleem et al., 2021; Lin et al., 2022). This suggests that long-term use of remdesivir is not feasible and should require new drug candidates with low toxicity. Prediction of targets and pathways in garciniaxanthone C aims to determine its relationship with possible inhibitory responses to pro-inflammatory proteins that contribute to the severity of the cytokine storm in COVID-19 (Daina et al. 2019; Szklarczyk et al. 2019). The prediction results of target and pathway interactions through SwissTargetPrediction and STRING servers showed that garciniaxanthone C, when entering the human body, can interact with nuclear factor *kappa* B subunit 1 (NFKB1) and prostaglandin-endoperoxide synthase 2 (PTGS2) (Fig. 6). Remdesivir works by only inhibiting proteins from SARS-CoV-2 such as helicase and M^{pro}. The drug provides an indirect therapeutic effect for cytokine storm treatment by inhibiting SARS-CoV-2 replication (Vulturar et al., 2022). Both proteins trigger the COVID-19 cytokine storm because they are identified as pro-inflammatory agents. Garciniaxanthone C is predicted to be a therapeutic agent for the COVID-19 cytokine storm through the molecular interaction mechanism and inhibition of the activity of pro-inflammatory proteins such as NFKB1 and PTGS2 in the human body.

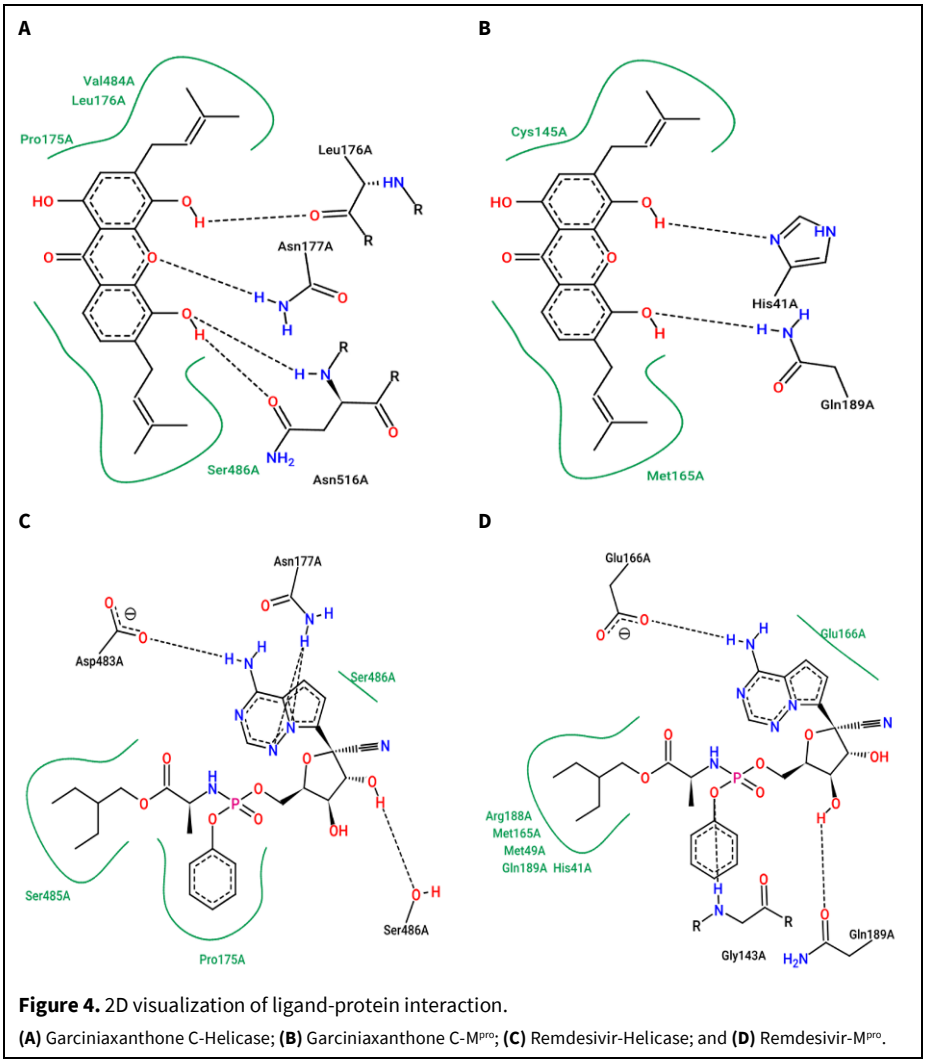

Figure 4. 2D visualization of ligand-protein interaction.
(A) Garciniaxanthone C-Helicase; **(B)** Garciniaxanthone C-M^{pro}; **(C)** Remdesivir-Helicase; and **(D)** Remdesivir-M^{pro}.

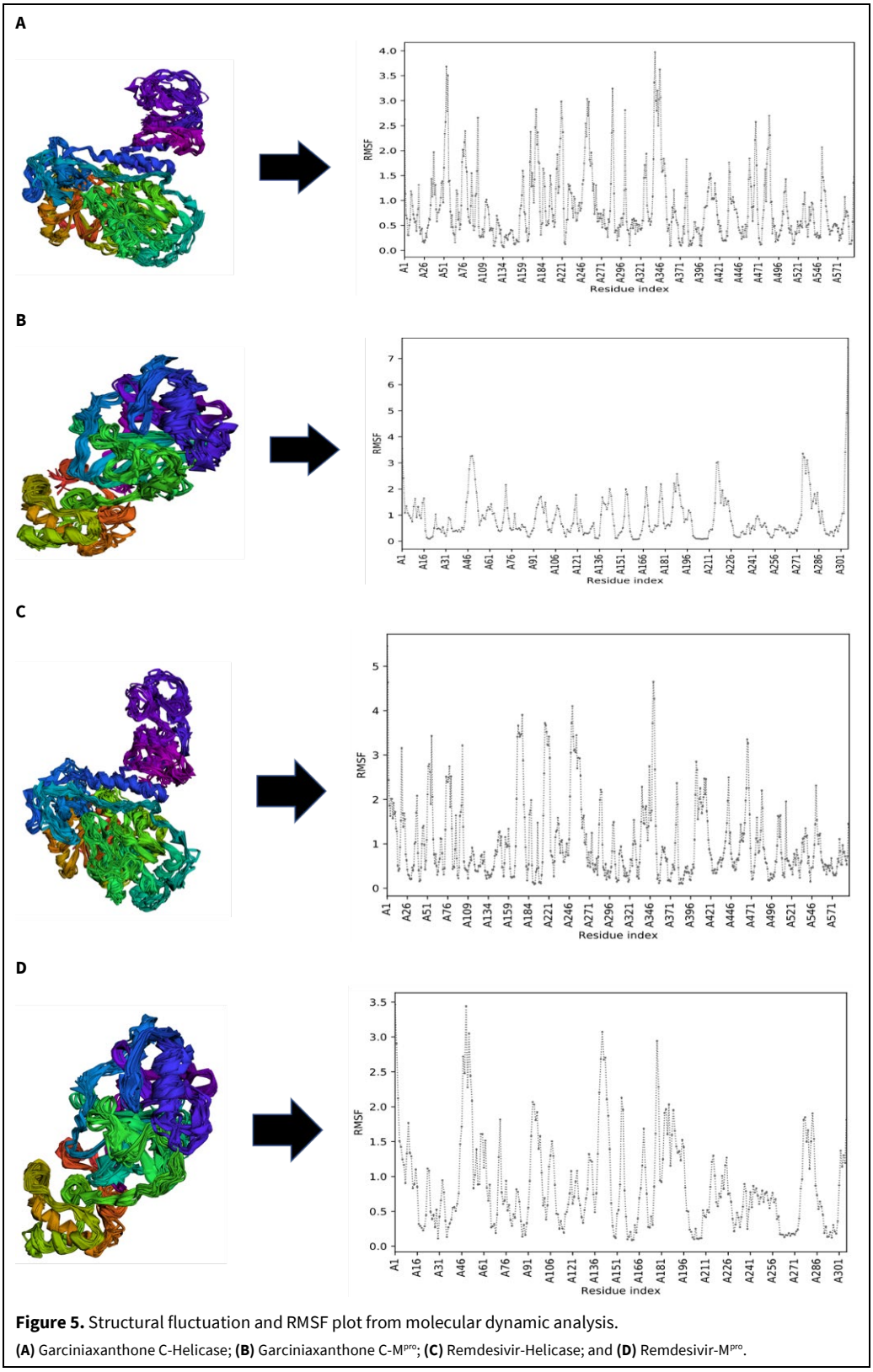

Figure 5. Structural fluctuation and RMSF plot from molecular dynamic analysis.
(A) Garciniaxanthone C-Helicase; **(B)** Garciniaxanthone C-M^{pro}; **(C)** Remdesivir-Helicase; and **(D)** Remdesivir-M^{pro}.

DISCUSSION

G. mangostana, also known as the "Queen fruit", is used by most people in the world in traditional medicine. Previous research revealed that mangosteen compounds can trigger a decrease in inflammatory gene expression to reduce the impact of insulin resistance (Bumrungpert et al., 2010). The presence of α-xanthones and γ-mangosteen compounds in *G. mangostana* pericarp can trigger memory improvement in the brain by restoring acetylcholinesterase activity in brain cells (Ovalle-Magallanes et al., 2017). Recent

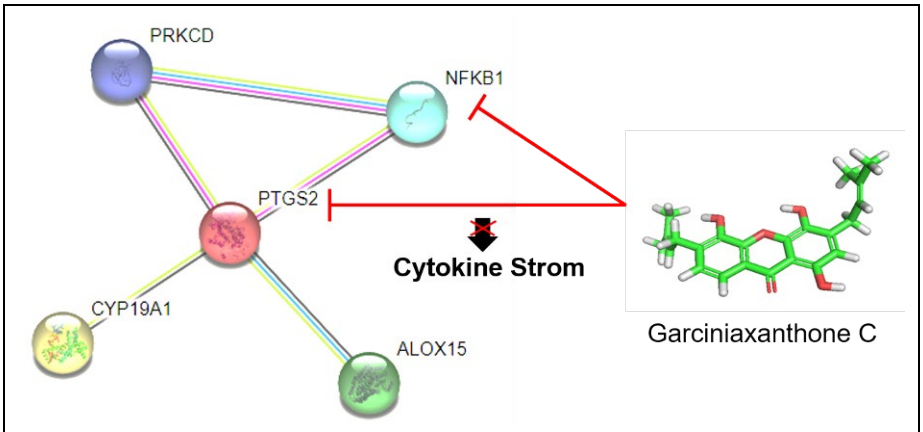

Figure 6. Predicted pathway of garciniaxanthone C from *G. mangostana* as cytokine storm therapeutic agent candidate through NFKB1 and PTGS2 inhibiton.

The color of interaction lines between shells indicates the strength based on the amount of experimental data such as gene neighborhood, gene fusions, gene co-occurrence, textmining, co-expression, and protein homology.

research on xanthones from *G. mangostana* revealed the potential of these compounds as anticancer and antioxidant through *in vitro* studies. Anticancer activity is shown by the cytotoxicity effect on SKLU-1, MCF7, and HT-29 cell lines with IC_{50} of 19.86-27.38 µM. Antioxidant activity was shown in the DPPH test with IC_{50} of 68.55, 63.05, and 28.45 µM (Tran et al., 2021).

In addition, α-mangostin and xanthonoids from *G. mangostana* have also been reported to have antiviral activity for treating chikungunya virus through *in vitro* and *in vivo* studies (Patil et al., 2021). *G. mangostana* contains garciniaxanthone derivate compounds such as garciniaxanthones A, B, C, D, E, F, and G with various potentials for antibacterial, anti-inflammatory, and antinociceptive (Espirito Santo et al., 2020; Ovalle-Magallanes et al., 2017). The potential of these derivative compounds as SARS-CoV-2 antivirals and agents for the treatment of cytokine storms has not been widely revealed by previous studies.

All garciniaxanthone derivatives were identified as drug-like molecules based on drug-likeness test. The drug-like molecule is a property of drug-candidate compounds that are similar to drugs. The similarity refers to how drugs work, which is determined by several rules such as Lipinski, Ghose, Veber, Egan, and Muege (Ansori et al., 2022; Dibha et al., 2022). Garciniaxanthone compounds exhibited a bioavailability score of 0.55. Previous research showed that the bioavailability score was ideal for the circulation of antiviral compounds in the human body to target cells (Adegboyega et al., 2021). All garciniaxanthones were also identified to act as antivirals because they presented a Pa score >0.3. Query compounds with a Pa score >0.3 indicate that the potential can be theoretically proven and used for further analysis through a wet lab approach (Khan et al., 2023).

Garciniaxanthone C could be potentially developed to be an inhibitor on both targets (dual inhibitor) since it has a low score or more negative binding affinity score than other compounds. Garciniaxanthone C acted through allosteric side inhibition consisting of Leu176A, Asn177A, Asn516A, Pro175A, Leu176A, Val484A, and Ser486A on helicase, then Gln189A, His41A, Cys145A, Met165A on M^{pro}. Antiviral candidate compounds may work by binding through allosteric domains on targets with more negative binding affinity and form weak binding interactions (Samrat et al., 2022). The ligand-protein complex on garciniaxanthone C with helicase and M^{pro} was identified to have a stable RMSF of <3 (Å) through molecular dynamic simulations. The ligand-protein complex must have an RMSF <3 (Å) to trigger molecular stability when the complex is formed (Wijaya et al., 2021).

Remdesivir is potentially toxic and cannot have an inhibitory mechanism on pro-inflammatory proteins that contribute to the SARS-CoV-2 cytokine storm; bonding interactions are weaker than garciniaxanthone C and are unstable. Garciniaxanthone C was identified as having low toxicity and can interact with pro-inflammatory agents, such as NFKB1 and PTGS2. NFKB1 is a transcription factor that regulates the inflammatory response through the release of cytokines like TNF-α, IL-2, IL-6, and IL-17, which play a role in the pathogenicity of SARS-CoV-2. These cytokines for inflammatory responses contribute importantly to cytokine storm conditions. PTGS2 also mediates inflammatory responses in the human body and is used as a drug target for NSAIDs (Agung et al., 2022; Capuano et al., 2020; Chen et al., 2020; Kovalchuk et al., 2021). Garciniaxanthone C is predicted to be a thera-

peutic agent for handling cytokine storm through interaction and inhibition of NFKB1 and PTGS2.

CONCLUSION

Garciniaxanthone compounds from *Garcinia mangostana* L. may be candidates for SARS-CoV-2 antiviral and preventing cytokine storm through garciniaxanthone C activity. Garciniaxanthone C binds to helicase and M^{pro} of SARS-CoV-2 with more negative binding affinity, produces weak binding interactions and is stable. The compound may interact and inhibit the activity of pro-inflammatory proteins such as NFKB1 and PTGS2. However, the dry laboratory potential of garciniaxanthone C must be reconfirmed by wet laboratory analysis.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Concepts or ideas	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Design	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Definition of intellectual content	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Literature search	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Experimental studies	x	x	x											x	x
Data acquisition	x	x	x											x	x
Data analysis	x	x	x	x	x									x	x
Manuscript preparation	x	x													
Manuscript editing	x	x	x	x	x	x	x							x	x
Manuscript review	x	x	x	x	x	x	x	x	x						

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