Herbal combination from *Moringa oleifera* Lam. and *Curcuma longa* L. as SARS-CoV-2 antiviral via dual inhibitor pathway: A viroinformatics approach

[Combinación de hierbas de *Moringa oleifera* Lam. y *Curcuma longa* L. como antiviral SARS-CoV-2 a través de la vía del inhibidor dual: Un enfoque de viroinformática]

Viol Dhea Kharisma1,2, Aggy Agatha2,3, Arif Nur Muhammad Ansori3,4, Muhammad Hermawan Widyanaanda3,5, Wahyu Choirur Rizky6, Tim Godfriedus Antonius Dings7, Marina Derkho8, Irina Lyksova9, Yulanda Antonius9, Imam Rosadi10, Rahadian Zainul11

1Master Program in Biology, Department of Biology, Faculty of Mathematics and Natural Sciences, Mulawa Doctoral Program in Veterinary Science, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia.
2Department of Life Sciences and Technology, Bandung Institute of Technology, Bandung, Indonesia.
3Generasi Biologi Indonesia Foundation, Gresik, Indonesia.
4Doctoral Program in Veterinary Science, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia.
5Laboratory of Animal Physiology, Structure, and Growth, Department of Biology, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang, Indonesia.
6College of Medicine, Sultanam Al Rajhi University, Al Bukayriyah, Qassim, Saudi Arabia.
7College of Medicine, Maastricht University, Maastricht, The Netherlands.
8Department of Natural Sciences, South-Urals State Agrarian University, Troitsk, Russian Federation.
9Faculty of Biotechnology, University of Surabaya, Surabaya, Indonesia.
10Department of Biology, Faculty of Mathematics and Natural Sciences, Mulawarman University, Samarinda, Indonesia.
11Department of Chemistry, Faculty of Mathematical and Natural Sciences, Universitas Negeri Padang, Padang, Indonesia.

*These authors contributed equally to this work.
*Email: rahadianzmsiphd@fmipa.unp.ac.id

**Abstract**

**Context:** The COVID-19 outbreak is caused by the transmission and infection of SARS-CoV-2 at the end of 2019. It has led many countries to implement lockdown policies to prevent the viral spreading. Problems arise in a COVID-19 patient because of viral infection that leads to a systemic response in the immune system, specifically due to cytokine storm. Moreover, the antiviral drugs that have not been found. Indonesia had a variety of traditional medicines, such as 'jamu'. It consists of a mixture of natural ingredients such as *Moringa oleifera* Lam. and *Curcuma longa* L.

**Aims:** To identify the activity of dual inhibitors as antiviral and anti-inflammatory agents from herbal combination compounds.

**Methods:** Sample was collected from PubChem (NCBI, USA) and Protein Data Bank (PDB), then drug likeness analysis using Lipinski rule of five in SCFBIO web server and bioactive probability analysis of bioactive compounds were conducted by PASS web server. Furthermore, the blind docking method was performed using PyRx 0.8 software to determine the binding activity and molecular interaction by PoseView web server and PyMol software v2.4.1 (Schrodinger, Inc, USA).

**Results:** Cryptochlorogenic acid and curcumin have been computationally proven as dual inhibitors for antivirals by inhibiting Mpro SARS-CoV-2 and as anti-inflammatory through inhibition of NFKB1 activity. However, the results are merely computational so that it must be validated through a wet lab research.

**Conclusions:** The combination of *Moringa oleifera* Lam. and *Curcuma longa* L. is predicted to have antiviral and anti-inflammatory activity through dual inhibitor mechanism played by cryptochlorogenic acid and curcumin.

**Keywords:** COVID-19; *Curcuma longa*; *Moringa oleifera*; Mpro; NFKB1.

**Resumen**

**Contexto:** El brote de COVID-19 es causado por la transmisión e infección del SARS-CoV-2. En un paciente con COVID-19 surgen problemas debido a una infección viral que conduce a una respuesta inmunológica sistémica. Además, no se han encontrado medicamentos antivirales. En Indonesia existe una preparación tradicional conocida como el "jamu". Esta es una mezcla de *Moringa oleifera* Lam. y *Curcuma longa* L.

**Objetivos:** Identificar la actividad de inhibidores duales como agentes antivirales y antiinflamatorios de compuestos de combinación de hierbas.

**Métodos:** Se recogió una muestra de PubChem (NCBI, EE. UU.) y Protein Data Bank (PDB), luego se realizó un análisis de similitud con el fármaco utilizando la regla de cinco de Lipinski en el servidor web SCFBIO y el servidor web PASS realizó un análisis de probabilidad bioactiva de los compuestos bioactivos. Además, el método de acoplamiento ciego se realizó utilizando el software PyRx 0.8 para determinar la actividad de unión y la interacción molecular mediante el servidor web PoseView y el software PyMol v2.4.1 (Schrödinger, Inc, EE. UU.).

**Resultados:** Se ha comprobado computacionalmente que el ácido criptoclorogénico y la curcumina son inhibidores duales de los antivirales al inhibir el Mpro SARS-CoV-2 y como antiinflamatorios mediante la inhibición de la actividad de NFKB1. Sin embargo, los resultados son meramente computacionales, por lo que deben validarse mediante una investigación de laboratorio húmedo.

**Conclusions:** Se predice que la combinación de *Moringa oleifera* Lam. y *Curcuma longa* L. tiene actividad antiviral y antiinflamatoria a través de un mecanismo inhibidor dual desempeñado por el ácido criptoclorogénico y la curcumina.

**Palabras Clave:** COVID-19; *Curcuma longa*; *Moringa oleifera*; Mpro; NFKB1.
The COVID-19 pandemic, which caused by SARS-CoV-2 infection at the end of 2019 has led several countries to implement lockdown policies to prevent the spread of the virus (Turista et al., 2020). WHO also announced that SARS-CoV-2 unfortunately is transmitted through airborne particles (Ansori et al., 2020; Fahmi et al., 2021). The status of the presence of effective antivirals used to treat SARS-CoV-2 infection in patients is also limited and there is insufficient information available (Li et al., 2020; Muttaqin and Ansori, 2020). The purpose of using antiviral drugs is to inhibit the activity of viral functional proteins, such as main protease (Mpro). This protein plays a role in polypeptide cleavage during viral assembly in host cells. Several antiviral drugs that have been tested on SARS-CoV-2 infection for Mpro inhibitors consist of lopinavir and ritonavir, both of which are still below expectations in controlling infection and viral pathogenesis. The reduced efficacy of both antivirals is caused by several factors, such as the position of the interaction, chemical bonds, and binding pockets in protein-specific domains (Muttaqin and Ansori, 2020; Song et al., 2020).

SARS-CoV-2 infection in human causes a cytokine storm with an excessive release of pro-inflammatory cytokines by immune cells and it can lead to patient death. SARS-CoV-2 infects cells in the human respiratory tract consisting of epithelium, macrophages, and dendritic cells. The virus binds to the host cell through a receptor binding domain (RBD) in the S1 domain of the spike protein with the angiotensin-converting enzyme 2 (ACE-2) (Vaninov, 2020; Parikesit and Nurdiansyah, 2021). Interestingly, there are several locations of organs that express ACE-2 in addition to the respiratory tract, such as the colon, ileum, digestive tract, and kidney. When the virus initiates replication through binding to ACE-2, it then triggers the expression of several non-structural proteins that can inhibit the IFN-1 activation response. In addition, SARS-CoV-2 can stimulate increased secretion of pro-inflammatory cytokines IL-6, TNF-α, and IL-1β through the activation of nuclear transcription factor kappa B subunit 1 (NF-κB/NFKB1). NFKB1 is the key to the activity of pro-inflammatory cytokines released by the immune system when a cytokine storm occurred (Guo et al., 2020).

The herbs combinations in traditional medicine such as ‘jamu’ has been used since long time in Indonesia to treat viral infections such as flu, herpes, and hepatitis (Ansori, 2021; Ansori et al., 2021; Khairullah et al., 2021). Some plants such as Moringa oleifera Lam. and Curcuma longa L. are used as mixtures in several types of ‘jamu’ (Ansori et al., 2021). The content of both bioactive compounds is predicted to have potential as antiviral and anti-inflammatory agent (Feustel et al., 2017; Hewlings and Kalman, 2017). The combination of Moringa oleifera Lam. and Curcuma longa L. has few evidence based on the potential of molecular mechanisms in triggering antiviral and anti-inflammatory pathways. The use of bioactive compounds from herbs for the treatment of COVID-19 and modulation of cytokine storm is currently very possible as a phytotherapeutic option since there has been no effective antiviral drugs found. Thus far, bioactive compounds from the combination of M. oleifera and C. longa are predicted to have a dual mechanism in inhibiting key proteins in SARS-CoV-2 replication and the cytokine storm.

**MATERIAL AND METHODS**

Sample preparation

The bioactive compounds contained in Moringa oleifera Lam. and Curcuma longa L. are elaidolinolenic acid, cryptochlorogenic acid, myoinositol, curcumin, curcumenol, and ar-curcumene, all these compounds from two herbal combination have antiviral activity based on previous in vitro and in vivo study but the mechanism is still unknown (Feustel et al., 2017; Praditya et al., 2019). The 3D structure and canonical SMILES of those compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in sdf format and canonical SMILES, respectively. Furthermore, it then termed as the ligands. The ligand minimization process was carried out by using PyRx 0.8 software. Moreover, the SARS-CoV-2 main proteinase (Mpro) and nuclear factor kappa B subunit 1 (NFKB1) were obtained from RCSB PDB (https://www.rcsb.org/) then the water molecules were eliminated by using PyMol software v2.4.1 (Schrödinger, Inc, USA) (Kharisma et al., 2020).
Table 1. Results of ligand sample preparation.

<table>
<thead>
<tr>
<th>Herbs source</th>
<th>Compound</th>
<th>ID</th>
<th>Formula</th>
<th>Canonical SMILES</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. oleifera</em></td>
<td>Elaidolinolic acid</td>
<td>528222</td>
<td>C₂₀H₃₀O₂</td>
<td>CCC=CCC=CCC=CCCCCCC(=O)O</td>
</tr>
<tr>
<td></td>
<td>Cryptochloalogenic acid</td>
<td>979866</td>
<td>C₂₀H₂₂O₇</td>
<td>C₁(C(C(C(C(O)O)O)O)O)OC(=O)C=C₂=CC(=C(=C₂)O)O</td>
</tr>
<tr>
<td></td>
<td>Myoinositol</td>
<td>892</td>
<td>C₆H₁₂O₅</td>
<td>C₁(C(C(C(C(O)O)O)O)O)O</td>
</tr>
<tr>
<td><em>C. longa</em></td>
<td>Curcumin</td>
<td>969516</td>
<td>C₂₀H₁₇O₅</td>
<td>COCl=C(C=CC=CC=CC(=O)OC(=O)C=C₂=CC(=C(=C₂)O)O</td>
</tr>
<tr>
<td></td>
<td>Curcumeneol</td>
<td>167812</td>
<td>C₁₅H₂₂O₂</td>
<td>C₁(C(C(C(C(O)O)O)O)O)O</td>
</tr>
<tr>
<td></td>
<td>Ar-Curcumene</td>
<td>92139</td>
<td>C₁₅H₁₈O₂</td>
<td>C₁(C(C(C(C(O)O)O)O)O)O</td>
</tr>
</tbody>
</table>

Drug-likeness analysis

The bioactive compounds of *M. oleifera* and *C. longa* obtained from PubChem were analyzed for drug-likeness using the SCFBIO web server (http://www.scfbio-ittd.res.in/software/drugdesign/lipinski.jsp). The Lipinski rule of five were comprised of various rules, such as molecular mass >500 Dalton, high lipophilicity (LogP) >5, hydrogen bond donor (HBD) >5, hydrogen bond acceptors (HBA) >10, and molar refractivity (MR) 40-130. Compounds that met at least 2 rules are categorized as drug-like molecules (Hartati et al., 2021).

Biological activity probability

Bioactivity prediction of *M. oleifera* and *C. longa* compounds were conducted by using PASS web server (http://way2drug.com/PassOnline/). Activity of antiviral and anti-inflammatory categories were selected for prediction. The score >0.3 (medium confidence) of potential activity (Pa) was selected as standard since that score was indicating computationally proof. Furthermore, the Pa score must be higher than probability score (Pi), which preventing the activity of compound in the human body (Susanto et al., 2018).

Virtual screening simulation

The binding simulations of ligands of *M. oleifera* and *C. longa* to Mpro and NFKB1 domains were identified by using molecular docking simulation. The grid docking was directed to the center position with certain coordinate (Å) X:-26.284 Y:12.597 Z:58.967 and dimension (Å) X:51.373 Y:66.973 Z:59.607 on Mpro, then for NFKB1 with center position (Å) X:42.462 Y:14.682 Z:38.0365 and dimension (Å) X:70.473 Y:61.765 Z:56.560. This study was using a blind docking method by enlarging the grid and directing the binding of ligands to all parts of the protein by PyRx 0.8 software. It aimed to identify of potential compounds as dual inhibitors (Luqman et al., 2020).

Molecular interaction and 3D visualization

The identification of the chemical bond interactions formed in the ligand-protein molecular complex in this study was conducted by using PoseView web server (https://proteins.plus/). The interactions of hydrogen and hydrophobic were visualized. Structural selection and staining through PyMol software were carried out on the 3D structure of the protein-ligand molecular complex (Purnama and Kharisma, 2018).

RESULTS

*M. oleifera* and *C. longa* compounds as drug-like molecule

Elaidolinolic acid, cryptochloalogenic acid, myoinositol, curcumin, curcumeneol, and ar-curcumene were derived from *M. oleifera* and *C. longa* with the information of CID, formula, and canonical SMILES from the PubChem database (Table 1). The 3D structures of the six compounds with pdb format were obtained from the ligand minimization process at PyRx 0.8 software. The visualization of the sticks model with staining of C, H, N, and O atoms were generated by using PyMol 2.5 software (Fig. 1). This study was using NFKB1 (ID: 1SVC) and Mpro SARS-CoV-2 (ID: 7ALH) retrieved from RCSB PDB. Both proteins are displayed by using PyMol software with cartoon structure, transparent surfaces, and homologous staining.

The predictions on the Lipinski server were considered as good drug candidates if the compounds are minimum two out of five parameters of Lipinski rule of five. The five rules consist of a molecular mass <500 Daltons, lipophilicity (LOGP) <5, hydrogen bond donor (HBD) <5, hydrogen bond acceptor (HBA) <10, and molar refractivity (MR) 40-130 (Hartati et al., 2021; Kharisma et al., 2021; Widyanyanda et al., 2021). Results showed that compounds of *M. oleifera* and *C. longa* had fulfilled more than two pa-
rameters of Lipinski rule of five. About six compounds are considered as drug-like molecules and predicted to trigger biological response activities when interacting with target proteins in the cytoplasm (Table 2).

**Antiviral and anti-inflammatory activity of herbs combination compound**

The canonical SMILES of each ligand derived from *M. oleifera* and *C. longa* is used for activity analysis by using PASS web server. Result showed that the compound had probability as antiviral and anti-inflammatory agent through the PASS web server. Prediction refers to the Pa and Pi score for each compound. The Pa score, which greater than 0.3 is categorized as capable for having activity according to the research objectives (Fig. 2). The Pa score >0.3 (medium confidence) indicated the potential of the query compound to be proven theoretically. The results showed that six compounds had Pa score >0.3 and those were theoretically proven as anti-inflammatory and antiviral agent.

**Revealing of herbs combination compound as dual inhibitor and its molecular interaction**

In this study, the molecular docking simulations was used to identify the binding activity of compounds from combination of *M. oleifera* and *C. longa* herbs with Mpro and NFκB1 through the level of binding affinity formed. The compound with the most negative binding activity with both target proteins is predicted to play an essential role. The results showed that the cryptochlorogenic acid from *M. oleifera* and curcumin from *C. longa* had lower binding affinity score. It was possible for those compounds to work synergistically by initiating the response to the target protein (Table 3). The 3D structure of the molecular docking simulation is visualized through PyMol software with cartoon structure (red/Mpro and blue/NFκB1) and transparent surfaces (grey). Then homologous staining for the target protein is selected and ligands are displayed with sticks structure with color based on atoms for C, H, O, and N (Fig. 3).

The results of the identification of molecular interactions from the docking simulation for those two compounds with the most negative binding energies indicate that there are specific types of chemical bonds formed in the binding pocket of the target protein. These bonds consist of hydrophobic, hydrogen, and π (Fig. 4). However, when referring to the results of this study, the composition of hydrogen bonds formed is greater than hydrophobic and π.

![Figure 1](http://jppres.com/jppres)

**Figure 1.** Visualization of ligands and protein samples.

Chemical compounds containing *M. oleifera* (A) and *C. longa* (B); (C) Target proteins consisting of SARS-CoV-2 Mpro and human NFκB1.
DISCUSSION

Elaidolinolenic acid, cryptochlorogenic acid, myo-inositol, curcumin, curcumenol, and ar-curcumene compounds from combination of *M. oleifera* and *C. longa* are predicted to act as drug-like molecules since those compounds fulfill minimum two out of five parameters of Lipinski rule of five. Drug-like molecules allowed the query compounds to bind to targets and pass-through cell membranes (Hartati et al., 2021). Probability tests on herbal combination compounds provide a general idea of their potency when they enter the body. All query compounds have a high probability activation level with Pa score >0.3 and those compounds are computationally proven as antiviral and anti-inflammatory (Kharisma et al., 2020). The inhibition of the potential activity of the compound content of the herbal combination (Pi) has a lower score than Pa. It indicated that there is no inhibition of antiviral and anti-inflammatory activity from the compound combination when it entered the human body.

This study uses molecular docking to predict the action mechanism of query compounds from herbal combinations when it acts as antiviral and anti-inflammatory responses. In this study, blind docking is used to identify the activity of a query compound to the target protein and it ranked based on the binding energy (Luqman et al., 2020). The activity of compounds combinations influences the dual activity on target proteins or act as dual inhibitors since it has more negative binding affinity. Binding affinity is energy, which refers to Gibbs law to indicate the negativity of a ligand to the target protein domain (Putra et al., 2020). The molecular docking results showed two compounds with the most potential as dual inhibitors, such as cryptochlorogenic acid and curcumin. Furthermore, it has ability to bind to the target with lower binding affinity. Moreover, the molecular
complex could form the weak bond interactions, which consist of hydrogen, hydrophobic, and π.

According to Kneller et al. (2020), Mpro protein had a catalytic region with an amino acid residue composition that consist of asparagine (Asn), glutamine (Gln), and proline (Pro). This position is potentially targeted by drug candidates to inhibit the Mpro activity during the SARS-CoV-2 replication. The cryptochlorogenic acid and curcumin may interact via Asn119, Pro108, and Gln69 by hydrogen bonding in the catalytic region of Mpro. The negative energy, which generated by cryptochlorogenic acid and curcumin could affect the activity of target protein since it binds to the functional domain and subsequently trigger the inhibitory response on the target. Inhibition of SARS-CoV-2 Mpro can interfere with viral replication activity and reduce the viral titer in patients tested positive for SARS-CoV-2 infection (Ye et al., 2020; Harisna et al., 2021).

NFKB1 is essential transcription factor for the regulation of proinflammatory agents to assist the immune system for eliminating pathogens. Likewise, NFKB1 is overexpressed during the cytokine storm phenomenon in COVID-19 and it triggers the systemic response that potentially causes death in the patients. This ultimately allows NFKB1 to be ideally targeted for drug candidates. Several proinflammatory cytokines that are regulated by NFKB1 consist of TNF-α, IFN-γ, IL-1, and IL-6, in which they can exacerbate cytokine storm events in the body of COVID-19 patients (Ahmed, 2020). The cryptochlorogenic acid and curcumin could inhibit the NFKB1 activity by producing the hydrogen bonds to the lysine (Lys), serine (Ser), and proline (Pro), in which their position is the active site of NFKB1 (Huxford and Ghosh, 2009; Mukund et al., 2019). Hydrogen bond interactions played an important role in the formation of protein-ligand complexes, initiated the biological response of a target protein, and it contributed to molecular stability. The cryptochlorogenic acid and curcumin have been computationally proven as dual inhibitors for antivirals through inhibition of SARS-CoV-2 Mpro and as anti-inflammatory through inhibition of NFKB1 activity. However, the results of this study remain theoretical and it must be further explored through in vitro and in vivo studies to validate the potential benefits of those bioactive compounds.

Figure 3. The 3D visualization of molecular docking results. (A) Cryptochlorogenic acid and curcumin 3D complex with SARS-CoV-2 Mpro; (B) Cryptochlorogenic acid and curcumin 3D complex with NFKB1.
CONCLUSION

Combination of herbs compound from Moringa oleifera Lam. and Curcuma longa L. is predicted to have antiviral and anti-inflammatory activity as dual inhibitor mechanism substantiated by cryptochlorogenic acid and curcumin. Those two compounds strongly bind to the active site of both proteins (SARS-CoV-2 Mpro and NFKB1) and exhibit an inhibitory response. However, further studies or approaches are necessary to support the evidence-based results from this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

This study was supported by the Generasi Biologi Indonesia Foundation, Indonesia (Grant Number: GENBINESIA/07/15/2021). Authors also thank the Government of the Republic of Indonesia, Ministry of Education, Technology, Research and Higher Education of Republic of Indonesia for PTUPT (Grant Number: 414/UN35.13/LT/2021), and Rector of Universitas Negeri Padang (Grant Number: 1008/ UN35.13/LT/2021).

REFERENCES


http://jppres.com/jppres

### AUTHOR CONTRIBUTION:

<table>
<thead>
<tr>
<th>Contribution</th>
<th>Kharisma VD</th>
<th>Aghata A</th>
<th>Ansori ANM</th>
<th>Widyananda MH</th>
<th>Rizky WC</th>
<th>Dings TGA</th>
<th>Derkho M</th>
<th>Lykosova I</th>
<th>Antonius Y</th>
<th>Rosadi I</th>
<th>Zainul R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concepts or ideas</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Design</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Definition of intellectual content</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Literature search</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Experimental studies</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Data acquisition</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Data analysis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Manuscript preparation</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Manuscript editing</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Manuscript review</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>