

Original Research Article

Targeting endometriosis, preserving receptivity: Molecular insights into glycitein's selective action

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Abstract

Purpose: To investigate the efficacy of glycitein a plant-derived isoflavone aglycone, in inhibiting endometriosis without interfering with endometrial receptivity.

Methods: Molecular docking studies were conducted to determine the interaction between glycitein and specific receptors associated with the pathogenesis of endometriosis, such as estrogen receptor- α (ER α), estrogen receptor- β (ER β), tumour necrosis factor- α (TNF- α), nuclear factor- κ B (NF- κ B), Prostaglandin EP3, and apoptosis proteins such as survivin, B-cell lymphoma 2 (BCL2), B-cell lymphoma-extra-large (BCL-XL), and Fas ligand (FASL). Binding properties of glycitein were compared with those of dienogest.

Results: Glycitein showed superior binding affinity to NF- κ B receptor (-6.4 kcal/mol) and stronger interaction with prostaglandin EP3 receptor (-9.2 kcal/mol) compared to dienogest. In contrast, glycitein showed weaker binding affinity to apoptosis-regulating proteins, including survivin (-4.5 kcal/mol), BCL2 (-6.4 kcal/mol), BCL-XL (-6.7 kcal/mol), and FASL (-5.6 kcal/mol), compared to dienogest (-5.7, -7.6, -8.3, and -6.9 kcal/mol, respectively).

Conclusion: The computational study has shown that glycitein exerted potent anti-inflammatory activity by inhibiting the NF- κ B pathway and prostaglandin EP3 receptor, but had minimal effects on endometrial apoptotic mediators. Such selectivity indicated that glycitein is likely to prevent endometriosis development without negatively affecting endometrial receptivity.

Keywords: Endometrial receptivity, Endometriosis, Glycitein, Molecular Docking, NF- κ B, Prostaglandin EP3

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INTRODUCTION

Endometriosis is an ongoing, estrogen-induced inflammatory disease affecting 10 % of women of reproductive age, where about 20 - 50 % develop infertility [1,2]. It occurs when the endometrial tissue develops outside the uterus, resulting in pelvic pain, dysmenorrhea, and decreased

quality of life [3]. Endometriosis is caused by several factors such as hormonal imbalance, inflammation, and increased cell survival capacity [4]. Estrogen is one of the major factors involved in endometriosis progression due to the activity of estrogen receptor α (ER α) and estrogen receptor β (ER β). Also, in endometriosis, there is overexpression of ER β in

ectopic lesions that induces local estrogen production, inflammation, cell proliferation, and apoptosis inhibition [5,6].

There are several other mechanisms such as inflammatory processes via nuclear factor- κ B (NF- κ B) activation and prostaglandin E₂ (PGE₂) involved in cell survival and growth. Also, NF- κ B promotes the expression of anti-apoptotic and pro-inflammatory molecules, while prostaglandin EP3 receptor activates cell proliferation, migration, and invasion [7-9].

Management of endometriosis involves the use of hormonal drugs such as combined oral contraceptives, progestin (such as dienogest), and GnRH (gonadotropin-releasing hormone) agonists or antagonists [10]. Although successful in pain treatment, these medications affect ovulation and reduce endometrial receptivity. Furthermore, conception cannot occur during medication, causing severe adverse effects [11,12]. There is therefore the need for new treatments targeting pathologic pathways of endometriosis without compromising fertility. Genistein, daidzein, and glycitein are three plant-based non-steroidal compounds, known as isoflavone aglycones, structurally similar to estradiol [13].

Studies have shown that isoflavones act as antioxidants, modulators, estrogenic agents with effects on various pathways [14]. It has been observed that genistein blocks the action of vascular endothelial growth factor A (VEGF-A) and regulates ER β /ER α ratio, while daidzein prevents inflammation caused by tumour necrosis factor- α (TNF- α) and blocks the expression of interleukin-6 (IL-6), IL-8, and cyclooxygenase-2 (COX-2) [15,16]. In previous studies on aglycone forms of isoflavones in endometriosis, glycitein was identified to have the strongest binding ability to EP3 prostaglandin receptor (-9.2 kcal/mol) compared to genistein (-8.6 kcal/mol), daidzein (-8.9 kcal/mol), and dienogest (-5.5 kcal/mol). Furthermore, glycitein exhibited the strongest predicted interaction with NF- κ B (-6.4 kcal/mol) compared to genistein (-6.3 kcal/mol), daidzein (-5.8 kcal/mol), and dienogest (-5.9 kcal/mol). These results suggest that glycitein may be a promising molecule in the treatment of endometriosis [17].

Despite these benefits, effects of glycitein on endometrial receptivity, which is essential in fertility-sparing treatment, have not been studied. Receptivity of the endometrium relies on a balanced interaction between apoptosis and cell survival mechanisms. Proteins, such as survivin, BCL2, BCL-XL, and FAS, regulate apoptosis and

are critical for endometrial reconstruction and embryo attachment throughout the menstrual cycle [18,19]. Excessive inhibition of these proteins would negatively affect endometrial function and fertility.

This study used a full molecular docking strategy to investigate the interactions between glycitein, the disease-causing molecules (ER α , ER β , TNF- α , NF- κ B, prostaglandin EP3), endometrial receptivity-related proteins (Survivin, B-cell lymphoma 2 (BCL2), B-cell lymphoma-extra large (BCL-XL), and Fas ligand (FASL)). The docking behaviour of glycitein was studied as a selective compound for controlling endometriosis without affecting endometrial conditions for embryo implantation compared to dienogest.

METHODS

Study design

This study applied an *in silico* molecular docking to investigate the interaction behaviour between glycitein and dienogest with nine endometriosis-related target proteins participating in the development of endometriosis and endometrial receptivity.

Ligand preparation

Three-dimensional (3D) structural information of glycitein and dienogest was downloaded from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) using their respective PubChem compound identifier ([CID]): glycitein (CID: 5317750) and dienogest (CID: 68861). Glycitein was the primary ligand used in this study, while dienogest was chosen as the control drug for endometriosis. The 3D structure of the ligands was prepared using UCSF Chimera 1.14 software, and energy minimisation was done before converting into PDB format for docking studies.

Protein preparation

The 3D structure information of the target receptors was extracted from the Structural Bioinformatics Protein Data Bank (RCSB PDB) (<http://www.rcsb.org/>) and the AlphaFold protein structure database (Table 1). Preparation of proteins involved eliminating the crystallographic waters and irrelevant co-crystallised ligands. Also, hydrogen was attached to improve geometry. The PDB files of protein structures were created using UCSF Chimera 1.14 software as with previous study [17].

Table 1: Receptor structures

Receptor	PDB ID / Source	Resolution (Å)
Estrogen Receptor α	5GS4	2.60
Estrogen Receptor β	5TOA	1.83
TNF- α Receptor	1TNF	2.60
NF- κ B Receptor	1NFK	2.30
Prostaglandin EP3 Receptor	6AK3	2.80
Survivin	AF-D2XQ53 (AlphaFold)	-
BCL2	8HTS	1.90
BCL-XL	1R2D	2.20
FASL	5L19	2.70

Molecular docking

The process of molecular docking was done using CB-Dock2 (<https://cadd.labshare.cn/cb-dock2/php/blinddock.php>). AutoDock Vina was used as the predictive binding affinity tool, according to the molecular docking approach [17].

Binding affinity

The score value generated by Vina for each receptor-ligand complex was used to determine the binding affinity, where negative values signified stronger predicted affinity.

Interaction profiling

Interaction profile of the receptor-ligand complex was done by preparing 2D and 3D visual images of the complex structures using Discovery Studio Visualizer 2024 and UCSF Chimera software.

This involved interactions such as hydrogen bonds, hydrophobic interaction, π - π stacking, π -cation interaction, and van der Waals interactions.

Comparative analysis

Glycitein binding interactions were compared with dienogest across all nine targets.

RESULTS

Binding affinities of Glycitein and Dienogest

The molecular docking experiments demonstrated varied binding properties of glycitein and dienogest with the nine protein targets (Figure 1). The Vina scores in kcal/mol of all the receptor-ligand complexes are shown in Table 2.

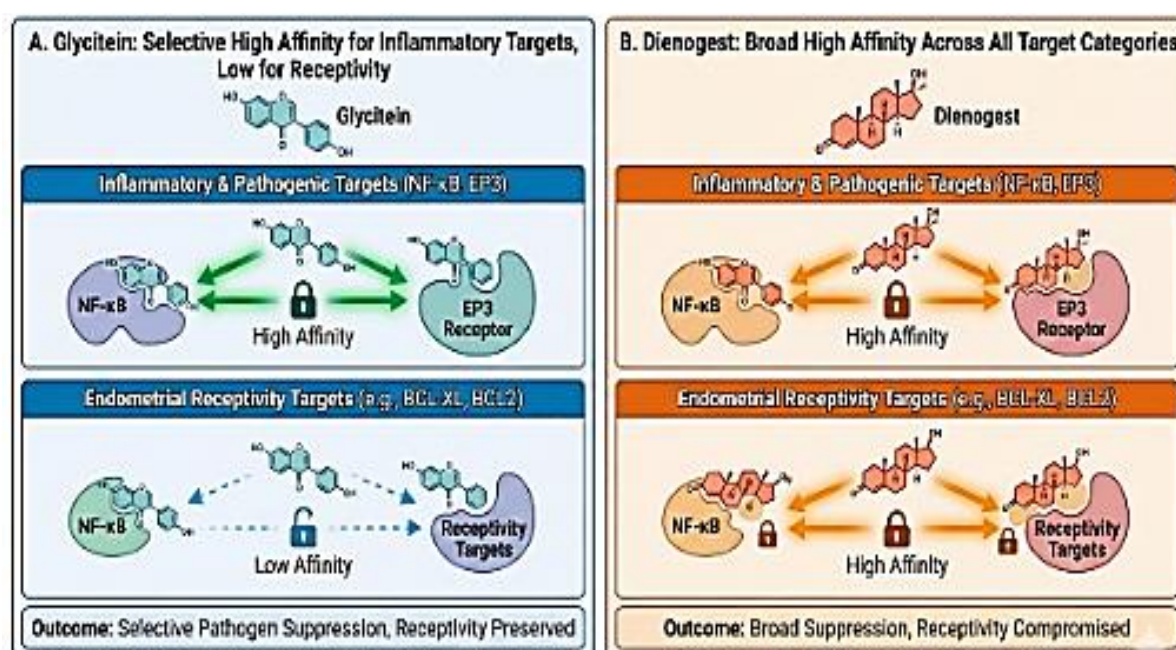
**Figure 1:** Comparative binding profiles of glycitein and dienogest based on molecular docking results

Table 2: Vina scores for ligand-receptor interactions (kcal/mol)

Receptor	Protein Data Bank identifier (PDB ID)	Glycitein	Dienogest
Endometriosis Pathogenesis Targets			
Estrogen Receptor α	5GS4	-5.6	-5.9
Estrogen Receptor β	5TOA	-8.3	-8.5
TNF- α Receptor	1TNF	-5.7	-6.5
NF- κ B Receptor	1NFK	-6.4	-5.9
Prostaglandin EP3 Receptor	6AK3	-9.2	-5.5
Endometrial Receptivity Targets			
Survivin	AF-D2XQ53	-4.5	-5.7
BCL2	8HTS	-6.4	-7.6
BCL-XL	1R2D	-6.7	-8.3
FASL	5L19	-5.6	-6.9

Interactions with endometriosis pathogenesis targets

Estrogen receptor β (ER β)

Glycitein had high affinity (-8.3 kcal/mol) for ER β binding, as observed with dienogest (-8.5 kcal/mol). Binding between glycitein and ER β occurred via hydrogen bonding with HIS A:475 and GLU A:305, van der Waals interactions with many residues including GLY A:472, MET A:479, MET A:295, LEU A:490, and ARG A:346, and alkyl/ π -alkyl interactions with ILE A:376, LEU A:476, LEU A:343, ALA A:302, and ILE A:373. A π -sigma interaction was observed with LEU A:339 (Table 3).

Estrogen Receptor α (ER α)

The two drugs displayed weak interactions (-5.6 kcal/mol and -5.9 kcal/mol for glycitein and dienogest respectively) with ER α relative to ER β , which were in agreement with previous reports on isoflavone specificity to ER β (Table 3).

NF- κ B Receptor

Glycitein had higher binding affinity (-6.4 kcal/mol) for NF- κ B binding compared to dienogest (-5.9 kcal/mol). The complex between

glycitein and NF- κ B receptor included Van der Waals interactions with HIS P:67, GLY P:68, ARG P:57, PHE P:56 (Table 3).

Prostaglandin EP3 receptor

The compound glycitein had better binding energy towards the EP3 receptor (-9.2 kcal/mol) compared to dienogest (-5.5 kcal/mol). The interaction network included Van der Waals contacts with GLN A:339, GLY A:102, GLN A:103, MET A:58, ARG A:333, LEU A:329, TYR A:114, PRO A:204, PHE A:133, VAL A:332, and SER A:336; conventional hydrogen bonding with THR A:107, π -sigma interactions with THR A:106 and VAL A:110, alkyl/ π -alkyl interactions with MET A:137 and PRO A:55, and π - π T-shaped stacking with TRP A:207 (Table 3).

TNF- α receptor

Dienogest showed stronger binding affinity to tumour necrosis factor- α receptor (TNF- α receptor) (-6.5 kcal/mol) compared to glycitein (-5.7 kcal/mol). Glycitein interactions included Van der Waals contacts with LEU A:29, ASN A:30, GLN A:27, ARG A:44, ASN A:46, and ASP A:45; conventional hydrogen bonding with TRP A:28; and a π -sigma interaction with LEU A:43 (Table 3).

Table 3: Key interactions of Glycitein with target proteins

Receptor	Key amino acid interactions	Bond types
ER β	HIS475, GLU305, LEU339, ILE376, LEU476, LEU343, ALA302, ILE373	Hydrogen bonds, π -sigma, alkyl/ π -alkyl, van der Waals
NF- κ B	VAL61, VAL115, LEU143, PRO65, HIS67, ARG57, PHE56	Hydrogen bond, π -sigma, alkyl/ π -alkyl, van der Waals
EP3	THR107, THR106, VAL110, MET137, PRO55, TRP207	Hydrogen bonds, π -sigma, alkyl/ π -alkyl, π - π T-shaped, van der Waals
BCL2	SER105, GLU152, ARG26, GLU160	Hydrogen bonds, π -cation
BCL-XL	SER145, GLU153, LYS20, GLU98, ALA149	Hydrogen bonds, π -cation, π -alkyl, van der Waals
FASL	MET224, ASN250, ASP255	Hydrogen bonds, attractive charge

Interactions with endometrial receptivity targets

Survivin

Dienogest demonstrated stronger binding affinity to survivin (-5.7 kcal/mol) than glycitein (-4.5 kcal/mol). Glycitein formed a conventional hydrogen bond with ASP2 and π -alkyl interactions with LYS5. Dienogest established a hydrogen bond with ARG8 and π -alkyl contact with LYS5, with deeper penetration into the binding pocket (Table 4 and Table 5).

B-cell lymphoma 2 (BCL2)

Dienogest displayed greater affinity for B-cell lymphoma 2 (BCL2) compared to glycitein (-7.6 kcal/mol versus -6.4 kcal/mol). Glycitein interacted with the protein via several stabilising modes of interaction, including hydrogen bonds with SER105 and GLU152 and π -cation interactions with ARG26 and GLU160. Dienogest, on the other hand, formed only hydrophobic π -alkyl interactions with HIS184 and TYR180, as expected from its steroid structure (Table 4 and Table 5).

B-cell lymphoma-extra large (BCL-XL)

The greatest affinity difference occurred between dienogest and glycitein for BCL-XL, with the former displaying better binding (-8.3 kcal/mol versus -6.7 kcal/mol). Glycitein participated in conventional hydrogen bonding with SER145, carbon-hydrogen bonding with GLU153, and π -cation/ π -alkyl interactions with LYS20, GLU98, and ALA149. Dienogest formed a hydrogen bond with SER145 and numerous van der Waals interactions (Table 4, 5).

Fas Ligand (FASL)

Dienogest displayed higher binding affinity for Fas ligand (FASL) (-6.9 kcal/mol) compared to glycitein (-5.6 kcal/mol). Glycitein interacted with

the protein through hydrogen bonds with MET224 and ASN250 and attractive charge interactions (Table 4, 5).

DISCUSSION

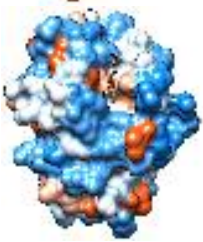
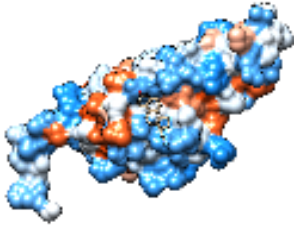
Glycitein showed favourable and promising binding properties with endometriosis-related targets. However, glycitein selectively binds to critical inflammatory and hormonal triggers of endometriosis without significant inhibition on apoptosis regulators needed for endometrial receptivity. Glycitein exhibited the strongest binding affinity toward the prostaglandin EP3 receptor and NF- κ B, with binding energies greater than dienogest against the same targets (-5.5 and -5.9 kcal/mol, respectively). This finding is consistent with a previous study on isoflavone aglycones, which revealed that glycitein has strong interactions with inflammatory mediators [17]. Nuclear factor- κ B (NF- κ B) is an essential factor in endometriosis initiation. It acts by encouraging the survival and proliferation of ectopic endometrial cells via activating anti-apoptotic genes and producing inflammatory cytokines [8,20]. The observed binding affinity of glycitein to NF- κ B may reflect its potential to modulate NF- κ B-mediated signalling. This observation is supported by earlier studies showing that glycitein inhibits NF- κ B activation through the MAPK/STAT3/NF- κ B signalling pathways in gastric cancer cells [21]. The EP3 receptors (showed highest affinity for glycitein), regulate the processes of proliferation, migration, and invasion in endometrial tissues [9].

Increased level of prostaglandin E₂ (PGE₂) in peritoneal fluid of patients with endometriosis via EP receptors has been described as the cause of pain, inflammation, and establishment of lesions [22]. Due to its high affinity to EP3, glycitein may compete with endogenous PGE₂ to reduce prostaglandin-induced inflammation and proliferation processes.

Table 4: Key interactions of Dienogest with target proteins

Receptor	Key amino acid interactions	Bond types
ER β	GLU305, HIS475, LEU339, ILE376, ILE373, LEU476, ALA302, LEU298, LEU343	Hydrogen bonds, π -sigma, alkyl/ π -alkyl, van der Waals
NF- κ B	TYR82, ARG59, ASN139, LYS80, GLY69, PRO71, PHE56	Hydrogen bonds, van der Waals
EP3	THR106, GLN339, GLY141, MET137	van der Waals, unfavourable bump, alkyl
Survivin	ASP2, LYS5	Hydrogen bond, π -alkyl
BCL2	HIS184, TYR180	π -alkyl
BCL-XL	SER145	Hydrogen bond, van der Waals
FASL	MET224, ASN250	Hydrogen bonds, hydrophobic

Table 5: 3D molecular interaction diagram

Ligand	Glycitein	Dienogest
Survivine (AF: D2XQ53)		
BCL2 (PDB: 8HTS)		
BCL XL (PDB:1R2D)		
FASL (PDB: 5L19)		

However, dienogest failed to interact strongly with this protein. Glycitein and dienogest showed preference for ER β over ER α , confirming the reported selectivity of isoflavones for ER β [23]. Binding affinity of glycitein with ER β was similar to that of dienogest, indicating similar potency for modulating estrogen-dependent signal transduction in endometriotic tissues characterized by high expression levels of ER β [5,6]. Such ER β -selective action is due to a narrower ligand-binding pocket in ER β than in ER α , allowing more efficient binding of isoflavone-like molecules [24]. Specific activity of ER β is beneficial from a therapeutic perspective because it preserves endometrial function by stimulating ER β in the eutopic endometrium and suppressing endometriotic lesions proliferation [25].

Combination of ER β selective activity and anti-inflammatory effect suggests that glycitein acts as a selective estrogen receptor modulator (SERM)-like agent exhibiting two therapeutic effects. Glycitein binds poorly to apoptosis

modulators compared to dienogest. Across all four endometrial receptivity targets, Survivin, BCL2, BCL-XL, and FASL, glycitein showed lower binding affinities than dienogest, with the largest differences observed for BCL-XL, and FASL. These proteins play essential roles in endometrial physiology and embryo implantation. The BCL2 family (including BCL2 and BCL-XL) regulates mitochondrial apoptosis and is critical for endometrial remodelling during the menstrual cycle and decidualization [18,26]. Survivin, a member of the inhibitor of apoptosis protein (IAP) family, is expressed in endometrial epithelium during implantation window and contributes to endometrial receptivity [19]. Furthermore, FASL mediates apoptosis of invading trophoblasts and regulates immune tolerance at the maternal-fetal interface by interacting with Fas cell surface death receptor (FAS) [27]. The endometrial stroma expresses the FAS receptor, while the invading trophoblast, as well as endometrial cells secrete FASL. Endometrial stromal cells are inherently resistant to FAS-mediated apoptosis, a mechanism that protects them from self-induced

cell death via their own FASL production. However, this resistance is overcome by inflammatory cytokines like interferon- γ and tumour necrosis factor- α , which are present at the implantation site. Expression of FASL in the endometrium is regulated by ovarian steroids and it plays a key role in establishing maternal immune tolerance. By inducing apoptosis in activated immune cells that express FAS, the endometrial FASL helps create an immunologically privileged site for the semi-allogeneic embryo [28,29]. Excessive inhibition of these proteins may compromise endometrial function and implantation. The high affinity of dienogest to these target proteins is likely responsible for suppressing endometrial proliferation and receptivity [11,12]. Minimal interactions of glycitein with these proteins suggest that, it may not significantly disrupt the apoptotic balance required for endometrial receptivity and embryo implantation.

From the comparison of all nine targets in this analysis, a therapeutic window theory for glycitein as a treatment for endometriosis may be postulated. This study revealed that glycitein demonstrated powerful anti-inflammatory activity (high affinity for NF- κ B and EP3 receptors), moderate hormonal balance regulation (ER β modulation) and low affinity to endometrial cell apoptotic factors (Survivin, BCL2, BCL-XL and FASL). This targeted action implies that glycitein may inhibit the progression of endometriosis via anti-inflammatory and antiproliferation actions while leaving intact endometrium suitable for implantation. Unlike glycitein, dienogest is known to possess potent effects on various targets including physiological targets, thus providing contraceptive action during the course of therapy. The selective binding of glycitein carries a number of implications for the clinical use of the drug, including fertility-sparing therapy. Through minimal interaction with endometrial apoptotic factors, glycitein would allow for conception to occur during the treatment process, circumventing a critical drawback of current hormone treatments. Another implication would include pain management. The strong affinity of glycitein for the prostaglandin EP3 receptor may ameliorate pain, which is a main symptom in women suffering from endometriosis. NF- κ B inhibition may reduce the survival and proliferation of ectopic lesions by modifying progression, rather than simply suppressing symptoms. Another benefit of using glycitein is safety. Being a natural isoflavone, glycitein is expected to be safer compared to artificial hormones. Further research should concentrate on validating these computational data by carrying out *in vitro* experiments using

endometrial stromal and epithelial cells, performing *in vivo* experiments in endometriosis models to assess the efficacy in decreasing lesions and pain behaviour, endometrial receptivity tests to prove that the implantation potential is retained, pharmacokinetics to establish bioavailability and proper dosage and finally, conducting clinical trials on patients suffering from endometriosis-associated infertility.

Limitation of the study

There are several limitations relating to the use of computational methods in this study. The binding affinity of molecular docking is determined by thermodynamic estimations which do not take into account possible biological interactions such as alterations in protein conformation, post-translational modifications and other parameters. The functional activity of the substances was not predictable since agonists and antagonists are not distinguishable without conducting experimental studies. Also, glycitein bioavailability was not determined.

CONCLUSION

Glycitein has demonstrated distinctive and beneficial binding capacity with NF- κ B and prostaglandin EP3 receptor, and negligible affinity for apoptosis mediators needed in endometrial receptivity compared to dienogest. Therefore, glycitein has the potential to inhibit endometriosis development through anti-inflammatory action without affecting the endometrial condition necessary for embryo implantation. There is need for further *in vivo* and *in vitro* studies to validate these predictions and establish the efficacy and safety of glycitein for the treatment of endometriosis.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Ethical approval

Not applicable

Availability of data and materials

Data and materials used in the study are available on request

Contribution of authors

The above study was carried out by the authors listed above in this paper and all responsibility for any claims associated with the content of this paper shall lie solely with them. Yakob Togar, Yosef Dwi Cahyadi Salan, Iwan Darma Putra, and Hardyan Sauqi conceived the study, Yakob Togar and Eko Suhartono carried out the docking analysis.

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