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Research Article

Identification of Targeted Therapeutic Compounds for the treatment of post-surgical adhesion: An in-Silico Study

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Abstract

Introduction: Intra-abdominal adhesions, especially intestinal adhesions and obstructions, are the most common complications after open abdominal and pelvic surgeries. Angiotensin Receptor Protein (ARB) is an essential protein involved in intestinal adhesion. This study aimed to identify new therapeutic compounds for preventing post-surgical adhesions.

Methods: The literature reviews identified ARBs as essential proteins in intestinal adhesion. Potential active sites for recognized target proteins were identified. The protein-ligand interaction was predicted by Molegro Virtual Docker (MVD) software. The interaction of ARBs with over 80000 drug-like compounds from the ZINC database was assessed by molecular docking. The designated compounds from the molecular docking were subjected to ADME prediction to assess drug limitations. The resulting molecules were subjected to Swiss Similarity software, and evaluation was performed using a Food and Drug Administration (FDA)- approved drugs library. Molecular dynamics (MD) simulations were performed using the GROMACS package version 2020.1 to assess the structural stability of the hit compounds.

Results: Four molecules, including ZINC000067920967, ZINC000161524911, ZINC000067587085, and ZINC000604511089, can block ARBs. ADME analysis demonstrated that these four molecules could be used as drugs. ADME analysis of these molecules revealed that they could be utilized as medicinal compounds. Additionally, the similarity screening against this molecule revealed that Teveten (Eprosartan), an FDA-approved drug, can be considered a therapeutic candidate for post-surgical adhesion.

Conclusion: The therapeutic compounds identified in this study, which block ARBs, can be utilized for post-surgical adhesion treatment. Additionally, Eprosartan, as an FDA-approved medication, exhibits anti-adhesion effects and may be a suitable candidate for preventing intestinal adhesions after abdominal surgery. However, more studies, such as clinical trials and animal studies, are essential.

Keywords: Post-Surgical Adhesion, Angiotensin Receptor Protein (ARBs), Virtual Screening, Molecular Docking, Eprosartan.

Introduction

Intra-abdominal adhesion is abnormal fibrotic tissue in the organs and tissues or abdominal cavities, which may be acquired or genetic [1-3]. The most common cause is following abdominal and pelvic surgeries. Rarely, it may develop secondary to intraperitoneal inflammatory responses, radiotherapy, infections, and abdominal trauma [2]. It is estimated that 93 to 100 percent of patients who undergo laparotomy will have some degree of adhesion [3]. The amount of adhesion varies among different patients and depends on the type of surgery and the complications that occur after it 4. Post-surgical adhesion is created following the healing of injuries caused by the surgeon's trauma [5]. Post-surgical adhesion can be asymptomatic [6] or appear with symptoms such as abdominal distension, vague

abdominal pains, nausea, and abnormal bowel movements, which may be intermittent or permanent, or cause diseases such as small intestine obstruction, infertility, and chronic pelvic pain [7]. In the United States, 117 people per 100,000 are hospitalized due to intraperitoneal adhesions, which cost 1.3 billion dollars to the healthcare system. Also, mortality is about 2,000 cases annually in the United States due to intestinal obstruction caused by adhesions [8-9]. In addition to the morbidity and financial burden, sometimes the complications caused by intraperitoneal adhesions provoke the need for repeated surgical intervention, which causes the creation of new adhesions and more complications for the patient. Additionally, this complication prolongs the duration of hospitalization and may necessitate subsequent surgeries. Various strategies have been proposed to prevent post-surgical adhesion, including modifying surgical procedures and using drugs such as antibiotics, NSAIDs, corticosteroids, and fibrinolytics. Although no clinical study has demonstrated the benefits of reducing adhesions using drug regimens to date, the use of intraperitoneal separators and laparoscopic surgery methods has been reported [10-11].

Angiotensin receptor blockers (ARBs) are used to manage high blood pressure. Recent studies have shown that these drugs can reduce inflammation and fibrosis in various organs. These results provided a new understanding that these drugs can theoretically reduce or prevent postoperative adhesions. These results recommend that the usage of these drugs might have the potential to avoid adhesions following surgery. Therefore, this study aimed to identify new therapeutic compounds for post-surgical adhesion by blocking angiotensin receptors through an in silico investigation.

Methods

Virtual screening and molecular docking

The literature reviews identified ARBs as essential proteins in intestinal adhesion. The 3D structure of the Human Angiotensin Receptor was obtained from the RCSB Protein Data Bank (PDB, https://www.rcsb.org/) with PDB ID: 4ZUD. Potential active sites for recognized target proteins were identified. Molegro Virtual Docker (MVD) software was used to prepare the input files and analyze the PDB files, and MVD was utilized to predict protein-ligand interactions in the study.The 3D structures of drug-like molecules were taken from the ZINC database. The Log P range of 4 to 5, molecular weight, neutral charge, and mild pH were used as selection criteria for compounds from the ZINC database. Regarding this, 80000 compounds were accidentally acquired. The MolDock score function, specifically the piecewise linear potential (PLP), was applied to assess the docking results [12].

ADME and similarity prediction

Output compounds from the molecular docking analysis were exposed to ADME prediction for authorization drug limitations. Pharmacokinetic limitations, including absorption, distribution, metabolism, and excretion (ADME) of the specific compounds, were investigated using the SwissADME web tool [10]. Moreover, the SwissSimilarity free web tool was used for identical prediction [11]. Output molecules were introduced to the SwissSimilarity software, and the Food and Drug Administration (FDA) approved drugs library was implemented for selection. Five procedures were used to select the library of FDA-approved drugs, including Electroshape, Shape-IT, fingerprints, Spectrophores, and Align-IT. Following, the communal screened compounds from a minimum of three procedures were selected.

Molecular dynamics simulation

Molecular dynamics (MD) simulations were performed using the GROMACS package version 2020.1 to assess the structural stability of the hit compounds. The chosen protein/ligand complexes were nominated as an input file for MD simulations via the docking study. PRODRG server-generated topology files [13]. The GROMOS96 54A7 force field was applied. A Cubic box filled with a TIP3P water model surrounded the complex. Neutralization of the system was done. The particle mesh Ewald (PME) technique was applied to estimate long-range electrostatic interactions following energy minimization, pressure, and temperature equilibration. 0.9 Å cut-off was fixed for short-range electrostatic cut-off and non-bonded Van der Waals interactions. The LINCS algorithm controlled the bond lengths. The Parrinello–Rahman barostat and modified Berendsen thermostat (V-rescale) maintained a constant pressure and temperature of 1 bar and 300 K. In conclusion, the Radius of gyration, root mean square fluctuation (RMSF), and root mean square deviation (RMSD) were investigated.

Results

Docking of ligands

To screen molecules that block the Human Angiotensin Receptor, molecular docking was first performed on over 80,000 drug-like molecules from the ZINC database. The finding was sorted regarding the MolDock score, and 3254 molecules were chosen with docking scores lower than -130 KJ/mol. The top 50 of these molecules are shown in Table 1.

Table 1: Virtual screening results

Ligand	MolDock Score	Rerank Score	RMSD	HBond	Docking Score	Similarity Score
ZINC000097015487	-159.088	-116.118	0	-4.36711	-166.865	0
ZINC000067920967	-158.489	-113.805	0	-4.88085	-163.567	0
ZINC000161524911	-158.345	-116.688	0	-2.6659	-155.715	0
ZINC000067587085	-157.658	-105.3	0	-2.5	-164.598	0
ZINC000067641979	-155.789	-104.636	0	0	-156.656	0
ZINC000604511089	-155.604	-117.549	0	-3.993	-164.215	0
ZINC000178752010	-154.972	-121.97	0	-11.6125	-149.601	0
ZINC000419756945	-154.895	-108.915	0	-4.18106	-157.603	0
ZINC000178752010_1	-154.655	-123.157	0	-11.7566	-149.72	0
ZINC000604511088	-154.59	-117.729	0	-4.3378	-161.769	0
ZINC000063835125	-154.117	-108.635	0	-2.5	-150.567	0
ZINC000579882522_1	-154.101	-113.88	0	-6.182	-151.107	0
ZINC000460725846	-153.63	-114.853	0	0	-156.767	0
ZINC000176088029	-152.449	-116.175	0	-3.44554	-155.522	0
ZINC000067654907	-152.391	-102.166	0	-2.5	-154.585	0
ZINC000161553275	-152.208	-119.35	0	-1.16609	-153.252	0
ZINC000656606425	-152.044	-111.026	0	-2.49864	-149.784	0
ZINC000067587083	-151.656	-98.0932	0	0	-157.912	0
ZINC000071755107_1	-151.574	-113.619	0	-6.82612	-156.574	0
ZINC000414613151	-151.539	-115.313	0	-11.7827	-151.374	0
ZINC000414619567	-151.256	-111.132	0	-10.9882	-154.174	0
ZINC000414651208	-150.976	-59.5243	0	-1.92969	-155.127	0
ZINC000436196344	-150.845	-108.916	0	-4.37333	-152.33	0
ZINC000520211296	-150.828	-115.741	0	-1.03279	-155.754	0
ZINC000436644126	-150.755	-118.923	0	-3.71596	-145.942	0
ZINC000067847619	-150.437	-97.994	0	-5.55027	-155.444	0
ZINC000582385839_1	-150.134	-58.4824	0	-2.21753	-156.818	0
ZINC000038767284	-149.979	-105.164	0	-3.27297	-156.274	0
ZINC000277072105	-149.586	-117.537	0	0	-152.145	0
ZINC000890668093	-149.342	-117.042	0	-2.5	-151.282	0
ZINC000737194301_1	-149.323	-111.71	0	-0.056853	-142.642	0
ZINC000419756946	-149.214	-98.9704	0	-2.5388	-153.024	0
ZINC000109695400	-149.07	-65.2399	0	-2.30758	-139.751	0
ZINC000514924890	-149.001	-99.9237	0	-3.83492	-149.814	0
ZINC000647170726	-148.968	-107.077	0	-0.234393	-152.942	0
ZINC000434983791	-148.806	-117.494	0	-2.47145	-149.687	0
ZINC000583001808	-148.789	-117.045	0	0	-147.912	0
ZINC000516112286	-148.616	-118.947	0	-0.961315	-151.843	0
ZINC000617921500	-148.506	-110.72	0	-1.44474	-147.716	0
ZINC000271740692	-148.464	-118.26	0	0	-153.215	0
ZINC000071755107	-148.362	-37.9213	0	-0.658203	-152.52	0
ZINC000826272927	-148.352	-108.904	0	-10.25	-159.041	0
ZINC000582327141_1	-148.251	-101.492	0	-2.48532	-154.766	0
ZINC000435138264	-148.243	-3.4854	0	-0.356039	-155.683	0
ZINC000176088010	-148.237	-111.171	0	-3.69499	-155.713	0
ZINC000020599749	-148.029	-111.828	0	-5.36868	-144.713	0
ZINC000515252379_1	-148.026	-106.633	0	-11.3719	-149.515	0
ZINC000656606424_1	-147.715	-108.64	0	-4.93604	-147.626	0
ZINC000065373445	-147.577	-109.489	0	0	-146.713	0

According to the results obtained from the first docking stage, when ligands were examined against the angiotensin II receptor protein, ZINC000067920967 had the highest score. This molecule establishes hydrogen bonds with amino acids tyrosine 92, tyrosine 87, tryptophan 284, arginine 167, serine 105, tyrosine 35, aspartate 281, isoleucine 288, methionine 284, and cysteine 180 of the angiotensin II receptor protein.

ADME and similarity prediction

The SwissADME web tool was used to investigate the ligands' pharmacokinetic and physicochemical factors (pharmacokinetic parameters ADME). Selected molecules from the docking study for ADME analysis were used (Table 2). Other features, such as human intestinal absorption, aqueous solubility, molecular weight, etc., were considered for all selected compounds (Table 1).

The library-related drugs were screened against ZINC000067920967, ZINC000161524911, ZINC000067587085, and ZINC000604511089, which were obtained from previous steps to discover a proper FDA-approved drug. It employs the five methods described in the Materials and Methods section: screened. The molecules whose similarity was proven using three methods were selected in the next step. Screening against ZINC000067920967 identified a similar molecule, Eprosartan.

Table 2: ADME analysis of screened Keap1 inhibitor compounds.

Molecule	Formula	MW	Fraction Csp3	#Rotatable bonds	TPSA	XLOGP3	ESOL Log S	ESOL Class	GI absorption	BBB permeant	CYP2D6 inhibitor	Lipinski #violations
Molecule 1	C21H20N4O2	360.41	0.24	5	79.87	2.2	-3.71	Soluble	High	No	Yes	0
Molecule 2	C20H25N5O2	367.44	0.5	7	96.7	3.1	-3.99	Soluble	High	No	Yes	0
Molecule 3	C20H23N7	361.44	0.3	6	77.21	2.78	-4.01	Moderately soluble	High	Yes	No	0
Molecule 4	C17H17N3O4S	359.4	0.24	7	119.45	3.78	-4.43	Moderately soluble	High	No	No	0
Molecule 5	C20H17N5O2	359.38	0.1	6	96.7	2.96	-4.14	Moderately soluble	High	No	Yes	0
Molecule 6	C20H23N5O2	365.43	0.3	6	91.9	2.42	-3.76	Soluble	High	No	Yes	0
Molecule 7	C17H17N3O4S	359.4	0.24	7	119.45	3.78	-4.43	Moderately soluble	High	No	No	0
Molecule 8	C19H17N5OS	363.44	0.11	6	104.92	3.13	-4.3	Moderately soluble	High	No	Yes	0
Molecule 9	C21H18N4O3	374.39	0.14	7	93.9	3.33	-4.38	Moderately soluble	High	No	Yes	0
Molecule 10	C19H16N6O2	360.37	0.16	5	98.56	2.87	-4.21	Moderately soluble	High	No	No	0

MW: Molecular weight/ Fraction Csp3: Fraction of carbons in the sp^3 hybridization/ TPSA: Topological polar surface area/ Log P: partition coefficient between n-octanol and water/ ESOL: Estimating aqueous solubility/ Log S: Logarithm of the molar solubility in water/ GI: Gastrointestinal/ BBB: Blood-brain barrier/ CYP2D6: Cytochrome P450 2D6.

Molecular dynamics simulations

The molecular dynamics simulation evaluated the structural stability of the Human Angiotensin Receptor-ZINC000067920967 complex in environmental and physiological conditions. H-Bond, RMSF, and RMSD were investigated in this study. The Root Mean Square Deviation (RMSD) for Human Angiotensin Receptor-ZINC00006792096 complex was between 0.2 and 0.4 nm. The RMSF was used to determine the flexibility and fluctuations of each residue in the Human Angiotensin Receptor during the last ten ns simulation period. No unwanted protein fluctuations were observed in RMSF for Human Angiotensin Receptor-ZINC00006792096 complex (Figure 1-2). The H-bond graph shows the number of H-bond interactions between the protein and the ligand during the simulation. Overall, we observed approximately two hydrogen bonds during the simulation for the Human Angiotensin Receptor-

ZINC000067920967 complex (Figure 3). These results confirmed that the selected compounds were stable.

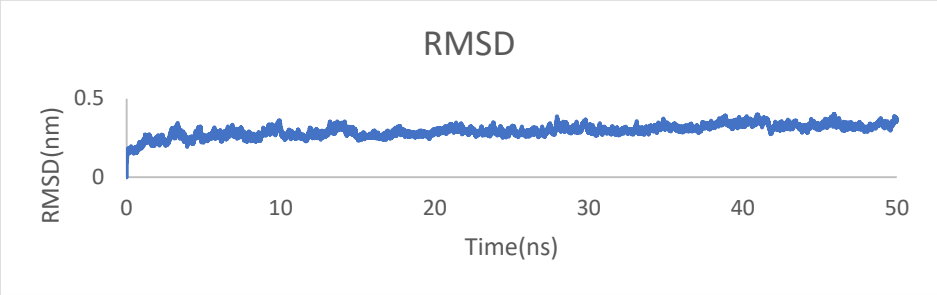

Figure 1: RMSD plots of Receptor-ZINC000067920967 complex.

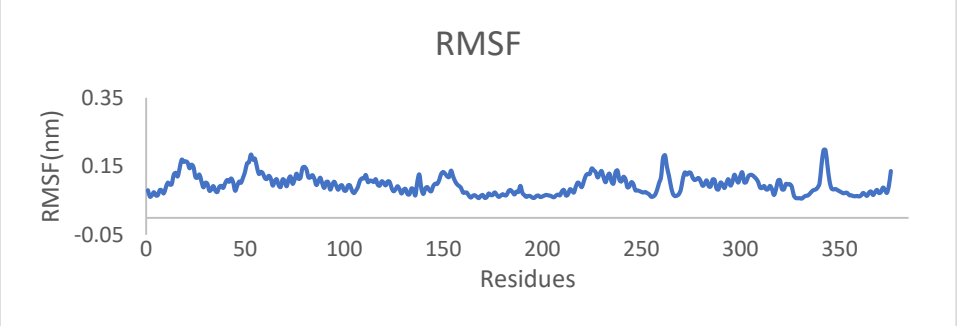

Figure 2: RMSF plots of Receptor-ZINC000067920967 complex.

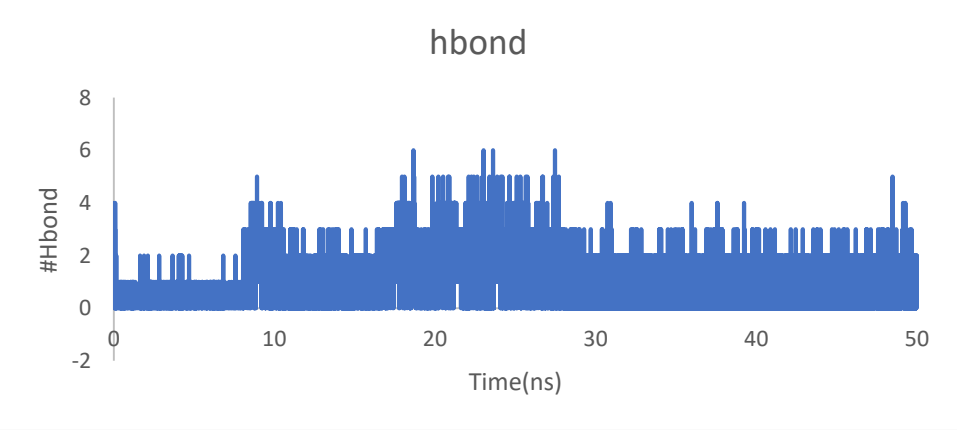

Figure 3: H- Bond plots of Receptor-ZINC000067920967 complex.

Discussion

Angiotensin receptor blockers (ARBs) are used to

manage high blood pressure. Recent studies have shown that these drugs can reduce inflammation and fibrosis in various organs. These results provided a new understanding that these drugs can theoretically reduce or prevent postoperative adhesions. The angiotensin receptor was targeted for drug discovery in this in silico study. The virtual screening was applied to recognize molecules that reduce or inhibit postoperative adhesions. The results showed that ZINC000067920967 could block the Angiotensin receptor. ADME analysis of this compound revealed that it could be applied as a therapeutic compound. However, this compound has not been involved in the clinical trial phase. In the next step, a similarity screening was conducted to identify analogous FDA-approved drugs with this molecule.

Similarity screening revealed that Eprosartan, an FDA-approved drug, can be considered a therapeutic candidate for post-surgical adhesion. Arjmand et al. [11] reported that telmisartan can significantly decrease fibrotic bands following surgery compared to the control group in a rat model. They showed that telmisartan could reduce inflammatory mediators, such as TGF-β, TNF-α, and IL-6; additionally, they demonstrated that the expression of fibrotic collagen 1 and 3 genes was significantly reduced in the telmisartan group [11]. Dinarvand et al. [14] reported that losartan decreases adhesion following surgery in a rat model. Intraperitoneal administration of losartan considerably decreased the fibrotic band. Following their adhesion induction model, they determined that losartan could reduce PAI-1 and TGF-β in serum and mRNA expression in the peritoneum. Other results showed that the tPA concentration and mRNA levels in peritoneal tissues were increased in animals treated with losartan [15]. Further research demonstrated that candesartan can decrease adhesion formation following an experimental model of peritoneal adhesions. Candesartan can decrease the severity of adhesion formation, as demonstrated in the experimental model of peritoneal adhesions in mice. Tokinaga et al. [16] demonstrated that intraperitoneal administration of candesartan reduced PAI-1 mRNA expression in traumatic tissues and was effective in reducing the adhesion score. These results recommend that the usage of these drugs might have the potential to avoid adhesions following surgery.

The renin-angiotensin system (RAS) comprises several peptides released into the bloodstream to regulate blood pressure and hemostasis, and to operate on target organs. AngII is an octapeptide that mainly regulates inflammation, vasoconstriction, and fibrosis through the AngII type 1 receptor (AT1R) [17, 18]. The AT1R, as a G-protein-coupled receptor, interacts with AngII and intervenes in the intracellular signaling pathways. It has been shown that local RAS elements such as AngII and AT1R are expressed in several organs, including the gastrointestinal tract, lung, and liver. AngII signaling via regional AT1R is associated with the extracellular matrix (ECM) precipitate following increased protein synthesis in the ECM, which contributes to a higher risk of fibrosis during scar formation in the skin [19], lung [20], and liver [17]. AngII/AT1R interactions can stimulate specific molecular mechanisms associated with fibrosis, such as nuclear factor kappa B (NF-κB) activation, transforming growth factor β (TGF-β) [21], and increased oxidative stress (OS) and inflammation [22-23].

It demonstrated that the interaction between AngII/AT1R and inflammation forms a positive feedback loop. Upregulation of AT1R may be involved in the raised expression of molecules associated with OS and inflammation [24]; therefore, AT1R stimulates OS and inflammation via various molecular mechanisms. Inflammation increases the release of ROS, leading to OS, a critical process in PSAB and fibrosis. Monocyte chemoattractant protein-1 is a crucial component of chemokine proteins involved in the inflammatory process, which AngII increases via AT1R signaling [25]. Moreover, AT1Rs directly induce the activation of NF-κB and its signaling pathway, leading to the production of various adhesive and inflammatory cytokines, including IL-1β, IL-6, ICAM-1, TNF-α, and TGF-β [26]. The AngII/AT1R axis can decrease peroxisome proliferator-activated receptor (PPAR) γ, which has an anti-inflammatory function [26]. Trauma to the abdominal or pelvic peritoneum during surgery activates AT1Rs on the surfaces of fibroblasts and mesothelial cells, inducing the release of adhesive and inflammatory molecules that prompt PSAB in the pelvic cavity or peritoneum [27]. One study demonstrated that the intraperitoneal administration of telmisartan following abdominal surgery in a rat model significantly decreased the expression of the inflammatory cytokines IL-6 and TNF-α through AT1R inhibition [28]. Following traumatic injuries to the tissues, the accumulation of fibroblasts and other immune cells at the injured site can trigger the NF-κB signaling pathway to increase the production of inflammatory cytokines, such as TNF-α, and stimulate

the generation of ROS [29]. Through the release of ROS, the AngII/AT1R pathway can decrease nitric oxide synthesis and indirectly trigger NF-κB. OS is a possible controller in the pathogenesis of PSAB. OS is related to elevated ROS levels, which include the hydroxyl radical, hydrogen peroxide, and superoxide, resulting from insufficient antioxidant activity. NOXs (NADH oxidase), as an enzyme, produce ROS localized in various tissues that catalyze the transformation of oxygen into a superoxide molecule (O2−) to raise OS [30-33]. Interaction of AT1R with activation of AngII leads to molecular mechanisms that stimulate NOX isoforms to produce OS and ROS. AngII with AT1R stimulation activates NOX isoforms and causes OS, leading to liver fibrosis [34].

Biological compounds rapidly developed as safe drugs and have been used to treat many diseases, including trauma. Therefore, it is recommended to research these compounds to identify a suitable drug for preventing intestinal adhesions [8, 35-36]. In addition, it is suggested that pathways and genes related to post-surgical adhesion be considered intelligent targets for treating at the molecular level [37]. Additionally, in silico studies, such as protein-protein interactions, are crucial for gaining a deeper understanding of the molecular events involved in post-surgical adhesion [38].

Conclusion

These findings indicate that the molecule ZINC00006792096 can decrease inflammation and fibrosis in various organs, making it a potential therapeutic compound. Additionally, Eprosartan, an FDA-approved drug, has the effects of Angiotensin receptor blockers and can be used to reduce or prevent postoperative adhesions; however, further studies, such as animal studies and clinical trials, are necessary.

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None.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

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None.

Authors' Contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Statement

This research was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran, under code: IR.BMSU.REC.1400.104.

Declaration of Generative AI and AI-assisted technologies

Not applicable.

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