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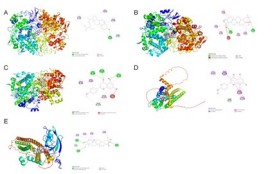
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RESEARCH ARTICLE

Title: The Mechanism Analysis of Digupi in Treating Acne Based on Network Pharmacology, Molecular Docking and Molecular Dynamics Simulations

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Abstract: Background: Digupi (also known as Lycium Cortex) is known for its antipyretic, blood-cooling, lung-clearing, and treatment of carbuncles and ulcers effects. However, the bioactive molecules of Digupi and its specific mechanisms for treating acne remain unclearunknown.Methods: Effective components of Digupi for acne treatment and their therapeutic targets were determined using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database, with target gene annotation through the UniProt database. Acne-related disease targets were identified from DisGeNET, GeneCards, and the Online Mendelian Inheritance in Man (OMIM) databases. The gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were used to analysis the molecular and pathway. Additionally, protein-protein interaction networks (PPI) and core targets selection were performed through the STRING database and Cytoscape software. Finally, chemical effective components and key targets of Digupi were analyzed by using Auto Dock Tools and GROMACS software.Results: In the "Drug-Ingredient-Potential Targets" network, 12 active components associated with Digupi for acne treatment were identified, they are aurantiamide, scopolin, hyoscyamine, stigmasterol, linoleyl,acetate, linarin, cholesterol, hederagenin, beta-sitosterol, sugiol, acacetin andatropine. Key targets such as TGFB1, PRKCA, TP53, AR, and PTGS2 were determined through protein-protein interaction network analysis. Enrichment analysis results indicate that potential core drug components of Digupi may treat acne through various pathways, including cancer-related signaling pathways like PI3K-Akt, lipid and atherosclerosis pathways, AGE-RAGE signaling pathway, relaxation signaling pathway, thyroid hormone signaling pathway, and MAPK signaling pathway. Molecular docking results suggest that the key targets in the regulatory network exhibit high binding affinity with the key active components of Digupi. Molecular dynamics (MD) simulations shows that acacetin, beta-sitosterol, and hederagenin have stable docking with PTGS2 (the main functional protein of Digupi), and acacetin having the most stable hydrogen bond distribution.Conclusion: Multi-target and multi-pathway provide preliminary insights into the molecular mechanisms underlying the treatment of acne by Digupi.

Keywords: network pharmacology; molecular docking; Digupi, acne; potential therapeutic targets; signaling pathways; molecular dynamics simulations

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1. Introduction

Acne, a prevalent and chronic inflammatory skin condition, primarily results from increased sebum production induced by androgens, abnormal follicular keratinization, inflammation, host immune reactions, and the presence of Propionibacterium acnes[1] . Approximately 80% of young adults and adolescents are clinically distinguished by the emergence of primary manifestations such as blackheads, whiteheads, papules, and pustules[2]. Currently, there are ways for treating acne, including topical approaches (such as vitamin A analogs, antibiotics, salicylic acid, benzoyl peroxide, chemical peels)[3, 4], systemic methods (comprising vitamin A analogs, antibiotics, hormones, isotretinoin, corticosteroids) [5, 6], and physical interventions (e.g., comedone extraction, cryotherapy, cryosurgery, electrocautery) [7-9]. However, due to the growing resistance of acne to antibiotic and hormonal treatments, the efficacy and safety of conventional therapies are not satisfactory [10]. Therefore, there is a need to explore more natural and safe

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complementary and alternative medicine (CAM) approaches for acne treatment.

Digupi is a traditional Chinese herbal medicine sourced from the root bark of Lycium barbarum [11]. It is characterized by a bitter taste and cold properties. It has been employed in traditional Chinese medicine for the treatment of conditions such as night sweats due to deficiency, pulmonary heat-induced coughing and wheezing, hemoptysis, hematuria, polydipsia, carbuncles, and ulcers[12, 13] . The chemical composition of Digupi is notably diverse, featuring a unique structural profile, and includes compounds such as terpenes, sterols, organic acids, phenolic compounds, alkaloids, and cyclic peptides[14]. Modern pharmacological studies have revealed that crude extracts or individual components of Digupi exhibit a range of pharmacological activities, including the treatment of acne, blood glucose reduction, blood pressure lowering, lipid-lowering, antibacterial, and antiviral effects [15]. However, the specific molecular mechanisms underlying the use of Digupi in acne treatment remain unclear.

Network pharmacology is a new discipline based on the theory of systems biology to design multi-target drug molecules for specific signaling nodes (Nodes). Precise and effective therapeutic intervention is achieved by synergistic multicompound network pharmacology and drug repurposing, obviating the need for drug discovery and speeding up clinical translation[16]. Molecular dynamics (MD) simulations have led to great advances in many scientific disciplines, such as chemical physics, materials science, and biophysics. This computational methodology has demonstrated high relevance in the detailed characterization of biomolecular systems, including complementarity with experimental data, experimental design optimization, and prediction of relevant properties for chemical systems that are expensive or difficult to handle experimentally. Among many applications, it has been employed to characterize disease development processes and has been used in the initial stages of drug design and development[17]. We utilized network pharmacology analysis and molecular dynamics (MD) simulations to identify the bioactive components associated with Digupi and predict the core targets and pathways involved in the Digupi's treatment of acne.

2. Materials and methods

2.1 Screening of active ingredients and potential targets of Digupi

The identification of active constituents in Digupi involved the utilization of the Traditional Chinese Medicine Systems Pharmacology database and analysis platform (TCMSP, https://old.tcmsp-e.com/tcmsp)[18]. Criteria for selection encompassed an oral bioavailability (OB) equal to or greater than 30% and a drug-likeness (DL) score of 0.18 or higher[19]. Additionally, gene names were annotated utilizing the Uniprot database (https://www.uniprot.org/).

2.2 Screening of acne-related Targets

To obtain targets associated with acne, a comprehensive search was performed in the GeneCard database (https://www.genecards.org/), Online Mendelian Inheritance in Man (OMIM, https://omim.org), and DisGeNET (https://www.disgenet.org) databases using the keyword "acne". Candidate targets were selected based on a reference score exceeding 30 points, while eliminating any duplicate targets.

2.3 Acquiring potential targets for acne treatment with dermatophytes

To determine potential therapeutic targets for Digupi in patients with acne, a cross-target analysis was performed utilizing the Venn tool (https://bioinfogp.cnb.csic.es/tools/venny/). Subsequently, a network titled "Drug Component-Potential Targets" was constructed using Cytoscape 3.7.2 software (https://cytoscape.org/).

2.4 Construction of protein-protein interaction network (PPI) and core target screening

We imported the cross-targets into the STRING database (https://string-db.org/), with a confidence threshold set at 0.4, and removed unrelated nodes from the network. Data downloaded from the STRING database were further utilized in Cytoscape software and the Metascape database to construct a protein target network. Some target proteins in cell biology activities are closely related and have the same or similar functions; these target proteins can be considered a cluster. Proteins in the same cluster are generally considered to play a synergistic role in disease progression. The MCC (Maximum Clique Centrality) algorithm from the Cytohubba plugin was employed to compute cluster associated with Digupi treatment for acne[20]. Finally, the top 10 core targets were presented[19].

2.5 GO and KEGG enrichment analysis

This section provides details of the methodology used along with information on any previous efforts with corresponding references. Any details for further modifications and research should be included. Sufficient details should be provided to the reader about the original data source in order to enable the analysis, appropriateness and verification of the results reported in the study.

2.6 Molecular docking

This section provides details of the methodology used along with information on any previous efforts with corresponding references. Any details for further modifications and research should be included. Sufficient details should be provided to the reader about the original data source in order to enable the analysis, appropriateness and verification of the results reported in the study.

2.7 Molecular dynamics (MD) simulations

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As the screening criterion of the binding energy ⩽ -9.0kJ/mol, the optimal docking combination was selected for dynamic simulation[20]. The protein was separated from the small molecule ligand, and a small molecule force field file was generated using the antechamber tool in Ambertools software, and the file was converted into a gromacs force field file using the acpype software. Small molecules were subjected to GAFF force field, while proteins were subjected to AMBER14SB force field and TIP3P water model. The files of proteins and small molecule ligands were merged to construct a simulation system for the complex. Then, GROMACS 2023.2 software was used to identify the complex. After energy minimization, the system underwent 100 ps of equilibration under both NVT and NPT conditions, followed by a 100 ns MD production run with coordinate saving at 2 fs intervals. Analysis of the final trajectory included measurements of root mean square deviation (RMSD), root mean square fluctuation (RMSF), and hydrogen bonds using GROMACS modules[21].

3. Results

3.1 The effective components and targets of digupi.

Digupi was screened for its active ingredients and targets in the Traditional Chinese Medicine Ingredients Database (TCMID). A total of 12 active ingredients were obtained, including aurantiamide, scopolin, hyoscyamine, stigmasterol, linoleyl acetate, linarin, cholesterol, hederagenin, beta-sitosterol, sugiol, acacetin, atropine. Duplicates were removed, resulting in a total of 87 relevant targets(Figure 1).

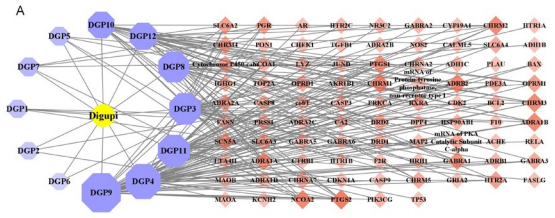


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3.2 The targets related to acne

A total 695 acne-associated targets were obtained from the DisGeNET, GeneCards, and OMIM databases based on a relevance score of ⩾30[19].

3.3 Acquisition of potential targets and construction of a "drug component-potential target" network network

The Venn tool was used to intersect the target genes of the active components of Digupi with acne-related genes, resulting in 13 potential target genes (Figure 2A) (Table 1). Furthermore, a network diagram of active herbal components was established (Figure 2B), where blue represents the active components, and orange represents the corresponding target proteins for these active components. From the diagram, it is evident that beta-sitosterol, hederagenin, and acacetin play prominent roles in Digupi.

Table 1. *Common targets of active ingredient and Acne*

nunmber	co-targets
1	PTGS1
2	PTGS2
3	RXRA
4	NOS2
5	AR
6	DPP4
7	BCL2
8	TP53
9	CYP19A1
10	F2R
11	KCNH2
12	PRKCA
13	TGFB1

3.4 Construction of PPI and core target screenings

The STRING database was utilized to obtain protein-protein interaction relationships among the potential targets, as depicted in Figure 3A. The network consisted of 12 nodes (excluding one independent target) and 30 edges, with nodes representing proteins and edges representing protein associations. To further analyze this network, it was imported into Cytoscape, where the MCODE plugin and the Metascape database were employed to identify core networks and hub proteins. Notably, the central targets in the protein-protein interaction network obtained from the STRING database included PTGS2, TP53, and PRKCA, as shown in Figure 3B. Meanwhile, the central targets in the protein-protein interaction network from the Metascape database were TGFB1, PRKCA, TP53, AR, and PTGS2 (Figure 3C).

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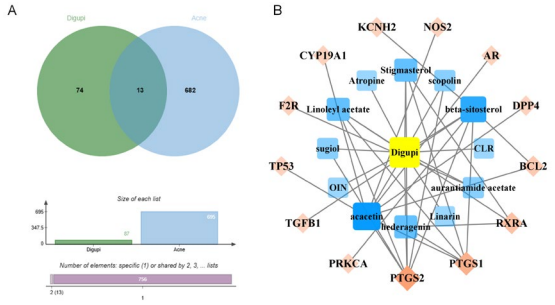


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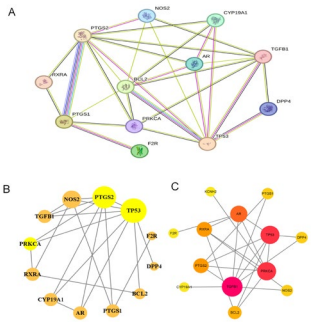


Fig. (3). If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

3.5 Results of enrichment analysis of Digupi in the treatment of acne

The GO analysis revealed that the enrichment of Biological Processes (BP) encompassed regulatory processes related to blood circulation, negative regulation of cell proliferation and migration, response to steroid hormone, regulation of system process, positive regulation of cell migration, response to hypoxia, negative regulation of cell migration, olefinic compound metabolic process, cellular response to xenobiotic stimulus, and organ growth. Cellular Components (CC) were mainly associated with the perinuclear cytoplasmic region and membrane rafts. Molecular Functions (MF) primarily involved protein homodimerization activity, protein domain specific binding, and heme binding. Additionally, the KEGG enrichment analysis revealed that the therapeutic effects of Digupi on acne were primarily linked to pathways, including cancer, the PI3K-Akt signaling pathway, lipid and atherosclerosis, the AGE-RAGE signaling pathway in diabetic complications, the sphingolipid signaling pathway, the thyroid hormone signaling pathway, the MAPK signaling pathway, the HIF-1 signaling pathway, and the relaxation signaling pathway (Figure 4A). Furthermore, a drug-compound-key target-pathway network was constructed using Cytoscape (Figure 4B).

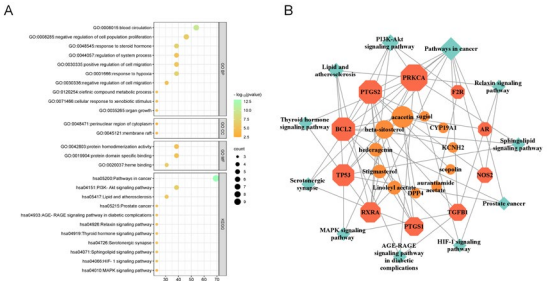


Fig. (4). If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

3.6 Molecular docking results

Docking was performed between three components of Digupi (acacetin, beta-sitosterol, and hederagenin) and five key targets (PRKCA, TP53, AR, PTGS2, and BCL2). The more stable the binding between the ligand and the receptor, the lower the binding energy of the two. Normally the binding energy ≤-6 kcal/mol can illustrate the ligand and receptor have strong connection[20], The binding energies of the active components with the receptors are presented in Table 2. Figure 5 illustrates the top 5 molecular docking results based on binding energies.

Table 2. *Binding energies of components and receptors*

Ligand	protein	Score
acacetin	PRKCA	-7.1
acacetin	TP53	-7.4
acacetin	AR	-8.7
acacetin	PTGS2	-9.3
acacetin	BCL2	-6.8
beta-sitosterol	PRKCA	-7.5
beta-sitosterol	TP53	-6.6
beta-sitosterol	PTGS2	-9.9
beta-sitosterol	BCL2	-6.4
hederagenin	PRKCA	-7.7
hederagenin	PTGS2	-9.6

3.7 Molecular dynamics (MD) simulations results

MD simulation can be exploited to visualize the real movement and structural modifications of a protein in a biological system. MD trajectories can be evaluated by calculation of Root-Mean-Square Deviation (RMSD) and the Root Mean Square Fluctuation (RMSF) of the compounds.The RMSD parameter which is the rate of the mean distance between the atoms is required for examining

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the equilibration and the structural stability of the protease in the presence of a docked ligand. The variation of flexibility in terms of RMSF parameter can be utilized to investigate inhibitor binding to the target, higher RMSF values mean that the protein has more flexible domains. The hydrogen bond is critical in providing a stable foundation for biological systems[22]. The MD simulation trajectories may be used to compute the hydrogen bonds in drug-protein combinations[23]. Assessment of RMSD outputs for acne main receptor PTGS2 and components acacetin, beta-sitosterol and hederagenin demonstrates the stability of the combinations. It was observed that all three components reach stability, the value of RMSD remains stable in the range of 0.10-0.30. And the results of RMSF describe the stability of protein and components. Fewer oscillations have been perceived in the later stage, maybe related to protein conformational adjustment. The hydrogen bonding results show that the number of hydrogen bonds in hederagenin and PTGS2 is distributed between 0-3, the number of hydrogen bonds in beta-sitosterol and PTGS2 is distributed between 0-2, and the number of hydrogen bonds in acacetin and PTGS2 is distributed between 0-6, which is relatively stable.(Figure 6)

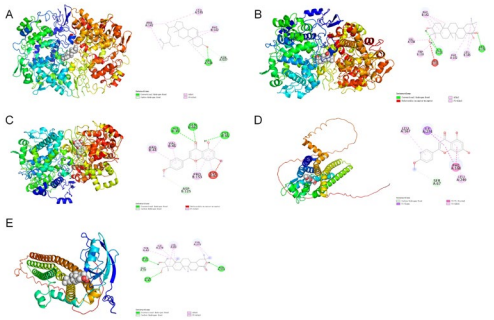


Fig. (5). If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

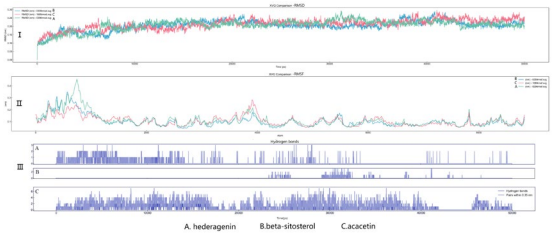


Fig. (6). If a figure is in separate parts, all parts of the figure must be provided in a single composite illustration file.

4. Discussion

Acne, a prevalent inflammatory skin condition characterized by pustules, papules, pimples, and blackheads, can also significantly impact individuals' psychological well-being and overall quality of life[24, 25]. Given the adverse effects and growing drug resistance associated with current acne treatments, there is an imminent need for the discovery of safe and effective anti-acne medications. Teratogenicity associated with retinoids, cutaneous adverse effects of topical anti-acne medications, and lack of long-term remission induction are a few hindrances that have to be tackled by novel therapies.In this investigation, we aimed to elucidate the intricate signaling pathways and networks involving acacetin, beta-sitosterol, and hederagenin(the ingredients of Digupi)by integrating data from publicly available sources related to Digupi and acne. Furthermore, we sought to predict the interactions between Digupi and potential protein targets associated with acne. Research has indicated that digupi has the potential to modulate key targets including PRKCA, TP53, AR, PTGS2, BCL2, as well as other critical targets by interacting with diverse chemical components, such as acacetin, beta-sitosterol, hederagenin, and more. This interaction results in a multi-faceted, multi-networked approach for achieving anti-acne effects. Notably, acacetin, a dihydroxy and mono methoxyflavonoid, exhibits properties with anticancer, anti-inflammatory, anti-infective, and therapeutic potential for metabolic diseases [26]. Beta-sitosterol modulates multiple cell signaling pathways, such as apoptosis, proliferation, invasion, angiogenesis, and metastasis, resulting in its diverse pharmacological effects, which encompass anti-inflammatory, anticancer, antioxidant, and antidiabetic properties [27]. Furthermore, Ersilia Tolino et al. demonstrated a significant improvement in efficacy among acne patients through the use of topical creams enriched with beta-sitosterol as an ingredient [28]. Hederacanthin (HG), a pentacyclic triterpenoid found in various medicinal plants, exhibits a range of pharmacological effects, including anticancer, anti-inflammatory, antidepressant, antidiabetic, antihyperlipidemic, and antiviral activities [29]. In summary, acacetin, beta-sitosterol, and hederagenin may play important roles in the treatment of acne as important components of digupi. In addition, molecular docking showed that PTGS2 had the lowest binding energy and more stable intermolecular binding with acacetin, beta-sitosterol, and hederagenin. Prostaglandin Endoperoxide Synthase 2 (PTGS2, also known as COX-2) has been shown to be a mediator of inflammation and oxidative stress induced by Propionibacterium acnes [30], and to play an important role in the pathology associated with inflammatory signaling [31]. In addition, several anti-acne drugs such as Punica granatum [32], Knautia drymeia Heuff [33], Pyrrolidine dithiocarbamate [34] and Kaempferia [35] target PTGS2, and the use of all of these drugs reduces PTGS2 expression; therefore, PTGS2 may be a key target of digupi in the treatment of acne.

In addition, enrichment analysis showed that digupi targets associated with acne were mainly enriched in the PI3K-Akt signaling pathway, lipid and atherosclerosis, AGE-RAGE signaling pathway in diabetic complications, sphingolipid signaling pathway, and thyroid hormone

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signaling pathway, among other pathways. Primary factors contributing to the development of acne vulgaris encompass increased sebum production, disrupted keratinization in follicular sebaceous gland ducts, the presence of Propionibacterium acnes, and associated inflammation [36]. Lipids can influence both bacterial growth and the host immune response. Lipids that accumulate within the follicular duct undergo oxidation via a lipase enzyme produced by Cutibacterium acnes (C. acnes), thereby promoting bacterial proliferation [37]. The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway regulates various cellular processes, including cell growth, proliferation, migration, angiogenesis, and skin development, and it holds significant relevance in the pathogenesis of acne [38, 39]. The dysregulated phosphatidylinositol-3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signaling pathway has been implicated in various immune-mediated inflammatory and hyperproliferative dermatoses such as acne, atopic dermatitis, alopecia, psoriasis, wounds, and vitiligo, and is associated with poor treatment outcomes. Several studies have revealed that certain natural products and synthetic compounds can obstruct the expression/activity of PI3K/Akt/mTOR, underscoring their potential in managing common and persistent skin inflammatory disorders [40]. Activation of the AGE-RAGE signaling pathway triggers a cascade of pathological events, including inflammation, oxidative stress, cell proliferation, and apoptosis, which are intricately involved in the development of diabetic complications. Consequently, the AGE-RAGE signaling pathway may also contribute to the pathogenesis of acne [41, 42]. Thyroid hormones play a pivotal role in the growth and differentiation of follicular sebaceous gland units (PSUs), and elevated circulating thyroxine levels have been associated with increased sebum secretion and the formation of acne [43, 44]. Therefore, Digupi may potentially impact acne development through its influence on these pathways.

This study also has several limitations. Firstly, the research approach based on network pharmacology cannot accurately predict whether the targets are upregulated or downregulated in the disease, and it may not provide a precise understanding of the mechanisms underlying the action of targets in the disease. Secondly, our study primarily relies on data from databases and network analyses, which may impact the accuracy of the data. Further experiments will be conducted to elucidate the specific molecular functions and mechanisms by which Digupi affects acne.

5. Conclusion

In this study, the mechanisms by which digupi affects acne were analyzed using network pharmacology. The findings demonstrated that Digupi's anti-acne treatment exhibits a multifaceted pharmacological effect involving multiple components, targets, and pathways. Additionally, molecular docking analysis substantiated the validity of the predictions made using a network pharmacology-based approach. Notably, this study provides a valuable foundation for understanding the therapeutic role of digupi in acne.

Ethical Approval

not applicable.

Funding

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Institutional Review Board Statement

Not applicable.

Data Availability Statement

The data that support the findings of this study are openly available in [TCMSP] at https://old.tcmsp-e.com/tcmsp, [Uniprot database] at https://www.uniprot.org/, [GeneCard database] at https://www.genecards.org/, [OMIM] at https://omim.org, [DisGeNET] at https://www.disgenet.org, [Venn tool] at https://bioinfogp.cnb.csic.es/tools/venny/, [Cytoscape 3.7.2 software] at https://cytoscape.org/, [STRING database] at https://string-db.org/, [Metascape database] at https://metascape.org, and [RCSB PDB database] at http://www.rcsb.org .

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Conflicts of Interest

The authors declare no conflict of interest.

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