Minireview

Therapeutic potential of HIV-1 entry inhibitor peptidomimetics

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Impact statement

Significant improvement has been made in the management of human immunodeficiency virus 1 (HIV-1) infection, but the use of highly active antiretroviral therapy (ART) is limited by multidrug resistance, prolonged use effects, and inability to purge the HIV-1 latent pool. Even though broadly neutralizing antibodies (bNAbs) have potential for HIV-1 infection as a therapeutic option, the antibodies are limited by cost of production and obligatory requirement for parenteral administration. Antibody mimetics/peptidomimetics of HIV-1 entry inhibitors could serve as an alternative for HIV-1 bNAbs and should therefore be explored as suitable candidates for HIV-1 therapy.

Abstract

Human immunodeficiency virus 1 (HIV-1) infection remains a public health concern globally. Although great strides in the management of HIV-1 have been achieved, current highly active antiretroviral therapy is limited by multidrug resistance, prolonged use-related effects, and inability to purge the HIV-1 latent pool. Even though novel therapeutic options with HIV-1 broadly neutralizing antibodies (bNAbs) are being explored, the scalability of bNAbs is limited by economic cost of production and obligatory requirement for parenteral administration. However, these limitations can be addressed by antibody mimetics/peptidomimetics of HIV-1 bNAbs. In this review we discuss the limitations of HIV-1 bNAbs as HIV-1 entry inhibitors and explore the potential therapeutic use of antibody mimetics/peptidomimetics of HIV-1 entry inhibitors as an alternative for HIV-1 bNAbs. We highlight the reduced cost of production, high specificity, and oral bioavailability of peptidomimetics compared to bNAbs to demonstrate their suitability as candidates for novel HIV-1 therapy and conclude with some perspectives on future research toward HIV-1 novel drug discovery.

Keywords: Human immunodeficiency virus 1, broadly neutralizing antibodies, peptidomimetics, entry inhibitors, antiretroviral therapy, HIV-1 novel drug discovery

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Introduction

An estimated 38 million people were living with HIV globally in 2019, of which 25.4 million had access to ART and about 690,000 had died from acquired immunodeficiency syndrome-related illnesses.[1] Human immunodeficiency virus (HIV) belongs to the genus *Lentivirus* and family *Retroviridae* and is a single-stranded, enveloped, positive-sense ribonucleic acid (RNA) virus. Although there is currently no sterilizing cure for HIV-1 infection, therapeutic management has been accomplished with antiretroviral (ARV) drugs.[2,3] Highly active antiretroviral therapy (HAART) suppresses viral replication to largely undetectable levels in plasma and allows the depleted CD4+ T cell population to recover.[4] The HAART regimen typically includes two or more classes of ARV drugs that target varied aspects of the HIV-1 life cycle.[5] Presently, four classes of ARV drugs have been approved for HIV-1 chemotherapy: reverse transcriptase inhibitors (RTIs), protease inhibitors, entry inhibitors, and integrase inhibitors.[6] HAART is limited because it is unable to reach the HIV-1 latent pool, has side effects with prolonged use, and selects for multidrug-resistant viral strains.[7,8] In view of the highlighted HAART-related limitations, there is the need for novel therapeutic options for HIV-1 infection.[9]

Currently, only enfuvirtide (a fusion inhibitor) and maraviroc (CCR5 antagonist) have been approved as entry inhibitors for clinical use in HIV-1 chemotherapy.[10] However, the subcutaneously administered, large polypeptide enfuvirtide is associated with painful injection sites, and maraviroc is associated with the emergence of CXCR4 tropic viruses and has therefore limited their clinical utility.[9,11,12] The development of highly specific small molecules and/or biologicals that inhibit HIV-1 entry could be the paradigm shift that is needed to make HIV-1 management more successful. Biologicals such as monoclonal antibodies have the advantage of high specificity in drug targeting compared to small molecules.[13,14]

Even though biologicals are susceptible to enzymatic degradation and protein unfolding if orally administered, and subcutaneous deliveries are prone to presystemic degradation by enzymes such as hydrolase and proteases, the exploration of efforts to maximize oral delivery of biological therapeutic agents is being pursued.[15] A particular research theme that may be promising in this vein is the utility of antibody mimetics or peptidomimetics.[16]

Peptidomimetics are organic molecules that have structural and functional similarity to the native peptide. They are developed by altering the structure of an existing peptide or by designing similar molecules that act as natural peptide equivalents and interact with receptors of a native peptide with equal or higher affinity to produce an agonistic or antagonistic effect.[17,18] Therefore, they have improved pharmacodynamic and pharmacokinetic properties such as selectivity, potency, oral bioavailability, and reduced side effect.[18] The principle of peptidomimetics has been used successfully in the development of clinically translated peptide inhibitors such as angiotensin-converting enzyme (ACE), thrombin, HIV-1 protease, B-cell lymphoma 2 (BCL-2), and inositol-requiring enzyme 1 (IRE1) inhibitors.[19–22] Peptidomimetics are also used as alternatives to antibody therapeutics to surmount drawbacks such as high production costs, complex formulation processes, subcutaneous delivery requirements, metabolic stability concerns, maintenance of cold chain during transport, and risk of treatment failure due to host variation.[23]

In this review, we discuss the limitations of HIV-1 broadly neutralizing antibodies (bNAbs) as HIV-1 entry inhibitors and explore the therapeutic use of antibody mimetics/peptidomimetics of HIV-1 entry inhibitors as an alternative for HIV-1 bNAbs. We highlight the reduced cost of production, high specificity, and oral bioavailability of antibody mimetics compared to bNAbs, and we conclude with some perspectives on future research to discover novel HIV-1 drugs.

HIV bNAbs as entry inhibitors

HIV entry into the host cell is mediated by a series of complex protein–protein interactions, the first of which involves relatively non-specific attachment of the viral envelop protein to the host cell membrane via the syndecan family of cell-surface heparan sulfate proteoglycans, alpha4beta7 integrin, or DC-SIGN pattern recognition receptors.[24–26] Subsequently, the HIV Env protein binds to the host receptor protein CD4, and this interaction causes the formation of a bridging sheet that enables co-receptor binding to one of two chemokine receptors (CCR5 and CXCR4), juxtapositioning of the viral and cell membranes, pore creation, and final deposition of the viral genetic material into the cytoplasm.[27–29]

Effective HIV-1 cell entry inhibitors remain an unmet need in HIV prevention and treatment. The Env gp120 protein is an attractive target in HIV drug discovery because it is an obligatory requirement for HIV-1 entry into host cell receptors.[30] This conceptual palatability has spawned a renewed interest in HIV-1 "entry and fusion inhibitor" drugs.[31] HIV-1 entry and fusion inhibitors are grouped into CD4 receptor inhibitors, co-receptor antagonists (CCR5 and CXCR4), and fusion inhibitors, based on their target, and represent a set of unique pharmacodynamic properties that prevent HIV entry into target host cells and therefore effective cessation of viral replication.[31–33] With the current limitations of HAART, entry and fusion inhibitors have the potential to transform HIV chemotherapy especially with regards to HIV-1 drug-resistant strains.[31,34] Ibalizumab (Trogarzo®) is a CD4 receptor-specific monoclonal antibody that binds to CD4 to prevent HIV-1 entry without compromising the immunological function of the CD4 receptor and has been approved for HIV treatment in patients with advanced and multidrug-resistant HIV-1 infection.[35–37] Ibalizumab demonstrates the utility of HIV-1 entry and fusion inhibition in managing multidrug resistance.

Early approaches in the 1980s used serum from HIV-infected patients with high titers of HIV-1 neutralizing antibodies that recognized the HIV-1 capsid.[38] However, by 1990, HIV-1 envelope protein was established as the sole target of the neutralizing antibodies and not the capsid.[39] Therefore, in the early 2000s, the first generation of monoclonal neutralizing antibodies (mNAbs) that targets various epitopes on the HIV-1 envelope protein were isolated, characterized, and translated as immunotherapy.[40,41] Although these antibodies were well tolerated and safe, they only showed modest suppression of viremia and escape variants developed, and this limited their practical use.[40,42–44]

Recent technological advances in HIV-1 pseudotype virus production, B-cell technology, and high throughput neutralization assays have reignited research efforts in the field of HIV-1 mNAbs.[45,46] Some persons living with HIV, referred to as "elite neutralizers," generate high titers of highly potent and bNAbs that have shown high efficacy in reducing viremia in both human and animal models.[47,48] bNAbs have been shown to completely prevent Simian-HIV infections in other primates, suppress viremia in HIV-1-infected individuals, and effectively suppress viremia in humanized mouse models, even after discontinuing therapy for up to 60 days.[49–53]

Limitations of HIV-1 bNAbs as entry inhibitors

Antibody engineering for therapeutic use is a cost-intensive process with several methodological constraints.[54] Murine-derived antibodies are limited by relatively less therapeutic efficacy, risk of target host immunogenic reactions, and short half-lives.[55,56] Chimeric antibodies developed to improve on the murine antibody shortfalls still provoke a human anti-chimeric antibody immune response.[57,58] Alternatively, humanized mice are used to generate affinity-matured and full-length antibodies ideal for therapeutic use.[59] However, the B-cell population in the spleen and antibody expression level in humanized mice is lower than in wild-type mice, indicative of compromised immunity in humanized mice.[60] Another platform for generating complete human antibodies for therapeutic use is the phage-displayed library.[61] Although phage display is suitable for large-scale production of antibodies, it is relatively

low throughput and tedious with increased risk of mismatched heavy and light chain pairing.[62]

The complexity of therapeutic antibody and the presence of undesired biophysical properties make large-scale manufacturing of clinically suitable antibodies exceedingly challenging.[63] As biologics, antibodies are highly unstable, and degradation can pose a substantial risk to patients' safety and impact negatively on clinical efficacy.[64,65] Production of biologically functional monoclonal antibodies is considered capital intensive, and this is because monoclonal antibodies are large proteins that often require post-translational modifications. Lower organisms such as yeast, bacteria, plant cell, and insects do not possess adequate machinery to produce functional antibodies.[66–68] Post-translational modification necessitates the use of machinery from mammalian cells to produce an active form of the protein suitable for clinical use.[59] These cell-based expression systems are considered expensive and inefficient, with a varying yield that is dependent on the expression system or the product.[68]

The large size of bNAbs limit tissue penetration, can result in off-target tissue accumulation, and directly impact its clinical efficacy.[69] Oral delivery of biotherapeutics is practically impossible, due to their larger size, and their preferred route of administration is through subcutaneous injection even though the pharmacokinetic profile of subcutaneously administered biotherapeutics is characterized by a slow rate of absorption.[15,70] Furthermore, therapeutic antibodies are prone to enzymatic degradation either at the site of administration or while in circulation, which can further reduce their bioavailability and clinical efficacy.[71]

The high cost of treatment is another significant factor that limits the clinical scalability and access of antibody therapy with bNAbs. The average annual cost of therapy is approximately USD100,000 per patient.[72] Although therapeutic antibodies cost differs according to their use, for example, antibody therapy used in oncology are more expensive than those used in autoimmune and viral diseases.[72] Furthermore, the market for antibody therapy in viral diseases is smaller, and this makes the high production cost a limitation in the profitability of HIV therapeutic antibodies from a commerce perspective.[73,74]

The limitations associated with therapeutic antibodies can be surmounted by developing mimetics of monoclonal antibodies known as peptidomimetics. Peptidomimetics are an important class of drugs that mirror the functionality of their corresponding peptide/protein, with improved stability and bioavailability, reduced immunogenicity, and less manufacturing complexity.[75,76]

HIV-entry inhibitors

The therapeutic utility of peptidomimetics has been demonstrated across varied fields such as oncology, cardiology, and infectious diseases.[77–85] Peptidomimetics offer a more target-specific approach compared with the low target specificity and accompanying side effects of conventional chemotherapeutic agents.[86] Furthermore, peptidomimetics provide better oral bioavailability and therapeutic potency and have shown promise in the fight against antimicrobial and antimalarial drug resistance.[87–94] In HIV chemotherapy, a number of peptidomimetics have already been approved and others are under development (Table 1) and thus demonstrated the feasibility of peptidomimetics for HIV-1 chemotherapy.

Peptidomimetic of NMWQKVGTPL, a natural peptide of CD4 binding, has been designed by removing all the non-binding amino acid residues, replacing hydrophobic leucine and tryptophan with synthetic analogue, and introducing non-peptide links. This peptidomimetic exhibited a 150-fold higher binding affinity to CD4, lower molecular weight, and increased proteolytic stability compared to the natural peptide.[112] Peptide triazoles (PTs) are a novel class of HIV inhibitors that interact with HIV gp120 and disrupt HIV infection by suppressing gp120 interactions with host cells receptor and co-receptor, resulting in the shedding from the virion particle. Furthermore, conjugation of thiol-containing PT on gold nanoparticles enhances viral membrane disruption and luminal p24 release. Peptidomimetics of peptide triazole provide a model that enhances the activity of PTs and helps in the development of HIV-1 inactivators that can prevent HIV entry into host cells.[124,125]

C-peptides, obtained from the C-terminal heptad repeat 2 (HR2) region of the HIV-1 gp41, are a potent fusion inhibitor. They prevent gp41 NHR-CHR interaction by binding to the coiled N-peptide region, which is transiently exposed in the prehairpin intermediate state.[126] C-peptide-based peptidomimetics have been designed for HIV fusion inhibitions. Amongst these peptidomimetics are D-peptide fusion inhibitors that were discovered using a D-amino acid variant of the HIV-1 gp41 through a mirror-image phage display and are stable in the presence of protease as well as being potentially orally bioavailable.[113,114] Foldamers are formed by replacement of selected amino acid residues from C-peptide fusion inhibitors with β-amino acid residues.[127] Like small-molecule drugs, these peptidomimetics present with oral bioavailability and stability and provide clues for the creation of small-molecule fusion inhibitors.[127]

Mimetics of soluble CD4 (sCD4) induce structural changes in gp120 that cause a short-term increase in infectivity of the virus but eventually lead to the inactivation of virus Env protein. Despite the implied clinical utility in HIV infection, sCD4 exhibits minimal efficacy in inhibiting viral infection in several HIV strains *in vivo*, due to the slow kinetics of inactivation of HIV Env caused by sCD4 and a failure to achieve adequate serum mimetic sCD4 levels. CCR5 co-receptor mimetics, derived by functionalizing interacting epitopes of CCR5 and gp120 with a palmitoyl group, improve the efficiency of sCD4-mediated HIV Env inactivation and HIV entry inhibition.[122] Furthermore, *in silico* approaches has led to the identification of a peptidomimetic inhibitor based on gp120-Scd4 interaction with high binding affinity to HIV-1 gp120 and good drug-like properties.[128]

Small-compound mimetics of CD4 receptors have been developed, and these CD4 mimetics have been shown to interact with the conserved CD4 binding site (CD4bs) on

Table 1. Approved and investigational new drug peptidomimetics for HIV-1 chemotherapy.

Peptidomimetics	Status	Properties
Saquinavir (SQV)	FDA approved (1997)	Hydroxyethylamine class peptidomimetic of HIV protease inhibitor with limited oral bioavailability[95,96]
Amprenavir (APV)	FDA approved (1999)	Higher aqueous solubility compared to SQV[97,98]
Indinavir (IDV)	FDA approved (1996)	Rapid absorption and oral bioavailability at low concentrations[99,100]
Ritonavir	FDA approved (1996)	Enhances the half-life of other protease inhibitors when co-administered[101,102]
Nelfinavir	FDA approved (1997)	An isostere of saquinavir with improved oral bioavailability[101,103]
Tipranavir (TPV)	FDA approved (2005)	Superior resistant profile[104–106]
Fosamprenavir	FDA approved (2003)	A phosphate prodrug of amprenavir with superior aqueous solubility and bioavailability[107]
Lopinavir	FDA approved (2000)	A ritonavir-based peptidomimetics with higher potency and activity against ritonavir-resistant virus[107–109]
Darunavir	FDA approved (2006)	A non-peptidic peptidomimetic with a high binding affinity with the substrate and increased bioavailability when it is administered with ritonavir[110]
Diol-based peptidomimetics	Experimental discovery	Potential inhibition of HIV with antitumor properties[111]
Peptidomimetic of NMWQKVGTPL	Experimental discovery	Exhibited a 150-fold higher binding affinity to CD4, lower molecular weight, and increased proteolytic stability compared to the natural peptide[112]
D-peptide fusion inhibitors	Experimental discovery	Designed using a D-amino acid variant of the HIV-1 gp41. They are stable in the presence of protease and potentially orally bioavailable[113–115]
BMS-378806 and analogues	Experimental discovery	Low-molecular-weight small-compound mimetics of soluble CD4 receptors that exhibited inhibitory activity against HIV-1 clade B isolates[116]
NBD-556 and analogues	Experimental discovery	Small-compounds mimetics that bind solely to the gp120 and inhibit viral infectivity at a micromolar range[117]
Peptidomimetics of bNAbs VRC01	*In silico* discovery	Binds to the conserved pocket of HIV-gp120 and were predicted to inhibit the gp120-CD4 interaction[118]
Novel scaffold peptidomimetics of 10E8	*In silico* discovery	Mimics the gp41 MPER region pharmacophore by binding to the critical amino acid residues of a highly conserved hinge region of the MPER peptide[119]
Peptidomimetic of an anti-CD4 antibody ST40	*In silico* discovery	Compared to the parent antibody, this mimetic has higher affinity for CD4; however, it displays low biological activity against HIV[120]
Peptidomimetics of VRC01 conformational epitopes	Experimental discovery	Mimetics that could potentially serve as part of a synthetic immunogen capable of eliciting reactive neutralizing antibodies[121]
A bivalent peptidomimetic of 34-mer fragment peptide (C34)	Experimental discovery	Increased anti-HIV-1 activity[121]
CCR5-peptidoliposomes mimetics	Experimental discovery	Increases HIV infection inhibition efficiency of sCD4[122]
CD4 mimetics	Experimental discovery	Induce antibody-dependent cell-mediated cytotoxicity (ADCC) in HIV-1-infected cells[123]

FDA: Food and Drug Administration; MPER: membrane-proximal external region.

HIV-1 gp120. BMS-378806 and analogues are low-molecular-weight HIV-entry inhibitors that target HIV-1 gp120[116]; they exhibited inhibitory activity against a panel of X4, R5, and R5/X4 HIV-1 clinical and laboratory isolates of the HIV-1 clade B. Structural analysis revealed that the BMS-378806 series exhibits functional mimicry of CD4 receptor through interaction with Phe43 cavity of the CD4bs in HIV-1 gp120. The BMS-series function by binding to and causing a conformational change in gp120 and consequently preventing CD4 binding.[129] NBD-556 and analogues are another set of small-compound mimetics that target HIV gp120 as HIV-entry inhibitors. NBD-556 binds solely to gp120 and inhibits viral infectivity at a micromolar concentration range.[117] Similar to CD4 receptor, NBD-556 also binds in the highly conserved Phe43 cavity in CD4bs, resulting in a conformational change in gp120 that is functionally akin to that of CD4 bound to gp120.[130]

The leading strategy toward eradication of HIV infection is the depletion of viral reservoirs through the reversal of viral latency, followed by clearance of persistently infected cells. Peptidomimetics of the N-terminal tetrapeptide region of the second mitochondrial-derived activator of caspases (SMACm) have shown potent latency reversal abilities. AZD5582, an example of these mimetics, enhances the expression of cell-associated HIV RNA in resting CD4+ T cells in virally suppressed HIV-infected individuals both *in vivo* and *in vitro* and without inducing pleiotropic cellular effects that are observed in other latency-reversing agents.[119]

Peptidomimetics of HIV-1 bNAbs

Computational approaches have allowed the discoveries of several potential peptidomimetics of CD4 binding site of HIV-1 bNAbs. N6 is a highly potent and broadly reactive

CD4-bs HIV bNAbs, and peptidomimetics of N6 that exhibit pharmacophoric mimicry of the features of the immunoglobulin by selective binding to the CD4bs of HIV-1 gp120 have been identified. These peptidomimetics had multiple intermolecular interactions with gp120, including van der Waals links with conserved residues of the Phe-43 cavity of gp120 and H-bond with Asp-368_{gp120}. HIV gp120 in complex with these peptidomimetics were shown to be stable with lesser values of free binding energy when compared to known entry inhibitors. Using molecular docking and molecular dynamics approaches, peptidomimetics of VRC01, another CD4bs antibody, were discovered based on the interaction between HIV-1 gp120 and the antigen-binding fragment of VRC01.[118] Similar to the mechanism of VRC01, these peptidomimetics bind to the conserved pocket of HIV-gp120 and were predicted to inhibit the gp120-CD4 interaction.[118] Novel scaffolds that mimic 10E8, an HIV-1 bNAbs that targets the membrane-proximal external region (MPER) of the HIV-1 gp41 as potential fusion inhibitor, have been identified using computational drug discovery approaches. These scaffolds functionally mimic the gp41 MPER region pharmacophore by binding to the critical amino acid residues of a highly conserved hinge region of the MPER peptide, which confers conformational flexibility that is required for host cell-virus membrane fusion.[119] A peptidomimetic of an anti-CD4 antibody (ST40), which comprise of antigen-binding residues from multiple complementarity-determining regions, has also been identified using computational approaches. Compared to the parent antibody ST40, the mimetic has a higher affinity for CD4; however, it displays low biological activity against HIV.[131]

Potential limitations of peptidomimetics for HIV-1 therapy

Peptidomimetics are gaining prominence as therapeutic agents due to their stability, specificity, fast tissue penetration and relative cost-effectiveness compared to natural antibodies. Despite these benefits that peptidomimetics have over natural antibodies, some potential limitations are inherent in their application.

The absence of an Fc receptor binding equivalent and the relatively smaller sizes of peptidomimetics reduce their *in vivo* half-life and are therefore cleared faster compared to natural antibodies. The absence of the Fc binding receptor motif in peptidomimetics suggests that they cannot utilize natural antibody effector functions like antibody-dependent cell cytotoxicity and opsonization. This limitation to a competition kinetics with the HIV-1 drug target sets the stage for the selection of drug-resistant variants. Conjugating peptidomimetics with the Fc component of the immunoglobulin, to merge the benefits of both peptidomimetics and natural antibodies, may enhance the overall efficacy of peptidomimetics.

To improve the molecular weight of peptidomimetics and lengthen their plasma half-life, bioengineering techniques such as PEGylation and proline-alanine-serine (PASylation) have been deployed. PEGylation, which involves the attachment of PEG polymer to the antibody mimetics and thereby decreasing renal clearance, has challenges like immunogenicity, possible protein-function suppression, high cost, and non-biodegradability that need to be surmounted. An alternative to PEGylation is PASylation, which increases plasma half-life of peptidomimetics without eliciting an immunogenic reaction. Additionally, conjugating antibody mimetics to a small protein that is called albumin binding domain can help extend their plasma half-life.[132]

While peptidomimetics have several advantages over natural antibodies as therapeutic agents, the use of protein scaffolds for the design and modification of these mimetics can increase the cost of their development. In order to gain competitive advantage against natural antibodies in the commercial arena of HIV-1 therapeutics, peptidomimetics must have a lower cost of identification from libraries, high-throughput selection, and decreased cost of the enrichment process. Intellectual property protection presents another bottleneck in the development and application of peptidomimetics as sequences and structures of peptidomimetics are closely guarded proprietary data and are not easily available to the entire scientific community. This may hinder efforts toward advancing the therapeutic potential of peptidomimetics. Therefore, reducing the cost of peptidomimetics identification and design would augur well for the field.

Concluding remarks and future perspectives

Many studies have highlighted the therapeutic potential of peptidomimetics. In HIV infection, the potential value of peptidomimetics and their suitability as alternatives to bNAbs in HIV chemotherapy stem from their oral available formulations, more stable composition, and relatively cheaper cost of production compared to bNAbs. Presently, HIV latency remains a stumbling block toward a cure for HIV-1 infection, and efforts at HIV drug discovery largely remain pathogen centered and small molecule dependent, which, in our opinion, has inadvertently contributed to the current limitations of HAART. To surmount the hurdles of HIV-1 latency and drug resistance, we propose a strategic shift to identifying druggable host targets that inhibit HIV-1 viral entry with a peptidomimetic. Taking this proposal into consideration, more drugs like Trogarzo are welcomed, and even more so, oral peptidomimetics that target host receptors like the CD4 receptor. We propose that this strategic approach is feasible in the light of strides that have already been made in HIV-1 peptidomimetic therapeutics and advocate for further studies in the field of HIV-1 entry inhibition using peptidomimetics toward host-druggable targets.

AUTHORS' CONTRIBUTIONS

The authors' contributions were as follows: conceptualization: NPUK, KZT, SKK, and OQ; methodology: NPUK, KZT, SKK, and OQ; manuscript draft: NPUK, KZT, SKK, and OQ; critical review and editing: NPUK, KZT, SKK, and OQ. All authors read and approved the final version of the manuscript.

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