ORIGINAL ARTICLE

Identification of PI3Kα inhibitors through pharmacophore design and drug repositioning

Paolo Wong Chero [1,a]; Daniel Ramírez Lupuche [1,b]; Richard Zapata Dongo [1,c]; Brenda Moy Díaz [1,d]; Stefany Infante Varillas [1,e]; Juan Faya Castillo* [1,f]

ABSTRACT

Objective: Phosphatidylinositol 3-kinase (PI3K) is one of the most frequently mutated proteins in cancer, resulting in changes to its roles in regulating metabolism, immunity and other cellular functions. Despite the identification of specific drugs targeting PI3K, significant resistance to these therapies has been observed. Therefore, the search for new inhibitors is crucial. This project proposes a strategy based on in silico tools for screening Food and Drug Administration (FDA)-approved drugs, aiming to evaluate their potential for drug repositioning.
Materials and methods: This study obtained the sequence of PI3Kα from UniProt Knowledgebase and its three-dimensional structure from AlphaFold Protein Structure Database, which were then coupled with adenosine triphosphate (ATP) and its selective inhibitors: inavolisib, taselisib, CH5132799, alpelisib and ZSTK474. Drug-protein interaction analysis was performed using Protein-Ligand Interaction Profiler (PLIP) and its visualization was done in PyMOL. Based on this information, pharmacophores were generated as models for virtual screening using the FDA-approved drug library available in Pharmit (https://pharmit.csb.pitt.edu/search.html).
Results: Key atomistic positions of drug-protein interactions were identified based on the selective PI3Kα inhibitors interaction, leading to the generation of nine pharmacophores. A virtual screening resulted in 22 drugs that met the proposed criteria, out of which 10 had binding energy values (kcal/mol) equal to or higher than those of the PI3Kα inhibitors. Subsequently, three drugs with potential use for drug repositioning were selected.
Conclusions: This study proposes fostamatinib, pralatrexate and entecavir as potential candidates for drug repositioning. Additionally, the nine pharmacophores can be utilized in other drug databases for identifying new molecules and/or drugs with potential for drug repositioning. Further in silico and in vitro studies of the proposed drugs are recommended.

Keywords: PI-3K, Molecular Docking Simulation; Computational Biology; Neoplasms; Pharmacophore (Source: MeSH NLM).

INTRODUCTION

The significant pathological variability of cancer and its growing drug resistance are increasingly limiting the efficacy of many treatments and worsening patient prognosis [1]. In the search for new therapeutic strategies to address these challenges, several studies have focused on the metabolic pathways involved in cancer development and progression to identify potential points of metabolic inhibition and halt tumor growth. Among these potential targets is phosphatidylinositol 3-kinase (PI3K), a key enzyme for regulating metabolism, immunity and other cellular functions. Notably, PIK3CA is one of the most frequently mutated genes in cancer, with alterations detected in approximately 14 % of all cases. Consequently, PI3K-targeted drugs have been developed in recent years [1-3]. Pan-PI3K inhibitors are expected to help overcome cancer resistance to a wide variety of therapies such as chemotherapy, radiation and targeted therapies [4,5].

PI3K is a family of lipid kinases categorized into three classes: I, II and III, with class I further subdivided into subtypes A and B [6]. These kinases act as signal transducers of receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs) and GTPases, ultimately regulating various cellular processes such as growth, proliferation, differentiation, migration, motility and apoptosis [1,2]. Class IA PI3K consists of a p85 regulatory subunit (p85α, p85β, p55α, p55γ, p50α) and a p110 catalytic subunit (p110α, p110β, p110γ, p110δ) [6]. The p110 catalytic subunit consists of an adaptor-binding domain (ABP), a RAS-binding domain (RBD), a membrane-binding C2 domain (C2), a helical domain, and a C-terminal catalytic domain (N- and C-terminal sections), which includes the hinge region where adenosine triphosphate (ATP) binds [2]. Meanwhile, the p85 regulatory subunit is composed of the SRC homology 3 (SH3) domain, breakpoint cluster region-homology (BH) domain, and internal SH2 (iSH2), C-terminal SH2 (cSH2) and N-terminal SH2 (nSH2) domains,

1 Universidad de Piura, School of Human Medicine, Lima, Peru.
[a] Doctor of Medicine, master's degree in Biomedical Research; [b] Human Medicine student; [c] Biologist, master's degree in Biomedical Research; [d] Pharmaceutical chemist; [e] Microbiologist, master's degree in Biomedical Research; [f] Biologist, master's degree in Bioinformatics.
*Corresponding author.

which must dissociate from the p110 subunit to activate PI3K [4]. Oncogenic mutations in PI3K are primarily found in the p110 catalytic subunit, specifically within RBD, helical (E542K, E545K) and catalytic (H1047R) domains [7]. These somatic mutations promote a gain of function, leading to excessive PI3K activity [4] and enhancing activation mechanisms between p110 and p85 [2]. Notably, studies have shown that eliminating PI3K activity halts tumor growth [8].

Based on the structural characterization of PI3K and its cytostatic effect upon inhibition, drugs have been developed to achieve tumor stabilization [2]. These drugs are generally ATP-competitive inhibitors and can be classified into pan-inhibitors, isoform-selective inhibitors and dual PI3K/mTOR inhibitors [6]. The first developed pan-inhibitors were wortmannin and LY294002 [9,10]. Later, in 2014, idelalisib (PI3Kδ inhibitor) became the first approved PI3K inhibitor [2]. To date, five PI3K inhibitors have been approved by the Food and Drug Administration (FDA): copanlisib, idelalisib, umbralisib, duvelisib and alpelisib [6]. Despite these advancements, some challenges have hindered clinical trials and drug approval, such as poor tolerance to pan-inhibitors and dual PI3Kα/PI3Kδ inhibitors, intrinsic and acquired drug resistance, and signaling feedback loops that neutralize PI3K inhibition [2]. Additionally, achieving isoform selectivity remains difficult, as even currently approved inhibitors can affect multiple PI3K isoform in clinical settings [2].

Cancer resistance to PI3K inhibitors arises through various mechanisms, including PI3K mutations and amplification, drug toxicity, positive feedback leading to compensatory mechanisms, non-coding ribonucleic acid (RNA) regulation of PI3K signaling, increased insulin production, and other miscellaneous mechanisms [6]. These challenges, along with the low isoform selectivity, have driven the search for novel therapeutic strategies. This study employs in silico drug repositioning techniques to identify FDA-approved drugs with potential PI3K inhibitory activity, despite their original indications [11]. A computational approach was used to rapidly screen for competitive PI3K inhibitors based on nine different pharmacophore models. This method provides a cost-effective and rapid strategy for identifying candidate drugs while leveraging their well-established safety profiles from preclinical and clinical studies required for approval [11].

MATERIALS AND METHODS

Study design and population

This descriptive study was conducted using in silico assays in the laboratories at Universidad de Piura. The in silico analyses employed specialized bioinformatics approaches and tools, with the catalytic domain of PI3K serving as the study population. To obtain the structure of PI3Kα (p110), the UniProt Knowledgebase (code: P42336) was initially used as a reference, since the crystallized structures available in Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (www.rcsb.org) were incomplete. The final model of the catalytic domain of PI3Kα was retrieved from AlphaFold Protein Structure Database (https://alphafold.ebi.ac.uk/), which provides high-confidence predictions.

PI3Kα inhibitors were identified from the literature and their co-crystal structures were obtained from RCSB PDB (inavolisib: 8EXV, taselisib: 8EXL, CH5132799: 3APC, alpesilib: 7MYO, ZSTK474: 2WXL). Subsequently, each structure was aligned to AlphaFold using PyMOL. The co-crystal structure of PI3Kα was removed, leaving only the inhibitor structure in complex with AlphaFold. The same process was performed with the ATP-bound co-crystal structure (PDB: 1E8X).

Variables and measurements

The in silico exploratory assays included the following variables: FDA-approved drugs identified through virtual screening, binding energies (kcal/mol) obtained from molecular docking between the catalytic domain of PI3K and the screened drugs, and the amino acids of the drug-protein interaction.

For virtual screening, pharmacophores were generated using the Pharmit web server (http://pharmit.csb.pitt.edu/). Each pharmacophore was designed with five key positions, determined based on the most important inhibitor-protein interactions (inavolisib, taselisib, alpesilib, CH5132799 and ZSTK474) identified via the Protein-Ligand Interaction Profiler (PLIP) web tool (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index). This was further complemented by a literature review on the key regions and amino acids involved in the phosphorylation process between ATP and PI3Kα. With this information, the key positions were defined and their XYZ coordinates were extracted using Pharmit and PyMOL. The virtual screening was conducted with the FDA-approved drug library. A tolerance of 0.5 was set in the "Receptor-Exclusive Shape" command to constraint the molecule size within the ATP-binding pocket.

Binding energies were calculated using the Yet Another Scientific Artificial Reality Application (YASARA) with the "BindEnergy" command. Prior to this, the structures were preprocessed with the "Clean" command and the missing hydrogens were added with the "AddHyd" command. A 10 Å box was generated around the system to encompass the entire protein, followed by energy minimization and docking. Drug-protein interaction amino acids were identified using the PLIP web tool.

Statistical analysis

Descriptive statistics were used to evaluate the binding affinity between the selected drugs and the catalytic domain of PI3K. The values were expressed in a bar graph to visualize the distribution of binding energies. In addition, the frequency of specific interactions was calculated for the selected drugs as candidates for drug repositioning.

Ethical considerations

This study was approved by the Institutional Research Ethics Committee at Universidad de Piura (Approval No. PREMED0820219). As an in silico study, it did not involve human participants or biological materials. The research was conducted in two laboratories at Universidad de Piura: Laboratorio de Cultivo Celular, Microbiología e Inmunología (Cell Culture, Microbiology and Immunology Laboratory) and Laboratorio de Análisis de Proteínas y Bioinformática (Protein Analysis and Bioinformatics Laboratory).

RESULTS

Based on the interactions analysis and literature findings, this study proposes nine pharmacophore models (Table 1), each comprising five key features that reflect the most critical positions used by the existing inhibitors and ATP-binding regions in kinases [12]. Pharmacophores 1, 2 and 3 include positions within the adenine and buried regions. Pharmacophores 4 and 5 incorporate positions in the solvent-accessible region, while pharmacophores 6 and 7 extend into the sugar pocket. Finally, pharmacophores 8 and 9 introduce positions in the phosphate-binding region.

Table 1. Pharmacophore models and their different characteristics

Model	Characteristics
Pharmacophore 1	HBA1, Hyd1, HBA2, Hyd2, HBA3
Pharmacophore 2	HBA1, Hyd1, HBA4, Hyd2, HBA3
Pharmacophore 3	HBA1, Hyd1, Hyd3, HBA5, HBA6
Pharmacophore 4	HBA1, Hyd1, HBD1, Hyd2, HBA3
Pharmacophore 5	HBA1, Hyd1, Hyd2, HBA3, HBA7
Pharmacophore 6	HBA1, Hyd1, Hyd2, HBA3, HBD2
Pharmacophore 7	HBA1, Hyd1, Hyd2, HBA3, HBA8
Pharmacophore 8	HBA1, Hyd1, Hyd2, HBA3, HBA9
Pharmacophore 9	HBA1, Hyd1, Hyd2, HBA3, HBA10

HBD: hydrogen bond donor; HBA: hydrogen bond acceptor; Hyd: hydrophobic; Aro: aromatic ring.

The generated pharmacophore models were used to screen for drugs containing these features in the FDA-approved drug library available in Pharmit. Initially, 33 drugs were identified across the nine proposed models (Table 2). To eliminate redundancy, repeated drugs appearing in more than one pharmacophore model were evaluated based on their binding energy, and only the most relevant candidate was retained. This process resulted in a final selection of 22 drugs.

Table 2. Drugs identified from each model

Model	FDA-approved drugs
1	Sulfadoxine, cefonicid, apalutamide
2	Entecavir
3	Cefamandole, dexamethasone, sulfamethazine, terazosin, trazodone
4	Azilsartan, larotrectinib, regadenoson, sildenafil
5	Ceftazidime, entecavir, omeprazole, regadenoson, ritodrine, vardenafil
6	Nelarabine, riboflavin
7	Azelastine, bosentan, entecavir, fostamatinib, riboflavin, tenofovir
8	Fostamatinib, pralatrexate
9	Entecavir, nizatidine, pralatrexate, tedizolid

For each identified drug, the binding energy (kcal/mol) of the complex formed between PI3K and FDA-approved drugs was measured. The same analysis was conducted for known PI3K inhibitors (inavolisib, taselisib, CH5132799, alpelisib, ZSTK474) with PI3K (Figure 1A).

Among the FDA-approved drugs, pralatrexate (57.2 kcal/mol) and entecavir (56.1 kcal/mol) exhibited the highest binding energy to PI3K, surpassing most PI3K inhibitors (alpelisib: 53.28 kcal/mol, inavolisib: 53.13 kcal/mol, CH5132799: 43.31 kcal/mol, ZSTK474: 47.02 kcal/mol). Among the existing PI3Kα inhibitors, taselisib had the highest binding energy (59.75 kcal/mol), exceeding all other tested drugs.

The individual binding energy values of the FDA-approved drugs obtained through virtual screening were compared against the average binding of existing PI3K-specific inhibitors. Based on this comparison, 10 potential drug candidates were identified with binding energy values within a range of -10 to +10 (Figure 1B). Table 3 provides a detailed description of the binding characteristics of these 10 candidates for drug repositioning within the active site of PI3Kα.

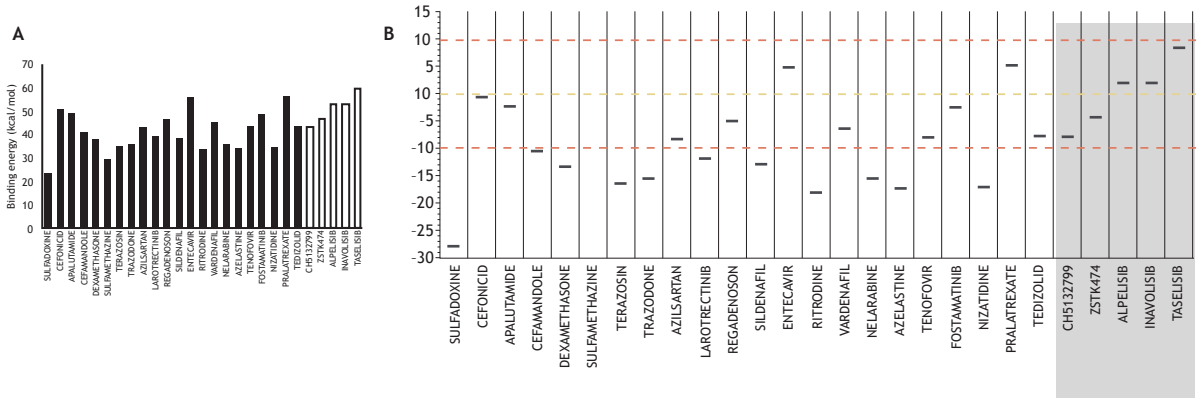

Figure 1. Binding energy between PI3K and tested drugs. (A) Black bars represent the binding energy of PI3K with FDA-approved drugs for other indications, whereas white bars represent the binding energy of PI3K with specific inhibitors. (B) Scatter plot of the binding energy between PI3Kα and tested drugs. Drugs with binding energy within a range of -10 to +10 kcal/mol (indicated by red lines) were considered acceptable candidates. Existing PI3Kα-specific inhibitors are shaded in gray.

Table 3. Characteristics of candidates for drug repositioning

Drugs	Binding energy (kcal/mol)	Hydrogen bonds	Hydrophobic interactions	Pi stacking	Salt bridges
Fostamatinib	48.7	Arg770 His855 Gln859 Asp933	-	-	Arg770
Entecavir	56.1	Ser773 Ser774 Val851 Gln859 Ser919 Asp933	Ile800 Ile932	-	-
Pralatrexate	56.4	Ser774 Lys802 Asn853 Ser854 Gln859	Ile800 Tyr836 Val850 Val851 Ile932	-	-
Tedizolid	43.6	Asp810 Gln859 Asp933	Ile800 Ile848 Ile932	Trp780	Asp810 Asp933
Tenofovir	43.5	Asp810 Gln859 Asp933	Trp780 Ile800 Val850 Gln859	Trp780	-
Vardenafil	45	Arg770 Val851 Ser854 Gln859	Trp780 Ile800 Ile932	Trp780	-
Regadenoson	46.2	Val851 Ser854 Gln859 Asp933	-	-	-
Apalutamide	49	Val851 Ser854 His855 Gln859 Asp933	Trp780 Ile848 Val851 Phe930 Ile932	-	-
Cefonicide	50.6	Val851 Asn853 Ser854 His855 Gln859	Ile800 Tyr836 Ile848 Ile932	-	-
Azilsartan	42.9	Arg770 Gln859 Asp933	Ile800 Lys802 Tyr836 Ile848 Val851 Thr856 Ile932	-	Lys802

DISCUSSION

Out of the 10 abovementioned drugs, three in particular—fostamatinib, pralatrexate and entecavir—have been selected as potential candidates for drug repositioning based on their in silico interactions and studies exploring their possible use in cancer treatment.

Fostamatinib is an inhibitor of spleen tyrosine kinase (Syk), approved for the treatment of chronic autoimmune thrombocytopenia in patients who have failed conventional therapy [13]. However, its use is also being evaluated for other conditions [14]. Previous studies have identified Syk protein as a key molecular mediator in the regulation of epithelial-mesenchymal plasticity (EMP) and the epithelial-mesenchymal transition (EMT), an essential process in the development of metastasis from a primary tumor [15]. Although initial studies found lower Syk expression in cancer patient tissues—indicating a potential tumor suppressor role [16]—experimental research has shown that Syk directly participates in EMT and suggests that its inhibition—using fostamatinib, for example—could reduce the likelihood of metastasis [15,17]. At the clinical level, fostamatinib has shown mixed results in terms of tolerance and limited efficacy against certain solid tumors, indicating that the results remain inconclusive [14,18]. Its interaction with kinases other than Syk, such as Flt3, JAK, c-Kit, Lck and RET, has already been reported [14], although its potential as a PI3K inhibitor has not yet been evaluated. In our in silico findings, fostamatinib interacts with PI3K by forming hydrogen bonds with His855, Gln859, Asp933 and Arg770, as shown in Figure 2A. These interactions are also observed in existing PI3Kα inhibitors and ATP. Bonds with His855 and Gln859 residues could enhance specificity for PI3Kα [19]. Notably, the carboxamide of alpelisib, taselisib and inavolisib also binds to Gln859 [2], suggesting that this residue plays a key role in determining the affinity between PI3Kα and other isoforms [19]. Asp933 is part of the conserved DFG (aspartate, phenylalalanine and glycine) motif found in all protein kinases, which plays a critical role in catalysis by binding Mg2+ ion to orient the ATP γ-phosphate for transfer [20]. This residue is also a common binding target of the aforementioned PI3Kα inhibitors [2].

On the other hand, pralatrexate is used to treat advanced or recurrent peripheral T-cell lymphoma. It is an antimetabolite inhibitor and folic acid analog that prevents DNA replication and disrupts the cell cycle. Preclinical studies have shown promising results for pralatrexate in high-risk neuroblastoma, demonstrating superior efficacy compared to methotrexate [21], as well as advantages over other antimetabolites in recurrent or refractory non-small cell lung cancer (NSCLC) and certain types of lymphomas [22]. Moreover, pralatrexate has been proposed for repositioning in the treatment of COVID-19 due to its viral effects in addition to its antineoplastic properties [23]. However, no studies have reported its effect on PI3Kα kinase or cancers with a high mutation rate in this enzyme, making our findings potentially relevant for future applications. As illustrated in Figure 2B, pralatrexate interacts with PI3Kα by binding not only to Gln85 but also to the catalytic residues Lys802 and Ser854. Lys802 is known to participate in the phosphate transfer reaction of p110α [20,24,25] and serves as an interaction target for the PI3Kα-specific inhibitor CH5132799 [2]. Additionally, Ser854 has been reported to interact with alpelisib, taselisib and inavolisib [2], indicating its importance as residue in the catalytic function of PI3Kα.

Entecavir is a nucleoside antiviral that has been used for nearly two decades to treat chronic hepatitis B virus infection by inhibiting viral replication [26]. As a guanine analog, its role in cancer therapy has been explored through in silico drug repositioning studies, suggesting its potential as a chemotherapeutic agent for breast, ovarian and prostate cancer, as well as in tissues with high PARP-1 activity [27,28]. However, its potential as an inhibitor of key kinases involved in cancer progression, such as PI3Kα, has not been evaluated. As shown in Figure 2C, entecavir interacts with PI3Kα similarly to fostamatinib, forming bonds with Gln859 and Asp933, which may confer the previously described characteristics. Additionally, it interacts with Val851, which is located in the kinase hinge region. This residue is also targeted by other known PI3Kα inhibitors, including alpelisib, taselisib, inavolisib and CH5132799 [2].

Finally, it is worth highlighting that other drugs with promising in silico results against PI3K are already being tested for cancer therapy. One example is tenofovir, a drug used to treat HIV infection, which has demonstrated potential effects in certain types of recurrent or advanced cancers, such as hepatocellular carcinoma [29,30].

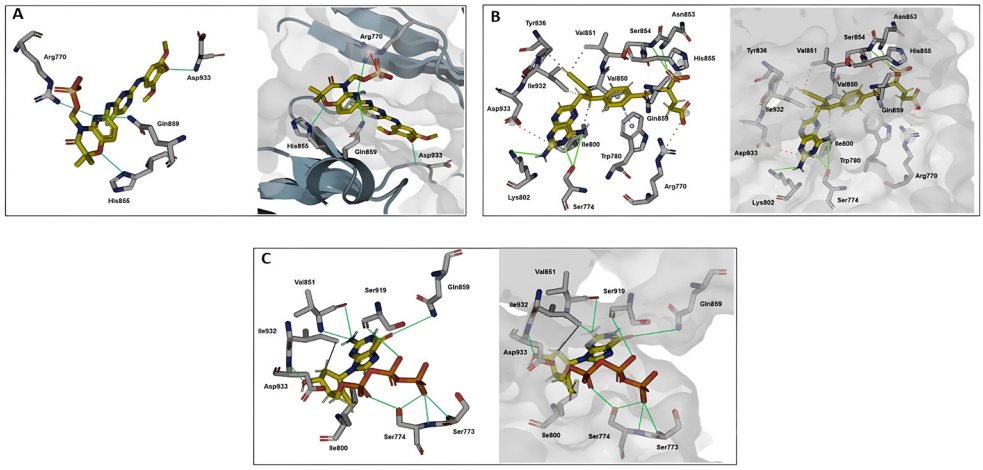

Figure 2. Drug-protein interaction. (A) Interaction between fostamatinib and PI3K. (B) Interaction between pralatrexate and PI3K. (C) Interaction between entecavir and PI3K. All interactions are shown in stick representation (left side of the panel) and surface representation (right side of each panel). Hydrogen bonds are represented by green lines.

In conclusion, this study identified 10 drugs with potential for repositioning in cancer treatment based on their interaction with PI3Kα. Among these, fostamatinib, pralatrexate and entecavir were selected due to their in silico interactions and prior studies supporting their potential applications in cancer treatment. These drugs are currently being tested experimentally or are undergoing clinical trials, primarily targeting kinase proteins, which makes their interaction with PI3Kα a viable possibility. Additionally, this project generated nine pharmacophores, which can be incorporated into specialized databases to facilitate the search for new molecules and/or drugs with potential for repositioning. Therefore, based on these findings, further in silico and in vitro research are recommended, focusing on their role in PI3Kα inhibition and in neoplasms where this kinase's activity or mutations play a crucial role.

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Author contributions: PWC, SIV and JFC conceptualized the study; PWC, DRL and JFC curated the data; and PWC, DRL, RZD and JFC utilized software for the analysis. Additionally, PWC, DRL, RZD, BMD and JFC conducted the formal analysis and research, while SIV and RZD secured funding from Consejo Nacional de Ciencia, Tecnología e Innovación (Concytec – National Council for Science, Technology and Innovation)–Programa Nacional de Investigación Científica y Estudios Avanzados (ProCiencia – National Program for Scientific Research and Advanced Studies). Data collection was carried out by PWC, DRL, RZD and JFC. Furthermore, SIV, RZD and JFC designed the research methodology, and PWC and DRL drafted the original manuscript. All authors contributed to the writing, review and editing of the manuscript.

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Conflicts of interest: The authors declare no conflicts of interest.

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Corresponding author:
Juan Enrique Faya Castillo
Address: C. Mártir José Olaya 162, Miraflores 15074
Telephone: (01) 213 9600 extension 2239
E-mail: juan.faya@udep.edu.pe / paolo.wong@udep.edu.pe

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ORCID iDs

Paolo Wong Chero	https://orcid.org/0000-0001-7635-0347
Daniel Ramírez Lupuche	https://orcid.org/0009-0003-9685-0375
Richard Zapata Dongo	https://orcid.org/0000-0001-7634-1029
Brenda Moy Díaz	https://orcid.org/0009-0008-3055-975X
Stefany Infante Varillas	https://orcid.org/0000-0002-3067-233X
Juan Faya Castillo	https://orcid.org/0000-0002-3408-7971