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A Protein Tyrosine Phosphatase 1B Inhibitor as a Potential Drug Against Prostate Cancer

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Abstract: Advances in developing new anticancer drugs continue, and one of the new therapeutic targets to reach is the Protein Tyrosine Phosphatase 1B (PTP1B), due to its functions, which are related to prognosis in a variety of types of cancer, and this protein is strongly related to tumor proliferation, migration, and apoptosis. This study evaluated a potential PTP1B ligandthe PT2 compound, whwhichup proposed as a compreviously pound directed to interact with the PTP1B´s activPTP1B´s in this wayto d,evelop a dru,g that could regulate the PTP1B´s functPTP1B´s The aim of this research is to evaluate the effects of the PT2 compound on PTP1B´s functions in prostate cancer cells (PC3) by in vitro cultures. We determined a regulation on messengers in PC3 cells, due to a regulation in the expression of p-FAK, p-P70S6K, and Glut-1; these proteins were correlated to decrease the function of PTP1B by the PT2 compound, whose effect is proportional to the concentration of the PT2 compound and cell. These results were determined by western blot, glucose uptake, and wound closure assays. We propose that the PT2 compound has a high probability of being selective for PTP1B, with an antimigration effect, allowing us to continue the evaluation. We also propose that this compound is likely to be used for security purposes in humans. These results showed the high potential of this compound as a new anticancer drug.

Keywords: anticancer; antimigration; glucose uptake; PC3; PTP1B.

1. Introduction

Prostate cancer is the most common cancer among men, with around 1.4 million new cases diagnosed annually worldwide (Globocan 2022, WHO). The develop of new anticancer drugs against new therapeutic targets is increasing worldwide, and we research group reported a compound against the Protein Tyrosine Phosphatase 1B (PTP1B) [1], which is a key enzyme to less / decreasing the messengers for Insulin and Leptin receptors [1-7] and the last years, PTP1B is proposes to signaling promotes tumor cell survival, proliferation, growth, inhibition of apoptosis, resistance, and metabolism by activating their pathways effectors [7,8]. PTP1B has been reported to be present in many cancer tissues and has been negatively associated with the poor condition and prognosis of cancer patients [7-9]. There are reports that identified a relationship between PTP1B overexpression and proliferation and migration for pancreas, prostate, breast, and gastric cancer [9,10].

Particularly in prostate cancer, PTP1B promotes mainly migration and tumorigenesis by several mechanisms [8,9], due to the PTP1B´s functions related in cancer; one of them is on the Src kinase (by dephosphorylating the inhibitory Tyr527 site in the C-terminus of this kinase) [11] with the subsequent activation of the PI3K/AKT and Ras/RAF/MEK/Erk pathways, this promoting cell proliferation and metastasis [8,9], and another function reported is on the PKM2/AMPK/mTOC1 signaling pathway, in deed is reported that the PTP1B inhibition significantly increased the phosphorylation of PKM2 at the residue Tyr105, resulting in the activation of AMPK which in turn decreased mTOC1 activity and led to the inhibition of P70S6K, and provokes cell death [12,13], and this which plays a key part in cancer cell growth and proliferation [8,9]. As well as Focal adhesion kinase (FAK) functioning, FAK signaling is important for increasing invasion and metastasis in prostate cancer [14,15], indicating that FAK is a potential target for this type of cancer as well.

Therefore, PTP1B could be a therapeutic target for prostate cancer, at least to decrease the proliferation and migration of this type of cancer [8,9,16]. Accordingly, there are studies on the inhibition of the P [17–19], and recently we evaluated the PT2 compound with the PTP1Ba recombinant protein [1], which showed a selective interaction, demonstrating the effect of this compound. Thus, in this study, we tested the PT2 compound in vitro using prostate cancer cells (PC3). The use of PC3 cells is promising because they contain key messengers that promote the viability of this cancer type, which makes it a possible object of study; some of these messengers, such as FAK [20,21], P70S6K [22-25], and Glut-1 [26-28], in which PTP1B could have functions. So, the PT2 compound could be selective for PTP1B, and, in this way, it could regulate PTP1B´s function related to the prognosis of prostate cancer [7-9,16], as determined in this study by proliferation, migration, glucose uptake, and western blot assays.

2. Materials and Methods

2.1. Reagents.

Cell culture reagents were purchased from Thermo-Fisher (Carlsbad, CA, USA), tissue culture plates and other plastic materials were obtained from Corning Inc. The following primary antibodies against p-FAK (Tyr397), p-P70S6K (Thr421 and Ser424), Glut-1, and β-actin were used from Santa Cruz Biotechnology, Inc. (TX, USA), and secondary antibodies conjugated with horseradish peroxidase were used from Sigma-Aldrich (MO, USA), and PT2 compound previously reported [29] was bought in Chembridge Corp. [30] (ID-Chembridge: PT2: 6463182; PubChem CID: 561165, Figure 1). Purity of the compound reported by the manufacturer was greater than 95% checked by LC/MS. The stock solutions for compounds were prepared in DMSO (1-10 mM), and MTT was obtained from Merck (Darmstadt, Germany).

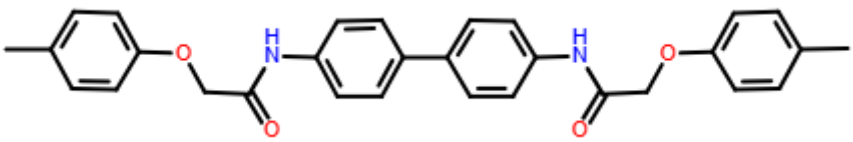

Figure 1. PT2 compound, PubChem CID: 561165.

2.2. Cell culture.

The prostate cancer (PC3) cells were obtained from the American Type Culture Collection (ATCC). Cells were cultured in 100 mm Petri dishes with Dulbecco's Modified

Eagle's Medium (DMEM) supplemented with 3.7 g/L sodium bicarbonate, 5% (PC3) fetal bovine serum (FBS), and antibiotics in a humidified atmosphere containing 5% CO_2 at 37°C.

2.3. Cytotoxicity assay in PC3 cell cultures determined by MTT.

The MTT viability assay was performed as described previously [31]. PC3 cells in 96-well microplates (10,000 cells per well) were treated for 48 h with concentrations between 1 and 200 µM of the PT2 compound, and DMSO at a final concentration of 0.5% was used as vehicle control. After treatment, the medium was replaced with medium containing MTT (0.5 mg/mL), and cells were incubated for 4 h. Later, lysis buffer (50% dimethylformamide, 20% SDS; pH = 4; Sigma Aldrich, USA) was added to the solution and incubated overnight to dissolve formazan crystals. Finally, the plate was read in a microplate reader at 595 nm. The assays were performed in triplicate and in three independent studies. The percentage viability was calculated according to the formula: % viability = [mean optical density (O.D.) treated cells × 100]/(mean O.D. control cells).

2.4. Scratch-wound migration assay.

PC3 cells were stimulated with PT2 compound and DMSO to test the inhibitor effect in cell migration with the scratch-wound assay as previously [32]. Briefly, confluent cells seeded in 35x12 mm cell plates were starved for 18 h with DMEM without FBS before the assay and treated with Mitomycin C at a 12 µM concentration (Santa Cruz Biotechnology, USA) for 2 h to inhibit cell proliferation. Then, cell cultures were scratch-wounded by a 200 µL micropipette tip and washed twice with PBS 1X to remove suspended cells. Later, cells were treated for 48 h with the PT2 compound at 50 and 100 µM concentrations in DMEM with 5% FBS. Cells were fixated with pure methanol, washed with PBS 1X, stained with Coomassie Brilliant Blue 0.125% in 45% Ethanol and 1% Acetic Acid (Coomassie Brilliant Blue R-250, Bio-Rad, Hercules, CA, USA), and photographed using a Vista Vision-VWR inverted microscope (Radnor, PA, USA) coupled to a camera. In this way, the progress of cell migration into the wound at the end of the experiment (48 h).

2.5. Glucose uptake assay.

PC3 cells were incubated with 50 and 100 µM of PT2 compound for 48 h; after, we used the Glucose Uptake Colorimetric Assay Kit from Sigma Cat#: MAK083. Briefly, the protocol indicates: after incubation with treatment, each well was washed 3 times with PBS and incubated with 10 mM 2-deoxyglucose (2-DG), a glucose analog, in glucose-free medium for 30 min. Following incubation, cells were washed 3 times with PBS and lysed with Extraction Buffer (Sigma Cat#: MAK083). Lysate was frozen/thawed in dry ice/ethanol, and then heated at 85°C for 40 min. Lysate was then cooled on ice for 5 min and then neutralized by Neutralization Buffer (Sigma Cat#: MAK083). Samples were spun down at 13,000 g to remove the insoluble fraction and then diluted 10-fold by adding Assay Buffer. Using the lysate, the glucose uptake was determined following the protocol of the Glucose Uptake Kit (Sigma Cat#: MAK083).

2.6. Western blot analysis.

Plates of six wells were used; 150,000 cells per well were seeded in 1.5 mL of supplemented DMEM medium for 48 h, incubated at 37°C and 5% CO_2, and allowed to reach

90 % confluence. The DMEM-supplemented medium was replaced with the DMEM experimental medium, and cells were incubated at 37°C for 18 h. The medium was removed, and 1 mL of experimental DMEM medium was placed under the PT2 compound at a concentration of 50 µM. Treatments were maintained for 48 h. Later, treatments were removed, and the cell monolayer was washed once with PBS. Total protein extraction was performed using the RIPA buffer system (ChemCruz sc-24948). For protein separation, 12% SDS-polyacrylamide gels were used for the characterization of proteins. Proteins were transferred overnight to PVDF membranes at 4°C, 90 mA. Membranes were blocked with 5% low-fat milk/TBST 0.1% and later incubated with the primary antibody overnight at 4°C under gentle agitation. We evaluated these targets: p-FAK (sc-81493), p-P70S6K (sc-377529), Glut-1 (sc-377228), and β-actin (sc-8432). The β-actin was used as a loading control. Anti-mouse secondary antibodies coupled to Horseradish peroxidase from Thermo-Fisher. Chemiluminescence detection was performed using Immobilon Western kit (Millipore, MA, USA) and X-ray film for some blots; for others, Bio-Rad ChemiDoc XRS+ was used, and a digital image was obtained. Analysis and quantification of pixel densities were performed using ImageJ software (version 1.54g) (NIH,262 DC, USA). Anti-β-actin was used as a loading control. The figures shown for Western Blot assays are representative of at least 3 independent experiments.

2.7. Statistical analysis.

Data´s results were expressed as mean ± standard deviation (SD) of at least three independent experiments. Averages and the statistical significance were determined using GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA), by one-way ANOVA statistical test with Dunnett post-hoc test, or paired t-Test. Differences were considered statistically significant at P <0.05 (* $p < 0.05$, ** $p < 0.002$, *** $p < 0.0002$, **** $p < 0.0001$).

3. Results and Discussion

3.1. Cytotoxic effect of PT2 compound on PC3 cell cultures and MTT results.

We determined a moderate cytotoxic effect at 48 h by in vitro PC3 cell cultures (Figure 2). After exposure to PT2 compound for 48 h at 50 µM, a moderate cytotoxic effect was observed; less expansion of the monolayer of culture (Figure 2), and we determined an IC_{50} at 40 µM by MTT assays (Figure 3).

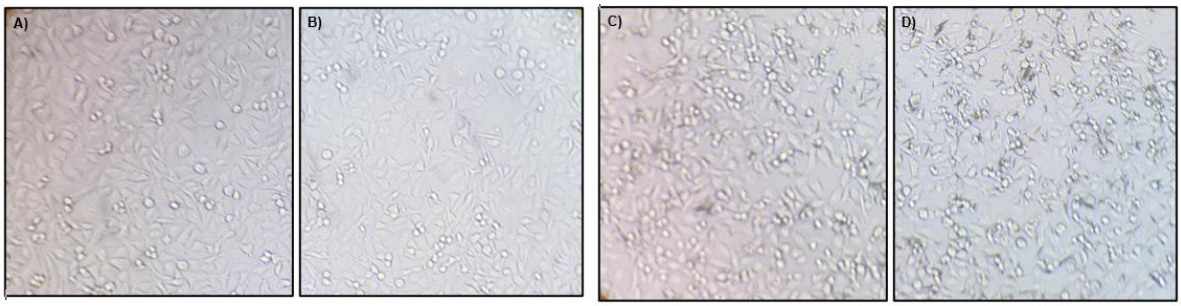

Figure 2. PC3 cells monolayer after 24h of incubation. **(A)** Without DMSO; **(B)** Control with DMSO as vehicle; **(C)** PT2 compound at 50 µM; **(D)** PT2 compound at 100 µM.

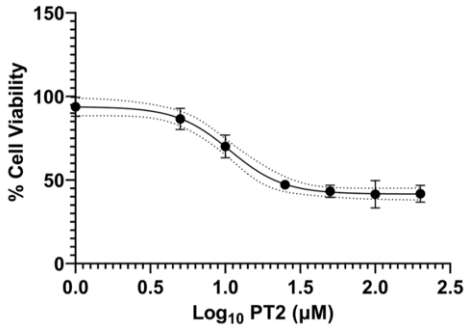

Figure 3. PC3 cells viability after 48 h of incubation with the PT2 compound between 1 and 200 µM. We determined the IC_{50} at 40 µM by MTT assays.

3.2. Scratch-wound migration assay.

We tested the migration in PC3 cell cultures to evaluate the effect of the PT2 compound, which probably decreased the PTP1B´s functions [9,10]. We determined this inhibitory effect using the previously reported scratch-wound migration assay [32,33], which is cell-dependent. After 48 h of incubation with a concentration of 10 and 50 µM of the PT2 compound, the results showed a clear decrease from the initial concentration (10 µM) in the migration cell with respect to controls with FBS 5% (Figure 4).

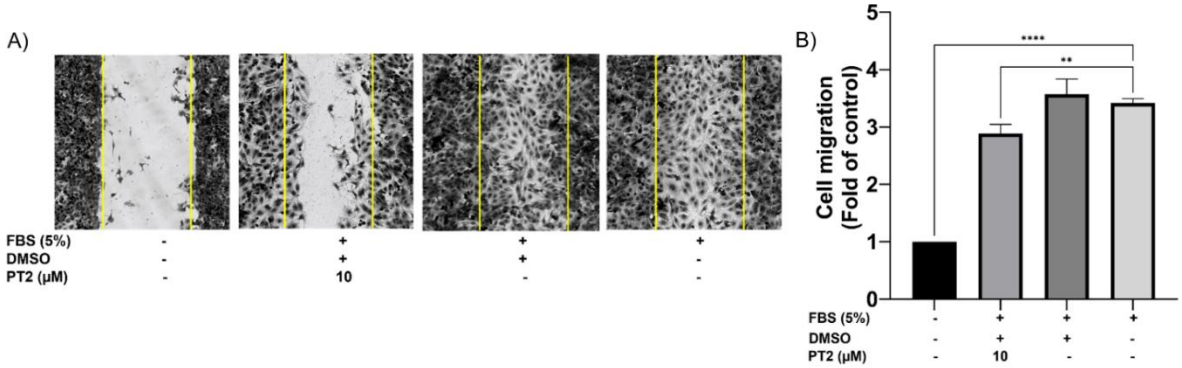

Figure 4. Results of migration in PC3 cell cultures, **(A)** Scratch-wound migration assay, after 48 h of treatment with 10 µM of PT2 compound, negative control, and controls with FBS 5%; **(B)** Statistical graphical of each group, they are represented as mean ± SD (*n* = 3); $p < 0.05$ vs the FBS control group.

3.3. Glucose uptake assay.

PC3 cells were incubated with 50 and 100 µM of the PT2 compound for 48 h, and then the capacity of glucose uptake was assessed for each concentration. The main results, at 100 µM of the PT2 compound, showed a decrease of nearly 40% with respect to the control. The concentration of 50 µM decreased to approximately 30% (Figure 5).

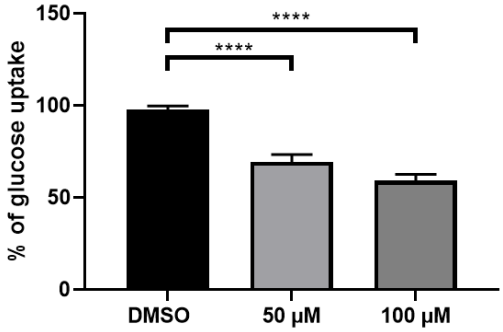

Figure 5. In the glucose uptake assay, PC3 cells were incubated with 50 and 100 µM of the PT2 compound for 48 h. The results for DMSO (vehicle), 50 and 100 µM of PT2 compound, are represented as mean ± SD (*n* = 3), $p < 0.05$ vs the control group (DMSO).

3.4. Messengers related to cellular migration.

We determined the expression of p-FAK and p-P70S6K, as these proteins are important in the proliferation messengers [20,21,34]. We tested 48 h the PT2 compound to 50 µM with PC3 cell cultures, and then we determined a lower expression of Glut-1, p-FAK, and p-P70S6K due to the PT2 compound effects regarding DMSO controls (Figure 6). These results were related to less migration generated by the PT2 compound in all assays tested (Figure 3).

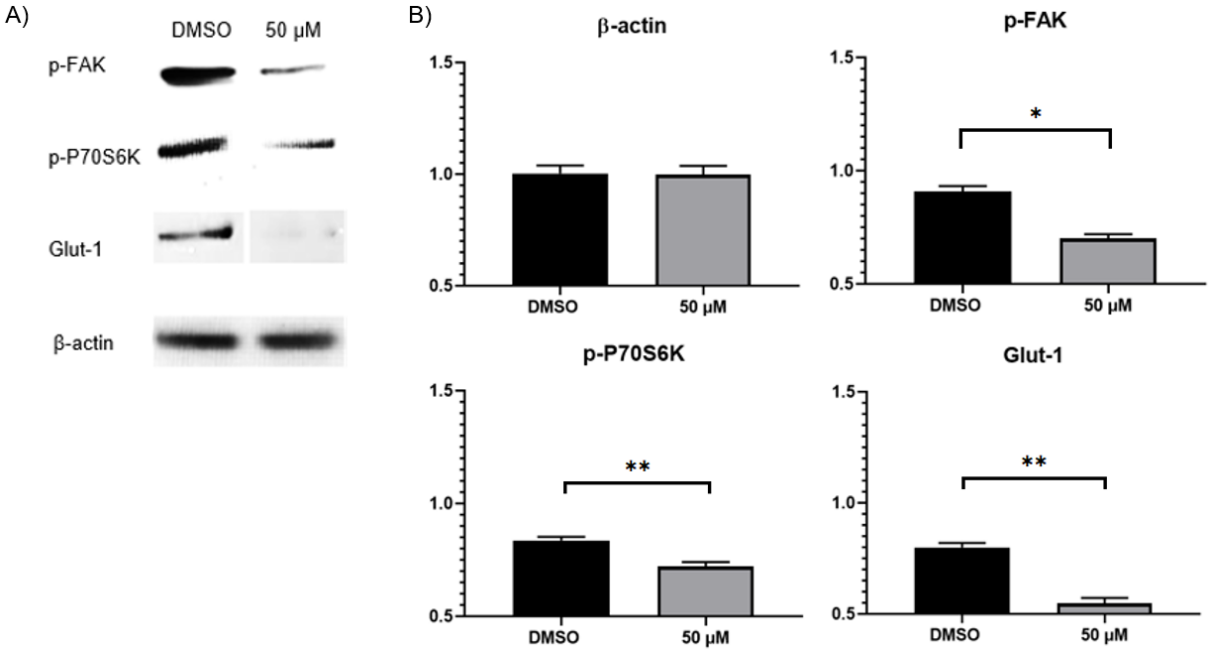

Figure 6. Impact of PT2 compound on proteins involved in cell migration within PC3 cell cultures. Cells were seeded with a seeding density of 1.5 x 10^5 cells and were treated with the PT2 compound at 50 µM for 48 h. The control cells were left untreated (DMSO). The whole cell protein lysate was prepared, and 20 µg of proteins was resolved in SDS-polyacrylamide gels. **(A)** Western blot analysis of p-FAK, p-P70S6K, Glut-1, and β-actin proteins; **(B)** Densitometry analysis of the data in Western blot analysis by ImageJ software. The values were normalized against β-actin (control), and they are represented as mean ± SD (n = 3) and expressed as fold-change in regard to loading control, $p < 0.05$ vs the control group (DMSO).

3.5. Discussion.

Prostate cancer is the most common cancer among men, with around 1.4 million new cases diagnosed annually worldwide (Globocan 2022, WHO). This shows the relevance of developing new anticancer drugs using new therapeutic targets, such as PTP1B [1], which is a key enzyme highly studied on messengers for Insulin and Leptin receptors [1-7]. In this study, we evaluated the effect of the PT2 compound on PC3 cell cultures, since PT2 is a potential PTP1B inhibitor, and we determined its effect on migration, messengers, and glucose uptake, which corresponds to probably regulating PTP1B´s functions within PC3 cells [8,9].

This research demonstrates advances in understanding the effects of the PT2 compound on PTP1B-related functions in cancer migration and proliferation [7-9,16], and these results are relevant to prostate cancer. So, for prostate cancer, there are signaling pathways in which PTP1B could be important, by activating or decreasing the expression of proteins involved in migration, viability, and drug resistance; and the expression of Glut-1 is important for these pathways [28,35].

We determined an anti-migration effect by the PT2 compound, due to a decrease in cell migration (Figure 4), related to the regulation of messengers in decreasing cell metabolism, and this without generating an immediate cell death; this is proposed because with all

concentrations tested for the IC_{50}, the cell cultures were viable (Figure 3). This result is related to reports showing that the effects on migration and proliferation are determined by inhibiting or knocking down PTP1B [8-10], and all of this supports PTP1B as a therapeutic target in this type of cancer.

Regarding proteins expression, Glut1 has been reported that this transporter contributes to the viability of several types of cancer, and in prostate cancer the expression of Glut1 may be related to the androgen receptor (AR), which increases the expression of Glut1 [26,27], and in this study the decrease in Glut-1 expression (Figure 5 and 6) is related to the inhibition of PTP1B by the compound PT2, which could regulate messengers in the AR signaling pathway, by regulating the PI3K/AKT and Ras/RAF/MEK/Erk pathways [8,9,36,37]. These regulations are related to lower expression of Glut-1, which could contribute to reducing mechanisms of resistance to treatments, stress, and responding to glucose starvation in various types of cancer [26,28,35]. On the other hand, PTP1B could regulate the PKM2/AMPK/mTOC1 signaling pathway, in deed it is reported that the PTP1B inhibition significantly increased the phosphorylation of PKM2 at the residue Tyr105, resulting in the activation of AMPK which in turn decreased mTOC1 activity and led to the inhibition the phosphorylation of P70S6K, and it is related to induce cell death [12,13], this which plays a key part in cancer cell growth and proliferation [8,9]. The functions of Focal adhesion kinase (FAK) are important for increasing migration and metastasis in prostate cancer [14,15]. Therefore, this study proposes that the PT2 compound dysregulates the phosphorylation of these proteins (P70S6J and FAK), determined by western blot assays (Figure 6), and in this way, justifies the anti-migration effect (Figure 4) and changes in the glucose uptake (Figure 5) by the PT2 compound.

Finally, we keenly recognize that the above correlation has limitations and is speculative to reach these results on prostate cancer, and it is necessary to validate these results at least in *in vivo* mice assays. We propose the PT2 compound that could interact with this therapeutic target (PTP1B) to develop a drug/adjuvant to treat prostate cancer, where it could be used as a sensitizer, and preclinical and clinical studies could be promoted to determine the PT2 compound´s therapeutic effect. In addition, the PT2 compound could probably be safe for humans, due to its toxicity results being favorable (citotoxicity and lethal dose 50) [35], which was determined in our laboratory.

4. Conclusions

We propose the PT2 compound as an adjuvant against prostate cancer, due to the findings shown in this study related to decreasing the PTP1B functions related to this cancer type. We determined that the PT2 compound could have a regulation over PTP1B, by the regulation of the expression proteins related to migration and proliferation of cancer cells (p-FAK and p-P70S6K) and glucose uptake (Glut-1). These results allow us to continue research on this PTP1B inhibitor and its applications in processes in which PTP1B plays a role.

Author Contributions

Conceptualization, J.L.V.S. and V.G.G.; methodology, J.L.V.S., O.G.H. and V.G.G.; software, J.L.V.S.; validation, J.L.V.S., B.R.S. and A.O.M.; formal analysis, V.G.G., B.R.S. and A.O.M.; investigation, J.L.V.S., B.R.S. and A.O.M.; resources, J.L.V.S. and V.G.G.; writing—original draft preparation, J.L.V.S., O.G.H. and V.G.G.; writing—review and editing, J.L.V.S.; project

administration, J.L.V.S., O.G.H. and V.G.G.; funding acquisition, J.L.V.S. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data presented in this study are openly available at PubMed. Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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