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ABSTRACT

Prolyl 4-Hydroxylase Subunit Alpha 1 (P4HA1) is a catalytic enzyme that involves synthesis of collagen and extracellular matrix interactions. Aberrant expression of P4HA1 promotes carcinogenetic invasion and metastasis in breast cancer. In this study, we combined transcriptomic and drug repositioning approach for the intervention of new targeted anti-cancer therapy for breast cancer. The mRNA expression, copy number variation, mutation and clinical patient’s outcome of P4HA1 validated through cBioportal. High-throughput virtual screening and MM-GBSA analysis were performed with Drugbank approved molecules (9,612) for identifying the potent therapeutic drug molecules against P4HA1 using Schrodinger. The cBioportal based gene expression of P4HA1 in the TCGA-breast cancer cohort revealed significant elevated expression in the breast tumor compared to the normal. Subsequently, the high copy number amplification and mRNA expression was high in the invasive breast carcinoma compared to the other subtypes. In addition, the overall survival was validated with median P4HA1 expression and conferred with poor prognosis of breast cancer patients. Further, receptor based virtual screening identified top hits of aminoglycoside derivatives, amikacin (glide score −9.58 kcal/mol) and gentamicin (glide score −7.02 kcal/mol) with best docking score and stable interaction with favorable amino acid residues of P4HA1 includes Glu171, Asp178, Lys213, Lys 206 and Leu174. Moreover, both the drug passed the drug-likeness property (ADME) and MM-GBSA energy model. This study integrates genomic and molecular docking approach, suggests P4HA1 as a prognostic biomarker and selective inhibition might be therapeutically involved in the breast cancer intervention.

KEYWORDS

Breast Cancer, P4HA1, Virtual Screening, DrugBank, ADME
INTRODUCTION

Cancer is a significant global threat to public health. Breast cancer is one of the world's most prevalent forms of cancer-related mortality in women. According to recent cancer figures, around 24.2% of women globally have new diagnoses (Global Cancer Estimates 2018) and nearly 6,27,000 died from the disease [1,2]. The diagnosis and treatment strategies are mainly focused on the clinicopathologic factors include hormonal response, grade, size, stage and subtypes. The breast cancer heterogeneity accounts for the drug resistance, metastasis and the patient’s survival still a big clinical issue [3-5]. Therefore, investigation on the potential candidates and its targeted inhibitory effect would majorly impact on the breast cancer therapeutic efficacy.

The prolyl-4-hydroxylase is a tetrameric, collagen synthesizing and α-KG dependent dioxygenase enzyme. Prolyl 4-hydroxylase, alpha polypeptide I (P4HA1) is the largest isoform that contributes to the majority of prolyl 4-hydroxylase activities. Initial studies focused mainly on its role in adhesion, protein folding and cell stability [6-8]. Subsequently, later P4HA1 was identified in association of hypoxic associated pathways, epithelial mesenchymal transition, tumor invasion and metastasis. The elevated expression of P4HA1 is substantially correlated with the progression, and poor survival in breast cancer [9-11]. Nevertheless, the targeted P4HA1 inhibitor is still in the inventory and screening approach.

The high-throughput technologies such as microarrays, next generation sequencing certainly accounts for the study of gene expression and alteration in the pathogenesis of disease [12]. Few studies reported the altered expression of P4HA1 in breast and other cancer using the gene profiling studies. For the targeted therapeutics scenario, insilico drug discovery techniques has become faster, cheaper and have been widely used in the investigation of molecular binding properties and its efficacy in the inhibitory effects of target protein for new drug development approaches [13-16].
In the present study, we aim to enumerate the transcriptomic expression, mutation and clinical significance of P4HA1 with the cancer genome atlas (TCGA) breast cancer cohorts using cBioportal. We proposed the virtual screening workflow for the identification of potent site and selective P4HA1 inhibitors from DrugBank small molecules. The affinities and stability of drug+P4HA1 was explored from free-binding energy calculations. Therefore, we combine functional genomic and structural virtual screening in a compendium for the potential diagnosis and effective tailored therapy for breast cancer patients.

METHODS

TRANSCRIPTOMIC DATA

The cBio Cancer Genomics Portal (http://cbioportal.org) [17,18] is an open access and multidimensional cancer open-source databases for visualization and interpretation. This portal includes nearly 56,250 tumor samples from 215 cancer trials. It comprises of the copy number variation, mRNA expressions, non-synonymous mutations, DNA methylation and minimal clinical data. The z-score of P4HA1 expression has been set for the comparison of expression and covariates. For the study, the TCGA dataset Breast METABRIC 2016 (2509 primary breast tumors with 548 corresponding normal) was selected. The primary parameters for the quest included amplifications, mutation, copy number variation (CNV), expression and the clinical attributes.

PREPARATION OF PROTEIN STRUCTURES

The X-ray crystal structure of wild type peptide-binding domain of human type I collagen prolyl 4-hydroxylase (PDB Id: 2V5F) at a resolution of 2.03 Å was retrieved from the RCSB PDB database (http://www.rcsb.org/pdb) [19]. Before docking the retrieved structure was subjected to protein-processing wizard implemented in maestro, Schrodinger. Bond orders and charges were altered and hydrogen atoms were added and all the water molecules were deleted. The energy minimization OPLS-AA (optimized capacity for liquid simulations) force fields also accompanied during protein preparation [20].

PREPARATION OF LIGAND
The molecular crystal structure of small molecules were downloaded from recently updated Drug Bank (v.5.1.7, released 2020-07-02), includes 9,612 entries including 4,051 (approved), 131 (nutraceuticals), 204 (Illicit) and 5,226 (non-redundant protein). All the compounds were imported to the LigPrep module of v2.3 from Schrödinger Suite 2018-1 for energy minimization, conformational analysis and ligand preparation before docking. [21]. LigPrep is applied to correct the structures of Lewis and remove ligand errors. It helps in generating ligand libraries with the necessary structural and chemical features for the virtual screening in Schrodinger software.

ACTIVE SITE / GRID GENERATION

SiteMap algorithm of maestro was used to identify and evaluate binding sites with a high degree of confidence and predict their pharmacological performance in P4HA1. It also spot the regions within the binding site which can be used by hydrophobic groups and/or ligand-bonded donors, acceptors or metal binders (Impact, v7.8, Schrödinger, LLC, New York, NY, 2018-1) [22,23]. For the prediction, stringent hydrophobicity and OPLS force filed were used. Glide (Grid-based Ligand Docking with Energetics) finds beneficial interactions between protein and ligands. The grid box was generated as the centroid of the sitemap binding site (96 Å x 96 Å x 96Å) in the protein and site region 35 Å x 35 Å x 35 Å (Glide, v7.8, Schrödinger, LLC, New York, NY, 2018-1) [2].

VIRTUAL SCREENING WORKFLOW

The molecular docking analysis was carried out using the Schrödinger software suite’s virtual screening workflow against DrugBank compound libraries. The scaling factor and the charge cut-off of the Van der Waals radius are 0.80 and 0.15 set for all ligand molecules respectively. The final score was assigned by the docked ligand in the receptor's active site. The lowest glide score ligand was regarded as the best ligand.

All the small molecular components were retrieved from the Ligprep module and output of P4HA1 protein preparation wizard subjected to the virtual screening workflow. Glide provides a wide selection of pace and precision, from HTVS (high-throughput virtual screening) to the efficient enrichment of a million compounds, to SP (standard accuracy) to effective docking of
tens to hundreds of tens with high precision, XP (extra accuracy) to further false positive deletion. In each selection criteria, a sequentially top 10% of hits were set as selection criteria for next parameter (HTVS-10% → SP-10% → XP-10%). The interaction results were analyzed and visualized on maestro.

ADME PROPERTIES

QikProp v5.10 program analyze the properties of ADME (absorption, distribution, metabolism, and excretion) of the compounds [24]. All the compounds have been neutralized and physiochemical properties have been predicted. The acceptance of the Lipinski law, aqueous solubility and human oral absorption are also tested.

MOLECULAR MECHANICS ENERGIES - GENERALIZED BORN AND SURFACE AREA (MM-GBSA)

The Prime's MM-GBSA (Prime, Schrödinger, LLC, New York, 2018-1) technology was implemented to measure the ligand binding and ligand tension energies for the docked complex protein poses. This employs a single minimal protein – ligand structure, thus rapidly optimize and rescore docking results. With the default setting, VSGB 2.0 for solvent model and OPLS3 force field incorporated, which performs analytical modifications for hydrogen-bond and μ stacking interactions.

RESULTS

THE EXPRESSION OF P4HA1 IN BREAST CANCER PATIENTS

The expression of P4HA1 was investigated using cBioPortal. The P4HA1 was altered in the breast cancer tissue with amplification, deep deletion and mRNA expression. The result depicts that P4HA1 expression was high in the breast carcinoma compared to the normal (Figure 1). We further investigated the association clinocopathologic parameters with the altered frequency of P4HA1. The high mRNA expression was correlated with the hormonal HER2 negative status, compared to the ER and PR status. Similarly, stage 2 of patients was highly
linked with the higher mRNA expression. Then we assessed the comparative amplification and expression of P4HA1 with the histological subtypes of breast cancer. The invasive ductal carcinoma subtypes found to with high frequency of amplification and expression compared to the lobular, mixed ductal & lobular, and mixed mucinous carcinoma (Figure 2). An mRNA expression z-score ±2.0 was set as the threshold.

Figure 1. Transcription level of P4HA1 in Breast cancer METABRIC (2016)- TCGA dataset (cBioportal). This graph depicts the association of amplification, expression, and deletion with clinicopathologic variables of breast cancer.
Figure 2. Correlation of copy number variations (CNVs) and expression of P4HA1. (A) Box plot of Putative CNVs (Amplification, Gain, Diploid, Shallow deletion and Deep deletion). (B) Bar chart of correlation of expression, CNVs and mutation to the different sub-types of breast cancer.

HIGH EXPRESSION OF P4HA1 CORRELATES WITH POOR OUTCOME

The prognostic significance of P4HA1 in breast cancer patients was estimated with cBioportal with preferable overall survival. The median expression value of P4HA1 was used for high and low expression criteria. The results showed that high expression of P4HA1 was significantly correlated with the poor overall survival clinical outcome (p-value 0.0170). (Figure 3)

Figure 3. Kaplan–Meier survival plot with P4HA1 alterations (red) compared to the unaltered group (blue).

PROTEIN AND LIGAND OPTIMIZATION

For analysis of the protein structure of P4HA1, the protein preparation wizard module was used. The prepared structures were then relaxed with the restrained minimization using
OPLS 2005 force field. In addition, it ensures the metal ionization, and deletes the water molecules that are crystallized (Figure 4 (A)). The Ramachandran plot produced by Maestro software after protein preparation, displays the distribution of phi and psi angles of the amino acid residues. The plot depicts almost all amino acids in the "favored" region (red), a few amino acids in allowed region (yellow) and only one amino acid in the disallowed region (white) (Figure 4 (B)). The strongest possible binding site has been predicted by SiteMap (Schrodinger). The best site score predicted was 0.480 Å, with 0.449 hydrogen bond score, 0.876 hydrophilic and 0.359 hydrophobic. Residues from the active locations have been identified with the Lys213, Lys206, Leu209, Glu171, Leu194, Leu174, Leu210, and Asp178. With this site location, grid has been generated for the receptor based virtual screen.

The extracted ligands (9,612) from DrugBank repository were rendered in SDF format and prepared using LigPrep. LigPrep was used with OPLS2005 force field enables to eliminate errors in ligands and with Epik at 7 ± 2.0 pH units. It generates accurate 3D molecular structures that are reduced in energy with correct chiralities. In addition, this allows the optimized output structures for the simulation programs without further user intervention. The virtual screening process was performed with these optimized ligands.

Figure 4. (A) Three-dimentaional cartoon model represenation of P4HA1 protein. (B) Ramachandran Plot depicts the stereochemical spatial arrangement of amino acid residues in the
P4HA1 structure. The favourable region represented in red color, additionally allowed in yellow, generously allowed in light yellow and disallowed region in white in color.

RECEPTOR BASED VIRTUAL SCREEN AND INTERACTION

A total of 9,612 compounds obtained from DrugBank library were docked into the predicted active site of P4HA1. A sophisticated filtering protocol has been used, where compounds were docked using HTVS and top 10% hits have been collected as output. These hit compounds were further docked with Glide SP, 10% hits were obtained. Finally, the hits from previous stage were subjected to Glide XP docking. Top 3 hits with glide score were shown in Table 1. Among the top 3 drugs, two drugs was aminoglycoside derivatives; Amikacin (Figure 5 (A), Gentamicin (Figure 5 (B)) and other lactulose (Figure 5 (C)). Thus, the approved drugs with stringent docking score and binding affinity can be considered for the therapeutic interventions for the P4HA1.
**Figure 5.** Chemical structure of potent inhibitors and binding interactions with the P4HA1. (A) Amikacin, (B) Gentamicin and (C) Lactulose

**Table 1.** The glide docking score, Emodel and hydrogen bond of the top 3 hits from DrugBank compounds interacted with the P4HA1 protein.

<table>
<thead>
<tr>
<th>DrugBank ID</th>
<th>Entry Name</th>
<th>Status</th>
<th>Docking score (kcal/mol)</th>
<th>XP GScore</th>
<th>XP_H Bond</th>
<th>Glide Emodel (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB00798</td>
<td>Gentamicin</td>
<td>approved</td>
<td>-7.02</td>
<td>-7.02</td>
<td>-4.31</td>
<td>-42.91</td>
</tr>
<tr>
<td>DB00581</td>
<td>lactulose</td>
<td>approved</td>
<td>-6.80</td>
<td>-6.98</td>
<td>-4.05</td>
<td>-45.04</td>
</tr>
</tbody>
</table>

Amikacin were found to be with a strong binding affinity (-9.58 kcal/mol) with the P4HA1. Protein-ligands hydrogen interactions pattern revealed with Asp295, Asn203, Gln110,
Arg105, Lys102, and Asp153. Other minor interactions include hydrophobic contacts with Cys152, and Pro108 (Figure 6 (A)). Gentamicin attributed to the high docking XP score (-7.02 kcal/mol). In the active site of P4HA1, it directly interacts with Asp245, Asp248, ARG 105, THR292, SER158, GLN110, LYS102, GLN107 forms hydrogen bond. Additionally, weak π-stacking interaction with Lys102, hydrophobic contacts with ILE152 and salt bridge with the Asp245 residue were exhibited (Figure 6 (B)).

Figure 6. (A) Superimposition of the P4HA1 protein structure (surface) and amikacin binding interaction (Sticks). A closeup view of the amikacin- P4HA1 and interacting amino acid residues are depicted. (B) Superimposition of the P4HA1 protein structure (surface) and gentamicin binding interaction (Sticks). A zoom view of the gentamicin- P4HA1 and interacting amino acid residues are depicted.
DRUG-LIKENESS PROPERTY

The significant drugs amikacin, gentamicin and lactulose were analyzed for its drug-likeness and ADME using Qikprop of Maestro. The drug-likeness was prioritized based on the Lipinski’s rule. Pursuant to Lipinski’s law of five for drug-like molecules, the molecular bond should be < 500, and the octanol-water fraction should be < 5.0, the hydrogen bonding donor groups < 5.0, and the hydrogen bond acceptor groups should be < 10. All the drugs, amikacin (3 violation), gentamicin (2 violation) and lactulose (2 violation) violated Lipinski’s law of five. Similarly, these drugs also violated Lipinski’s law of three. In the assessment of the adsorption and delivery of drugs, octanol/water partition coefficient QPlogPo / w and aqueous solubility QPlog S both the aminoglycoside drugs were in acceptable range amikacin (-8.8, -0.46) and gentamicin (-3.5, -0.46). The other parameter which are important in assessing the ADME/T were binding to human serum albumin (QPlogKhsa), Caco-2 cell permeability in nm/sec (QPPCaco) and brain/blood partition coefficient (QPlogBB), which aminoglycoside drugs was in acceptable range. The drug-likeness and ADME/T properties were listed in Table 2. From the results it was noticed that both the best lead molecules fulfill all the essential criteria.

Table 2: The ADME (Adsorption, Distribution, Metabolism, Excretion) properties of the top hits of small molecule compounds

<table>
<thead>
<tr>
<th>Name of the Compound</th>
<th>QPlogPo /w</th>
<th>QPlogS</th>
<th>Rule Of Five</th>
<th>Rule Of Three</th>
<th>HOA</th>
<th>QPlog Khsa</th>
<th>QPPCaco</th>
<th>QPlogBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>-8.282</td>
<td>-0.462</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>-2.23</td>
<td>0.004</td>
<td>-5.62</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>-3.519</td>
<td>-0.465</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>-1.13</td>
<td>1.08</td>
<td>-1.67</td>
</tr>
<tr>
<td>lactulose</td>
<td>-3.398</td>
<td>1.74</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-1.05</td>
<td>28.67</td>
<td>-2.38</td>
</tr>
</tbody>
</table>

Predicted octanol/water partition coefficient (QPlogPo/w = – 2.0 to 6.5),
Predicted aqueous solubility, (QPlogS = –6.5 to 0.5),
Rule Of Five = Number of violations of Lipinski’s rule of five,
Rule Of Three = Number of violations of Lipinski’s rule of three.
Predicted qualitative human oral absorption (HOA): 1, 2, or 3 for low, medium, or high.
Prediction of binding to human serum albumin. (QPlogKhsa = −1.5 to 1.5)
Predicted apparent Caco-2 cell permeability in nm/sec. (QPPCaco = <25 poor, >500 great)
Predicted brain/blood partition coefficient (QPlogBB = –3.0 – 1.2)
FREE BINDING ENERGY - MM-GBSA

MM-GBSA calculations were carried out to determine the relative ligand affinity to the receptor after glide docking. MM-GBSA is commonly used for the free-energy ligands in a congeneric sequence. The negative and weak value (ΔGBind score) of the molecule's binding energy considered to be highly preferred. The drug binding energies of P4HA1 for amikacin and gentamicin were -56.56 Kcal/mol and -66.83 Kcal/mol respectively. Table 3. shows the MM-GBSA results for the top 3 drugs. The result has revealed a strong binding affinity of aminoglycoside derivatives and may serve as effective inhibitor to suppress P4HA1 levels.

Table 3. The free binding calculations (MM-GBSA) of top 3 hits from DrugBank compounds interacted with the P4HA1 protein.

<table>
<thead>
<tr>
<th>DrugBank ID</th>
<th>Entry Name</th>
<th>dG Bind (ΔGbind = kcal/mol)</th>
<th>Complex Energy</th>
<th>dG Bind Coulomb</th>
<th>Receptor Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB00479</td>
<td>Amikacin</td>
<td>-21.673</td>
<td>-3478.21</td>
<td>-162.872</td>
<td>-3484.15</td>
</tr>
<tr>
<td>DB00798</td>
<td>Gentamicin</td>
<td>-20.526</td>
<td>-3435.87</td>
<td>-213.415</td>
<td>-3484.15</td>
</tr>
<tr>
<td>DB00581</td>
<td>lactulose</td>
<td>-16.641</td>
<td>-3509.64</td>
<td>-10.986</td>
<td>-3484.15</td>
</tr>
</tbody>
</table>

DISCUSSION

A large volume of knowledge available to the public integrating gene expression knowledge related to clinical results is generated by the TCGA. Online-portal allows the scientific community to conduct effective broad genomic research and explore onco-regulators and biomarkers. In this study, we have thoroughly examined P4HA1 expression in TCGA METABRIC breast cancer and reported its aberrant expression. In addition, the copy number gain was high in the breast cancer tissue compared to the normal. The overall survival outcome of patients was directly proportional to the poor prognosis. Further, the pharmacological aminoglycoside derivatives (Amikacin and Gentamicin) were identified as a potent selective inhibitor for P4HA1 through virtual screen of drug-target interaction with DrugBank compound library. Our findings provided the potential candidate identification and therapeutic targeted drugs, thus contributing to insight into the treatment strategy.
Prolyl hydroxyl hydroxylation of collagen is important for folding, stabilization and secretion of the fibrillar collagen triple collagen helix [25,26]. The latest findings have shown that straightened and oriented collagen fibers are a predictor of cell proliferation and cell migration and patient mortality [27,28]. Expression of P4HA1 helps to deposit collagen, invade breast cancer and contributing to the lymph node and lung metastases [11]. We found P4HA1 to be highly expressed in the breast carcinoma and strongly correlated with the clinicopathologic features, especially hormonal status. P4HA1 expression has recently been associated with the diameter of the tumor microvessel and matrix metalloproteinase 1 (MMP1) thereby regulates glioma's neovascularization and prostate cancer progression [29]. In addition, P4HA1 have been identified as bifunctional growth and invasive regulators in melanoma [30]. The knockdown of P4HA1 in breast cancer cells contributed to significant decrease in collagen production and tumor rigidity in-vivo. P4HA1 found to be overexpressed in oral squamous cell carcinoma, hepatocellular carcinoma, lung cancer, and pancreas cancer [31-33,11]. In the TCGA-BC METABRIC breast cancer patients, P4HA1 strongly correlate with the patient’s clinical significance. P4HA1 mRNA levels were shown as an independent prognostic indicator of local recurrence and OS in high-grade gliomas, squamous carcinoma and colorectal cancer [34,31]. In the case of triple-negative breast cancer, its expression associated to short relapse-free survival [9]. Therefore, these finding suggests that targeting P4HA1 for the selective inhibition might overcome the breast cancer proliferation and invasion.

The molecular docking resulted in the strong binding relationship between the aminoglycoside derivatives and the active site of P4HA1. Aminoglycoside antibiotics are natural or semisynthetic products of fermentation. They are water-soluble that have a bactericidal potency against Gram negative bacteria by inhibiting the synthesis of proteins [35,36]. Strengthening research indicates that aminoglycosides can activate the acute signals from the renal cells, which eventually contribute to a pro-inflammatory response by allosterically stimulating phosphatidylinositol phospholipidase C (PPC) [37,38]. Furthermore, they demonstrate significant involvement in suppressing premature termination codons PTC and counteracted degradation of p53 mRNA degradation thus actively contributes to apoptosis in tumor cell [39-41].
The P4HA1 protein residues establishes significant interactions with amikacin atoms (-9.58 kcal/mol). Amikacin is found to be the first semisynthetic kanamycin-A aminoglycoside antibiotic used specifically for joint inflammation, intra-abdominal infections, meningitis, sepsis, diarrhoea and urinary tract disease [42,43]. A study established the role of amikacin in cancer, that mainly used in the routine treatment of granulocytopenic cancer patients in conjunction with beta-lactam antibiotics [44]. Similarly, we found that gentamicin showed strong binding with the residues of P4HA1 (-7.02 kcal/mol). Gentamicin is another gram-negative aminoglycoside antibiotic. Recently, the application of gentamicin has shown that cell growth and cell death in lymphoma cells are delayed by cell cycle arrest in the G1 phase [45,46]. Furthermore, in breast cancer cells, the addition of gentamicin to culture media promotes the dissemination of glycolytic enzymes and glucose transporters by stimulating the inducer hypoxia alpha factor 1 (HIF1a) and inducing DNA damage [47]. Thus, the aminoglycoside antibiotic agents that bind to the P4HA1 protein might serve in controlling the proliferation of breast cancer.

Our study explored the molecular insights of P4HA1 in the progression and may be prognostic biomarker in breast cancer. Further, aminoglycoside derivatives showed strong binding efficacy with the active site of P4HA1 and provide the foundation for precise inhibitors in breast cancer management.

CONCLUSION

We employed integrative genomic and virtual screening approach in investigating the potential expression of P4HA1 in breast cancer and to predict selective targeted inhibitor from DrugBank small molecular drugs. Our results indicated that P4HA1 is strongly expressed with high amplification and closely associated with poor prognostic in breast cancer. In addition, computational methods such as virtual screening predicted the lead molecules aminoglycoside derivatives (amikacin and gentamicin) as a potent selective inhibitor for P4HA1. The overall results suggested that aminoglycoside derivatives for the inhibition of P4HA1 could be a promising therapeutic strategy for the intervention of breast cancer.

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ETHICS DECLARATIONS

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

HUMAN AND ANIMAL RIGHTS AND INFORMED CONSENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

AUTHOR'S CONTRIBUTIONS

M.M., Conceptualization, Methodology, Data analysis and interpretation, drafted the manuscript. K.PK., Supervision, Reviewing and Editing. All authors approved with final drafted manuscript.

REFERENCES


