RESEARCH ARTICLE

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Ferroptosis Mediated Novel Drug Design Approach in the Treatment of Oral Squamous Cell Carcinoma

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Abstract

Background: Globally, Oral Squamous Cell Carcinoma (OSCC) is the highest prevalent type of oral cancer. Implementing a successful treatment plan for the aforementioned tumor has always been a primary concern. There are numerous targeted therapies of which Ferroptosis has been receiving increasing attention in the recent decade. A novel form of controlled cell death "Ferroptosis' is caused by iron-dependent lipid peroxidation. A well-known mechanism for controlling ferroptosis is the Cysteine/GSH/GPX4 axis, in which System X_c^- is crucial. System X_c^- inhibitors have been proven earlier to improve chemotherapy sensitivity. **Materials and methods:** Five System X_c^- inhibitors were selected from the literature. The structure of these molecules from Zinc15 and the protein sequence of the target from Protein Data Bank were obtained. Twenty new molecules were identified following pharmacophore modeling and were docked with the target protein using SwissDock. The binding energies of the new molecules with the target were compared with that of the reported molecules. **Result:** The molecular docking study showed that two new molecules (ZINC89362298 and ZINC1730544) resulted in the highest binding pattern (-8.64) than that of the reported molecules (-7.75). **Conclusion:** The present study concluded that ZINC89362298 and ZINC1730544 had better binding efficiencies than that of the reported System xc- inhibitors. Hence these two molecules could be used in targeted drug therapy and could be a promising lead in the management of oral cancer in the future.

Keywords: Drug designing- ferroptosis- Insilico- oral cancer- OSCC

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Introduction

Oral squamous cell carcinoma (OSCC) remains a challenge for head and neck surgeons with a low 5-year survival rate despite improvements in diagnostic techniques and therapies (Bugshan and Farooq, 2020). Various factors including depth of invasion, tumor grade, and biomarkers predict the survival rate of cancer patients (Rivera et al., 2017). Numerous studies support identifying factors that affect the course of the treatment (Massano et al., 2006). Similar to how they aid with prognosis, medications also have their own role in a patient's survival and quality of life. The role of apoptosis and the genes involved have been sufficiently understood for decades to be used in diagnosis, prognosis, and treatment with targeted therapy being in trend (Dwivedi et al., 2020). Inducing apoptosis in oral malignant epithelial cells has shown encouraging outcomes to combat cancer (Hsu et al., 2004). Recently many other forms of regulated cell death have emerged with the motive to modify disease outcomes. A few other non-apoptotic cell death includes iron-dependent ferroptosis, vacuole-presenting methuosis, immune-reactive pyroptosis, and necroptosis (Yan et al., 2020). For instance, studies on pyroptosis were reported to influence tumor cell proliferation, metastasis, and invasion (Fang et al., 2020). Another form of cell death that researchers found exponential growth in the treatment of cancer in recent decades is Ferroptosis (Jiang et al., 2021). Ferroptosis, an oxidative stress-dependent regulated necrosis is a novel pathway for preventing cancer progression (Li et al., 2020). Ferroptosis has a complex and integrated pathway regulated precisely at multiple levels that includes transcriptional, epigenetic, post-transcriptional, and post-translational factors (Tang et al., 2021). The central role involved in ferroptosis is cysteine metabolism in which the glutamate-cystine antiporter, system X_c^- is the prime target in cancer treatment (Xu et al., 2019). Tumors with overexpression of System X_c^- are associated with increased cell proliferation and metastasis according to previous literature. Hence inhibition of System X_c^- enhances chemotherapy sensitivity (Liu et al., 2021). System X_c^- inhibitors reported in the literature are Artesunate, trigonelline, lanperisone, sulfasalazine, and sorafenib. Hence the study aims to identify existing drugs that can be potentially bound against System X_c^- and to suggest potential substitutes as prospective leads

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for future stable drug designing. The objective of the study is to assess and compare the differences between the novel molecules' binding energies and those of the reported molecules with the target using computer-aided drug design in an in silico setting.

Materials and Methods

The study was carried out after obtaining approval from the scientific review board (SRB/SDC/UG-2102/22/OPATH/013), in the Department of Oral Pathology. In this study, System Xc was chosen as the target protein and its potential inhibitors were identified from the databases such as PubMed and Google Scholar. The five System Xc- inhibitors obtained from the search were Artesunate, Trigonelline, Lanperisone, Sulfasalazine and Sorafenib. These drugs have varied functions and clinical applications. Artesunate is an artemisinin derivative that has been used as an antimalarial agent, trigonelline is a plant alkaloid used as anti-diabetic drug (Roh et al., 2017), sulfasalazine is an anti-inflammatory drug used to treat ulcerative colitis (Patel et al., 2019), lanperisone is a muscle relaxant and sorafenib is a kinase inhibitor and has been known for its role in renal cancer (Liu et al., 2022). Hence this study attempts to assess the affinity of these drugs with the target System Xc in the form of binding pattern with that of the new compounds derived from the molecular structure of these five molecules keeping them as a template. The steps to develop new pharmacophores and to assess the binding pattern of these molecules with the target are as follows with the abstract of the workflow presented in Figure 1.

Zinc 15 Database

Zinc15 is a free chemical database with purchasable compounds which are ready to dock (Irwin et al., 2005). The structure of the selected molecules (Artesunate, trigonelline, sulfasalazine, lanperisone, and sorafenib) was collected from the ZINC15 database. (Figure 2) The molecules' SDF (structure data file) format and SMILES (Simplified Molecular Input Line Entry Specification) format were also obtained for further assessment in SWISS ADME.

SWISS ADME (Absorption, Distribution, Metabolism and Excretion)

Swiss ADME is a free tool to assess the pharmacokinetic properties, drug-like nature, and medicinal chemistry friendliness of the selected molecules aiding in drug discovery (Daina et al., 2017). The SMILES format from Zinc15 of each molecule was used in Swiss ADME, where the properties were assessed such as Log P, drug likeliness rules such as Lipinski (Rule 1), Ghose (Rule 2), Veber (Rule 3), Egan (Rule 4) and Muegge (Rule 5) (Table 1) and topological polar surface area (TPSA).

RCSB PDB (Research Collaboratory for Structural Bioinformatics Protein Data Bank)

This an excellent tool that provides experimentally determined 3D structures of proteins, nucleic acids and other macromolecules along with its computed structure models (Rose et al., 2016). Protein sequence of the target System Xc was collected from this Protein Data Bank (PDB) (Figure 3)

Pharmacophore Modeling

Pharmacophore modeling is done to develop pharmacophore models using the structural information about the molecules or compounds under study. To develop novel compounds from the existing System Xc inhibitors, this study used ZINCPharmer, to identify the biologically relevant compounds related to the existing five System Xc inhibitors and SwissDock, to determine the binding energies of the compounds with the target.

PharmaGist

PharmaGist is a free web server used to detect pharmacophores that enables a molecule to interact with a specific target (Duhovny et al., 2008). The sdf format of the molecules from the ZINC15 database was converted to mol2 (Molecule structure format) format using OpenBabel software which was then uploaded in PharmaGist. The results were obtained which were used for further analysis.

ZINCPharmer

ZINCPharmer, a free pharmacophore search software, identifies biologically relevant compounds automatically (Koes et al., 2012). The results from PharmaGist were loaded into ZINCPharmer where possible pharmacophores were obtained. Of these, the twenty best molecules with the highest score were selected for further analysis (Table 2).

Swiss dock

Swiss dock, a web service to predict the interaction between a target and a molecule was used in this study (Grosdidier et al., 2011). Each of the resulting 20 molecules from ZINCPharmer and the chosen 5 original molecules from the literature were docked individually with the target protein using SwissDock. The binding energies which were obtained from the results were then tabulated and compared.

This study where System Xc is chosen as the target protein identified drugs/ molecules from the literature that bind with it. We searched various databases and articles related to System Xc and its role in ferroptosis. The five system xc- inhibitors that resulted from the search were Artesunate, Trigonelline, Lanperizone, Sulfasalazine, Sorafenib. The drugs have varied functions and clinical applications. Artesunate is an artemisinin derivative that has been used as an antimalarial agent, trigonelline is a plant alkaloid used as anti diabetic drug, sulfasalazine is an anti inflammatory drug used to treat ulcerative colitis, lanperizone, a muscle relaxant and sorafenib is a kinase inhibitor has been known for its role in renal cancer. The structure of these molecules was collected from the ZINC15 database in order to assess its properties for which, Swiss ADME was used (Figures 1, 2). Protein sequence of the target system xc- was collected from Protein Data Bank (PDB) (Figure 3). Pharmacophore modeling was done using Pharmagist. Using Zinc Pharmer, which resulted in compounds with various

combinations from the selected five drugs, the best 20 molecules were selected. Each of these resulted molecules and the chosen molecules were docked individually with the target protein for which Swissdock is used. The results showed binding energies which were then assessed and compared with the original molecules.

Results

The structure of the five selected System $\overline{X}c$ inhibitors from literature was obtained using ZINC15 (Figure 2). The properties of the molecules were assessed using SwissADME (Table 3). The structure of the protein System $\overline{X}c$ was obtained from protein data bank (Figure 3). The twenty new pharmacophore models with the highest score were filtered for the docking. The results of the molecular docking analysis using SwissDock showed two new molecules (ZINC89362298 and ZINC1730544) with the highest binding pattern (-8.64) than that of the existing System $\overline{X}c$.

The results of the molecular docking analysis using SwissDock showed two new molecules (ZINC89362298 and ZINC1730544) with the highest binding pattern (-8.64) than that of the existing System XC- inhibitors (-7.75) (Figure 4). The properties of all the molecules were tabulated for comparison in which these two novel compounds had better properties satisfying the rules required for a drug such as Lipinski (Rule 1), Ghose (Rule 2), Veber (Rule 3), Egan (Rule 4) and Muegge (Rule 5) (Table 2). Other parameters such as bioavailability, LogP, and topological polar surface area (TPSA) were also compared (Table 3).

The molecular docking study showed that two new molecules (ZINC89362298 and ZINC1730544) resulted with the highest binding pattern (-8.64) than that of the reported molecules (-7.75) (Figure 4). The properties of all the molecules were tabulated for comparison in which the two novel compounds had better properties satisfying all the rules (Table 1). Other parameters such as bioavailability, LogP and topological polar surface area (TPSA) were also compared.

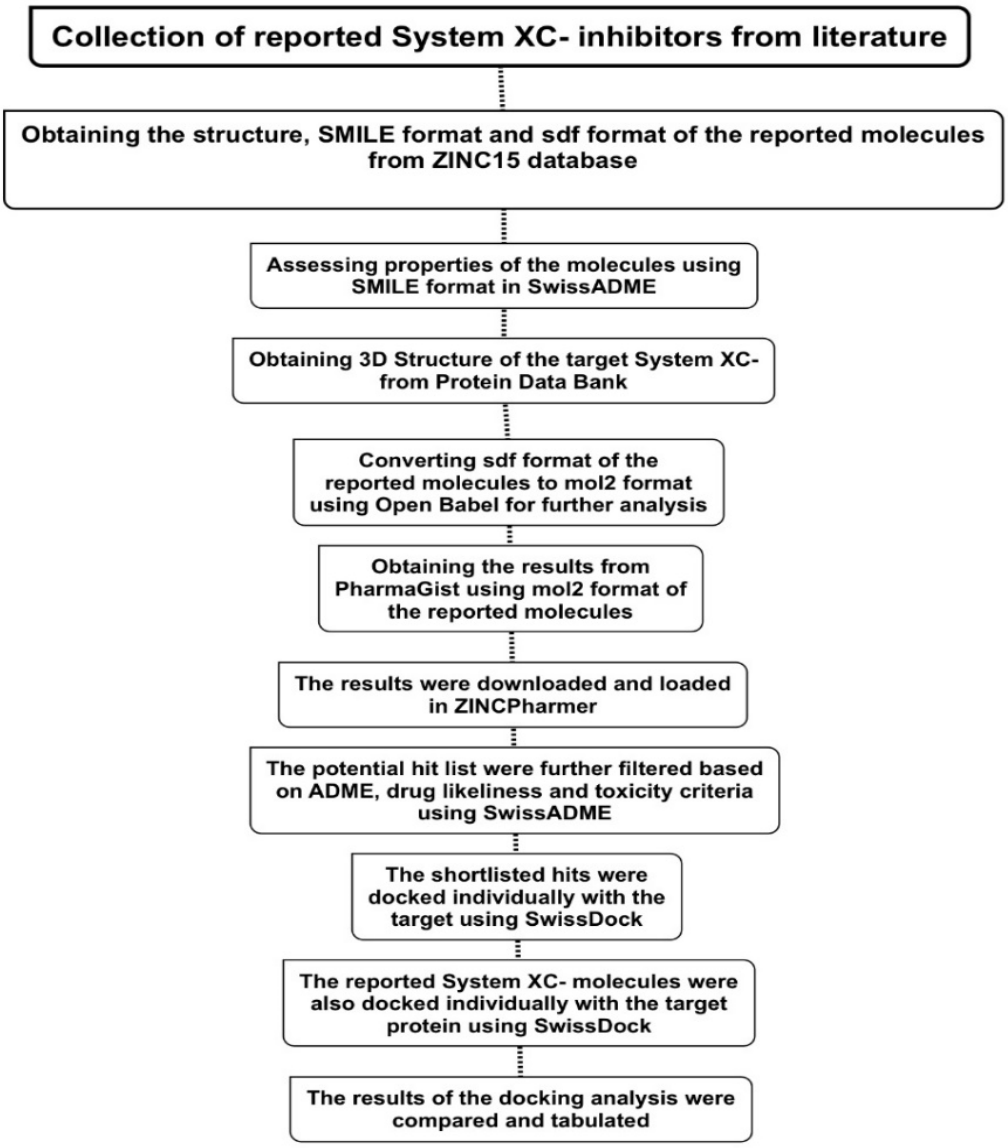

Figure 1. Step by Step Representation of the Study Workflow

Table 1. Drug Likeliness Rules Considered for Novel Drug Designing

S.no	RULES	PROPERTIES
1	Lipinski rule of 5	Molecular weight < 500
		LogP < 5
		< 5 H-bond donors
		< 10 H-bond acceptors
2	Ghose	Molecular weight 160-480
		LogP 0.4-5.6
		Molar refractivity 40-130
		Total number of atoms 20-70
3	Veber	Good bioavailability
		< 10 rotatable bonds
		Polar surface area <140
4	Egan	Good bioavailability with -1.0
		LogP ≤5.8
		TPSA ≤130 A°
5	Muegge	Molecular weight 200-600 Da
		XLogP -2 to 5
		TPSA <150
		Number of rings <7
		Number of carbon <4
		Number of heteroatoms <1
		Number of rotatable bonds <15
		HBA <10
		HBD <5

Ferroptosis mediated novel drug design approach in the treatment of OSCC

Discussion

The present study reported two molecules (ZINC89362298 and ZINC1730544) with better binding energies when compared to that of original molecules from the literature. Compounds binding with the concerned target is utmost important while developing a drug for which the ligands discovered from the present study demonstrated clearly that they bind strongly to the target protein.

A well-known, globally burden and the most prevalent oral malignancy, oral squamous cell carcinoma is derived from the epithelial lining of the oral mucosa. As easily accessible, the oral lesions should be detected more earlier than any other disorders. Light-based detection systems, fluorescence visualization, and brush cytology are a few emerging diagnostic techniques for oral cancer detection. (Lane et al., 2006).

A study by Yang et al investigated the importance of natural products in the treatment of cancer and infectious diseases in which they stressed on the fact that natural substitutes have their own place in drug discovery (Yang et al., 2012). Similarly this project included one natural compound trigonelline and it proved to be highly efficacious with the binding energy of -9.4 which is more than that of the reported compounds but with a disadvantage of violating few rules (Table 2).

Establishment of oral sorafenib (400 mg bid) as the drug of choice for metastatic renal cell carcinoma following the phase I and phase II results (Wilhelm et al., 2006) indicated selecting sorafenib as one of the drugs

Table 2. New Pharmacophores with the Properties

S. No	Name	Rule1	Rule2	Rule3	Rule4	Rule5	LogP	Bioavailability	TPSA	Binding Energy
1	ZINC70666569	Yes	Yes	Yes	Yes	Yes	2.46	0.56	121.83	-7.95
2	ZINC35264558	Yes	Yes	Yes	Yes	Yes	3.17	0.55	60.67	-7.67
3	ZINC93115728	Yes	Yes	Yes	Yes	Yes	2.76	0.85	60.36	-7.58
4	ZINC57952376	Yes	Yes	Yes	Yes	Yes	2.82	0.55	43.6	-7.57
5	ZINC93326888	Yes	NO	Yes	Yes	Yes	2.23	0.55	80.12	-7.33
6	ZINC93326895	Yes	NO	Yes	Yes	Yes	2.38	0.55	84.7	-7.23
7	ZINC72205469	Yes	Yes	Yes	Yes	Yes	3.2	0.55	72.7	-7.94
8	ZINC31625677	Yes	Yes	Yes	Yes	Yes	2.9	0.55	70.7	-7.64
9	ZINC93327041	Yes	Yes	Yes	Yes	Yes	2.25	0.55	76.88	-7.58
10	ZINC15785639	Yes	Yes	Yes	Yes	Yes	3.16	0.55	73.25	-7.83
11	ZINC11730642	Yes	Yes	Yes	Yes	Yes	1.52	0.56	80.07	-8.56
12	ZINC11730544	Yes	Yes	Yes	Yes	Yes	2.34	0.56	89.3	-8.63
13	ZINC11730476	Yes	Yes	Yes	Yes	Yes	1.72	0.56	80.07	-8.21
14	ZINC07499120	Yes	Yes	Yes	Yes	Yes	3.21	0.55	43.6	-7.56
15	ZINC69677058	Yes	Yes	Yes	Yes	Yes	2.05	0.85	64.64	-7.65
16	ZINC49422890	Yes	Yes	Yes	Yes	Yes	1.81	0.55	86.69	-7.2
17	ZINC40460846	Yes	Yes	Yes	Yes	Yes	1.81	0.55	86.69	-7.34
18	ZINC69345384	Yes	Yes	Yes	Yes	Yes	3.68	0.55	63.91	-8.51
19	ZINC89362298	Yes	Yes	Yes	Yes	Yes	3.38	0.55	90.21	-8.64
20	ZINC69677058	Yes	Yes	Yes	Yes	Yes	2.05	0.85	64.64	-7.63

Ferroptosis mediated novel drug design approach in the treatment of OSCC

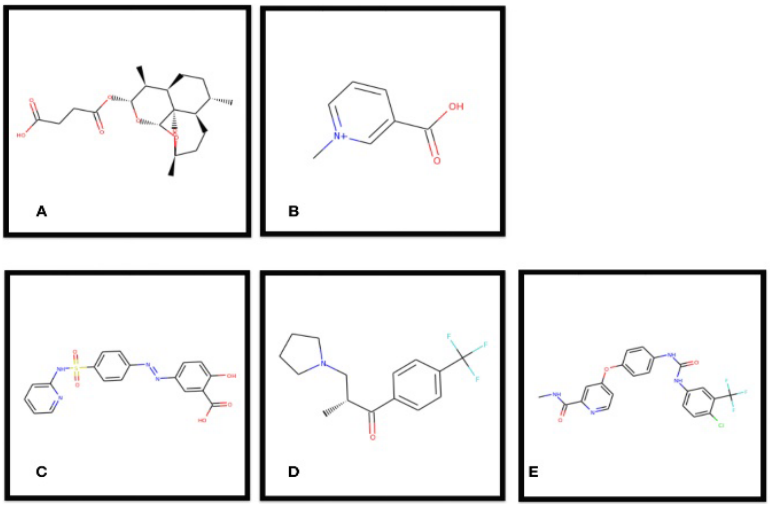

Figure 2. Showing Structures of Selected System XC Inhibitors from the ZINC15 Database. A, Artesunate; B, Trigonelline; C, Sulfasalazine; D, Lanperisone; E, Sorafenib

Table 3. Showing Properties the Molecules

S. No	Ligands	Rule1	Rule2	Rule3	Rule4	Rule5	LogP	Bioavailability	TPSA	Binding Energy
1	Artesunate	Yes	Yes	Yes	Yes	Yes	2.92	0.56	100.52	-7.84
2	Trigonelline	Yes	No	Yes	Yes	No	-2.82	0.55	41.18	-9.4
3	Lanperisone	Yes	Yes	Yes	Yes	Yes	2.82	0.55	20.31	-7.75
4	Sulfazalazine	Yes	Yes	No	No	Yes	2.11	0.56	149.69	-8.29
5	Sorafenib	Yes	No	Yes	No	Yes	3.42	0.55	92.35	-8.45
6	ZINC11730544	Yes	Yes	Yes	Yes	Yes	2.34	0.56	89.3	-8.63
7	ZINC89362298	Yes	Yes	Yes	Yes	Yes	3.38	0.55	90.21	-8.64

Ferroptosis mediated novel drug design approach in the treatment of OSCC

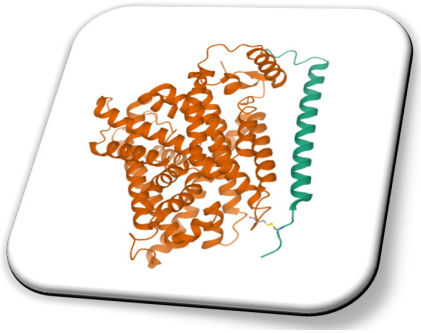

Figure 3. Protein Structure of the Target - System XC

in the current study would be more appropriate to induce ferroptosis as it is already proven to resist tumorigenesis. It was studied that sulfasalazine and curcumin, by depleting glutathione and by increasing ROS induced ferroptosis binding with system xc- in breast cancer (Wang et al., 2021) which justifies the inclusion of sulfasalazine in this study. The side effects of these five molecules include metabolic and phenotypic alterations resulting in reduced anticancer activity (Dang et al., 2022). In accordance with these study findings the molecules such as Trigonelline, sulfasalazine and sorafenib violated one or two rules while the new identified molecules are in accordance with all 5

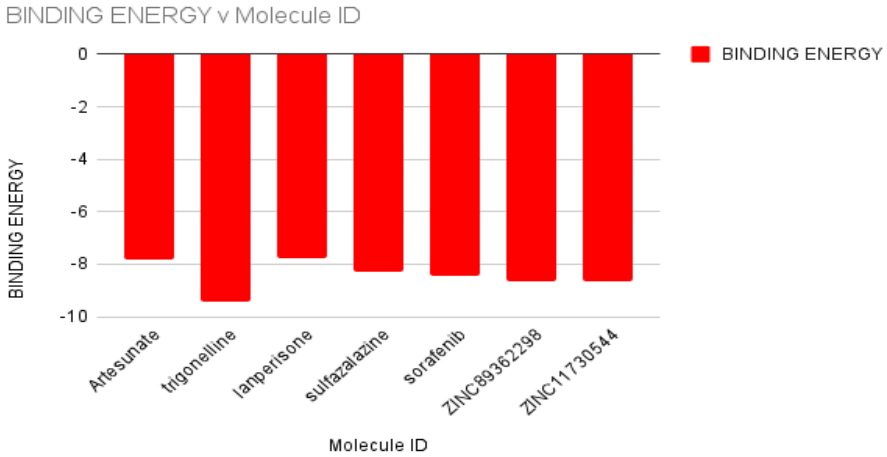

Figure 4. Represents the Binding Energies of the Existing and New Molecules.

rules. Hence the reported molecules can serve as a potent anti cancer agent. Analyzing molecular dynamics of the drugs and the resulting molecules that were not performed in the present study is one of the major limitations of this study. Many more targets with respect to the ferroptosis pathway and their potential drugs/compounds need to be assessed which could be future recommendations.

In conclusion, the goal of this research is to identify ferroptosis-specific ligands that can be used to create commercial medications that are more effective and less harmful for an earlier diagnosis and potential treatment option. The two pharmacophore models (ZINC89362298 AND ZINC1730544) obtained from the reported System X_c^- inhibitors could be a promising lead in developing commercial anticancer drugs. If proven successful in animal models, these molecules can be translated into novel therapeutic agent followed by human trials. Future in vitro studies and clinical trials are needed to be performed with these therapeutic combinations.

Author Contribution Statement

Conception and design of the study was done by Dr. Mukesh Doble and Dr. Dharini, data acquisition was carried out by Dr. Dharini. Analysis of data was carried out by Dr. Mukesh Doble and Dr. Dharini. Drafting of the article was done by Dr. Abilasha and Dr. Dharini. Final approval was done by Dr. Pratibha Ramani and Dr. Abilasha.

Acknowledgements

Ethical approval

Not applicable as no human subjects were involved.

Scientific Review Board Approval

SRB/SDC/UG-2102/22/OPATH/013

Availability of data

Raw data available.

Conflict of interest

The authors declare no conflict of interest.

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