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MOLECULAR DOCKING OF PHYTOCHEMICAL AS FTSZ CELL DIVISION PROTEIN INHIBITOR IN *MYCOBACTERIUM TUBERCULOSIS*

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ABSTRACT: *Mycobacterium tuberculosis* is the causal agent of tuberculosis which is an infectious disease responsible for more than 2 million deaths per annum worldwide, mainly in developing countries. Cell division of this microbe is very crucial for propagation. Filamenting temperature sensitive mutant Z (FtsZ) is very important player that seems to assemble into a dynamic ring (Z- ring) on the inner surface of the cytoplasmic membrane which involved in stabilizing Z-rings at the place where the division occurs and the formation of the ring is the signal for septation to begin. To control this disease researchers have investigated many naturally occurring bioactive molecules from different medicinal plants. In the present docking study, we screened a total of fifty-one different bioactive molecules found in three medicinal plants namely *Justicia adhatoda, Abrus precatoriu s*and *Dracaena angustifolia* to determine the inhibition against *M. tuberculosis* FtsZ cell divisional protein. No inhibitory effect was observed for the molecule found in *D. angustifolia* on the other hand, three compounds namely abrectorin, precatorine and gallic acid of *A. precatorius* and one compound namely vasicine of *J. adhatoda* showed inhibition. Among the four dock compounds, only abrectorin showed very good Moldock and Rerank Score (-121.394KJmol^{-1} and -108.71KJmol^{-1}) with H-Bond (-9.03613KJmol^{-1}). From, this investigation it could be contemplated that the plant species *A. precatorius* and *J. adhatoda* may be the good sources of FtsZ protein inhibitor. Validation of the compound in wet laboratory will help to explore its usability.

INTRODUCTION: Tuberculosis (TB) is the most frequently occurring infectious disease in the world and also stands out as a major cause of morbidity, disability and 2-3 million deaths per annum, globally. It is caused by mainly *Mycobacterium tuberculosis* in Humans [1, 2, 3] and process of cell division is instead by FtsZ protein [4]. It is a GTPase [5] that polymerizes in a nucleotide-dependent manner head-to-tail to form single-stranded filaments that assemble into a contractile ring [6].

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It is called the Z-ring and forms on the inside of the cytoplasmic membrane where it marks the future site of the septum of a dividing bacterial cell. Although FtsZ polymerization rapidly reaches steady state, the Z-ring is dynamically maintained through the course of cell division by continuous and rapid turnover of FtsZ polymers [7, 8] likely fueled by FtsZ's GTP hydrolysis [5, 9]. FtsZ is the first protein to localize at the division site and recruits other proteins involved in bacterial cell division. Besides serving as a scaffold for the other cell division proteins, FtsZ itself may exert cytokinetic forces that lead to cell division [7, 8, 9].

The unprecedented increase in antibiotic-resistant pathogens and lack of new antibiotic development [10] highlights the need for new anti-microbial drugs active against novel targets such as bacterial cell division proteins [11, 12]. In this current work we

hypothetically report inhibition of *M. tuberculosis* FtsZ protein by fifty-one bioactive molecules found in three medicinal plants namely *Justicia adhatoda, Abrus precatorius* and *Dracaena angustifolia.*

MATERIALS AND METHODS:

Ligand Preparation:

A literature was searched to find *J. adhatoda, A. precatorius* and *D. angustifolia* phytochemicals and their structure file (in .pdb, .smile format) were downloaded from PubChem (http: //puBChEm. ncbi.nlm.nih.goc/) and Chem Spider (http: //www.chemspider. com/) database. The tuberculosis FtsZ inhibitor database comprises 51 bioactive compounds from three medicinal plants. The inhibitors were converted to .pdb format and optimized by means of ligand preparation using default settings in Molegro Virtual Docker (MVD-2010,4.2.0) [13].

Preparation of receptor:

The X-ray crystal co-ordinates of FtsZ (PDB ID: 2Q1Y) are retrieved from protein data bank. Since FtsZ have their crystal structure in a state that represent the pharmacological target for the development of new drugs to cure tuberculosis. It is well known that PDB files often have poor or missing assignments of explicit hydrogens and the PDB file format cannot accommodate bond order information. Therefore, proper bonds, bond orders, hybridization and charges were assigned using the MVD. The potential binding sites of FtsZ receptor was calculated using the built-in cavity detection algorithm implemented in MVD. The search space of the simulation exploited in the docking studies was studied as a subset region of 25.0 Angstroms around the active side cleft.

Molecular docking:

MVDs docking search algorithms and scoring functions:

Ligand docking studies were performed by MVD, which has recently been introduced and gained attention among medicinal chemists. MVD is a fast and flexible docking program that gives the most likely conformation of ligand binding to a macromolecule. MolDock software is based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm [14]. It has an interactive optimization technique inspired by Darwinian Evolution Theory (Evolutionary Algorithms - EA), in which a population of individuals is exposed to competitive selection that weeds out poor solutions. Recombination and mutation are used to generate new solutions. The scoring function of MolDock is based on the Piecewise Linear Potential (PLP), which is a simplified potential whose parameters are fit to protein-ligand structures and a binding data scoring function [15, 16] that is further extended in GEMDOCK (Generic Evolutionary Method for molecular DOCK) [17] with a new hydrogen bonding term and charge schemes

Parameters for docking search algorithms:

MolDock Optimizer:

In MVD, selected parameters were used for the guided differential evolution algorithm: number of runs =5 by checking constrain poses to cavity option), population size=50, maximum interactions =2000, cross over rate=0.9, and scaling factor=0.5.Ao variance-based termination scheme was selected rather than root mean square deviation (RMSD). To ensure the most suitable binding mode in the binding cavity, Pose clustering was employed, which lead to multiple binding modes.

Parameters for scoring functions:

MolDock score:

They ignore-distant-atoms option was used to ignore atoms far away from the binding site. Additionally, hydrogen bond directionality was said to check whether hydrogen bonding between potential donors and acceptors can occur. The binding site on the protein was defined as extending in X, Y & Z directions around the selected cavity with a radius of 25 Angstroms.

RESULTS:

Docking results:

During cavity generation it was found 5 cavities generated out of which the cavity having volume 289.104 had selected for the docking study. All the fifty one compounds were loaded to the MVD environment and docked with the active site of FtsZ. During docking we have used MolDock Score as the energy scoring function with resolution 0.30 A^0 and the MolDock Simplex Evolution search algorithm. Out of 51 compounds 15 from *D.angustifolia*, 6 from *A.precatorius* and 19 from *J.adhatoda*, where most of the compounds

showing good binding affinities toward the protein. The top most four molecule are abrectorin(-121.394KJmol^{-1}, -83.6817KJmol^{-1}, -9.03613KJmol^{-1}), precatorine (-99.6725KJmol^{-1}, -76.0147KJmol^{-1}, -7.77213KJmol^{-1}), galic acid (-72.4461KJmol^{-1}, -34.3573KJmol^{-1}, -8.77058KJmol^{-1}) and vasicine (-83.4599KJmol^{-1}, -71.794KJmol^{-1}, -7.03174 KJmol^{-1}) **(Table 1).** After screening through docking study the final selected dock-complex were subjected for H-bond annotation **(Table 2)**.

TABLE1: DOCKING OF PHYTOCHEMICALS FOUND IN *DRACAENA ANGUSTIFOLIA, JUSTICIA ADHATODA* AND *ABRUS PRECATORIU* AGAINST TUBERCULOSIS CELL DIVISIONAL PROTEIN FtsZ

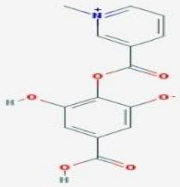
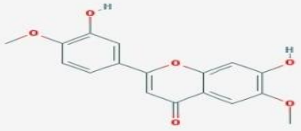
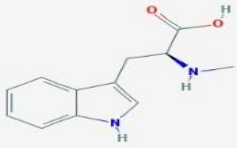
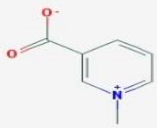
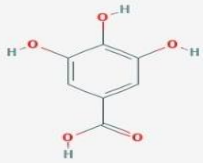
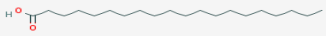
Dracaena angustifolia			
Name of ligand	**MolDock Score**	**Rerank Score**	**HBond**
Phytene-1	-133.575	-108.71	0
Namonins D	8833.43	-54.7534	-3.47281
NamogeninsB	3897.27	-45.933	-0.190545
Angudracanoside F	5878.08	-41.2418	-1.67443
AngudracanosideE	4873.59	-40.5113	-6.87843
NamogeninsA	5904.85	-37.73	-0.191252
Angudracanoside D	5878.29	-24.9747	-0.475568
(25Z)-26-methylstrongylosterol	900.056	-19.0775	-1.18376
Angudracanoside C	5884.3	-16.0315	-0.474638
Angudracanoside A	5886.25	-15.0695	-0.478535
Angudracanoside B	4887.69	-14.6567	-0.51568
Sitostenone	917.576	-8.82243	-0.954966
Cholesterol	916.428	-3.44468	-3.43592
Namonin E	3847.54	0.849978	-0.320171
Namonins C	7843.14	18.8501	-5.78423
Justicia adhatoda			
Name of ligand	**MolDock Score**	**Rerank Score**	**HBond**
Behenic acid	-132.811	-115.463	-0.179187
Cerotic acid	-135.757	-113.272	2.19902
Lignoceric acid	-134.409	-112.617	0
Arachidic acid	-132.617	-111.366	-1.1524
Linoleic acid	-89.0314	-94.5023	-0.130342
Beta carotene	-51.6142	-94.288	0
Anisotine	-108.319	-92.0953	-0.821308
Vasicinolone	-100.57	-79.489	-4.75321
Ascorbic acid	-47.9399	-78.739	-4.60792
Scopolamine	-88.7211	-73.6933	-5
Vasicine	-83.4599	-71.794	-7.03174
Beta-Sitosterol	-58.6843	-69.8993	0
Lyoniside	-47.0349	-69.2404	0
Vasicinol	-77.8818	-64.1643	-6.93674
Peganine	-75.6067	-63.7937	-6.56234
Vasicinone	-70.4087	-59.839	-6.47827
Deoxyvasicinone	-69.378	-55.5117	-3.92806
Taraxerol	1921.34	-54.6283	0
Betaine	-46.3362	-43.4197	-0.1272
Scopoline	-40.2978	-40.7777	-2.7245
Abrus precatorius			
Name of ligand	**MolDock Score**	**Rerank Score**	**HBond**
Abrectorin	-121.394	-83.6817	-9.03613
Precatorine	-99.6725	-76.0147	-7.77213
Abrin	-93.2101	-69.2098	-4.93034
Gallic acid	-72.4461	-34.3573	-8.77058
Choline	-57.1776	-42.2583	-2.5
Trigonelline	-52.31	-51.3188	-3.15832

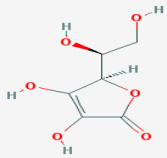
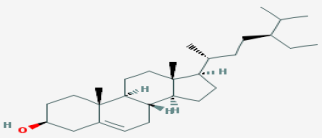
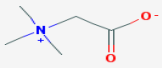
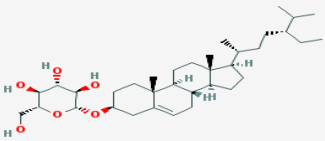
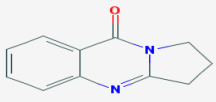
Binding interactions of Ligands and Protein:

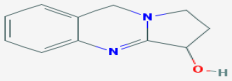
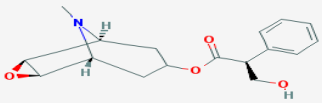
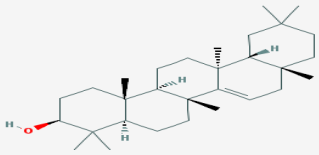
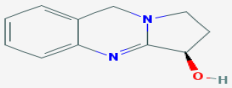
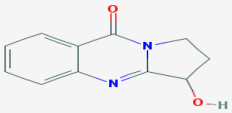
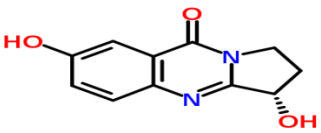
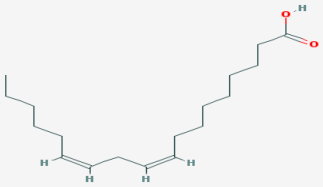
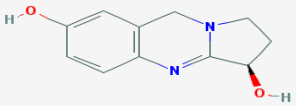
The most active abrectorine was ranked as first on the docking score. It is clear from that this compound was bound deep into the binding cavity of FtsZ making interactions with the residues N141 (Arg26B), N144 (Arg26B), N178 (Glu30B), O313 (Met49B) and N332(Lys55A) with interaction energy (-1.78 KJmol^{-1}, -2.50 KJmol^{-1}, -1.61 KJmol^{-}

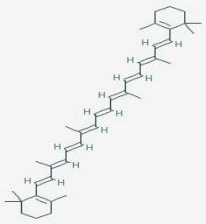
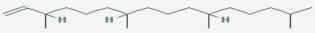
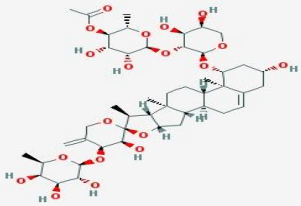
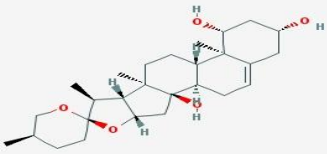
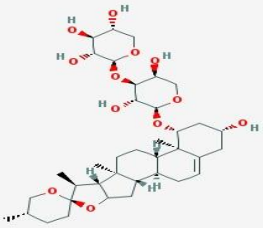
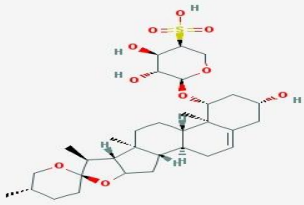
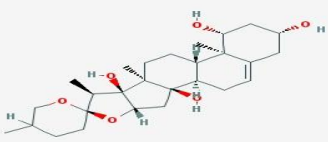
^{1}, -2.50 KJmol^{-1}, -2.25 KJmol^{-1}) and interaction distance (3.08A^{0}, 2.65A^{0}, 3.28A^{0}, 2.61A^{0}, 3.15A^{0}) **(Table3, Figure 1)**.

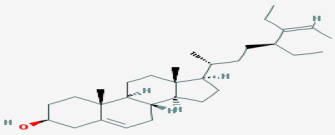
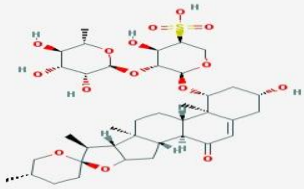
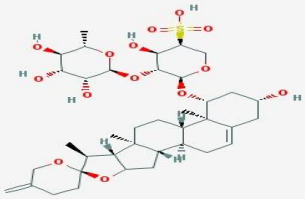
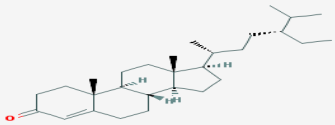
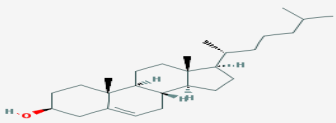
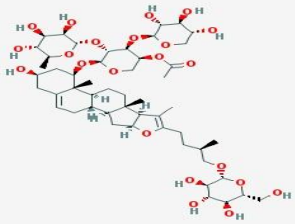
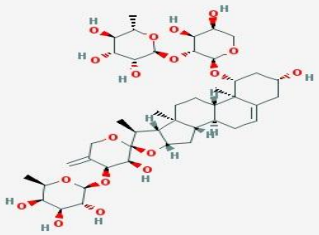
TABLE 2: CHARACTERISTICS FEATURES OF PHYTOCHEMICALS FOUND IN THREE PLANT *ABRUS PRECATORIU, JUSTICIA ADHATODA* AND *DRACAENA ANGUSTIFOLIA.*

Name of compound	Structure of Compound	Properties
	Abrus precatorius	
Precatorine		ID: 54704420 Molecular Weight: 289.24024 [g/mol] XLogP3-AA: 1.9 H-Bond Donor: 2 H-Bond Acceptor: 6
Abrectorin		ID: 44257585 Molecular Weight: 314.28946 [g/mol] XLogP3-AA: 2.4 H-Bond Donor: 2 H-Bond Acceptor: 6
Abrine		ID: 160511 Molecular Weight: 218.25176 [g/mol] XLogP3: -0.5 H-Bond Donor: 3 H-Bond Acceptor: 3
Trigonelline		ID: 5570 Molecular Weight: 137.13598 [g/mol] XLogP3-AA: 1.2 H-Bond Donor: 0 H-Bond Acceptor: 2
Gallic Acid		ID: 370 Molecular Weight: 170.11954 [g/mol] XLogP3: 0.7 H-Bond Donor: 4 H-Bond Acceptor: 5
Choline		ID: 305 Molecular Weight: 104.17076 [g/mol] XLogP3-AA: -0.4 H-Bond Donor: 1 H-Bond Acceptor: 1
	Justicia adhatoda	
Arachidic acid		ID: 10467 Molecular Weight: 312.5304 [g/mol] XLogP3: 8.5 H-Bond Donor: 1 H-Bond Acceptor: 2

Ascorbic acid		ID: 54670067 Molecular Weight: 176.12412 [g/mol] XLogP3: -1.6 H-Bond Donor: 4 H-Bond Acceptor: 6
Behenic acid		ID: 8215 Molecular Weight: 340.58356 [g/mol] XLogP3: 9.6 H-Bond Donor: 1 H-Bond Acceptor: 2
Beta-Sitosterol		ID: 222284 Molecular Weight: 414.7067 [g/mol] XLogP3-AA: 9.3 H-Bond Donor: 1 H-Bond Acceptor: 1
Betaine		ID: 247 Molecular Weight: 117.14634 [g/mol] XLogP3-AA: 0.5 H-Bond Donor: 0 H-Bond Acceptor: 2
Cerotic acid		ID: 10469 Molecular Weight: 396.68988 [g/mol] XLogP3: 11.8 H-Bond Donor: 1 H-Bond Acceptor: 2
Lyoniside		ID: 5742590 Molecular Weight: 576.8473 [g/mol] XLogP3-AA: 7.7 H-Bond Donor: 4 H-Bond Acceptor: 6
Deoxyvasicinone		ID: 68261 Molecular Weight: 186.2099 [g/mol] XLogP3-AA: 0.9 H-Bond Donor: 0 H-Bond Acceptor: 2
Lignoceric acid		ID: 11197 Molecular Weight: 368.63672 [g/mol] XLogP3: 10.7 H-Bond Donor: 1 H-Bond Acceptor: 2

Peganine		ID: 72610 Molecular Weight: 188.22578 [g/mol] XLogP3-AA: 0.4 H-Bond Donor: 1 H-Bond Acceptor: 2
Scopolamine		ID: 3000322 Molecular Weight: 303.35294 [g/mol] XLogP3: 0.9 H-Bond Donor: 1 H-Bond Acceptor: 5
Taraxerol		ID: 92097 Molecular Weight: 426.7174 [g/mol] XLogP3-AA: 9.3 H-Bond Donor: 1 H-Bond Acceptor: 1
Vasicine		ID: 442929 Molecular Weight: 188.22578 [g/mol] XLogP3-AA: 0.4 H-Bond Donor: 1 H-Bond Acceptor: 2
Vasicinone		ID: 10242 Molecular Weight: 202.2093 [g/mol] XLogP3-AA: 0.4 H-Bond Donor: 1 H-Bond Acceptor: 3
Vasicinolone		ChemSpider ID**: 139625** Molecular Weight: 218.20869[g/mol] LogP: -0.981 H-Bond Donor: 2 H-Bond Acceptor: 5
Linoleic Acid		ID: 5280450 Molecular Weight: 280.44548 [g/mol] XLogP3: 6.8 H-Bond Donor: 1 H-Bond Acceptor: 2
Vasicinol		ID: 6452262 Molecular Weight: 204.22518 [g/mol] XLogP3-AA: 0.1 H-Bond Donor: 2 H-Bond Acceptor: 3

Anisotine		ID: 442884 Molecular Weight: 349.38316 [g/mol] XLogP3-AA: 3 H-Bond Donor: 1 H-Bond Acceptor: 5
Beta Carotene		ID: 5280489 Molecular Weight: 536.87264 [g/mol] XLogP3: 13.5 H-Bond Donor: 0 H-Bond Acceptor: 0
Dracaena angustifolia		
1-Phytene		ID: 529408 Molecular Weight: 280.5316 [g/mol] XLogP3-AA: 9.5 H-Bond Donor: 0 H-Bond Acceptor: 0
Namonin D		ID: 11147371 Moleculer Weight: 927.0366[g/mol] XLogP3-AA: 9.5 H-Bond Donor: 9 H-Bond Donor: 19
Namogenin B		ID: 44567203 Molecular Weight: 446.61938 [g/mol] XLogP3-AA: 3.5 H-Bond Donor: 3 H-Bond Acceptor: 5
Angudracanoside F		ID: 49866278 Molecular Weight: 694.84922 [g/mol] XLogP3-AA: 1.6 H-Bond Donor: 6 H-Bond Acceptor: 12
Angudracanoside E		ID: 49866277 Molecular Weight: 626.7984 [g/mol] XLogP3-AA: 3.3 H-Bond Donor: 4 H-Bond Acceptor: 10
Namogenin A		ID: 10885068 Molecular Weight: 462.61878 [g/mol] XLogP3-AA: 2.4 H-Bond Donor: 4 H-Bond Acceptor: 6

Angudracanoside D		ID: 49866276 Molecular Weight: 786.92312 [g/mol] XLogP3-AA: 0.5 H-Bond Donor: 7 H-Bond Acceptor: 15
(25Z)-26-methylstrongylosterol		ID: 52931388 Molecular Weight: 440.74398 [g/mol] XLogP3-AA: 9.9 H-Bond Donor: 1 H-Bond Acceptor: 1
Angudracanoside C		ID: 49866275 Molecular Weight: 786.92312 [g/mol] XLogP3-AA: 0.5 H-Bond Donor: 7 H-Bond Acceptor: 15
Angudracanoside A		ID: 49866273 Molecular Weight: 786.92312 [g/mol] XLogP3-AA: 1.1 H-Bond Donor: 6 H-Bond Acceptor: 15
Angudracanoside B		ID: 49866274 Molecular Weight: 770.92372 [g/mol] XLogP3-AA: 1.6 H-Bond Donor: 6 H-Bond Acceptor: 14
Sitostenone		ID: 5484202 Molecular Weight: 412.69082 [g/mol] XLogP3-AA: 9.3 H-Bond Donor: 0 H-Bond Acceptor: 1
Cholesterol		ID: 5997 Molecular Weight: 386.65354 [g/mol] XLogP3: 8.7 H-Bond Donor: 1 H-Bond Acceptor: 1
Namonin E		ID: 10964186 Molecular Weight: 1045.1677 [g/mol] XLogP3-AA: -1.2 H-Bond Donor: 11 H-Bond Acceptor: 22
Namonin C		ID: 10440733 Molecular Weight: 884.99992 [g/mol] XLogP3-AA: -1.7 H-Bond Donor: 10 H-Bond Acceptor: 18

DISCUSSION:

The introduction of CADD approach to modern drug development sector makes it very fast and reliable due to its less cost and time consuming effort. The ligand-receptor docking and interaction analysis are the great effort to the *in-silico* drug development. Herein we have used the MVD docking environment a reliable docking tool where our plant compounds with receptor protein FtsZ were docked. It was found that except the *D.angustifolia* plant compounds only four compounds from *A. precatorius* and *J. adhatoda* showed good inhibitory effect **(Table 10).**

The Moldock, Rerank and H-Bond Score of top most molecules are abrectorin (-121.394 $KJmol^{-1}$, -83.6817 $KJmol^{-1}$, -9.03613 $KJmol^{-1}$), precatorine (-99.6725 $KJmol^{-1}$, -76.0147 $KJmol^{-1}$, -7.77213 $KJmol^{-1}$), galic acid (-72.4461 $KJmol^{-1}$, -34.3573 $KJmol^{-1}$, -8.77058 $KJmol^{-1}$) and vasicine (-83.4599 $KJmol^{-1}$, -71.794 $KJmol^{-1}$, -7.03174 $KJmol^{-1}$), respectively **(Table 1)**.

Among them abrectorine was ranked as top docked molecule on the basis of score obtained from MVD (Molegro virtual Docker) docking algorithm. *A. precatorius* plant derives antioxidants especially polyphenols and flavonoids have recently attracted medicinal attention as bioactive agents with anticancer, antidiabetic, antimicrobial, hepatoprotective, neuroprotective and cardioprotective properties [20, 21,18].

The abrectorin is extracted from the seeds of *A. precatorius* plant. Its leaves, roots and seeds are used as a medicament in traditional system of Indian medicine for antihelminthic, antidiarrhoeal, antiemetic and inhibits intestinal motility. Re-searchers have reported that seeds are used for the treatment of diabetes and chronic nephritis [19]. Thus, it can be concluded that this compound can serve as competitive inhibitor against FtsZ protein. Validation of the compound in wet laboratory will help to explore its usability

CONCLUSION: Screening studies of 51 phytochemical of three medicinal plant *A. precatorius, J.adhatoda* and *D. angustifolia* obtained from pubchem database are docked against *M. tuberculosis* FtsZ protein using Molegro Virtual Docker software, and four bioactive molecule abrectorine, Precatorine, Gallic Acid and Vasicine was found to inhibit FtsZ protein. Hence, this study confirmed that these four compounds can be utilise to use as an anti tuberculotic agents.

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