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Identification of Natural Compounds as CTX-M-15 Inhibitors for the Management of Multidrug-Resistant Bacteria: An in-silico study

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Abstract

Background: Antibiotic resistance is a major global threat to the efficacy of bacterial infection treatment. Resistance to beta-lactam antibiotics in bacteria is primarily caused by the production of extended-spectrum β -lactamases, with the CTX-M variant, particularly CTX-M-15, being the most common. The need for an effective CTX-M-15 inhibitor is currently pressing.

Methods: This study screened a library of natural compounds from the ZINC database against the CTX-M-15 protein using the PyRx 0.8 tool. The SwissADME web platform was used to predict the ADMET properties of the five most promising compounds.

Result: The identified hit compounds, ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591, exhibited strong binding with CTX-M-15. These compounds interacted with crucial catalytic site residues in the CTX-M-15 protein, particularly Ser70 and Ser130. Notably, the binding energies of these compounds were higher than those of the reference compound avibactam. Furthermore, they exhibited pharmacologically favorable characteristics.

Conclusion: These compounds show promise as potential CTX-M-15 inhibitors to combat bacterial resistance. However, more experimental research is needed to optimize these compounds for their role as CTX-M-15 inhibitors.



Introduction

The global threat of pathogenic microorganisms that are resistant to established antibiotics has had significant ramifications for the treatment of infectious diseases. This situation is primarily caused by increased or inappropriate use of antibiotics in human medical practice, agricultural activities, and veterinary medicine [1,2]. Evidently, there has been a concerning increase in the prevalence of antibiotic resistance among bacterial strains responsible for both community-based and nosocomial infections. Mitigating the persistent and impending threat of antibiotic resistance remains a difficult task for clinicians and microbiologists worldwide [3-6].

The production of beta-lactamases is the primary cause of resistance to beta-lactam antibiotics in Gram-negative bacteria [7]. These enzymes aid in the cleavage of the amide linkage within the beta-lactam ring structure, effectively neutralizing the antibacterial efficacy of beta-lactam antibiotics [8]. Extended-spectrum beta-lactamases (ESBLs) play an essential role in providing bacterial pathogens with resistance to a variety of antibiotics, most notably advanced-generation cephalosporins [9]. CTX-M is one of the most common ESBLs, with the CTX-M-15 variant emerging as the most common form [10,11].

The discovery and development of novel beta-lactamase inhibitors to combat the persistent and imminent threat posed by multidrug-resistant bacteria remains a primary focus in clinical practice, microbiology, and drug discovery research [12]. The current demand for a potent CTX-M inhibitor is high. Computer-aided drug design represents a paradigm shift away from traditional pharmacological approaches and toward computational approaches [13,14]. The substantial financial and time investments associated with the attrition of candidate drugs in conventional pharmacology drive this transition, making it necessary. The use of computational database screening in pharmaceutical research has grown significantly. Virtual screening (VS) methodologies use computer-driven techniques to identify novel ligands by using biological structural information as a foundation for discovery [15-17]. This study aimed to find a natural CTX-M-15 inhibitor using the in-silico tools.

Methods

Protein preparation

The 3D conformation of the CTX-M-15 protein in conjunction with avibactam (PDB ID: 4HBU) was acquired from the Protein Data Bank. Following that, the avibactam co-crystal ligand was excised, and

preparatory procedures were carried out on the protein structure before it was saved in .pdb format.

Natural compound library

The ZINC database, an open-access repository designed for VS purposes, was used to obtain natural compounds from their respective database websites [18]. Subsequently, 500 natural compounds were acquired and subjected to docking-based screening procedures.

Virtual screening

The compounds were screened using the PyRx 0.8 tool against the CTX-M-15 protein [19]. The SDF-formatted compound library was imported into the PyRx workspace and subjected to a series of minimization procedures. The refined ligand structures were then converted into the pdbqt format using the PyRx platform's Open Babel functionality. Finally, the most promising compounds based on binding energy (BE) were subjected to an in-depth interaction analysis.

Drug-Likeness

The SwissADME web platform [20] was used to predict the Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties of the five most promising compounds. ADMET prediction is an essential part of the discovery process, where the precise results aid in the identification of optimal pharmaceutical candidates.

Results

This study screened the natural compounds against one of the most prevalent beta-lactamases, i.e., CTX-M-15. Following the preparation of the compound library, VS was conducted to evaluate their efficacy against the CTX-M-15 protein, using the avibactam as a reference compound. After this procedure, the top 10 compounds were chosen based on their higher BE relative to the avibactam (Table 1). Figure 1 depicts the top ten compounds along with avibactam in the CTX-M-15 binding pocket.

Compound	Binding energy (Kcal/mol)
ZINC1857626342	-8.8
ZINC403692	-8.6
ZINC408773	-8.5
ZINC57926	-8.2
ZINC790938591	-8.0
ZINC6143155	-7.7
ZINC250411	-7.4
ZINC6783868	-7.2
ZINC34348680	-7.1
ZINC149277742	-7.0
Avibactam*	-6.6

Table 1: Binding energy of the top ten compounds.

Based on their BE and interactions with CTX-M-15 key residues (Ser70 and Ser130), the top five compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591) were

chosen for comprehensive interaction analysis. ZINC1857626342 interacted with Ser70, Lys73, Asn104, Tyr105, Ser130, Asn132, Asn170, Thr216, Lys234, Thr235, Gly236, Ser237, Thr243, Ser272, and Arg274 residues of CTX-M-15 protein. The Ser70, Lys73, Asn132, Ser130, Thr235, and Arg274 residues were H-bonded with ZINC1857626342 (Figure 2A). ZINC403692 was found to bind with Ser70, Lys73, Tyr105, Ser130, Asn132, Asn170, Thr216, Ala219, Thr235, Gly236, Ser237, and Arg274 residues of CTX-M-15 protein. The Ser70, Lys73, and Ser130 residues were H-bonded with ZINC403692 (Figure 2B). ZINC408773 interacted with Ser70, Lys73, Asn104, Tyr105, Ser130, Asn132, Asn170, Thr216, Ser220, Lys234, Thr235, Gly236, Ser237, Gly238, Thr243, and Arg274 residues of CTX-M-15 protein. The Asn104, and Ser130, residues were H-bonded with ZINC408773 (Figure 2C). ZINC57926 was found to bind with Ser70, Lys73, Asn104, Tyr105, Ser130, Asn170, Thr216, Ser220, Thr235, Gly236, Ser237, Thr243, and Arg274 residues of CTX-M-15 protein. The Ser70 and Ser237 residues were H-bonded with ZINC57926 (Figure 2D). In addition, ZINC790938591 interacted with Ser70, Lys73, Asn104, Tyr105, Ser130, Asn132, Asn170, Thr216, Ala219, Thr235, Gly236, Ser237, and Arg274 residues of CTX-M-15 protein. The Ser70, Asn104, Ser130, and Asn132 residues were H-bonded with ZINC790938591 (Figure 2E).

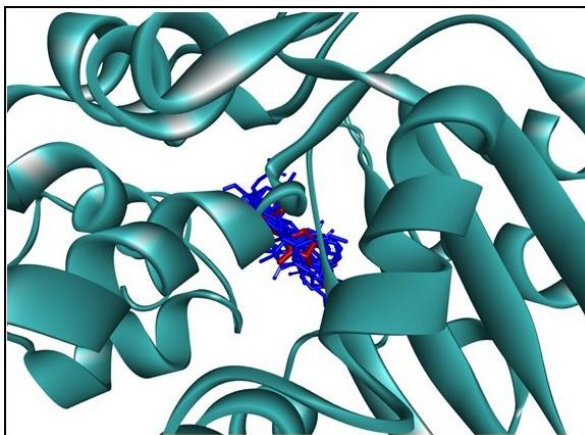


Figure 1: Visualization of the top ten compounds, as well as avibactam (red color), in the CTX-M-15 binding pocket.

Furthermore, the co-crystal ligand avibactam was found to interact with Ser70, Lys73, Tyr105, Ser130, Asn132, Asn170, Thr216, Ser220, Ala219, Thr235, Gly236, Ser237, and Arg274 residues of the CTX-M-15 protein (Figure 2F). The structures of selected compounds are shown in Table 2.

A comprehensive analysis of the physicochemical properties, adherence to drug-like criteria, and toxicity profiles of the hit compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and

ZINC790938591) in the current study demonstrates that they exhibit virtually all of the essential attributes required for their potential as future drug candidates (Table 3).

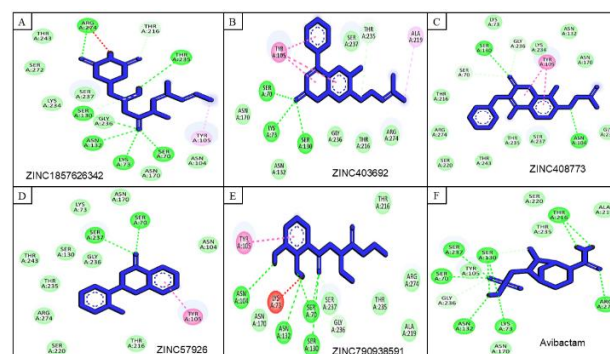


Figure 2: Interacting residues of CTX-M-15 with ZINC1857626342 (A), ZINC403692 (B), ZINC408773 (C), ZINC57926 (D), ZINC790938591 (E), and avibactam (F).

Compounds	Structure	H-bonded residues
ZINC1857626342		Ser70, Lys73, Ser130, Asn132, and Arg274
ZINC403692		Ser70, Lys73, and Ser130
ZINC408773		Asn104, and Ser130
ZINC57926		Ser70, and Ser237
ZINC790938591		Ser70, Asn104, Ser130, and Asn132
Avibactam		Ser70, Lys73, Ser130, Asn132, Thr216, Ser237, and Arg274

Table 2: Structure of selected compounds and H-bonded residues of CTX-M-15 with the compounds.

Discussion

Beta-lactamase inhibitors have emerged as a viable option for mitigating the effects of beta-lactam antibiotic resistance [21]. Here, the natural compounds from the ZINC database were screened against the CTX-M-15. The top five compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591) were chosen for in-depth interaction analysis based on their BE and interactions with CTX-M-15 key residues.

Property	Model Name	Predicted Value				
		ZINC1857626342	ZINC403692	ZINC408773	ZINC57926	ZINC790938591
Physico-chemical Properties	MW (g/mol)	307.38	340.80	334.41	240.25	269.25
	HBA	4	3	3	3	6
	HBD	2	0	0	1	4
	TPSA	83.47	39.44	39.44	46.53	116.09
Lipophilicity	iLOGP	2.26	3.79	3.87	2.09	1.89
	XLOGP3	1.43	5.18	5.36	2.78	0.68
	WLOGP	1.53	5.46	4.96	2.77	-0.25
	MLOGP	1.51	4.08	4.03	1.85	-0.19
	Silicos-IT Log P	3.11	5.83	6.40	3.06	0.27
	Consensus Log P	1.97	4.87	4.92	2.51	0.48
Estimated Solubility	Log S	-2.18	-5.45	-5.43	-3.51	-1.71
	Solubility(mg/ml)	5.01e-01	5.99e-04	3.83e-04	9.28e-02	5.44e-01
	Solubility (mol/l)	1.63e-03	1.76e-06	1.14e-06	3.86e-04	2.02e-03
	Class	Soluble	Moderately soluble	Moderately soluble	Soluble	Soluble
Pharmaco-kinetics	GI absorption	High	High	High	High	High
	BBB permeant	No	Yes	Yes	Yes	No
	log Kp (cm/s)	-7.16	-4.70	-4.53	-5.79	-7.46
Drug likeness	Number of violations	Lipinski	0	0	0	0
		Ghose	0	0	0	0
		Veber	0	0	0	0
		Egan	0	0	0	0
		Muegge	0	0	0	0

Table 3: Druglike properties of selected compounds.

To gain a comprehensive understanding of the interacting residues within the CTX-M-15 protein for the selected compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591), an analysis was conducted by re-docking the co-crystal ligand avibactam into the CTX-M-15 protein which revealed that Ser70, Lys73, Tyr105, Ser130, Asn132, Asn170, Thr216, Ser220, Ala219, Thr235, Gly236, Ser237, and Arg274 residues participated in the binding with avibactam. Notably, Ser70, Lys73, Tyr105, Ser130, Asn170, Thr216, Thr235, Gly236, Ser237, and Arg274 were common CTX-M-15 binding residues with the top five compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591) as well as the avibactam. This indicates that these compounds bind to the same binding pocket within the CTX-M-15 protein as avibactam.

Docking serves as an alternative strategy for preliminary compound evaluation before in vivo experimental validation [22]. This method helps predict the energetically favorable binding orientations of ligands within the active site of a receptor/protein. Therefore, docking has received widespread recognition in the scientific community for its ability to reduce the time and money required for drug development [23]. In a docking study, a high negative BE signifies robust interactions within the ligand-protein complex [24-26]. Notably, the selected compounds—ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591 have higher BEs than the reference compound avibactam, indicating potent interactions with the CTX-M-15 protein.

The CTX-M-15 enzyme is essential in the hydrolysis of beta-lactam antibiotics during both the acylation and deacylation phases of its catalytic cycle. The

interaction of these antibiotics with CTX-M-15 significantly enhances the deacylation rate, allowing for rapid regeneration of the CTX-M-15 enzyme. CTX-M-15 inhibitors, on the other hand, exert their inhibitory effects by lowering the deacylation rate or the enzyme's ability to regenerate, which is accomplished by the creation of stable acyl complexes with CTX-M-15. As a result, the efficiency of CTX-M-15 inhibitors is dependent on the enzyme's interaction between high acylation rates and low deacylation rates [27]. Ser70 and Ser130 are essential interaction residues of CTX-M-15 in the context of the acylation process with its inhibitor [28-30]. It is worth noting that the identified hits in this investigation (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591) were found to bind to Ser70 and Ser130 residues of the CTX-M-15 enzyme.

A compound's absorption is influenced by characteristics such as intestinal absorption in humans, water solubility, and Caco2 permeability [31]. Indeed, the therapeutic compounds must go via several routes in the body before reaching their destination. A compound's water solubility is critical in regulating absorption and subsequent distribution. Low water solubility compounds often have inferior absorption characteristics. Numerous examples of failed drug development can be attributed to poor pharmacokinetic profiles and unsatisfactory bioavailability, which are factors other than potency and toxicity. The hit compounds (ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591) demonstrate druglike properties.

Given the increasing prevalence of life-threatening bacterial infections, as well as their proclivity to develop resistance to current therapeutic approaches, there is an urgent need for the discovery and development of novel compounds capable of combating them. These molecules must have low toxicity, precise

target action, and high bioavailability. Natural products have emerged as a critical source of potential pharmacological agents, serving as key templates for the development of new pharmaceuticals ranging from anti-cancer therapy to antibiotics [32,33]. The primary motivation for researching natural products with antimicrobial activity stems from the ongoing spread of plasmid-mediated antibiotic resistance genes, as well as the emergence of diseases, particularly those affecting the respiratory and nervous systems, that remain unaddressed by existing natural or plant-derived compounds. In the absence of conventional medicines, the WHO encourages the use of medicinal plants as supplementary therapy. This approach emphasizes extensive research into bioactive substances, their chemical compositions, and the pharmacological potential of various plant species in producing drugs with lower toxicity profiles than existing ones. Natural substances have found use in the treatment of a variety of ailments, including microbial infections, inflammatory processes, and cancer, due to their numerous benefits [34]. The hit compounds described in this study are natural compounds that have shown strong binding affinities with the CTX-M-15 protein and may thus be effective in tackling the challenge of bacterial resistance.

ESBLs play a pivotal role in the development of antibiotic resistance in bacteria. CTX-M is a common ESBL, with the CTX-M-15 variant emerging as the most prominent. This study used computational tools to screen natural compounds against the CTX-M-15 protein in order to identify promising CTX-M-15 inhibitors. Notably, the compounds ZINC1857626342, ZINC403692, ZINC408773, ZINC57926, and ZINC790938591 demonstrated strong binding affinities to CTX-M-15, interacted with critical residues (Ser70 and Ser130) of the CTX-M-15 protein, and exhibited pharmacologically favorable properties. These compounds could be used as potential CTX-M-15 inhibitors to combat bacterial resistance. Nonetheless, additional experimental studies are required to optimize these compounds as CTX-M-15 inhibitors.

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Author Contributions

MZA and AH conceived the study. MZA collected and analyzed the data. AH prepared the graphs and tables. Both authors contributed to writing and reviewing the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, et al. The global threat of antimicrobial resistance: science for intervention. *New Microbes and New Infections*, (2015); 6: 22-29.
2. Mancuso G, Midiri A, Gerace E, Biondo C. Bacterial Antibiotic Resistance: The Most Critical Pathogens. *Pathogens*, (2021); 10(10): 1310.
3. Larsson DGJ, Flach CF. Antibiotic resistance in the environment. *Nature Reviews Microbiology*, (2022); 20(5): 257-269.
4. Shakil S, Rizvi SMD, Greig NH. High Throughput Virtual Screening and Molecular Dynamics Simulation for Identifying a Putative Inhibitor of Bacterial CTX-M-15. *Antibiotics (Basel)*, (2021); 10(5): 474.
5. Yasir M, Ajlan AM, Shakil S, Jiman-Fatani AA, Almasaudi SB, et al. Molecular characterization, antimicrobial resistance and clinico-bioinformatics approaches to address the problem of extended-spectrum beta-lactamase-producing *Escherichia coli* in western Saudi Arabia. *Scientific Reports*, (2018); 8(1): 14847.
6. Bush K, Courvalin P, Dantas G, Davies J, Eisenstein B, et al. Tackling antibiotic resistance. *Nature Reviews Microbiology*, (2011); 9(12): 894-896.
7. Bush K, Bradford PA. Epidemiology of beta-Lactamase-Producing Pathogens. *Clinical Microbiology Reviews*, (2020); 33(2): e00047-19.
8. Peirano G, Pitout JDD. Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae: Update on Molecular Epidemiology and Treatment Options. *Drugs*, (2019); 79(14): 1529-1541.
9. Smet A, Martel A, Persoons D, Dewulf J, Heyndrickx M, et al. Broad-spectrum beta-lactamases among Enterobacteriaceae of animal origin: molecular aspects, mobility and impact on public health. *FEMS Microbiology Reviews*, (2010); 34(3): 295-316.
10. Bevan ER, Jones AM, Hawkey PM. Global epidemiology of CTX-M beta-lactamases: temporal and geographical shifts in genotype. *Journal of Antimicrobial Chemotherapy*, (2017); 72(8): 2145-2155.
11. Quinones D, Aung MS, Carmona Y, Gonzalez MK, Pereda N, et al. High Prevalence of CTX-M Type Extended-Spectrum Beta-Lactamase Genes and Detection of NDM-1 Carbapenemase Gene in Extraintestinal Pathogenic *Escherichia coli* in Cuba. *Pathogens*, (2020); 9(1): 65.
12. Mwangi J, Hao X, Lai R, Zhang ZY. Antimicrobial peptides: new hope in the war against multidrug resistance. *Zoological Research*, (2019); 40(6): 488-505.
13. Sabe VT, Ntombela T, Jhamba LA, Maguire GEM, Govender T, et al. Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: A review. *European Journal of Medicinal Chemistry*, (2021); 224: 113705.
14. Giordano D, Biancaniello C, Argenio MA, Facchiano A. Drug Design by Pharmacophore and Virtual Screening Approach. *Pharmaceuticals (Basel)*, (2022); 15(5): 646.
15. Reddy AS, Pati SP, Kumar PP, Pradeep HN, Sastry GN. Virtual screening in drug discovery -- a computational perspective. *Current Protein & Peptide Science*, (2007); 8(4): 329-351.
16. Cavasotto CN, Orry AJ. Ligand docking and structure-based virtual screening in drug discovery. *Current Topics in Medicinal Chemistry*, (2007); 7(10): 1006-1014.
17. Good AC, Cheney DL. Analysis and optimization of structure-based virtual screening protocols (1): exploration

- of ligand conformational sampling techniques. *Journal of Molecular Graphics and Modelling*, (2003); 22(1): 23-30.
18. Irwin JJ, Shoichet BK. ZINC--a free database of commercially available compounds for virtual screening. *Journal of Chemical Information and Modeling*, (2005); 45(1): 177-182.
 19. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods in Molecular Biology*, (2015); 1263: 243-250.
 20. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, (2017); 7: 42717.
 21. Drawz SM, Papp-Wallace KM, Bonomo RA. New beta-lactamase inhibitors: a therapeutic renaissance in an MDR world. *Antimicrobial Agents and Chemotherapy*, (2014); 58(4): 1835-1846.
 22. Pinzi L, Rastelli G. Molecular Docking: Shifting Paradigms in Drug Discovery. *International Journal of Molecular Sciences*, (2019); 20(18): 4331.
 23. Gupta M, Sharma R, Kumar A. Docking techniques in pharmacology: How much promising? *Computational Biology and Chemistry*, (2018); 76: 210-217.
 24. Meng XY, Zhang HX, Mezei M, Cui M. Molecular docking: a powerful approach for structure-based drug discovery. *Current Computer-Aided Drug Design*, (2011); 7(2): 146-157.
 25. Sait KHW, Mashraqi M, Khogeer AA, Alzahrani O, Anfinan NM, et al. Molecular docking analysis of HER-2 inhibitor from the ZINC database as anticancer agents. *Bioinformation*, (2020); 16(11): 882-887.
 26. Sait KHW, Alam Q, Anfinan N, Al-Ghamdi O, Malik A, et al. Structure-based virtual screening and molecular docking for the identification of potential novel EGFRkinase inhibitors against ovarian cancer. *Bioinformation*, (2019); 15(4): 287-294.
 27. Faheem M, Rehman MT, Danishuddin M, Khan AU. Biochemical characterization of CTX-M-15 from *Enterobacter cloacae* and designing a novel non-beta-lactam-beta-lactamase inhibitor. *PLoS One*, (2013); 8(2): e56926.
 28. Lahiri SD, Mangani S, Durand-Reville T, Benvenuti M, De Luca F, et al. Structural insight into potent broad-spectrum inhibition with reversible recyclization mechanism: avibactam in complex with CTX-M-15 and *Pseudomonas aeruginosa* AmpC beta-lactamases. *Antimicrobial Agents and Chemotherapy*, (2013); 57(6): 2496-2505.
 29. King DT, King AM, Lal SM, Wright GD, Strynadka NC. Molecular Mechanism of Avibactam-Mediated beta-Lactamase Inhibition. *ACS Infectious Diseases*, (2015); 1(4): 175-184.
 30. Winkler ML, Papp-Wallace KM, Taracila MA, Bonomo RA. Avibactam and inhibitor-resistant SHV beta-lactamases. *Antimicrobial Agents and Chemotherapy*, (2015); 59(7): 3700-3709.
 31. Larregieu CA, Benet LZ. Drug discovery and regulatory considerations for improving in-silico and in vitro predictions that use Caco-2 as a surrogate for human intestinal permeability measurements. *The AAPS Journal*, (2013); 15(2): 483-497.
 32. Rossiter SE, Fletcher MH, Wuest WM. Natural Products as Platforms To Overcome Antibiotic Resistance. *Chemical Reviews*, (2017); 117(19): 12415-12474.
 33. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of Natural Products*, (2020); 83(3): 770-803.
 34. Mayegowda SB, Ng M, Alghamdi S, Atwah B, Alhindi Z, et al. Role of Antimicrobial Drug in the Development of Potential Therapeutics. *Evidence-Based Complementary and Alternative Medicine*, (2022); 2500613.



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