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Research Article

Virtual Screening of *Coffea arabica* Phytochemicals as Natural β-Lactamase Inhibitors

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Abstract: One of the key contributors to antimicrobial resistance is the enzymatic hydrolysis of β-lactam antibiotics by β-lactamases, becoming one of the leading public health challenges. In order to overcome this issue, the current work utilizes advanced *in-silico* grid-based molecular docking and post-docking analysis to identify potential β-lactamase inhibitors from *Coffea arabica* beans. Based on past experimental evidence of coffee's antimicrobial activity, this research aimed to explore the inhibitory potential of its bioactive compounds through computational modeling to identify natural alternatives to synthetic inhibitors. Seventy-three phytochemicals were then screened and molecularly docked by AutoDock against four clinically relevant β-lactamases, namely, AmpC, CTX-M9, CTX-M14, and SHV-1, and subsequently subjected to toxicity and ADMET analysis. Among these, tannin, epicatechin, quercitrin, and quercetin exhibited the highest binding affinities (-8.5 kcal/mol, -7.7 kcal/mol, -8.6 kcal/mol, and -8.6 kcal/mol, respectively), outperforming the reference inhibitor, Avibactam. ADMET analysis also revealed favorable pharmacokinetic, low toxicity, and oral bioavailability of the top-ranked phytocompounds. Collectively, the results indicate the novelty of *C. arabica's* phytochemicals as promising natural β-lactamase inhibitors. However, further *in-vitro* and *in-vivo* studies are required for validating their therapeutic efficacy against resistant bacteria. The current study also establishes a framework for integrating computational approaches in phytochemical research to accelerate antibacterial drug discovery.

Keywords: Antibiotic Resistance, ADMET, β-lactamase Inhibitors, *In-silico* Modeling, Phytochemicals, *Coffea arabica*.

1. INTRODUCTION

Antimicrobial resistance (AMR) has become one of the most severe threats to global public health, resulting in the failure of traditional antibiotic therapies [1, 2]. The production of β-lactamases (βLs) (enzymes capable of hydrolyzing β-lactam antibiotics) represent the most formidable challenge, particularly in Gram-negative pathogens [3]. Moreover, the continuous and rapid evolution of these βLs variants such as SHV-1, TEM-1, AmpC, CTX-M, and NDM-1, and NDM-1, has rendered many clinically relevant β-Lactams ineffective, emphasizing the urgent search for novel inhibitors to restore their efficacy [4]. Natural products are invaluable sources of bioactive compounds of structural complexity and biological specificity with a long history of combating infectious diseases [5]. Over the last few years, phytochemicals of medicinal plants have gained more attention as potential adjuvants or alternatives to traditional synthetic antibiotics [6]. These phytocompounds often have diverse bioactivities (anti-inflammatory, antioxidant, antibacterial, and antiviral), which makes them promising candidates for developing multitarget drug [7]. Plants can produce various secondary metabolites or phytochemicals in response to environmental stress, such as microbial invasion, oxidative stress, high salinity, exposure to ultraviolet radiations, drought or elevated temperatures [8]. Several phytochemicals have shown potential to inhibit βLs, which are bacterial enzymes conferring resistance against β-lactam antibiotics [9]. Among these natural sources, *Coffea arabica* (*C. arabica*) is recognized not only as a globally consumed beverage crop but also as

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a reserve of structurally diverse phytochemicals, including alkaloids, flavonoids, saponins, polyphenols, and tannins [10, 11]. *C. arabica* is acknowledged for its abundance of bioactive compounds with potent inhibitory action against various pathogens [12]. Coffee extract contains a variety of bioactive compounds, including chlorogenic acid (CGA), catechins, quercetins, caffeic acids, tannins, and caffeine with inhibitory effects on both Gram-negative and Gram-positive bacteria [13]. Antibacterial components in coffee can inhibit DNA synthesis and inactivate enzymes that are essential to bacterial survival and replication [12]. Despite the increasing evidence of its biological efficacy, the specific molecular mechanisms underlying the antibacterial activities of *C. arabica* remain poorly understood. In particular, the βLs inhibitory potential of its phytochemicals has not yet been thoroughly explored. Computational studies of these natural compounds may, therefore, reveal novel scaffolds for βLs inhibition as well as provide important insights for future antibacterial drug development.

Multi-drug-resistant (MDR) bacteria have become a significant global health challenge due to their widespread resistance to conventional antibiotics [14]. There is an urgent need to discover new antimicrobial drugs to address this issue. A promising recent strategy involves the use of secondary metabolites of plants. Medicinal plants are increasingly recognized as a potential alternative treatment for resistant pathogens compared to synthetic drugs [15]. Plant-derived chemicals possess notable antibacterial properties with fewer adverse effects, making them suitable candidates for antimicrobial drug development. These phytochemicals interact with bacterial systems via several mechanisms such as disrupting the cell membrane integrity, altering the cell permeability, chelating the essential metal ions, inhibiting the nucleic acid or protein synthesis, and directly binding to key bacterial enzymes to block their catalytic activities [16-18]. Thus, natural compounds can be utilized successfully to inhibit bacterial survival and suppress resistance by targeting these mechanisms.

Currently, various advanced bioinformatics tools are available to identify the drug-like properties of phytochemicals more efficiently than traditional, time-consuming experimental procedures [19, 20]. *In-silico* molecular docking is a technique that analyzes the binding interactions between phytochemicals and target enzymes based on binding affinities or docking scores. By combining virtual screening and pharmacoinformatics, the current study aims to investigate the phytochemicals of *C. arabica* for their potential to inhibit βLs, thereby enhancing the efficacy of β-lactam antibiotics against resistant pathogens. The findings are also expected to not only highlight the significant role of *in-silico* modeling in accelerating the drug discovery process but also provide potential scaffolds capable of counteracting βLs-mediated antibiotic resistance.

2. MATERIALS AND METHODS

2.1. Retrieval of Phytocompounds

The Dr. Duke's Phytochemical and Ethnobotanical Database (https://phytochem.nal.usda.gov/) was used to obtain the information about the nature and types of various phytochemicals present in *C. arabica* [21, 22]. A total of 73 phytocompounds belonging to different classes were screened and their 3D structures were downloaded from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. These phytochemicals were selected based on their documented abundance, chemical diversity as well as previously reported bioactivities. The structure of Avibactam was also downloaded in SDF format, which was used as reference compound for comparative docking.

2.2. Preparation of Ligands

The SDF format of all the ligands (phytochemicals as well as Avibactam) was then converted into PDB using PyMOL software. Then, all these ligands were saved in PDBQT format with the help of AutoDock Tools v1.5 [21, 23].

2.3. Retrieval and Preparation of Target Enzymes

Four commonly reported βLs, AmpC, SHV-1, CTX-M9 and CTX-M14, were selected as target enzymes in this study based on their high prevalence in increasing β-Lactam resistance in Gram-negative pathogens [24, 25]. The 3D structures of these enzymes were downloaded from Protein DataBank (https://www.rcsb.org/) in PDB format. The PDB

IDs of SHV-1, AmpC, CTX-M9 and CTX-M14 βLs were 4JPM, 5GZW, 3HLW and 6CYU, respectively. The AutoDock tools v1.5.7 were then used to save these structures in PDBQT format, as required by AutoDock Vina [26]. Moreover, the water molecules and native ligands were removed, polar hydrogens were added, and Kollman charges were also assigned to target proteins using AutoDock tools.

2.4. Identification of Active Site

All these enzymes had different ligands already bound to their active sites such as CE4 in CTX-M14, AMP in AmpC, 1OG in SHV-1 and CE3 in CTX-M9 βLs. These ligands provided basic information about the active sites of these enzymes.

2.5. Grid Box Preparation

The grid box was prepared around the already bound ligands using AutoDock tools [27, 28]. Briefly, the grid spacing set at 1Å, the dimensions and central coordinates adjusted at 25 × 27 × 25 Å, x = 8.679, y = 6.851, z = 9.225 for AmpC βL, 27 × 27 × 27 Å, x = 10.101, y = 9.983, z = 10.295 for CTX-M9 βL, 25 × 20 × 23 Å, x = 8.026, y = 12.521, z = 10.42 for SHV-1 βL, and 23 × 21 × 23 Å, x = 15.784, y = 32.761, z = 40.973 for CTX-M14 βL. All this information on grid boxes was then recorded for docking.

2.6. Molecular Docking

Docking was performed via AutoDock Vina using the vina command ("\vina\vina.exe" --config conf. txt --log log.txt) in command prompt [29]. The Lamarckian Genetic Algorithm (LGA) was run at default parameters at 10 distinct sites [19]. To ensure the reliability of docking, native ligands were also redocked into the same binding sites. The output files were saved in PDB format to analyze the binding interactions of ligands at the binding sites of target enzymes, and RMSD values below 2.0 Å were considered acceptable for validation [27].

2.7. Pharmacokinetic Profiles of Phytochemicals

The druglike and toxicity profiles of top scoring phytochemicals were also determined by submitting their canonical SMILES to admetSAR (http://lmmd.ecust.edu.cn/admetsar2/) and PROTOX-II (https://tox-new.charite.de/protox_II/). Compounds were screened according to Lipinski's Rule of Five, Ghose and Veber filters, and toxicity thresholds; molecules satisfying at least four criteria were considered as drug-like candidates [30]. The overall *in-silico* workflow included compound selection, protein preparation, docking validation, screening, and ADMET profiling.

3. RESULTS AND DISCUSSION

The rise in antibiotic resistance is largely attributed to the inappropriate and indiscriminate use of antimicrobial agents. This situation is becoming increasingly critical as many of the bacterial strains have adopted the mechanism of hydrolytic inactivation of β-lactam antibiotic via βLs [3]. This study primarily investigated AmpC, CTX-M-9, CTX-M-14, and SHV-1 βLs, which contribute to the inactivation of β-lactam antibiotics, with the aim of identifying potential inhibitors against these enzymes. Docking analysis of 73 phytocompounds from *C. arabica* against four selected enzymes revealed significant variations in the binding affinities. Among these, tannin (AmpC), quercetin (SHV-1), epicatechin (CTX-M9), and quercitrin (CTX-M14) displayed strongest interactions with binding energies of -8.5, -8.6, -7.7, and -8.6 kcal/mol, respectively, outperforming the reference inhibitor Avibactam. Strikingly, all these phytocompounds showed stable hydrogen and hydrophobic bonding with active side residues such as Lys73, Ser130, Asp123, and Gly32. These amino acid residues are considered essential for the β-lactam hydrolyzing activity of the enzymes.

Plants are well known reservoirs of bioactive compounds guiding modern therapeutic development. Phytocompounds have demonstrated antimicrobial, antiviral, anticancer, anti-Alzheimer, anti-inflammatory, and antioxidant activities [31]. However, screening of these thousands of phytochemicals was traditionally labor-intensive and time-consuming, which, with the advent of various bioinformatic tools, has become comparatively easy [32]. Molecular docking, one of the most widely used bioinformatic tools, screens compounds based on their affinity towards target enzymes. Thus, it enables virtual screening and identification of phytocompounds with the best activity in a cost-effective and time-efficient manner [33]. Molecular docking was also utilized in this

study to identify the phytocompounds of *C. arabica* that exhibit the highest inhibitory activity against target βLs. Table 1 enlists the phytocompounds and their binding affinities for respective target enzymes.

In-silico docking analysis showed that tannin exhibited a strong binding affinity of -7.6 kcal/mol against AmpC βL and was 28.8% more effective compared to synthetic inhibitor Avibactam (-5.9 kcal/mol). Figure 1 shows the 3D interactions of tannin at the binding site of target AmpC βL. Other phytochemicals including quercetin, epicatechin, naringenin, and caffeic acid also showed comparatively high binding affinities for AmpC βL relative to Avibactam (Table 1).

Tannin, a phenolic component naturally occurring in coffee and various types of teas, has been reported to exhibit several beneficial pharmacological properties, including high antioxidant properties and immune system stimulation [34, 35]. Moreover, it may help lower blood cholesterol levels [36]. Several studies have also reported its antibacterial activities against both Gram-positive and Gram-negative pathogens, primarily by disrupting bacterial membranes and inducing cellular damage [37, 38]. Figure 2 presents the 2D interaction of both tannin and Avibactam with active site residues, showing that tannin formed many conventional hydrogen bonds as well as van der Waals interactions with several active site residues, whereas Avibactam formed conventional hydrogen bonds with only four amino acid residues of AmpC βL. The antimicrobial activity of tannin and other polyphenols derived Thai medicinal plant against extended spectrum βL (ESBL) producing *Escherichia coli* has also been reported [39].

Among the tested phytochemicals, quercetin exhibited the highest binding affinity towards SHV-1 βL (-8.6 kcal/mol), followed by tannin (-6.5 kcal/mol), epicatechin (-6.5 kcal/mol), and

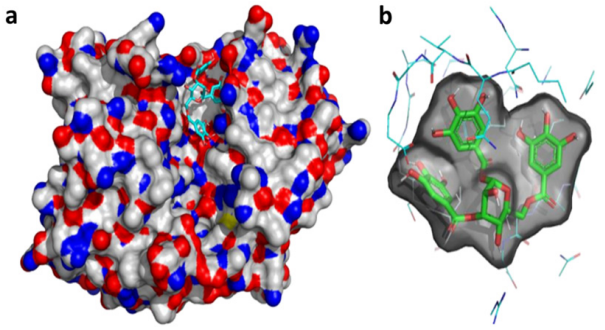

Fig. 1. 3D interactions of tannin at the binding site of AmpC βL.

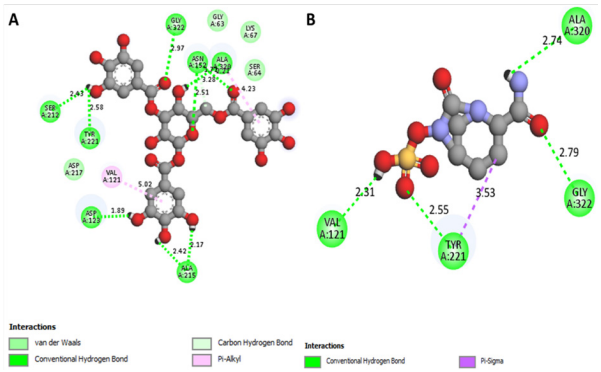

Fig. 2. 2D interactions of tannin (A) and Avibactam (B) with the active site residues of AmpC βL.

Table 1. The binding energies of top scoring phytochemicals as well as synthetic inhibitor (Avibactam).

S. No.	Phytochemicals	Pubchem ID	Binding energies (kcal/mol)			
			AmpC	SHV-1	CTX-M9	CTX-M14
1	Tannin	16129778	-8.5*	-6.5	-7	-6.4
2	Quercetin	5280343	-7.4	-8.6*	-7.2	-7.6
3	Epicatechin	72276	-7.3	-6.5	-7.7*	-7.2
4	Quercitrin	5280459	-7.3	-6.2	-6.5	-8.6*
5	Hyperoside	5281643	-7.3	-6.3	-6.1	-7.7
6	Naringenin	932	-7.1	-6.2	-6.4	-7.1
7	Kaempferol	5280863	-6.9	-6.1	-7	-7.6
8	Caffeic acid	689043	-6.5	-6.3	-7.1	-7.2
9	Avibactam	9835049	-5.9	-5.4	-5.5	-5.2

** highest binding affinities*

quercitrin (-6.2 kcal/mol), as summarized in Table 1. Avibactam, however, exhibited a comparatively lower binding affinity of -5.4 kcal/mol. Figure 3 illustrates the 3D interactions of quercetin within the active site of SHV-1 βL.

Quercetin, also referred to as quercetine or quertine, is a flavanol belonging to the flavonoids subclass, and is found abundantly in various plants such as red onions, broccoli, and various fruits. It's a natural pigment present in significant amounts in several edible plant species. Vafadar *et al.* [40] reported that quercetin shows significant cytotoxic activities against ovarian cancer *in-vitro* and *in-vivo*. Several studies have also reported the therapeutic benefits including anti-inflammatory, antioxidant, anti-diabetic, and anti-microbial effects of quercetin [41]. In addition, quercetin has also exhibited protective effects against COVID-19 due to its immunomodulatory properties [42]. A more recent study by Jian *et al.* [43] has highlighted that quercetin and its derivatives have high potential for treating premature ovary failure (POF), polycystic ovary syndrome (PCOS), endometrial carcinoma (EC) and other gynecological disorders. Figure 4 illustrates the 2D binding interactions of quercetin and Avibactam with the amino acid residues of SHV-1 βL. Lys73 was identified as a common residue interacting with both ligands via van der Waals interaction. The results were in coherence with finding of another study which reported the *in-vitro* inhibition of βL enzyme of *Ficus religiosa* bark extract likely due to presence of quercetin and related flavonoids [9].

Epicatechin, a flavanol abundantly found in tea, cocoa, and several fruits, exhibited the highest binding affinity against CTX-M9 βL, with a docking score of -7.7 kcal/mol. Avibactam, in comparison, exhibited a lower binding affinity of -5.5 kcal/mol for CTX-M9 βL. Although several phytocompounds demonstrated higher binding affinities than Avibactam, only the top-performing compounds are listed in Table 1. Figure 5 illustrates the 3D docking interactions between CTX-M9 βL and epicatechin.

Epicatechin is a monomeric flavonoid with several reported therapeutic benefits. Seo *et al.* [44] reported that epicatechin and gallic acid can enhance muscle mass and potentially ameliorate age-related muscle decline. Epicatechin and its derivatives also exhibit potent antioxidant and anti-inflammatory activities, significantly improving neuronal health following brain injury [45, 46]. 2D interactions of epicatechin and Avibactam within the active site of the CTX-M9 βL are represented in Figure 6. Epicatechin interacted with several active site residues of CTX-M9 βL via conventional and non-conventional hydrogen bonds, van der Waals forces, and hydrophobic interactions. Avibactam, on the other hand, did not establish any conventional hydrogen bonding. Asn132 and Thr216 were identified as common residues interacting with both epicatechin and Avibactam, though the nature of interactions differed. Buchmann *et al.* [47] also highlighted the synergistic potential of using epicatechin-antibiotic combination in fighting against βL-producing ESKAPE pathogens through time-kill assay. Additionally, epicatechin and its derivatives also show significant inhibitory activities against *Staphylococcus aureus* by suppressing its biofilm formation and βL enzymatic activity [48].

Quercitrin exhibited the highest binding affinity of -8.6 kcal/mol for CTX-M14 βL. In contrast, Avibactam displayed a comparatively

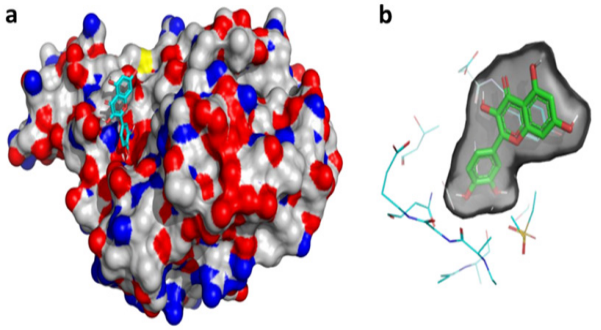

Fig. 3. 3D interactions of quercetin at the binding site of SHV-1 βL.

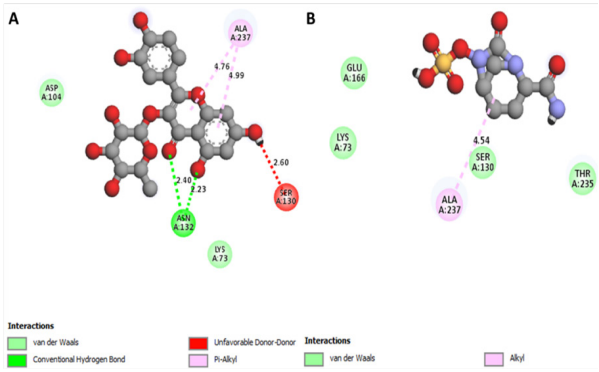

Fig. 4. 2D interactions of quercetin (A) and Avibactam (B) with the active site residues of SHV-1 βL.

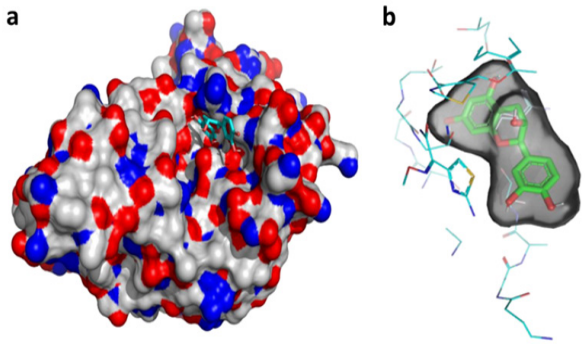

Fig. 5. 3D interactions of epicatechin at the binding site of CTX-M9 βL.

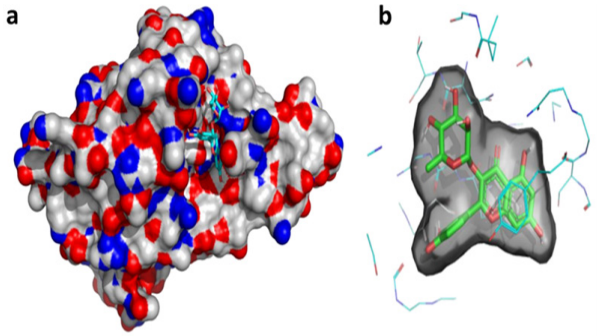

Fig. 7. 3D interactions of quercitrin at the binding site of CTX-M14 βL.

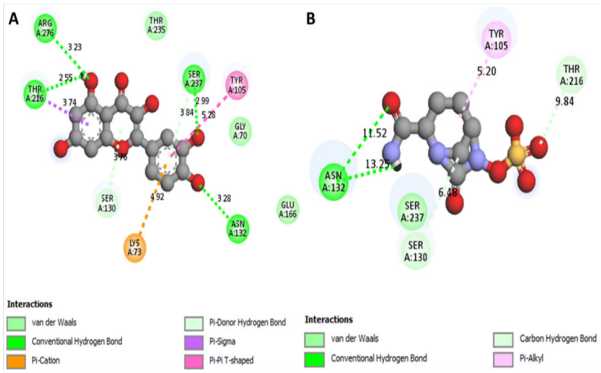

Fig. 6. 2D interactions of epicatechin (A) and Avibactam (B) with the active site residues of CTX-M9 βL.

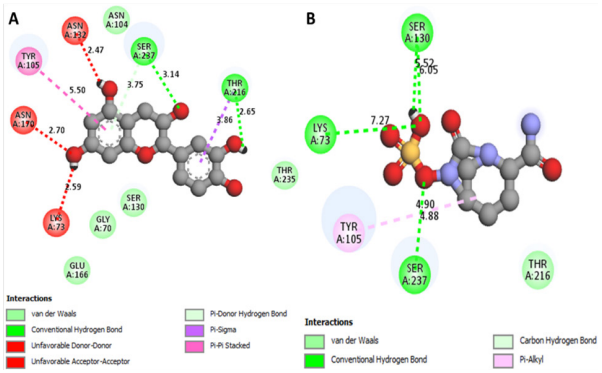

Fig. 8. 2D interactions of quercitrin (A) and Avibactam (B) with the active site residues of CTX-M14 βL.

lower binding energy of -5.2 kcal/mol. Several other *C. arabica* phytocompounds also demonstrated stronger affinities than Avibactam, as summarized in Table 1. The 3D interactions of CTX-M14 βL and quercitrin are shown in Figure 7, illustrating hydrogen bonds and hydrophobic contacts with key catalytic site residues.

Quercitrin is also a flavonoid glycoside derivative of quercetin linked with rhamnose sugar. Like other phytocompounds, it is ubiquitously found in several grains, leaves and other parts of vegetables and fruits [49]. Quercitrin has been reported to have significant anti-inflammatory and anti-tumorigenic activities, especially against prostate and bladder cancers [50, 51]. Li *et al.* [52] reported that quercitrin induced treatments significantly reduced tumor cell viability in lung adenoma induced mice. It is also reported to show hair stimulating activities by activating the expression of growth factors through MAPK pathway in follicle cells [53]. The 2D interactions of quercitrin and Avibactam at the binding site of CTX-M14 βL are shown in Figure 8. Lys73, Tyr105, Ser130, Thr216, and Ser237 were some of the common amino acids of CTX-M14 βL interacting with both quercitrin and Avibactam in different types of bonding interactions.

The pharmacological profiles of top-scoring phytochemicals and Avibactam were also evaluated to analyze their drug-likeness and therapeutic potential [30]. This analysis was based on Lipinski's Rule of Five, which evaluates key physicochemical properties such as molecular weight, hydrogen bond donor and acceptor counts, molar refractivity, and other relevant descriptors to predict the potential of a compound to serve as a drug candidate [54-56]. As summarized in Table 2, majority of the phytochemicals satisfied the drug-likeness criteria. The favorable pharmacokinetic properties of these phytocompounds also highlight their potential as lead compounds for further therapeutics development. In summary, *C. arabica* harbors diverse array of phytochemicals with significant potential to inhibit βLs responsible for antibiotic resistance in Gram-negative pathogens. These compounds may not only enhance the activity of β-lactam antibiotics but also help restore their efficacy against resistant bacterial strains.

Table 2. Drug-like properties of top scoring phytocompounds and Avibactam.

Compounds	Lipinski's rules					Rule of 5's violations
	MW	Log $P_{o/w}$	Molar Ref.	HBA	HBD	
	< 500	≤ 5	40-130	≤ 10	≤ 5	
Tannin	1701.21	4.84	391.5	46	25	4
Quercetin	302.24	1.99	78.04	7	5	0
Epicatechin	290.27	1.55	74.33	6	5	0
Quercitrin	448.38	0.49	109	10	7	1
Hyperoside	464.38	-0.54	110.16	11	8	2
Naringenin	272.26	2.51	71.57	5	3	0
Kaempferol	286.24	2.28	76.01	6	4	0
Caffeic acid	180.16	1.2	47.16	4	3	0
Avibactam	265.25	-1.53	60.27	5	2	0

4. CONCLUSIONS

In conclusion, plant-derived natural compounds are receiving growing attention in the field of drug discovery due to their diverse therapeutic benefits. The integration of bioinformatic approaches in this field has also significantly accelerated the process of identifying and characterizing potential drug candidates from plants. This study also employed multiple *in-silico* approaches to screen and identify the phytocompounds of *C. arabica* that can inhibit the βLs, which contribute significantly to antibiotic resistance in Gram-negative pathogens such as *E. coli* and *Klebsiella pneumoniae*. Among the screened phytocompounds, tannin (-8.5 kcal/mol), epicatechin (-7.7 kcal/mol), quercetin (-8.6 kcal/mol) and quercitrin (-8.6 kcal/mol) displayed stronger binding affinities for the four target enzymes (AmpC, CTX-M9, SHV-1 and CTX-M14 βLs), respectively, as compared to the Avibactam, a synthetic βLs inhibitor. Moreover, the pharmacological analysis of the top scoring phytochemicals also confirmed their drug-like properties and safety profiles. Further *in-vitro*, *in-vivo*, and molecular dynamics studies are required that can validate the potential therapeutic benefits of these natural compounds in controlling β-Lactam resistance.

5. CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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