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Virtual Toxicity Screening and Molecular Docking of Natural Compounds to Discover New Antibiotics for Methicillin-Resistant *Staphylococcus aureus*

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) is a strain whose resistance against existing antibiotics is a serious threat to life. MRSA causes mild skin infections, invasive infections, newborn infections, and surgical patient infections that can lead to death. MRSA quickly develops resistance to new treatments, contributing to the global antimicrobial resistance pandemic. In Uganda, MRSA is now resistant to commonly used antibiotics like ceftriaxone, cefixime, levofloxacin, ciprofloxacin, and chloramphenicol, thus a need to explore new antibiotics to treat diseases caused by MRSA. Its resistance against these drugs continues to worry the health sector, given that in the past two decades, very few drugs successfully entered the market. This is because the well-known traditional experimental drug development and testing process is lengthy and slow and requires huge investments. In this study, we performed virtual screening to discover potential compounds that have antibacterial activity against MRSA. We conducted an extensive literature search and found 180 compounds with antibacterial activity against MRSA. On further screening, only 21 out of 180 compounds were common in Uganda. Thereafter, we conducted both virtual toxicity and molecular docking on the identified 21 compounds. PES12 had score values below the acceptable physicochemical properties considered for toxicity analysis. The molecular docking analysis between the interaction of 21compounds with two macromolecular targets of MRSA, namely, nitrocefin acyl-Penicillin binding protein 2a (1MWS) and SeMet Penicillin binding protein 2a (1MWR), showed binding energy ranging from −2.7 and −18.6 kcal/mol. Compound PES01 has an excellent binding affinity value of −18.6 kcal/mol, which is far greater than that of known drugs (−6.9 to 8.7 kcal/mol) for treating infection due to MRSA. This study's findings could inform the development of new and more potential antibiotics; however, there is a need to conduct animal studies and clinical trials to understand the effectiveness of the identified 21 compounds.

Keywords: MRSA, binding affinity, toxicity, molecular docking

1. Introduction

Bacterial antimicrobial resistance (AMR) occurs when bacterial alteration makes antibiotics less effective. AMR has become one of the leading public health threats with higher morbidity and mortality rates globally [1, 2]. A number of bacterial resistant infections resulting from AMR are rapidly increasing mainly due to the interactions among humans, animals, the environment, and the continued excessive use of antibiotics [3]. In February 2017, WHO announced that with the evolution of bacterial resistance to antibiotics, normal medical procedures would be at risk, and the lives of many people diagnosed with resistant bacterial infections would potentially be jeopardized [4]. About 700,000 people are estimated to die annually due to AMR, and if nothing is done, 10 million people are expected to lose their lives annually by 2050 [5]. In 2019, AMR burden was common at 27.3 % deaths per 100,000 in western sub-Saharan Africa and 6.5 deaths per 100,000 in Australasia [2].

According to the World Bank, it is estimated that AMR costs could range from $300 billion to $1 trillion annually by 2050. AMR would raise the poverty rate and impact developing countries like Uganda. It is estimated that global GDP could decline by around 1% by 2050, with a significant impact on labor through the loss of productivity due to illness and untimely death. According to WHO, *Staphylococcus aureus* was among the six notable organisms responsible for 929,000 deaths associated with AMR [2] in 2019. Furthermore, the WHO and Centers for Disease Control and Prevention recognize methicillin-resistant

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Staphylococcus aureus (MRSA) as a notorious threat to life [6]. MRSA is the leading cause of hospital-acquired infections in newborns, surgical patients, malnourished individuals, diabetic patients, and those with chronic conditions. MRSA quickly develops resistance to new treatments, contributing to the global antimicrobial resistance pandemic. Furthermore, *Staphylococcus aureus* infects both humans and animals and leads to food contamination. These infections can survive in several environmental settings with major resistance to most of the commonly used antibiotics including ampicillin, erythromycin, tetracycline, cephalosporins, methicillin, and all beta-lactamase manufacturers. The resistance to these antibiotics continues to worry the health sector since they have to spend millions of dollars to buy antibiotics that can no longer treat the infections due to *S. aureus*, and also, the rate of discovery of new antibiotics has fallen to almost zero since the 1990s. In Uganda, there is a high prevalence of AMR amongst commonly used antibiotics like cotrimoxazole, ampicillin, and ceftriaxone [7–9]. Furthermore, the presence of multidrug-resistant bacteria like MRSA was reported in Ugandan hospitals [10]. To be part of the WHO global action plan, Uganda launched a national action plan (NAP) to reduce AMR in 2018. The AMR NAP focused on AMR surveillance and the optimized use of antibiotics in both human and animal treatment [11]. The resistance to these antibiotics continues to worry the health sector, given that in the past two decades, very few drugs successfully entered the market [12]. This may be due to varying factors that include the inability to identify and isolate toxic compounds from a pool of potential drug candidates in the early stages of development.

Discovering new antibiotics is challenging because the well-known traditional experimental drug development and testing process is lengthy and slow and requires huge investments that are estimated to be approximately over 1 billion dollars. Drug discovery is a dynamic process involving several stages, ranging from target identification to animal studies, which all take time. In addition, several evaluation requirements such as safety, pharmacokinetics, efficacy, testing, and regulatory clearances further slow down the entire process. Therefore, with the lack of new antibiotics for the management of bacterial infections, the majority of patients and the overall healthcare setting continue to suffer [13]. Furthermore, the health sector experiences difficulties in treating such infections and incurs heavy financial burdens, which in most cases are extended to the patients or their caregivers [14]. Thus, new strategies must be put in place to speed up the discovery of new antibiotics if life is to be saved.

It is against this background that this research project seeks to perform virtual screening of natural compounds to discover new potential antibiotics to treat infections due to MRSA. In this research, we adopted and used bioinformatics tools like PyRx and dataWarrior to discover new potential drugs for MRSA. Thus, this research seeks to address the following research questions:

1) *RQ1: Which natural product compounds have inhibitory activity against MRSA?* We performed an in-depth literature search and identified 180 natural product compounds with antibacterial activity against MRSA. On further screening, only 21 out of 180 natural product compounds were extracted from plants that are common in Uganda.
2) *RQ2: What is the toxicity of the identified natural product compound?* We used computer-aided virtual toxicity analysis to study the toxicity of the 21 natural product compounds whose plant extracts are available in Uganda.
3) *RQ3: How does the identified natural product compound interact with MRSA?* We performed docking to establish the binding affinity of the 21 compounds with MRSA by looking at drug–target interaction (DTI) between the compounds and MRSA. Higher affinity implied that the compound may be a potential drug to treat diseases due to MRSA.

2. Literature Review

This section presents related work in regard to our study, and it is divided into three major sub-sections as listed below.

2.1. Natural product compounds

A number of studies have shown the use of natural products as treatment options; for example, Egra et al. [15] reported the use of the *Selaginella* plant by the local communities to treat illnesses such as wounds, menstrual disorders, heart diseases, and anti-inflammation. Similarly, anti-malaria drugs named quinine and artemisinin were discovered from natural products and have effectively contributed to the treatment of malaria, with artemisinin additionally supporting the treatment of type 1 diabetics and cancer [16]. A study by Schultz [17, 18] is another good example that shows the use of Ugandan plants to treat ailments such as acute inflammation, fever, stomach pain, cancer, gastrointestinal tract infections, nausea, skin infections, lung infections, wound infections, fever, and sore throat. A similar study on colonization, epidemiology, and genetic mechanisms of MRSA studied medicinal plants with anti-MRSA properties and tested five compounds on different strains including the resistant strains. The authors identified a compound named plumbagin from *Plumbago zeylanica* to have anti-MRSA. Additionally, a series of quinoline products were extracted and tested for antibacterial effect against resistant bacterial strains, and zeaxanthin from *Delonix regia* had a promising anti-agent for MRSA [19]. Butler et al. studied the antimicrobial activity of Ugandan *Ficus natalensis*, where plant extracts from the leaves, fruits, and bark clot were collected, and the strains of MRSA were also characterized and incubated at 37°C for 24 h. The results of this study indicated inhibitory activity against MRSA, with the leaves and fruits extracts showing antibacterial effect against bacteria, whereas the bark extract only exhibited inhibitory activity against MRSA. Despite the findings, this study did not explore the active compounds in the bark cloth.

Bocquet et al. [20] studied the antibacterial potential of xanthohumol, desmethylxanthohumol, and lupulone, which are compounds extracted from the hop plant, against MRSA. Hop is a plant that is globally available and comes from the Cannabaceae family, and its antibacterial activity is well known; however, it is less researched and documented for resistant strains like MRSA. This study looked at the extracts of leaves, stems, and rhizomes of hop and observed a desirable antibacterial activity, particularly on the rhizomes. Findings from this study also portrayed antibacterial activity in *S. aureus* strains. Lupulone was observed to be active, with the Minimum Inhibitory Concentration ranging from 0.6 to 1.2 and 78 to 156/mL against the resistant strain. Xanthohumol showed activity against *S. aureus* and showed less activity on desmethylxanthohumol. This study also elaborates on the need to combine any of the three compounds to increase the antibacterial action of hop compounds but, importantly, weaken the ability of MRSA.

2.2. Computational docking

Docking has been used to study the phytochemical properties of natural product compounds with the proteins/disease under investigation. Kurian [21] conducted docking analysis to discover new antifungal drugs against Yeast Se14p protein as a target by interacting it with five heterocyclic quinone compounds, and he discovered that among the five compounds, atovaquone showed the strongest binding affinity compared to known antifungal drugs. Verma et al. [22] used docking to study the effect of parthenium compounds on the multidrug resistance of *Candida albicans* using computational methods. In this study, the protein structures were downloaded from the Protein Data Bank. Docking was conducted using the PyRx software to identify the hit lead compounds with preferred biological functions against *Candida albicans*. The physicochemical compounds were independently docked to the proteins, and the docked compounds with the lowest energies were chosen. The results have a high indication of binding between the parthenium compounds isolates and the proteins, which serve as a good inhibition of all proteins of multidrug resistance and treatment of fungal infections. Elijah et al. [23] used molecular docking to study the interaction between 2, 4-disubstituted quinoline derivatives with the Tuberculosis receptor as a possible therapeutic target. After conducting molecular docking, the binding energies of all derivatives ranged from −3.2 and −18.5 kcal/mol. Two compounds had binding affinity values of −15.4 and 18.5 kcal/mol, which were greater than the indicated medicine isoniazid's −14.6 kcal/mol.

A similar study that employed molecular docking was reference by Rowaiye et al. [24]; this study was conducted to search for natural products with better binding affinities for natural killer cells. The study identified a total of over 1697 natural compounds from 83 plant species that were subjected to docking against 18 proteins. The findings of this study presented 17 compounds with good binding energies against the natural receptor cell. Kumar et al. [25] used molecular docking to study the interaction of MRSA with pyridine and pyrimidine derivatives. Their study revealed that pyridine derivatives yielded better targets for the development of anti-MRSA agents compared to standard anti-MRSA agents.

Cortes et al. [26] conducted molecular docking on 24 cannabinoids active against MRSA. The full dataset was compared to penicillin-binding protein, iso-tyrosyl tRNA synthetase, and DNA gyrase. The most active cannabinoids had a strong affinity for penicillin-binding protein (PBP), whereas the least active compounds had weak affinities for all targets. Among the cannabis compounds, cannabis 2 was emphasized due to its appropriate mix of antibacterial action and higher score values against the specified target; thus, its docking performance was compared to that of oxacillin, a commercial PBP inhibitor. Both drugs' 2D structures interact with the protein in the active site using a similar chemical mechanism.

Furthermore, Guan et al. [27] discovered that theaflavin binds the allosteric site of penicillin-binding protein 2a, causing its active site to open. This allows β-lactam antibiotics to treat MRSA infection, rather than directly exerting antibacterial activity at the active site. Kalalo et al. [28] used molecular docking to study possible tea polyphenol compounds that can inhibit PBP2a in MRSA. They discovered that the majority of these tea compounds had better binding energy than existing medicines. They discovered that theaflavin (−9.7 kcal/mol), a tea polyphenol molecule, had a higher binding energy with ceftaroline (9.5 kcal/mol) and hence is projected to have superior antibacterial action. Docking has also been used in drug repurposing, for example, Houshmand and Houshmand [29] used PyRx-Vina to discover drugs for COVID-19 from a list of existing approved drugs in the drug bank. After a thorough docking analysis, they discovered that known vitamin B_9, protease inhibitors, which are presently utilized in the treatment of HIV and cancer, had strong interaction and could potentially be a drug for COVID-19. They recommended vitamin B_9 as a therapy because it can be administered orally and has no side effects.

2.3. Gaps in literature

In summary, as a common practice in Uganda, most studies are based on the use of wet laboratory experiments, which involve the analysis and testing of biological chemicals, plant extracts, compounds, or drugs using liquid substances. With the wet lab experiments, there are high chances of missing out on potential lead compounds since the process is limited to a small number of phytochemicals. In addition, it is hard to determine potential compounds before the web lab experiments, and this lengthens the entire drug development process for MRSA and thus very costly. Owing to the drawbacks associated with wet laboratory drug development, in this research study, we carried out virtual screening by looking at both toxicity and binding affinity of potential compounds to select the best lead compounds before subjecting all compounds to a wet lab experiment. Furthermore, in Uganda, a few studies have used docking during drug discovery but not specifically on MRSA.

3. Research Methodology

3.1. Identification of natural product compounds

In this section, we present how we obtained data for *RQ1: Which natural product compounds have inhibitory activity against MRSA?* Considering the abundance of plants and herbs in Uganda, this research study focused on using compounds from the natural product database as a starting point. Using existing knowledge from literature and compound description, activities against MRSA, we screened and identified compounds in the natural product database that have shown inhibition activity against MRSA. Specifically, we were interested to know the compound chemical structures and their respective Simplified Molecular Input Line Entry System. Also, we identified the plants from which the compounds were extracted, and this guided us to know where to find that particular plant in Uganda. The expected output of this phase was a list of natural product compounds with antibacterial activity against MRSA.

3.2. Natural product compound toxicity analysis

In this section, we present how we obtained data for *RQ2*: *What is the toxicity of the identified natural product compound?* Predicting drug toxicity is critical to avoiding adverse effects. We adopted Computer-Aided Drug Design tools called DataWarrior [30], FAF-Drugs41, and PreADMET2 to evaluate the molecular properties and toxicity risk parameters of the identified 21 natural product compounds. The physicochemical properties and toxicity parameters considered include aqueous solubility (cLogS), partition coefficient between n-octanol and water (cLogP), molecular weight (MW), drug likeness, hydrogen bond donor

(HD), hydrogen bond acceptor (HA), mutagenic, irritant, tumorigenic, and reproductive effective, polar surface area (PSA). PreADME was used to evaluate ADMET characteristics like blood brain barrier (BBB) penetration, human intestinal absorption (HIA), CYP_2C19_inhibition, Pgb inhibition, and plasma protein binding. FAF-Drugs4 tool was used to find other physicochemical characteristics of compounds like oral bioavailability (VEBER), oral bioavailability (EGAN), phospholipidosis, and Fsp3. To perform toxicity analysis, natural product compounds files were entered as input files in DataWarrior, PreADME, and FAF-Drugs4. All these tools produced output files with physicochemical properties and toxicity parameters. The output values obtained were then compared to the accepted standard, for example, MW < 500, HD < 10, HA< 5, cLogS >-4, cLogP<5. In addition, in this study, we used the Microsoft Excel package to perform the analysis.

3.3. Determine the binding affinity between natural product compounds and MRSA

In this section, we present how we addressed *RQ3: How does the identified natural product compound interact with MRSA?* We established the compound-protein interactions, also commonly known as drug–target interactions (DTIs), between the 21 natural product compounds with MRSA. The efficacy of therapeutic compounds is determined by having a stronger affinity for proteins or receptors. Compounds that do not demonstrate any interaction with the targeted protein cannot be potential drugs. We conducted molecular docking by interacting natural product compounds with two macromolecular targets of MRSA, namely, nitrocefin acyl-Penicillin binding protein 2a (1MWS) and SeMet Penicillin binding protein 2a (1MWR). We considered 1MWS and 1MWR because these MRSA strains were the most common among patients who visited the microbiology laboratory of Mbarara University of Science found in Uganda. Molecular docking was done using the PyRx tool [31] in order to establish the compound-protein binding affinity. A strong binding energy of interaction between natural product compounds and the target protein (MRSA) indicates a potential drug candidate. The protein structures were obtained and downloaded from the Protein Data Bank, whereas the compound ligands were obtained from PubChem. We used PyRx to convert the protein targets from pdb to pdbqt files. In preparation for protein target for docking, all available water molecules, native ligand, and unwanted chains were removed to obtain pdbqt files to be used for docking. The SDF formats of all ligands were converted to the pdbqt format in readiness for docking, and ligands were uploaded into PyRx through Open Babel. Conformation clustering was done by looking at root mean square deviation (RMSD) cut-off of 2.0 Å for a cluster, and the most favorable conformation was represented by the lowest free binding energy and the lowest inhibition constant. Lamarkin's geometric algorithm was used as the optimization algorithm, and the universal force field was used as an energy minimization parameter. The grids were maximized to cover the entire binding site of the ligands, and 10 maximum exhaustiveness was calculated for each ligand. Before the initiation of the docking operation, charges were assigned to protein and ligand structures by Auto Dock Vina. The PyRx tool generates an Excel output report file that contains compounds together with their respective binding affinities. We consider this output report for further analysis.

4. Results and Discussion

4.1. Natural product compounds with antibacterial activity against MRSA

From the literature, we discovered 180 natural product compounds extracted from plants that had antibacterial activity against MRSA. The majority of these plants' extracts were from foreign countries. Only 21 compounds were extracted from plants found in Uganda, and no research study had been carried out to understand the toxicity and MRSA interactions with these compounds. Due to restrictions from the funder of this research, authors are not allowed to disclose the name of these compounds; thus, we shall label them PES01 to PES21.

4.2. Natural product compound physicochemical properties and toxicity analysis

From Table 1, looking at the column labeled MW<500, it is observed that the majority of the compounds have molecular weight (MW) within the acceptable range of less than 500, except for compound PES01, whose MW is 823.901. The large MW of PES01 implies that it has both a poor absorption rate and limited diffusion across the biological membrane. However, compounds below the acceptable MW have good absorption and diffusion across the biological membrane. Looking at the compound's lipophilicity expressed as cLogP<5, 20 compounds had their cLogP below the accepted range except for PES19 with 6.8665 as its lipophilicity. The higher lipophilicity of PES19 may indicate a slow diffusion across the lipid bilayer. Four compounds, PES10, PES11, PES13, and PES19, possess aqueous solubility cLogS values out of accepted ranges, and thus, the low aqueous solubility will influence their distribution property. Compounds PES01, PES02, PE03, and PES04 have hydrogen bond acceptor (HA) and hydrogen bond donor (HD) not within the acceptable range and thus affecting their permeability due to a great number of hydrogen bond donor and acceptor groups. Also, the same compounds have PSA greater than 140 square angstroms; thus, compounds PES01, PES02, PE03, and PES04 may be very poor at permeating cell membranes.

The majority of compounds have rotatable bonds (RB) <10 except for PES05 and PES19; thus, the latter have poor oral bioavailability. From Table 2, we observe that the majority of the compounds show negative druglikeness scores, except compounds PES01, PES02, PES08, PES10, PES12, PES15, and PES20 possess positive druglikeness scores; thus, these compounds contain molecular fragments commonly found in commercial drugs. The majority of compounds were non-mutagenic, with the exceptions of PES08, PES13, PES15, PES16, PES18, PES20, and PES21. Most compounds were non-tumorigenic except for PES03, PES08, and PES21. The majority of compounds had no side effects on reproductive health except for PES03 and PES18. Most compounds were nonirritant except for PES13, PES17, PES18, and PES19. Furthermore, 11 compounds are non-mutagenic, non-tumorigenic, and nonirritant and have no reproductive health adverse effect as shown in Table 3.

Table 4 shows more physicochemical characteristics of compounds like oral bioavailability by considering VEBER and

Table 1. Physicochemical properties of the selected 21 compounds calculated using DataWarrior

Compound	MW<500	cLogP<5	cLogS>-4.0	HA<10	HD<5	PSA<140A	RB<10
PES01	823.901	0.6952	−3.513	17	4	224.72	6
PES02	422.389	−0.4109	−2.551	11	3	143.86	7
PES03	446.407	−0.0864	−2.927	10	5	155.14	5
PES04	418.397	−1.026	−2.903	9	7	167.91	3
PES05	385.503	1.3798	−2.751	8	4	118.97	11
PES06	388.415	2.1004	−2.428	7	2	86.61	5
PES07	386.399	3.7625	−3.301	7	4	116.45	4
PES08	211.172	0.0016	−1.14	6	2	79.23	1
PES09	284.266	2.6095	−3.211	5	2	75.99	2
PES10	271.271	2.3596	−4.112	5	2	70	1
PES11	326.391	4.6855	−4.093	4	1	47.92	4
PES12	270.283	2.6964	−3.137	4	2	66.76	2
PES13	254.24	2.6177	−4.452	4	1	63.6	1
PES14	166.175	0.5754	−1.465	3	2	57.53	3
PES15	188.182	1.3675	−2.901	3	0	43.37	1
PES16	178.186	1.4183	−2.188	3	1	46.53	0
PES17	158.24	2.8817	−2.349	2	1	37.3	7
PES18	136.15	1.5229	−1.958	2	0	26.3	2
PES19	256.472	6.8665	−4.527	1	1	20.23	15
PES20	208.259	3.3038	−3.84	1	0	17.07	3
PES21	158.199	2.2567	−3.106	1	1	20.23	1

Table 2. Physicochemical properties of the selected 21 compounds calculated using DataWarrior

Compound	Druglikeness	Mutagenic	Tumorigenic	Reproductive effective	Irritant
PES01	7.8074	None	None	None	None
PES02	0.32355	None	None	None	None
PES03	−3.4398	None	High	High	None
PES04	−3.0467	None	None	None	None
PES05	−5.1812	None	None	None	None
PES06	−0.8225	None	None	None	None
PES07	−0.16737	None	None	None	None
PES08	1.0646	High	Low	None	None
PES09	−0.10513	None	None	None	None
PES10	1.1795	None	None	None	None
PES11	−2.3404	None	None	None	None
PES12	0.052524	None	None	None	None
PES13	−0.94415	Low	None	None	High
PES14	−0.6215	None	None	None	None
PES15	0.60625	Low	None	None	None
PES16	−1.8585	Low	None	None	None
PES17	−25.216	None	None	None	High
PES18	−3.9857	High	None	High	High
PES19	−32.166	None	None	None	High
PES20	0.1125	High	None	None	None
PES21	−2.2456	Low	High	None	None

EGAN rule, phospholipidosis, and Fsp3. These characteristics were calculated using the FAF-Drugs4 tools. From Table 4, we observe that all compounds have good bioavailability except for compound PES05. Still from the same table, all compounds are non-inducers of phospholipidosis. Table 5 shows ADMET characteristics, which include BBB penetration, HIA, CYP_2C19_inhibition, Pgb inhibition, and plasma protein binding calculated using the PreADMET tool. In vivo, drugs can bind reversibly to plasma proteins and lipids, a process known as plasma protein binding, which is utilized in clinical trials to monitor drug concentration and predict therapeutic dose. Plasma protein binding analysis was performed using the following criteria: (i) compounds highly bound with a score greater than 90% and (ii) compounds weakly bound with a score less than 90%. Compounds PES07, PES11, PES12, PES13, PES17, PES19, and PES20 are strongly bound to plasma protein binding with scores above 90%, whereas the rest are weakly bound. The BBB is a highly selective barrier

Table 3. 11 Compounds that possess none characteristics across four physicochemical properties

Compound	Mutagenic	Tumorigenic	Reproductive effective	Irritant
PES01	None	None	None	None
PES02	None	None	None	None
PES04	None	None	None	None
PES05	None	None	None	None
PES06	None	None	None	None
PES07	None	None	None	None
PES09	None	None	None	None
PES10	None	None	None	None
PES11	None	None	None	None
PES12	None	None	None	None
PES14	None	None	None	None

between the brain and the rest of the body, and medications that target the central nervous system (CNS) should have higher BBB penetration, whereas treatments that target peripheral organs should have lower BBB penetration to reduce CNS side effects. The following criteria were used to assess BBB penetration: (i) high absorption to the CNS for BBB> 2.0; (ii) BBB has a middle absorption to the CNS of 2.0 to 0.1; and (iii) BBB has minimal absorption into the CNS (<0.1). Six compounds (PES01-PES06) have low absorption since their BBB<0.1. However, the majority of compounds have middle absorption because their BBB ranges between 0.1 and 2.0 except for PES19 with a high absorption with a BBB of 19.0873.

The following criteria were used to evaluate the prediction of HIA, which is significant in the design, optimization, and selection of oral medications: (i) compounds with low absorption for HIA (0%–20%); (ii) compounds with moderate HIA absorption between 20% and 70%; and (iii) compounds with high HIA absorption between 70% and 100%.

The majority of the compounds have high HIA absorption except for PES02-PES05 with a moderate HIA absorption. The majority of the compounds were inhibitors of CYP_2C19, a cytochrome P450b, an enzyme responsible for the metabolism of known drugs in humans except for PES01, PES02, PES05, PES08, PES10, and PES14. Furthermore, it was also revealed that most of the compounds were found to be non-inhibitors of P-glycoprotein (Pgb) except for PES06, PES07, PES11, PES19, and PES20. P-glycoprotein is a member of the ATP-binding cassette superfamily of membrane transport proteins responsible for drug efflux and is a crucial component of the BBB. Furthermore, note that only compound PES12 possesses scores within the acceptable range, looking at all physicochemical properties displayed in Tables 1–5.

4.3. Molecular interaction of compounds with MRSA strains results

Table 6 presents results for molecular docking analysis obtained after interacting natural product compounds with two macromolecular targets from MRSA, namely, nitrocefin acyl-Penicillin binding protein 2a (1MWS) and SeMet Penicillin binding protein 2a (1MWR). The binding energy for compound interactions with 1MWR ranges from −3.8 to −18.6 Kcal/mol. However, the binding energy after interacting compounds with 1MWS ranges from −2.7 to −15.2 Kcal/mol as shown in Table 6. Table 7 shows binding energy after interacting MRSA strains with known drugs for treating MRSA, and it is observed that their binding energy ranges from −6.9 to −8.7 Kcal/mol. Comparing binding energies of compounds and those of known drugs for treating MRSA and assuming that −6.9 Kcal/mol of chloramphenicol as a cut-off, PES01–PES13 have high binding energy compared with those of known drugs. The higher binding energies for compounds under investigation are not totally unique because previous studies by Mustafa et al. [32], Pantelić et al. [33] and Ahmad et al. [34] also revealed that higher binding energies of compounds imply that such compounds may be potential drug candidates against the protein target under investigation.

Table 4. Physicochemical properties of the selected 21 compounds calculated using FAF-Drugs4

Compound	Oral bioavailability (VEBER)	Oral bioavailability (EGAN)	Phospholipidosis	Fsp3
PES01	Good	Good	Noninducer	0.42
PES02	Good	Good	Noninducer	0.42
PES03	Good	Good	Noninducer	0.32
PES04	Good	Good	Noninducer	0.38
PES05	Low	Good	Noninducer	0.84
PES06	Good	Good	Noninducer	0.43
PES07	Good	Good	Noninducer	0.29
PES08	Good	Good	Noninducer	0.22
PES09	Good	Good	Noninducer	0.06
PES10	Good	Good	Noninducer	0.13
PES11	Good	Good	Noninducer	0.3
PES12	Good	Good	Noninducer	0
PES13	Good	Good	Noninducer	0.07
PES14	Good	Good	Noninducer	0.22
PES15	Good	Good	Noninducer	0.09
PES16	Good	Good	Noninducer	0.3
PES17	Good	Good	Noninducer	0.89
PES18	Good	Good	Noninducer	0.13
PES19	Good	Good	Noninducer	1
PES20	Good	Good	Noninducer	0
PES21	Good	Good	Noninducer	0.09

Table 5. ADMET properties of the selected 21 compounds calculated using PreADMET

Compound	BBB	HIA	CYP_2C19_inhibition	Pgp_inhibition	Plasma_Protein_Binding
PES01	0.0410089	89.283662	Non	Non	69.840552
PES02	0.0665572	61.267981	Non	Non	48.653671
PES03	0.0344379	65.902238	Inhibitor	Non	60.371924
PES04	0.0502051	33.636872	Inhibitor	Non	50.093116
PES05	0.0970856	66.693864	Non	Non	70.431583
PES06	0.0364783	93.849263	Inhibitor	Inhibitor	78.53712
PES07	0.376467	84.127222	Inhibitor	Inhibitor	100
PES08	0.359984	83.136922	Non	Non	22.684433
PES09	0.595872	93.042707	Inhibitor	Non	84.729106
PES10	0.843006	92.614826	Non	Non	84.598231
PES11	1.91134	95.74939	Inhibitor	Inhibitor	99.692242
PES12	1.39253	100	Inhibitor	Non	100
PES13	1.07168	95.860591	Inhibitor	Non	91.393789
PES14	0.663054	90.758331	Non	Non	46.71105
PES15	1.30657	98.233788	Inhibitor	Non	80.348626
PES16	0.622139	94.020109	Inhibitor	Non	72.120791
PES17	0.826691	94.784959	Inhibitor	Non	100
PES18	1.65265	100	Inhibitor	Non	31.723859
PES19	19.0873	100	Inhibitor	Inhibitor	100
PES20	1.51574	100	Inhibitor	Inhibitor	94.831826
PES21	1.56093	100	Inhibitor	Non	79.860886

Table 6. Binding energy of the selected 21 compounds after interaction with MRSA strains calculated using PyRx

Compound	1 MWR binding energy Kcal/mol	1 MWS binding energy Kcal/mol
PES01	−18.6	−15.2
PES02	−7.2	−6.9
PES03	−7.7	−3.8
PES04	−7.1	−6.7
PES05	−6.7	−5.7
PES06	−8.2	−6.6
PES07	−7.9	−6.7
PES08	−6.9	−5.1
PES09	−7.9	−5.6
PES10	−7.4	−6.1
PES11	−7.2	−6.5
PES12	−8.0	−4.6
PES13	−7.2	−6.3
PES14	−5.7	−3.3
PES15	−6.2	−6.2
PES16	−6.5	−5.5
PES17	−4.7	−4.4
PES18	−5.1	−4.6
PES19	−3.8	−2.7
PES20	−6.1	−5.5
PES21	−6.0	−5.2

Table 7. Binding energy of the known drugs after interaction with MRSA strains calculated using PyRx

Known drugs	1 MWR binding energy Kcal/mol
Ceftriaxone	−8.7
Cefixime	−8.0
Levofloxacin	−7.6
Ciprofloxacin	−7.5
Chloramphenicol	−6.9

5. Conclusion

In this research study, we performed an in-depth literature search and identified 180 natural product compounds with antibacterial activity against MRSA. On further screening, only 21 out of 180 natural product compounds were extracted from plants that are common in Uganda. We later conducted computer-aided virtual toxicity analysis to study the toxicity of the 21 natural product compounds, and we found that the majority of them passed toxicity analysis tests. Furthermore, we performed docking to establish the binding affinity of the 21 compounds with MRSA by looking at the DTI between the compounds and MRSA. We found that all compounds had binding energies between −2.7 Kcal/mol and −18.6 Kcal/mol. Compound PES01 had an excellent binding energy value of −18.6 kcal/mol, which was far greater than that of known drugs (−6.9 to 8.7 kcal/mol). Looking at the binding energy of PES01–PES13, it can be concluded that these compounds may be new potential drugs for treating MRSA. As a starting point, PES12 should be given the highest priority since it passed all toxicity screening compared to the others.

Recommendations

This study discovered 21 potential compounds that have antibacterial activity against MRSA. Although PES01 had an excellent binding energy, its chemical structure had to be redesigned to reduce its MW. This can be achieved through various methods, including breaking down large molecules into smaller ones, removing substituent groups, or altering the arrangement of atoms within the molecule. Although we performed virtual toxicity and docking analysis, there is a need to carry out animal studies and clinical trials on these identified compounds before they can be considered for the treatment of MRSA. In a follow-up study, these compounds can be studied on other diseases; for example, some could be good anti-cancer agents.

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Ethical Statement

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

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support the findings of this study are openly available in Ressource Parisienne en BioInformatique Structurale (RPBS) at https://bioserv.rpbs.univ-paris-diderot.fr/services.html and in PreADMET at https://preadmet.qsarhub.com/.

Author Contribution

Simon Kawuma: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **David Sabiiti Bamutura:** Methodology, Software, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Izath Nura:** Investigation, Writing – original draft, Writing – review & editing. **Daniel Zziwa Ashiraf:** Investigation, Writing – original draft, Writing – review & editing. **Joel Bazira:** Methodology, Validation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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