UNIVERSITI PUTRA MALAYSIA

ANTIBACTERIAL, ANTIBIOFILM PROPERTIES AND MECHANISM OF ACTION OF PHOSPHANEGOLD(I) THIOLATE COMPLEXES ON Staphylococcus aureus STRAINS

ANMAR AMEER MOHAMMED SADEQ ALRAWAS

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By

ANMAR AMEER MOHAMMED SADEQ ALRAWAS

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

February 2022

DEDICATION

With my deepest gratitude and most humble effort, I would like to dedicate this thesis:
To my dear supervisor **Prof. Ts .Dr. Cheah Yoke Kqueen** who keep supporting me and encourage me throughout my PhD program.

To the soul of my father and sister, who were wishing to see my finishing my PhD before their past away, to my family members for their never ended help, support, and patience during all time.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfilment of the Requirement for the degree of Doctor of Philosophy

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Chairman : Professor Ts. Cheah Yoke Kqueen, PhD
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With the widespread increase of bacterial resistance to available antibiotics and the lack of resources for the discovery of new classes of antibiotics, the multidrug-resistant *S. aureus* has become a global concern. The methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported as a serious threat in health settings. There is now a strong demand for new antibacterial agents as only a few antibiotics can combat MRSA infections. The notable development of transition metals for medicinal purposes and advanced designs of metal complexes as antibacterial agents have been extended in the research area. These offer good choices as alternative antibacterial agents despite the fact that they have not been explored intensively. Recent *in vitro* studies have highlighted the potential use of gold-based compounds to inhibit the growth of important pathogens, such as MRSA without classifying the mode of action (MOA) or explaining the potential of the growth inhibition mechanism. This research study was aimed at evaluating and investigating the antibacterial activity, anti-biofilm activity, synergistic interaction, and classification of the mode of action of the novel 3F2 phosphanegold(I) thiolate compound. Preliminary screening using the disc diffusion method showed that the novel 3F2 gold compound possesses a noticeable antibacterial activity against MRSA strains with an average inhibition zone ranging between 8 mm to 12 mm. The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of the 3F2 gold compound against MRSA strains was in range of 4 µg/mL to 8 µg/mL. Moreover, the dose-dependent 3F2 gold compound exhibited bactericidal activity against MRSA during the first twelve hours. The interaction of the novel 3F2 compound in combination with ciprofloxacin showed a partially synergistic activity with FICI = 0.53 using the checkerboard method. Also, the 3F2 gold compound showed an anti-biofilm activity, whereby cell viability was reduced by more than 50 percent. InCelligence technology and the CLSM microscopic results proved the inhibition/eradication of *S. aureus* biofilm formation with MIBC in the range of 3.125 µg/mL to 12.5 µg/mL. Furthermore, the predicted mode of action (MOA) of the 3F2 gold compound was classified based on a data analysis of the phenotypic microarray.

The Pearson correlation and clustering analysis showed that the mode of action was similar to that of vancomycin in targeting the MRSA cell wall. However, the TEM and RT-PCR results supported the predicted mode of action. Finally, all the findings showed promising antibacterial activity by the new 3F2 gold compound, with a unique potential MOA against MRSA. Overall, the thesis results are beneficial for both the development of antibacterial agents and gaining an understanding of the mechanism of action to minimize the multi-drug resistance, and to develop new methods of identifying and classifying the mode of action of new antibacterial agents

.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

AKTIVITI ANTIBAKTERIA, ANTIBIOFILM DAN MEKANISME TINDAKAN LOGAM PERALIHAN *PHOSPHANGOLD*(I) *THIOLATE* TERHADAP *Staphylococcus aureus*

Oleh

ANMAR AMEER MOHAMMED SADEQ ALRAWAS

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Pengerusi : Profesor Ts. Cheah Yoke Kqueen, PhD
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Peningkatan tahap kerintangan bakteria terhadap antibiotik yang sedia ada secara meluas dan kekurangan sumber dalam penemuan kelas antibiotik baru telah menyebabkan *S.aureus* yang rintang pelbagai antibiotik menjadi kebimbangan global. *Staphylococcus aureus* (MRSA) yang rintang metisilin telah dilaporkan sebagai ancaman serius terhadap kesihatan. Kini, terdapat permintaan yang tinggi untuk penemuan agen antibakteria yang baru kerana hanya beberapa antibiotik boleh menangani jangkitan MRSA. Perkembangan penting logam peralihan untuk tujuan perubatan dan rekaan unggul kompleks logam sebagai agen antibakteria telah diperluaskan dalam bidang penyelidikan. Ini menyebabkan ia adalah pilihan yang baik sebagai agen antibakteria alternatif walaupun hakikatnya ia belum diterokai secara intensif. Kajian in vitro terbaru menekankan potensi penggunaan sebatian berasaskan emas untuk menghalang pertumbuhan patogen yang penting, seperti MRSA tanpa mengklasifikasikan mod tindakan (MOA) atau menjelaskan potensi mekanisme perencatan pertumbuhan. Oleh itu, kajian ini bertujuan untuk menilai dan menyelidik aktiviti antibakteria, anti-biofilem, interaksi sinergistik, dan klasifikasi mod tindakan sebatian novel *phosphangold (I) thiolate* 3F2. Saringan awal menggunakan kaedah penyebaran cakera menunjukkan bahawa sebatian novel emas 3F2 mempunyai aktiviti antibakteria yang ketara terhadap strain MRSA dengan zon perencatan purata di antara 8 mm hingga 12 mm. Kepekatan perencatan minimum (MIC) dan kepekatan bakteria minimum (MBC) sebatian emas 3F2 terhadap strain MRSA adalah di antara 4 µg/mL hingga 8 µg/mL. Selain itu, sebatian emas 3F2 yang bergantung kepada dos menunjukkan aktiviti bakteria terhadap MRSA dalam tempoh dua belas jam pertama. Interaksi sebatian novel 3F2 dengan kombinasi ciprofloxacin menunjukkan aktiviti separa sinergistik dengan FICI = 0.53 menggunakan kaedah papan dam. Selain itu, sebatian emas 3F2 menunjukkan aktiviti anti-biofilem, di mana kehidupan sel berkurangan lebih daripada 50 peratus. Teknologi InCelligence dan keputusan mikroskopik CLSM membuktikan perencatan/pembasmian pembentukan biofilem *S. aureus* dengan julat MIBC sebanyak 3.125 µg/mL hingga 12.5 µg/mL. Tambahan pula, mod tindakan (MOA) yang diramalkan bagi sebatian emas 3F2

dikelaskan berdasarkan analisis data mikrotatasusunan fenotip. Analisis korelasi dan pengelompokan Pearson menunjukkan bahawa mod tindakan adalah serupa dengan vankomisin dalam menyasarkan dinding sel MRSA. Walau bagaimanapun, keputusan TEM dan RT-PCR menyokong mod tindakan yang diramalkan. Akhir sekali, semua penemuan menunjukkan aktiviti antibakteria oleh sebatian emas 3F2 dengan potensi MOA yang unik terhadap MRSA. Secara keseluruhannya, hasil tesis ini adalah bermanfaat untuk pembangunan agen antibakteria dan pemahaman tentang mekanisme tindakan untuk meminimumkan rintangan pelbagai antibiotik dan untuk membangunkan kaedah baru untuk mengenal pasti dan mengklasifikasikan mod tindakan agen antibakteria baru.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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AIP	Auto-inducing peptide
ALI assay	Air-liquid interface assay
AO/ PI	Acridine Orange / propidium Iodide
ATCC	American type culture collection
CLMS	Confocal leaser scanning microscopy
CLSI	Clinical laboratory standards institure
CUF	Colony forming unit
CWA	Cell wall anchored
DHFR	Dihydrofolate reductase
DMSO	Dimethylsulphoxide
ECM	Extra cellular matrix
eDNA	Extracellular DNA
FAO	The Food and Agriculture Organization
FICI	Fractional inhibitory concentration index
HSA	Highest single agent
INT	Iodonitrotetrazolium violet
LCMS	Liquid chromatography mass spectrometry
MBC	Minimum bactericidal concentration
MDR	Multi-drug resistance
MHB	Muller-hinton broth
MIC	Minimum inhibitory concentration
MOA	Mode of Action / Mechanism of Action
MRSA	Methicillin- resistant *Staphylococcus arues*

MSCRAMMs	Microbial surface components recognizing adhesive matrix molecules
NA	Nutrient agar
NAM / NAG	Acetylmuramic acid / N-acetylglucosamine
NMR	Magnetic resonance
O.D	Optical density
OIE	World Organization for Animal Health
PBS	Phosphate buffered saline
PG	Peptidoglycan
PIA	Polysaccharide intercellular adhesion
PM	Phenotype microarray
PSM	Phenol soluble modulins
RT_PCR	Real-time Polymerase Chain Reaction
RTCA	Real-time cell analysis
SCC*mec*	*S*taphylococcal *c*assette *c*hromosome *mec*
SD	Standard deviation
SEM	Scanning electron microscope
SSS	Scalded-skin syndrome
ST	Sexual transmitted diseases
TEM	Transmission electron microscope
TSA / TSB	Tryptic soya Agar / Broth
TSS	Toxic shock syndrom
ViSA	Vancomycin intermediate *Staphylococcus aureus*
WGS	Whole genome sequencing
WHO	World health organization

WTA	Wall teichoic acid
^{0}C	Degree Centigrade / Celsius
µg/mL	Microgram per Millilitre
3F2	Tricyclohexylphosphanegold(I)-O-methyl-N-(3-fluoropheny) thiocarbamato
3F3	Bis(diphenylphosphino)ferrocene-di gold(I)- O-methyl N-(3-fluorophenyl)-thiocarbamato
3FL	O-methyl-N-(3-fluorophenyl)-thiocarbamato

CHAPTER 1

INTRODUCTION

1.1 Background

Over the years, the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE) have become increasingly concerned about the serious health problems posed globally to humans and animals by multidrug-resistant (MDR) pathogenic bacteria. However, infectious diseases remain one of the main causes of many illnesses and deaths around the world. Microbes, such as multidrug-resistant bacteria, are the major cause of severe fever, sepsis, diarrhoea, respiratory diseases, skin infections, sexually transmitted diseases (STD) and many others, and very serious actions are required to stop or reduce the threat of these MDR pathogens and to save the lives of many people. The advance of phenotypic resistance in microorganisms, specifically MDR bacteria, to current antibiotics and the emergence of new infectious diseases have become global issues in the twenty-first century, thereby making it essential that novel, safe and effective antimicrobial agents be discovered (Rojas et al., 2003)

The Gram-positive bacterium, *S. aureus*, is one of the main pathogenic bacteria that is emerging increasingly due to the rapid development of resistance against a series of first, second and third line antibiotics that are usually used to treat infectious diseases caused by the *S. aureus* (Harris et al., 2002; Theuretzbacher, 2011).

The methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most difficult infections to treat due to its ability to develop resistance against available antibiotics, despite the introduction of new derivatives, and the abuse of these antibiotics (Rodvold and McConeghy, 2014). Many of these antibiotics and their derivatives are linked to dose limitations, development of resistance, and expensive costs. This will be discussed in detail in Chapter 2. In addition, over the last two decades, there has been a noticeable increase in the number of cases of vancomycin intermediate-resistant *Staphylococcus aureus* (ViSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) around the world, and the resistance mechanisms of the aforementioned strains are quite different, thus, making it difficult to treat them with the same antibiotics (Fridkin, 2001; Hiramatsu et al., 2014). Vancomycin is still the drug of choice for the treatment of MRSA infections, despite the fact that resistance to this antibiotic has been increasing noticeably (Bérdy, 2012; Tegos and Hamblin, 2005; McGuinness et al., 2017). Thus, the demand for active drug discovery approaches for the development of new antimicrobial agents is being highlighted. Moreover, infectious diseases associated with the *Staphylococcus aureus* biofilm are another challenge as it is well known that the biofilm population is physiologically different from its planktonic counterpart, and is better able to persist in the infected host, even under harsh environmental stress. As a result, the resistance mechanism of bacterial cell biofilms is different from that of planktonic cells (Petrelli et al., 2017; Pozo and Patel, 2007).

The ability of the *S. aureus*, specifically the MRSA, to form biofilms is one of the main factors for the virulence of nosocomial infections. Moreover, infections caused by *S. aureus* strains that possess the ability to form biofilms are more difficult to treat with existing antibiotics as these antibiotics have not been specifically designed to treat biofilm infections (Agarwal and Jain, 2012; Costerton, 2012; Lynch and Abbanat, 2010). Hence, there is now a strong demand for the discovery, design or synthesis of new antibacterial agents to treat biofilm-forming bacteria.

In addition to the remarkable therapeutic success of some existing antibacterial agents, metal-based antimicrobial agents have shown promising results in the laboratory. Metallodrugs have been used for a long time prior to the discovery of organic antibiotics. Since then, there has been a general decline in the use of metal-based drugs, particularly antibacterial compounds, with the exception of silver compounds (Bharti and Singh, 2009; Hobman and Crossman, 2015). The use of metal-based antibacterial agents is one of the strategies adapted by many researchers to combat the challenges of bacterial resistance to antibiotics worldwide. Metal-based agents *in vitro*, in the form of complexes or salt complexes, in particular, have been able to combat bacterial resistance (Hobman and Crossman, 2015).

The gold element (Au) and its complexes have also been used in medicine throughout civilization until the present day. A gold complex was clinically used as treatment for rheumatic disease. Later on, in the middle of the 20th century, gold complexes were screened and evaluated for their potential use as antibacterial agents (Glisic and Djuran, 2014). Interest in the potential antibacterial properties of gold(I) and gold(III) complexes was sparked by Robert Koch, who used potassium dicyanoaurate(I) to treat tuberculosis, a disease caused by the *Mycobacterium tuberculosis* (Tiekink, 2002). Later on, a great number of gold(I) and gold(III) complexes were used against a wide spectrum of bacterial pathogens, although the majority of the studies were carried out on gold(I) compounds, perhaps because of their greater stability compared to gold(III) compounds (Glisic and Djuran, 2014).

Notwithstanding that metal-based antibacterial agents have been shown to be effective against a wide range of Gram-positive and Gram-negative pathogens, some studies have revealed that these pathogens have started to develop a resistance to metal ions, especially towards silver ions, but this is not the case with gold-based antibacterial agents (Hobman and Crossman, 2015). This resistance to metal ions is probably due to a lack of knowledge and understanding on the mechanism of action of metal-based antibacterial agents.

There is a rising clinical demand for new antibacterial agents as the therapeutic efficacy of current antibiotics against Gram-positive cocci is very limited due to the emergence of MDR *S. aureus* strains, such as MRSA and VRSA (Fricker, 1996). Hence, the aim of this study was to investigate and evaluate *in vitro* the antibacterial activity of

phosphanegold(I) thiolate complexes against a wide range of pathogens, including *S. aureus* strains, as well as to investigate the ability of phosphanegold(I) thiolate to inhibit or remove the *S. aureus* biofilm. This study was also aimed at investigating and predicting the mechanism of action of phosphanegold(I) thiolate against *S. aureus* strains.

1.2 Problem Statement

Bacterial infections caused by pathogens, such as the multidrug-resistant *S. aureus*, are still a global concern, and one of the main reasons for the increasing morbidity and mortality rates is bacterial resistance to current antibiotics, which is growing dramatically and threatening public health globally. Besides that, for many years now, no new classes of antimicrobial agents have been introduced into the market, and the rate of discovery of new antimicrobial agents has been very low and insufficient to counter the challenging growth of antibacterial resistance. The *S. aureus* has developed a resistance against a series of first, second and third-line antibiotics, including beta-lactam and glycopeptide antibiotics, to be classified as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA), respectively. Therefore, this pathogen is a risk factor for hospital-acquired and community-acquired infections. In addition, diseases associated with the *S. aureus* biofilm have displayed a greater resistance to antibiotics and combinations of different antibacterial agents. In contrast to organic antibacterial agents, less attention has been paid to inorganic antibacterial agents, such as metal-based drugs. Many attempts have been made to overcome the issue of bacterial resistance by the *S. aureus*. Researchers have investigated the antibacterial effectiveness of metal and metal-based medicines *in vitro* against several strains of the *S. aureus.* Silver, copper, lead, platinum, gold, and other metal complexes have been reported to have antibacterial properties. However, bacteria, including the *S. aureus*, may develop a resistance against some of these metal compounds. Moreover, lack of knowledge on the mode of action or mechanism of action of metal compounds has limited their usage recently as antibacterial agents. Indeed, a few gold-based drugs, such as gold(I) with phosphine ligand or N-heterocyclic carbene ligand complexes, have been reported to possess potential antibacterial properties against the *S. aureus* without having developed any resistance as yet. However, the mechanism of action of these gold compounds on bacterial cells is still not fully understood. Thus, a study that can provide enough information about the mechanism of action of gold-based antibacterial agents may help to reduce the bacterial resistance of the *S. aureus.*

1.3 Justification for the Study

Metal-based drugs are reported to have multiple uses in health settings due to their antimicrobial, anticancer, anti-inflammatory, and many other properties. It has been disclosed in the literature that gold-based drugs are purported to be promising antibacterial agents against critical human pathogens, including the *S. aureus.*

In this study, the novel phosphanegold(I) thiolate compounds known as the 3F series (containing 3F2, 3F3,3F4, 3F5, 3F6, and 3FL) were investigated for their antibacterial and antibiofilm properties individually or in combination with other standard antibiotics against *S. aureus* strains. Also, the mechanism of action of the phosphanegold(I) thiolate compounds was predicted and determined against the methicillin-resistant *Staphylococcus aureus* using new Phenotype MicroArray (PM) technology. The outcomes of this study may contribute richly to the further development of antibacterial agents derived from metal-based drugs. Moreover, the prediction of the mode of action using PM technology may open the door to a better understanding of the mechanism of action of metal-based drugs and, therefore, lead to the designing of more potent gold-based compounds as antibacterial agents.

1.4 Hypothesis

Novel phosphanegold(I) thiolate compounds under the 3F series (3F2, 3F3, 3F4, 3F5, 3F6, and 3FL), either individually or in combination, have a unique mechanism of action and potent antibacterial activity against *S. aureus* strains. Thus, an investigation into the antibacterial activity of the abovementioned phosphanegold(I) thiolate compounds was carried out *in vitro*, and subsequently, the anti-biofilm ability of the compounds against the *S. aureus* biofilm-producing strains and the synergistic interaction of the most potent phosphanegold(I) thiolate compound were investigated. Furthermore, the mechanism of action of the best phosphanegold(I) thiolate compound among the above six compounds was predicted and determined using Phenotype MicroArray technology.

1.5 Objectives

1.5.1 General Objective

To investigate and characterize the biological properties of phosphanegold(I) thiolate complexes (3F series) as potential antibacterial agents against *S. aureus* strains, and to predict the general mechanism of action of the best phosphanegold(I) thiolate complex among the 3F series.

To achieve the above general objective, the following specific objectives were set.

1.5.2 Specific objectives

1- To conduct a preliminary screening and evaluation of the antibacterial properties of phosphanegold(I) thiolate complexes (3F series) *in vitro* against Gram-negative and Gram-positive pathogens.

2- To investigate the synergistic activity of the 3F2 (phosphanegold(I) thiolate) complex in combination with antibiotics with a known mode of action against the methicillin-resistant *Staphylococcus aureus* (ATCC43300).

3- To investigate the ability of the 3F2 (phosphanegold(I) thiolate) complex to inhibit/eradicate the *Staphylococcus aureus* (ATCC43300) biofilm.

4- To predict the mechanism of action (MOA) of the 3F2 phosphanegold(I) thiolate complex by studying the phenotypic profile of the methicillin-resistant *Staphylococcus aureus* (ATCC43300).

1.6 Conceptual framework

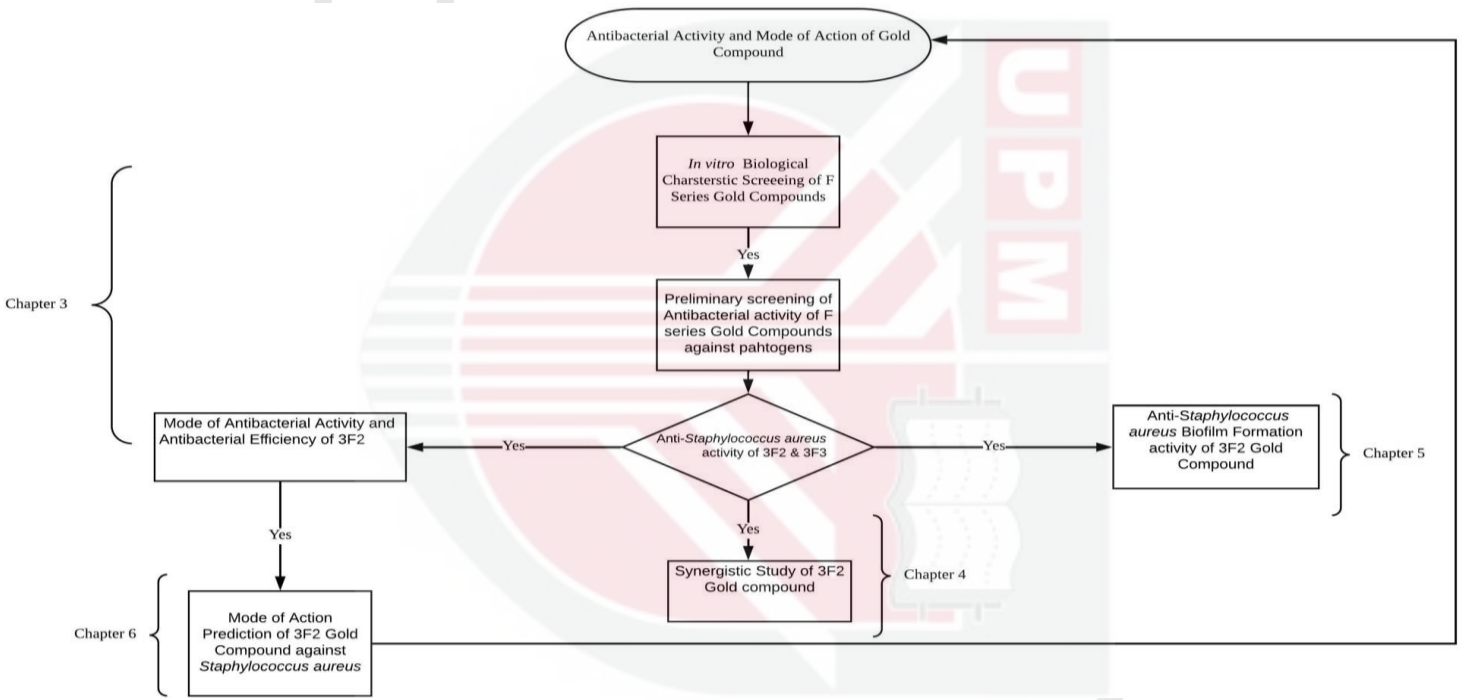

Figure 1.1 : Conceptual framework illustrates concept map of the antibacterial activity and mode of action of phosphanegold(I) thiolate complexes. Four working chapters indicated by curly brackets are relevant to be discussed in this thesis

REFERENCES

Abdulamir., A. S., Jassim., S. A. A., Hafidh., R. R., and Bakar., F. A. (2015). The potential of bacteriophage cocktail in eliminating Methicillin-resistant Staphylococcus aureus biofilms in terms of different extracellular matrices expressed by PIA, ciaA-D and FnBPA genes. *Annals of Clinical Microbiology and Antimicrobials*. https://doi.org/10.1186/s12941-015-0106-0

Acar., J. F. (2000). Antibiotic synergy and antagonism. *Medical Clinics of North America*, *84*(6), 1391–1406. https://doi.org/10.1016/S0025-7125(05)70294-7

Agarwal., A., and Jain., A. (2012). Association between drug resistance & production of bioflm in staphylococci. *Indian Journal of Medical Research*, *135*(4), 562–564.

Agarwal., A., and Jain., A. (2013). Glucose & sodium chloride induced biofilm production & ica operon in clinical isolates of staphylococci, (August), 262–266.

Ala'Aldeen., D. a. a., and Hiramatsu., K. (2004). *Staphylococcus aureus: molecular and clinical aspects*. Retrieved from http://books.google.com/books?id=2NNnA98Pbi8C&pgis=1

Alhanout., K., Malesinki., S., Vidal., N., Peyrot., V., Rolain., J. M., and Brunel., J. M. (2010). New insights into the antibacterial mechanism of action of squalamine. *Journal of Antimicrobial Chemotherapy*, *65*(8), 1688–1693. https://doi.org/10.1093/jac/dkq213

American Society for Microbiology. (2005). *Manual of antimicrobial susceptibility testing*. *Manual of antimicrobial susceptibility testing*. https://doi.org/10.1007/s13398-014-0173-7.2

Angeles., D. M., and Scheffers., D. (2021). The Cell Wall of Bacillus subtilis, 539–596.

Appelbaum., P. C. (2007). Microbiology of Antibiotic Resistance in Staphylococcus aureus. *Clinical Infectious Diseases*, *45*(Supplement 3), S165–S170. https://doi.org/10.1086/519474

Archer., N., Mazaitis., M., and Costerton., J. (2011). Staphylococcus aureus biofilms: properties, regulation, and roles in human disease. …, *2*(5), 445–459. https://doi.org/10.4161/viru.2.5.17724

Armbruster., C. R., Wolter., D. J., Mishra., M., Hayden., H. S., Radey., M. C., Merrihew., G., Maccoss., M. J., Burns., J., Wozniak., D. J., Parsek., M. R., and Hoffman., R. (2016). Staphylococcus aureus Protein A Mediates Interspecies Interactions at the Cell Surface of Pseudomonas aeruginosa, *7*(3), 1–9. https://doi.org/10.1128/mBio.00538-16.Editor

Bandow., J. E., Brötz., H., Ole., L. I., Labischinski., H., Hecker., M., Bro., H., Ingo., L., and Leichert., O. (2003). Proteomic Approach to Understanding Antibiotic Action Proteomic Approach to Understanding Antibiotic Action. *Antimicrobial Agents and Chemotherapy*, *47*(3), 948–955. https://doi.org/10.1128/AAC.47.3.948

Beaudoin., T., Kennedy., S., Yau., Y., and Waters., V. (2016). Visualizing the Effects of Sputum on Biofilm Development Using a Chambered Coverglass Model. *Journal of Visualized Experiments*, (118), 2–7. https://doi.org/10.3791/54819

Beckingsale., T. (2008). *Staphylococcus aureus : salt stress , cell wall de ciency , and Biofilm formation Staphylococcus aureus : Salt Stress , Cell Wan Deficiency , and Biofilm Formation* . Durham University. Retrieved from http://etheses.dur.ac.uk/2513/1/2513_525.pdf

Beenken., K. E., Dunman., P. M., Mcaleese., F., Macapagal., D., Murphy., E., Projan., S. J., Blevins., J. S., and Smeltzer., M. S. (2004). Global Gene Expression in Staphylococcus aureus Biofilms, *186*(14), 4665–4684. https://doi.org/10.1128/JB.186.14.4665

Belley., A., Neesham-grenon., E., Arhin., F. F., Mckay., G. A., Parr., T. R., and Moeck., G. (2008). Assessment by Time-Kill Methodology of the Synergistic Effects of Oritavancin in Combination with Other Antimicrobial Agents against Staphylococcus aureus , *52*(10), 3820–3822. https://doi.org/10.1128/AAC.00361-08

Benson., T. E., Harris., M. S., Choi., G. H., Cialdella., J. I., Herberg., J. T., Martin., J. P., and Baldwin., E. T. (2001). A Structural Variation for MurB : X-ray Crystal Structure of Staphylococcus aureus, 2340–2350.

Bérdy., J. (2012). Thoughts and facts about antibiotics: Where we are now and where we are heading. *Journal of Antibiotics*, *65*(8), 385–395. https://doi.org/10.1038/ja.2012.27

Beveridge., T. J. (1999). Structures of gram-negative cell walls and their derived membrane vesicles. *Journal of Bacteriology*, *181*(16), 4725–4733. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10438737

Beveridge., T. J., and Graham., L. L. (1991). Surface layers of bacteria. *Microbiological Reviews*, *55*(4), 684–705. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1723487

Bharti., S. K., and Singh., S. K. (2009). Metal Based Drugs : Current Use and Future Potential. *Library*, *1*(2), 39–51.

Bimanand., L., Taherikalani., M., Jalilian., F. A., Sadeghifard., N., Ghafourian., S., Mahdavi., Z., Mohamadi., S., Sayehmiri., K., Hematian., A., and Pakzad., I. (2018). Association between biofilm production, adhesion genes and drugs resistance in different SCCmec types of methicillin resistant Staphylococcus aureus strains isolated from several major hospitals of Iran. *Iranian Journal of Basic Medical Sciences*, *21*(4), 400–403. https://doi.org/10.22038/ijbms.2018.19378.5132

Bochner., B. R. (2003a). New technologies to assess genotype-phenotype relationships. *Nature Reviews Genetics*, *4*(4), 309–314. https://doi.org/10.1038/nrg1046

Bochner., B. R. (2003b). New technologies to assess genotype–phenotype relationships. *Nature Reviews Genetics*, *4*(4), 309–314. https://doi.org/10.1038/nrg1046

Bochner., B. R., Gadzinski., P., and Panomitros., E. (2001). Phenotype Microarrays for high-throughput phenotypic testing and assay of gene function. *Genome Research*, *11*(7), 1246–1255. https://doi.org/10.1101/gr.186501

Boswihi., S. S., and Udo., E. E. (2018). Methicillin-resistant Staphylococcus aureus : An update on the epidemiology, treatment options and infection control. *Current Medicine Research and Practice*, *8*(1), 18–24. https://doi.org/10.1016/j.cmrp.2018.01.001

Bourne., C. R., Wakeham., N., Bunce., R. A., Nammalwar., B., Darrell Berlin., K., and Barrow., W. W. (2012). Classifying compound mechanism of action for linking whole cell phenotypes to molecular targets. *Journal of Molecular Recognition*, *25*(4), 216–223. https://doi.org/10.1002/jmr.2174

Brambilla., L. Z. S., Endo., E. H., Cortez., D. A. G., and Dias Filho., B. P. (2017). Anti-biofilm activity against Staphylococcus aureus MRSA and MSSA of neolignans and extract of Piper regnellii. *Revista Brasileira de Farmacognosia*, *27*(1), 112–117. https://doi.org/10.1016/J.BJP.2016.08.008

Cabral., M. P., García., P., Beceiro., A., Rumbo., C., Pérez., A., Moscoso., M., and Bou., G. (2017). Design of live attenuated bacterial vaccines based on D-glutamate auxotrophy. *Nature Communications*, *8*(May). https://doi.org/10.1038/ncomms15480

Carneiro., C. R. W., Postol., E., Nomizo., R., Reis., L. F. L., and Brentani., R. R. (2004). Identification of enolase as a laminin-binding protein on the surface of S taphylococcus aureus, *6*, 604–608. https://doi.org/10.1016/j.micinf.2004.02.003

Carr., H., Wlodkowski., J., Rosenkranz., H., Carr., S., Wlodkowski., T., and Rosenkranz., H. (1973). Silver Sulfadiazine: In vitro antibacterial activity. *Antimicrobial Agents and Chemotherapy*, *4*, 585–587.

Castro., W., Navarro., M., and Biot., C. (2013). Medicinal potential of ciprofloxacin and its derivatives. *Future Medicinal Chemistry*, *5*(1), 81–96. https://doi.org/10.4155/fmc.12.181

Chang., E. L., Simmers., C., and Knight., D. A. (2010). Cobalt complexes as antiviral and antibacterial agents. *Pharmaceuticals*, *3*(6), 1711–1728. https://doi.org/10.3390/ph3061711

Chen., B. J., Jamaludin., N. S., Khoo., C. H., See., T. H., Sim., J. H., Cheah., Y. K., Halim., S. N. A., Seng., H. L., and Tiekink., E. R. T. (2016). In vitro antibacterial and time kill evaluation of mononuclear phosphanegold(I) dithiocarbamates. *Journal of Inorganic Biochemistry*, *163*, 68–80. https://doi.org/10.1016/j.jinorgbio.2016.08.002

Chohan., Z. H., Supuran., C. T., and Scozzafava., A. (2005). Metal binding and antibacterial activity of ciprofloxacin complexes, *20*(3), 303–307. https://doi.org/10.1080/14756360310001624948

Choo., E. J., and Chambers., H. F. (2016). Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia, *48*(4), 267–273.

Chou., T. (2010). Drug Combination Studies and Their Synergy Quantification Using the Chou-Talalay Method, *70*(2), 440–447. https://doi.org/10.1158/0008-5472.CAN-09-1947

Chudobova., D., Cihalova., K., Dostalova., S., Ruttkay-Nedecky., B., Merlos Rodrigo., M. A., Tmejova., K., Kopel., P., Nejdl., L., Kudr., J., Gumulec., J., Krizkova., S., Kynicky., J., Kizek., R., and Adam., V. (2014). Comparison of the effects of silver phosphate and selenium nanoparticles on Staphylococcus aureus growth reveals potential for selenium particles to prevent infection. *FEMS Microbiology Letters*, *351*(2), 195–201. https://doi.org/10.1111/1574-6968.12353

Cihalova., K., Chudobova., D., Michalek., P., Moulick., A., Guran., R., Kopel., P., Adam., V., Kizek., R., Cihalova., K., Chudobova., D., Michalek., P., Moulick., A., Guran., R., Kopel., P., Adam., V., and Kizek., R. (2015). Staphylococcus aureus and MRSA Growth and Biofilm Formation after Treatment with Antibiotics and SeNPs. *International Journal of Molecular Sciences*, *16*(10), 24656–24672. https://doi.org/10.3390/ijms161024656

Coelho., L. R., Souza., R. R., Ferreira-carvalho., B. T., Sa., A. M., Sa., A. M., and Janeiro., R. De. (2017). agr RNAIII divergently regulates glucose-induced biofilm formation in clinical isolates of Staphylococcus aureus, (2008), 3480–3490. https://doi.org/10.1099/mic.0.2007/016014-0

Costerton., J. W. (2012). Bacterial Biofilms : A Common Cause of Persistent Infections, *1318*(1999). https://doi.org/10.1126/science.284.5418.1318

Cramariuc., O., Rog., T., Javanainen., M., Monticelli., L., Polishchuk., A. V., and Vattulainen., I. (2012). Mechanism for translocation of fluoroquinolones across lipid membranes. *Biochimica et Biophysica Acta - Biomembranes*, *1818*(11), 2563–2571. https://doi.org/10.1016/j.bbamem.2012.05.027

Cucarella., C., Solano., C., Valle., J., Amorena., B., Lasa., I. G. O., and Penade., R. (2001). Bap , a Staphylococcus aureus Surface Protein Involved in Biofilm Formation, *183*(9), 2888–2896. https://doi.org/10.1128/JB.183.9.2888

Dakheel., K. H., Abdul Rahim., R., Neela., V. K., Al-Obaidi., J. R., Hun., T. G., and Yusoff., K. (2016). Methicillin-Resistant Staphylococcus aureus Biofilms and Their Influence on Bacterial Adhesion and Cohesion. *BioMed Research International*, *2016*. https://doi.org/10.1155/2016/4708425

de Kievit., T. R., and Iglewski., B. H. (2000). MINIREVIEW Bacterial Quorum Sensing in Pathogenic Relationships, *68*(9), 4839–4849.

Deresinski., S. (2009). Vancomycin in combination with other antibiotics for the treatment of serious methicillin-resistant staphylococcus aureus infections. *Clinical Infectious Diseases*, *49*(7), 1072–1079. https://doi.org/10.1086/605572

Di Veroli., G. Y., Fornari., C., Wang., D., Mollard., S., Bramhall., J. L., Richards., F. M., and Jodrell., D. I. (2016). Combenefit: An interactive platform for the analysis and visualization of drug combinations. *Bioinformatics*, *32*(18), 2866–2868. https://doi.org/10.1093/bioinformatics/btw230

Dobinsky., S., Kiel., K., Rohde., H., Bartscht., K., Knobloch., J. K., Horstkotte., M. A., and Mack., D. (2003). Glucose-Related Dissociation between icaADBC Transcription and Biofilm Expression by Staphylococcus epidermidis : Evidence for an Additional Factor Required for Polysaccharide Intercellular Adhesin Synthesis, *185*(9), 2879–2886. https://doi.org/10.1128/JB.185.9.2879

Doern., C. D. (2014). When does 2 plus 2 equal 5? A review of antimicrobial synergy testing. *Journal of Clinical Microbiology*, *52*(12), 4124–4128. https://doi.org/10.1128/JCM.01121-14

Doublet., P., Van Heijenoort., J., Bohin., J. P., and Mengin-Lecreulx., D. (1993). The murI gene of Escherichia coli is an essential gene that encodes a glutamate racemase activity. *Journal of Bacteriology*, *175*(10), 2970–2979. https://doi.org/10.1128/jb.175.10.2970-2979.1993

Downer., R., Roche., F., Park., P. W., Mecham., R. P., and Foster., T. J. (2002). The Elastin-binding Protein of Staphylococcus aureus (EbpS) Is Expressed at the Cell Surface as an Integral Membrane Protein and Not as a Cell Wall-associated Protein *. *The Journal of Biological Chemistry*, *277*(1), 243–250. https://doi.org/10.1074/jbc.M107621200

Drago., L., De Vecchi., E., Nicola., L., and Gismondo., M. R. (2007). In vitro evaluation of antibiotics' combinations for empirical therapy of suspected methicillin resistant Staphylococcus aureus severe respiratory infections. *BMC Infectious Diseases*, *7*, 1–7. https://doi.org/10.1186/1471-2334-7-111

El-Azizi., M. (2016). Novel Microdilution Method to Assess Double and Triple Antibiotic Combination Therapy in Vitro. *International Journal of Microbiology*, *2016*. https://doi.org/10.1155/2016/4612021

El Zoeiby., A., Sanschagrin., F., and Levesque., R. C. (2003). Structure and function of the Mur enzymes: Development of novel inhibitors. *Molecular Microbiology*, *47*(1), 1–12. https://doi.org/10.1046/j.1365-2958.2003.03289.x

Elkashif., A., and Seleem., M. N. (2020). Investigation of auranofin and gold-containing analogues antibacterial activity against multidrug-resistant Neisseria gonorrhoeae. *Scientific Reports*, *10*(1), 1–9. https://doi.org/10.1038/s41598-020-62696-3

Elsome., A. M., Hamilton-Miller., J. M. . T., Brumfitt., W., and Noble., W. C. (1996). Antimicrobial activities in vitro and in vivo of transition element complexes containing gold (I) and osmium (VI). *Journal of Antimicrobial Chemotherapy*, *37*, 911–918. Retrieved from http://jac.oxfordjournals.org/

Elsome., A. M., Hamilton-miller., J. M. T., Bmmfitt., W., and Noble., W. C. (1996). Antimicrobial activities in vitro and in vivo of transition element complexes containing gold (I) and osmium (VI), 911–918.

Farrel., N. (1989). *Transition Metal Complexes as Drugs and Chemotherapeutic Agents*. *Biochemical Education* (Vol. 18). https://doi.org/10.1016/0307-4412(90)90247-L

Fayyaz., M., Mirza., I. A., Ahmed., Z., Abbasi., S. A., Hussain., A., and Ali., S. (2013). In vitro susceptibility of chloramphenicol against methicillin-resistant Staphylococcus aureus. *Journal of the College of Physicians and Surgeons--Pakistan : JCPSP*, *23*(9), 637–640. https://doi.org/09.2013/JCPSP.637640

Ferrer., M. D., Rodriguez., J. C., Álvarez., L., Artacho., A., Royo., G., and Mira., A. (2017). Effect of antibiotics on biofilm inhibition and induction measured by real-time cell analysis. *Journal of Applied Microbiology*, *122*(3), 640–650. https://doi.org/10.1111/jam.13368

Fillat., M. F., Gimeno., M. C., Laguna., A., Latorre., E., Ortego., L., and Villacampa., M. D. (2011). Synthesis , Structure and Bactericide Activity of (Aminophosphane) gold (I) Thiolate Complexes, (I), 1487–1495. https://doi.org/10.1002/ejic.201001195

Finberg., R. W., Moellering., R. C., Tally., F. P., Craig., W. A., Pankey., G. A., Dellinger., E. P., West., M. A., Joshi., M., Linden., P. K., Rolston., K. V, Rotschafer., J. C., and Rybak., M. J. (2004). The Importance of Bactericidal Drugs : Future Directions in Infectious Disease, *01655*.

Fisher., S. L. (2008). Glutamate racemase as a target for drug discovery. *Microbial Biotechnology*, *1*(5), 345–360. https://doi.org/10.1111/j.1751-7915.2008.00031.x

Foster., T. J., Savolainen., K., Paulin., L., Korhonen., T. K., and Kuusela., P. (2001). Expression of pls , a Gene Closely Associated with the mecA Gene of Methicillin-Resistant Staphylococcus aureus , Prevents Bacterial Adhesion In Vitro, *69*(5), 3013–3020. https://doi.org/10.1128/IAI.69.5.3013

Foucquier., J., and Guedj., M. (2015, June 1). Analysis of drug combinations: current methodological landscape. *Pharmacology Research and Perspectives*. Wiley-Blackwell Publishing Ltd. https://doi.org/10.1002/prp2.149

Fowles., C. C., Smoak., E. M., and Banerjee., I. A. (2010). Interactions of zeatin with gold ions and biomimetic formation of gold complexes and nanoparticles. *Colloids and Surfaces B: Biointerfaces*, *78*(2), 250–258. https://doi.org/10.1016/j.colsurfb.2010.03.010

Francius., G., Domenech., O., Mingeot-Leclercq., M. P., and Dufrêne., Y. F. (2008). Direct observation of Staphylococcus aureus cell wall digestion by lysostaphin. *Journal of Bacteriology*, *190*(24), 7904–7909. https://doi.org/10.1128/JB.01116-08

Frei., A. (2020). Metal complexes, an untapped source of antibiotic potential? *Antibiotics*, *9*(2). https://doi.org/10.3390/antibiotics9020090

French., G. L. (2006). Bactericidal agents in the treatment of MRSA infections - The potential role of daptomycin. *Journal of Antimicrobial Chemotherapy*, *58*(6), 1107–1117. https://doi.org/10.1093/jac/dkl393

Fricker., S. P. (1996). *Medical Uses of Gold Compounds: Past, Present and Future*. Retrievedfromhttps://link.springer.com/content/pdf/10.1007%2FBF03215464.pdf

Fridkin., S. K. (2001). Vancomycin-Intermediate and -Resistant Staphylococcus aureus: What the Infectious Disease Specialist Needs to Know, *30333*.

Frieden., T. (2013). *Antibiotic resistance threats in the United States. Centers for Disease Control and Prevention*. https://doi.org/http://dx.doi.org/10.15620/cdc:82532. U.S.

Garrett., T. R., Bhakoo., M., and Zhang., Z. (2008). Bacterial adhesion and biofilms on surfaces. *Progress in Natural Science*, *18*(9), 1049–1056. https://doi.org/10.1016/j.pnsc.2008.04.001

Garza-Cervantes., J. A., Chávez-Reyes., A., Castillo., E. C., García-Rivas., G., Ortega-Rivera., O. A., Salinas., E., Ortiz-Martínez., M., Gómez-Flores., S. L., Peña-Martínez., J. A., Pepi-Molina., A., Treviño-González., M. T., Zarate., X., Cantú-Cárdenas., M. E., Escarcega-Gonzalez., C. E., and Morones-Ramírez., J. R. (2017). Synergistic antimicrobial effects of silver/transition-metal combinatorial treatments. *Scientific Reports*, *7*(1), 1–16. https://doi.org/10.1038/s41598-017-01017-7

George P. Tegos and Michael R. Hamblin. (2005). Disruptive innovations: new anti-infectives in the age of resistance. *Biophysical Chemistry*, *257*(5), 2432–2437. https://doi.org/10.1016/j.immuni.2010.12.017.Two-stage

Gerits., E., Blommaert., E., Lippell., A., O'Neill., A. J., Weytjens., B., De Maeyer., D., Fierro., A. C., Marchal., K., Marchand., A., Chaltin., P., Spincemaille., P., De Brucker., K., Thevissen., K., Cammue., B. P. A., Swings., T., Liebens., V., Fauvart., M., Verstraeten., N., and Michiels., J. (2016). Elucidation of the mode of action of a new antibacterial compound active against Staphylococcus aureus and Pseudomonas aeruginosa. *PLoS ONE*, *11*(5), 1–17. https://doi.org/10.1371/journal.pone.0155139

Gli., B. Đ., and Djuran., M. I. (2014). overview of di ff erent biological activities in relation to the oxidation state of the gold ion and the ligand structure, 5950–5969. https://doi.org/10.1039/c4dt00022f

Glisic., B. D., and Djuran., M. I. (2014). Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of the gold ion andGlisic, B. D., & Djuran, M. I. (2014). Gold complexes as antimicrobial agents: an overview of different biological. *Dalton Transactions*, *43*(16), 5950–5969. https://doi.org/10.1039/C4DT00022F

Glišić., B. Đ., and Djuran., M. I. (2014). Gold complexes as antimicrobial agents: an overview of different biological activities in relation to the oxidation state of the gold ion and the ligand structure. *Dalton Trans.*, *43*(16), 5950–5969. https://doi.org/10.1039/C4DT00022F

Gowrishankar., S., Kamaladevi., A., Balamurugan., K., and Pandian., S. K. (2016). In Vitro and in Vivo Biofilm Characterization of Methicillin-Resistant Staphylococcus aureus from Patients Associated with Pharyngitis Infection. *BioMed Research International*, *2016*. https://doi.org/10.1155/2016/1289157

Grace., A. N., and Pandian., K. (2008). Quinolone Antibiotic-Capped Gold Nanoparticles and Their Antibacterial Efficacy Against Gram Positive and Gram Negative Organisms. *Journal of Bionanoscience*, *1*(2), 96–105. https://doi.org/10.1166/jbns.2007.018

Grein., F., Müller., A., Scherer., K. M., Liu., X., Ludwig., K. C., Klöckner., A., Strach., M., Sahl., H., Kubitscheck., U., and Schneider., T. (2020). T. Ca2+-Daptomycin targets cell wall biosynthesis by forming a tripartite complex with undecaprenyl-coupled intermediates and membrane lipids. *Nature Communications*, (2020), 1–11. https://doi.org/10.1038/s41467-020-15257-1

Gross., M., Cramton., S. E., Götz., F., and Peschel., A. (2001). Key Role of Teichoic Acid Net Charge in Staphylococcus aureus Colonization of Artificial Surfaces Key Role of Teichoic Acid Net Charge in Staphylococcus aureus Colonization of Artificial Surfaces. *Infection and Immunity*, *69*(5), 3423–2426. https://doi.org/10.1128/IAI.69.5.3423

Gu., Y. G., Florjancic., A. S., Clark., R. F., Zhang., T., Cooper., C. S., Anderson., D. D., Lerner., C. G., Mccall., J. O., Cai., Y., Black-schaefer., C. L., Stamper., G. F., Hajduk., P. J., and Beutel., B. A. (2004). Structure – activity relationships of novel potent MurF inhibitors, *14*, 267–270. https://doi.org/10.1016/j.bmcl.2003.09.073

Guerra., W., de Andrade Azevedo., E., de Souza Monteiro., A. R., Bucciarelli-Rodriguez., M., Chartone-Souza., E., Nascimento., A. M. A., Fontes., A. P. S., Le Moyec., L., and Pereira-Maia., E. C. (2005). Synthesis, characterization, and antibacterial activity of three palladium(II) complexes of tetracyclines. *Journal of Inorganic Biochemistry*, *99*(12), 2348–2354. https://doi.org/10.1016/J.JINORGBIO.2005.09.001

Gutiérrez., D., Fernández., L., Martínez., B., Ruas-Madiedo., P., García., P., and Rodríguez., A. (2017). Real-Time Assessment of Staphylococcus aureus Biofilm Disruption by Phage-Derived Proteins. *Frontiers in Microbiology*, *8*, 1632. https://doi.org/10.3389/fmicb.2017.01632

Gutiérrez., D., Hidalgo-Cantabrana., C., Rodríguez., A., García., P., and Ruas-Madiedo., P. (2016). Monitoring in Real Time the Formation and Removal of Biofilms from Clinical Related Pathogens Using an Impedance-Based Technology. *PLOS ONE*, *11*(10), e0163966. https://doi.org/10.1371/journal.pone.0163966

Hafidh., R. R., Abdulamir., A. S., and Abu Bakar., F. (2012). Phenotype microarray profiling of the antibacterial activity of red cabbage. *Functional Foods in Health and Disease*, *2*(6), 212–227.

Harbut., M. B., Vilchèze., C., Luo., X., Hensler., M. E., Guo., H., Yang., B., Chatterjee., A. K., Nizet., V., Jacobs., W. R., Schultz., P. G., and Wang., F. (2015). Auranofin exerts broad-spectrum bactericidal activities by targeting thiol-redox homeostasis. *Proceedings of the National Academy of Sciences*, *112*(14), 4453–4458. https://doi.org/10.1073/pnas.1504022112

Harris., L. G., Foster., S. J., Richards., R. G., Lambert., P., Stickler., D., and Eley., A. (2002). An introduction to Staphylococcus aureus, and techniques for identifyingand quantifying S. aureus adhesins in relation to adhesion to biomaterials:Review. *European Cells and Materials*, *4*, 39–60. https://doi.org/10.22203/eCM.v004a04

Hibbitts., A., and O'Leary., C. (2018). Emerging nanomedicine therapies to counter the rise of Methicillin-resistant Staphylococcus aureus. *Materials*, *11*(2). https://doi.org/10.3390/ma11020321

Hiramatsu., K., Kayayama., Y., Matsuo., M., Aiba., Y., Saito., M., Hishinuma., T., and Iwamoto., A. (2014). Vancomycin-intermediate resistance in Staphylococcus aureus. *Integrative Medicine Research*, *2*(4), 213–224. https://doi.org/10.1016/j.jgar.2014.04.006

Hobman., J. L., and Crossman., L. C. (2015). Bacterial antimicrobial metal ion resistance. *Journal of Medical Microbiology*, *64*(2014), 471–497. https://doi.org/10.1099/jmm.0.023036-0

Hoerr., V., Duggan., G. E., Zbytnuik., L., Poon., K. K. H., Große., C., Neugebauer., U., Methling., K., Löffler., B., and Vogel., H. J. (2016). Characterization and prediction of the mechanism of action of antibiotics through NMR metabolomics. *BMC Microbiology*, *16*(1), 1–14. https://doi.org/10.1186/s12866-016-0696-5

Hu., Y., Chen., L., Ha., S., Gross., B., Falcone., B., Walker., D., Mokhtarzadeh., M., and Walker., S. (2003). Crystal structure of the MurG : UDP-GlcNAc complex reveals common structural principles of a superfamily of glycosyltransferases, *100*(3), 845–849.

Hwang., I. -s., Hwang., J. H., Choi., H., Kim., K.-J., and Lee., D. G. (2012). Synergistic effects between silver nanoparticles and antibiotics and the mechanisms involved. *Journal of Medical Microbiology*, *61*(Pt_12), 1719–1726. https://doi.org/10.1099/jmm.0.047100-0

IAGC. (2019). *No Time to Wait: Securing The Future From Drug-Resistant Infection*. *World Health Organization* (Vol. 54). Retrieved from https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/

Ing Yeo., C., and Tiekink., E. R. (2020). Crystal structure of (μ2-1,1′-bis(diphenylphosphino)hexane-κ2P,P′)-bis [(Z)-N-(3-fluorophenyl)-O-methylthiocarbamato-κS]digold(I), C46H46Au2F2N2O2P2S2. *Z. Kristallogr. NCS*, *1*(ahead-of-print), aop. https://doi.org/10.1515/ncrs-2020-0354

Ito., T., Hiramatsu., K., Oliveira., D. C., De Lencastre., H., Zhang., K., Westh., H., O'Brien., F., Giffard., P. M., Coleman., D., Tenover., F. C., Boyle-Vavra., S., Skov., R. L., Enright., M. C., Kreiswirth., B., Kwan., S. K., Grundmann., H., Laurent., F., Sollid., J. E., Kearns., A. M., Goering., R., John., J. F., Daum., R., and Soderquist., B. (2009). Classification of staphylococcal cassette chromosome mec (SCCmec): Guidelines for reporting novel SCCmec elements. *Antimicrobial Agents and Chemotherapy*, *53*(12), 4961–4967. https://doi.org/10.1128/AAC.00579-09

Iwata., Y., Satou., K., Furuichi., K., and Yoneda., I. (2020). International Journal of Infectious Diseases Collagen adhesion gene is associated with bloodstream infections caused by methicillin-resistant Staphylococcus aureus. *International Journal of Infectious Diseases*, *91*, 22–31. https://doi.org/10.1016/j.ijid.2019.11.003

Jacobsen., J. S., Joyner., D. C., Borglin., S. E., Hazen., T. C., Arkin., A. P., and Bethel., E. W. (n.d.). Visualization of Growth Curve Data from Phenotype Microarray Experiments Earth Sciences Division , Lawrence Berkeley National Laboratory , Physical Biosciences Division , Lawrence Berkeley National Laboratory , Virtual Institute for Microbial Stress and S.

Ji., Y., Yin., D., Fox., B., Holmes., D. J., Payne., D., and Rosenberg., M. (2004). Validation of antibacterial mechanism of action using regulated antisense RNA expression in Staphylococcus aureus. *FEMS Microbiology Letters*, *231*(2), 177–184. https://doi.org/10.1016/S0378-1097(03)00931-5

Jindal., H. M., Zandi., K., Ong., K. C., Velayuthan., R. D., Rasid., S. M., Samudi Raju., C., and Sekaran., S. D. (2017). Mechanisms of action and *in vivo* antibacterial efficacy assessment of five novel hybrid peptides derived from Indolicidin and Ranalexin against *Streptococcus pneumoniae*. *PeerJ*, *5*, e3887. https://doi.org/10.7717/peerj.3887

Jürgens., S., and Casini., A. (2017). Mechanistic Insights into Gold Organometallic Compounds and their Biomedical Applications. *CHIMIA International Journal for Chemistry*, *71*(3), 92–101. https://doi.org/10.2533/chimia.2017.92

Konaté., K., Mavoungou., J. F., Lepengué., A. N., Aworet-Samseny., R. R., Hilou., A., Souza., A., Dicko., M. H., and M 'batchi., B. (2012). Antibacterial activity against β- lactamase producing Methicillin and Ampicillin-resistants Staphylococcus aureus: fractional Inhibitory Concentration Index (FICI) determination. ???, *11*, 1. https://doi.org/10.1186/1476-0711-11-18

Kong., E. F., Tsui., C., and Kucharíková., S. (2017). crossm Modulation of Staphylococcus aureus Candida albicans Quorum Sensing.

Kot., B., Sytykiewicz., H., and Sprawka., I. (2018). Expression of the Biofilm-Associated Genes in Methicillin-Resistant Staphylococcus aureus in Biofilm and Planktonic Conditions. *International Journal of Molecular Sciences Article*. https://doi.org/10.3390/ijms19113487

Kumar., R. S., and Arunachalam., S. (2008). Synthesis, micellar properties, DNA binding and antimicrobial studies of some surfactant–cobalt(III) complexes. *Biophysical Chemistry*, *136*(2–3), 136–144. https://doi.org/10.1016/J.BPC.2008.05.007

Laddomada., F., Miyachiro., M. M., Jessop., M., Patin., D., Job., V., Mengin-lecreulx., D., Roy., A. Le, Ebel., C., Breyton., C., Gutsche., I., and Dessen., A. (2019). The MurG glycosyltransferase provides an oligomeric scaffold for the cytoplasmic steps of peptidoglycan biosynthesis in the human pathogen Bordetella pertussis, (November 2018), 1–17. https://doi.org/10.1038/s41598-019-40966-z

Lade., H., and Kim., J. (2021). Bacterial Targets of Antibiotics in Methicillin-Resistant Staphylococcus aureus.

Leite., G. C. (2015). Effect of Antibiotics Combination and Comparison of Methods for Detection of Synergism in Multiresistant Gram-Negative Bacteria. *Journal of Infectious Diseases and Therapy*, *03*(02). https://doi.org/10.4172/2332-0877.1000207

Lemire., J. a, Harrison., J. J., and Turner., R. J. (2013). Antimicrobial activity of metals: mechanisms, molecular targets and applications. *Nature Reviews. Microbiology*, *11*(6), 371–384. https://doi.org/10.1038/nrmicro3028

Levison., M. E. (2004). Pharmacodynamics of antimicrobial drugs, *18*, 451–465. https://doi.org/10.1016/j.idc.2004.04.012

Lien., L. T. Q. (2018). *ANTIBIOTIC RESISTANCE : IMPLICATIONS OF HOSPITAL PRACTICES FOR PUBLIC HEALTH A study from Hanoi , Vietnam La Th i Quynh Lien From the Department of Public Health Sciences HOSPITAL PRACTICES FOR PUBLIC HEALTH A study from Hanoi , Vietnam*. Karolinska Institutet. Retrieved from https://openarchive.ki.se/xmlui/handle/10616/46214

Liu., H., Ritter., T. K., Sadamoto., R., Sears., P. S., and Wu., M. (2003). Acceptor Specificity and Inhibition of the Bacterial Cell-Wall Glycosyltransferase MurG, *92037*, 603–609. https://doi.org/10.1002/cbic.200300557

Liu., Y., and Breukink., E. (2016). The Membrane Steps of Bacterial Cell Wall Synthesis as Antibiotic Targets. https://doi.org/10.3390/antibiotics5030028

Lorian., V. (1971). The Mode of Action of Antibiotics on Gram-Negative Bacilli. *Archives of Internal Medicine*, *128*(4), 623–632. https://doi.org/10.1001/archinte.1971.00310220131022

Lundqvist., T., Fisher., S. L., Kern., G., Folmer., R. H. A., Xue., Y., Newton., D. T., Keating., T. A., Alm., R. A., and De Jonge., B. L. M. (2007). Exploitation of structural and regulatory diversity in glutamate racemases. *Nature*, *447*(7146), 817–822. https://doi.org/10.1038/nature05689

Lynch., A. S., and Abbanat., D. (2010). New antibiotic agents and approaches to treat biofilm-associated infections, 1373–1387.

Man., N. Y. T., Knight., D. R., Stewart., S. G., Mckinley., A. J., Riley., T. V, and Hammer., K. A. (2018). Spectrum of antibacterial activity and mode of action of a novel tris- stilbene bacteriostatic compound. *Scientific Reports*, 1–9. https://doi.org/10.1038/s41598-018-25080-w

Mann., P. A., Müller., A., Xiao., L., Pereira., P. M., Yang., C., Lee., S. H., Trzeciak., J., Schneeweis., J., Moreira., M., She., X., Gill., C., Balibar., C. J., Labroli., M., Su., J., Flattery., A., Sherborne., B., Maier., R., Tan., C. M., Black., T., Önder., K., Monsma., F. J., Pinho., M. G., Schneider., T., and Roemer., T. (2013). Murgocil is a Highly Bioactive Staphylococcal-specific Inhibitor of the Peptidoglycan Glycosyltransferase Enzyme MurG. https://doi.org/10.1021/cb400487f

Manna., A. C., and Cheung., A. L. (2006). Expression of SarX , a Negative Regulator of agr and Exoprotein Synthesis , Is Activated by MgrA in Staphylococcus aureus †, *188*(12), 4288–4299. https://doi.org/10.1128/JB.00297-06

Manner., S., Goeres., D. M., Skogman., M., Vuorela., P., and Fallarero., A. (2017). Prevention of Staphylococcus aureus biofilm formation by antibiotics in 96-Microtiter Well Plates and Drip Flow Reactors: critical factors influencing outcomes. *Scientific Reports*, *7*, 43854. https://doi.org/10.1038/srep43854

Martens., E., and Demain., A. L. (2017). The antibiotic resistance crisis, with a focus on the United States. *Journal of Antibiotics*, *70*(5), 520–526. https://doi.org/10.1038/ja.2017.30

Mccarthy., H., Rudkin., J. K., Black., N. S., Gallagher., L., O'neill., E., O'gara., J. P., Geoghegan., J. A., and Otto., M. (2015). Methicillin resistance and the biofilm phenotype in Staphylococcus aureus. https://doi.org/10.3389/fcimb.2015.00001

McGuinness., W. A., Malachowa., N., and DeLeo., F. R. (2017). Vancomycin resistance in *Staphylococcus aureus*. *The Yale Journal of Biology and Medicine*, *90*(2), 269–281.

McPhillie., M. J., Cain., R. M., Narramore., S., Fishwick., C. W. G., and Simmons., K. J. (2015). Computational Methods to Identify New Antibacterial Targets. *Chemical Biology & Drug Design*, *85*(1), 22–29. https://doi.org/10.1111/cbdd.12385

Mei., M. L., Li., Q. L., Chu., C. H., Lo., E. C. M., and Samaranayake., L. P. (2013). Antibacterial effects of silver diamine fluoride on multi-species cariogenic biofilm on caries. *Annals of Clinical Microbiology and Antimicrobials*, *12*(1), 1–7. https://doi.org/10.1186/1476-0711-12-4

Merino., N., Toledo-arana., A., Vergara-irigaray., M., Valle., J., Solano., C., Calvo., E., Lopez., J. A., Foster., T. J., and Penade., R. (2009). Protein A-Mediated Multicellular Behavior in Staphylococcus aureus □, *191*(3), 832–843. https://doi.org/10.1128/JB.01222-08

Merritt., J. H. (2015). growing and analyzing static Biofilm, 1–29. https://doi.org/10.1002/9780471729259.mc01b01s00.Growing

Mesak., L. R., and Davies., J. (2009). Phenotypic changes in ciprofloxacin-resistant Staphylococcus aureus. *Research in Microbiology*. https://doi.org/10.1016/j.resmic.2009.09.013

Miragaia., M. (2018). Factors Contributing to the Evolution of mecA -Mediated β -lactam Resistance in Staphylococci : Update and New Insights From Whole Genome Sequencing (WGS), *9*(November), 1–16. https://doi.org/10.3389/fmicb.2018.02723

Mishra., A., Kaushik., N. K., Verma., A. K., and Gupta., R. (2008). Synthesis, characterization and antibacterial activity of cobalt(III) complexes with pyridine–amide ligands. *European Journal of Medicinal Chemistry*, *43*(10), 2189–2196. https://doi.org/10.1016/J.EJMECH.2007.08.015

Mizdal., C. R., Stefanello., S. T., da Costa Flores., V., Agertt., V. A., Bonez., P. C., Rossi., G. G., da Silva., T. C., Antunes Soares., F. A., de Lourenço Marques., L., and de Campos., M. M. A. (2018). The antibacterial and anti-biofilm activity of gold-complexed sulfonamides against methicillin-resistant Staphylococcus aureus. *Microbial Pathogenesis*, *123*, 440–448. https://doi.org/10.1016/j.micpath.2018.08.002

Mizdal., C. R., Stefanello., S. T., Nogara., P. A., Antunes Soares., F. A., de Lourenço Marques., L., and de Campos., M. M. A. (2018). Molecular docking, and anti-biofilm activity of gold-complexed sulfonamides on Pseudomonas aeruginosa. *Microbial Pathogenesis*, *125*, 393–400. https://doi.org/10.1016/j.micpath.2018.10.004

Monecke., S., Jatzwauk., L., Müller., E., Nitschke., H., Pfohl., K., Slickers., P., Reissig., A., Ruppelt-Lorz., A., and Ehricht., R. (2016). Diversity of SCCmec Elements in Staphylococcus aureus as Observed in South-Eastern Germany. *PLOS ONE*, *11*(9), e0162654. https://doi.org/10.1371/journal.pone.0162654

Moormeier., D. E., and Bayles., K. W. (2017). Staphylococcus aureus biofilm: a complex developmental organism. *Molecular Microbiology*, *104*(3), 365–376. https://doi.org/10.1111/mmi.13634

Mueller., M., Pen., A. De, and Derendorf., H. (2004). MINIREVIEW Issues in Pharmacokinetics and Pharmacodynamics of Anti-Infective Agents : Kill Curves versus MIC, *48*(2), 369–377. https://doi.org/10.1128/AAC.48.2.369

Navid., A. (2012). *Microbial Systems Biology*. *Springer*. https://doi.org/10.1007/978-1-61779-827-6

Nazari., Z. E., Banoee., M., Sepahi., A. A., Rafii., F., and Shahverdi., A. R. (2012). The combination effects of trivalent gold ions and gold nanoparticles with different antibiotics against resistant Pseudomonas aeruginosa, 53–59. https://doi.org/10.1007/s13404-012-0048-7

Nira Rabin., Y. Z., Opoku-Temeng., C., Yixuan Du., E. B., and Sintim., & H. O. (2015). Biofilm formation mechanisms and targets for developing antibiofilm agents, *8*, 697–711.

Novelli., F., Recine., M., Sparatore., F., and Juliano., C. (1999). Gold (I) complexes as antimicrobial agents, *54*, 232–236.

O.I.E. (2012). Laboratory Methodologies for Bacterial Antimicrobial Susceptibility Testing. *OIE Terrestrial Manual*, 1–11. https://doi.org/10.4065/mcp.2010.0639

O'Neill., E., Pozzi., C., Houston., P., Smyth., D., Humphreys., H., Robinson., D. A., Gara., J. P. O., and Icrobiol., J. C. L. I. N. M. (2007). Association between Methicillin Susceptibility and Biofilm Regulation in Staphylococcus aureus Isolates from Device-Related Infections □ †, *45*(5), 1379–1388. https://doi.org/10.1128/JCM.02280-06

O'Toole., G. A. (2011). Microtiter dish biofilm formation assay. *Journal of Visualized Experiments : JoVE*, (47). https://doi.org/10.3791/2437

Odds., F. C. (2003). Synergy, antagonism, and what the chequerboard puts between them. *Journal of Antimicrobial Chemotherapy*, *52*(1), 1–1. https://doi.org/10.1093/jac/dkg301

Oehninger., L., Rubbiani., R., and Ott., I. (2013). N-Heterocyclic carbene metal complexes in medicinal chemistry. *Dalton Transactions*, *42*(10), 3269–3284. https://doi.org/10.1039/C2DT32617E

Oliva., B., O'Neill., A. J., Miller., K., Stubbings., W., and Chopra., I. (2004). Anti-staphylococcal activity and mode of action of clofazimine. *Journal of Antimicrobial Chemotherapy*, *53*(3), 435–440. https://doi.org/10.1093/jac/dkh114

Ortego., L., Gonzalo-asensio., J., Laguna., A., Villacampa., M. D., and Gimeno., M. C. (2015). (Aminophosphane) gold (I) and silver (I) complexes as antibacterial agents. *Journal of Inorganic Biochemistry*, *146*, 19–27. https://doi.org/10.1016/j.jinorgbio.2015.01.007

Ortego., L., Gonzalo-Asensio., J., Laguna., A., Villacampa., M. D., and Gimeno., M. C. (2015). (Aminophosphane)gold(I) and silver(I) complexes as antibacterial agents. *Journal of Inorganic Biochemistry*, *146*, 19–27. https://doi.org/10.1016/j.jinorgbio.2015.01.007

Owings., J. P., McNair., N. N., Mui., Y. F., Gustafsson., T. N., Holmgren., A., Contel., M., Goldberg., J. B., and Mead., J. R. (2016). Auranofin and N-heterocyclic carbene gold-analogs are potent inhibitors of the bacteria Helicobacter pylori. *FEMS Microbiology Letters*, *363*(14), 1–6. https://doi.org/10.1093/femsle/fnw148

Özdemir., İ., Temelli., N., Günal., S., and Demir., S. (2010). Gold(I) Complexes of N-Heterocyclic Carbene Ligands Containing Benzimidazole: Synthesis and Antimicrobial Activity. *Molecules* . https://doi.org/10.3390/molecules15042203

Pankey., G. A., and Sabath., L. D. (2004a). Clinical Relevance of Bacteriostatic versus Bactericidal Mechanisms of Action in the Treatment of Gram-Positive Bacterial Infections. *Clinical Infectious Diseases*, *38*(6), 864–870. https://doi.org/10.1086/381972

Pankey., G. A., and Sabath., L. D. (2004b). Clinical Relevance of Bacteriostatic versus Bactericidal Mechanisms of Action in the Treatment of Gram-Positive Bacterial Infections. *Clinical Infectious Diseases*, *38*(6), 864–870. https://doi.org/10.1086/381972

Pawar., A., Jha., P., Chopra., M., Chaudhry., U., and Saluja., D. (2020). Screening of natural compounds that targets glutamate racemase of Mycobacterium tuberculosis reveals the anti-tubercular potential of flavonoids. *Scientific Reports*, *10*(1), 1–12. https://doi.org/10.1038/s41598-020-57658-8

Peach., K. C., Bray., W. M., Winslow., D., Linington., P. F., and Linington., R. G. (2013). Mechanism of action-based classification of antibiotics using high-content bacterial image analysis. *Molecular BioSystems*, *9*(7), 1837. https://doi.org/10.1039/c3mb70027e

Petersen., P. J., Jones., C. H., and Bradford., P. A. (2007). In vitro antibacterial activities of tigecycline and comparative agents by time-kill kinetic studies in fresh Mueller-Hinton broth, *59*, 347–349. https://doi.org/10.1016/j.diagmicrobio.2007.05.013

Petrelli., D., Repetto., A., Ercole., S. D., Rombini., S., Ripa., S., Prenna., M., and Vitali., L. A. (2017). Analysis of meticillin-susceptible and meticillin- resistant biofilm-forming Staphylococcus aureus from catheter infections isolated in a large Italian hospital, (2008), 364–372. https://doi.org/10.1099/jmm.0.47621-0

Pietiäinen., M., François., P., Hyyryläinen., H., Tangomo., M., Sass., V., Sahl., H., Schrenzel., J., and Kontinen., V. P. (2009). Transcriptome analysis of the responses of Staphylococcus aureus to antimicrobial peptides and characterization of the roles of vraDE and vraSR in antimicrobial resistance, *15*. https://doi.org/10.1186/1471-2164-10-429

Pozo., J. L., and Patel., R. (2007). The Challenge of Treating Biofilm-associated Bacterial Infections, *82*(2). https://doi.org/10.1038/sj.clpt.6100247

Pradeep Kumar., M., Tejaswi., S., Rambabu., A., Kalalbandi., V. K. A., and Shivaraj. (2015). Synthesis, crystal structure, DNA binding and cleavage studies of copper(II) complexes with isoxazole Schiff bases. *Polyhedron*, *102*, 111–120. https://doi.org/10.1016/J.POLY.2015.07.052

Rani., N., Kumar., C., Arunachalam., A., and Ptv., L. (2018). Rutin as a potential inhibitor to target peptidoglycan pathway of Staphylococcus aureus cell wall synthesis, *3*(3), 1–9. https://doi.org/10.15761/CMID.1000142

Redgrave., L. S., Sutton., S. B., Webber., M. A., and Piddock., L. J. V. (2014). Fluoroquinolone resistance: Mechanisms, impact on bacteria, and role in evolutionary success. *Trends in Microbiology*, *22*(8), 438–445. https://doi.org/10.1016/j.tim.2014.04.007

Resch., A., Rosenstein., R., Nerz., C., Go., F., and Icrobiol., A. P. P. L. E. N. M. (2005). Differential Gene Expression Profiling of Staphylococcus aureus Cultivated under Biofilm and Planktonic Conditions, *71*(5), 2663–2676. https://doi.org/10.1128/AEM.71.5.2663

Rizzotto., M. (2012). Metal Complexes as Antimicrobial Agents. In *A Search for Antibacterial Agents*. https://doi.org/10.5772/45651

Rodvold., K. A., and Mcconeghy., K. W. (2014). Methicillin-resistant staphylococcus aureus therapy: Past, present, and future. *Clinical Infectious Diseases*, *58*(SUPPL. 1), 20–27. https://doi.org/10.1093/cid/cit614

Rojas., R., Bustamante., B., Bauer., J., Fernández., I., Albán., J., and Lock., O. (2003). Antimicrobial activity of selected Peruvian medicinal plants. *Journal of Ethnopharmacology*, *88*(2–3), 199–204. https://doi.org/10.1016/S0378-8741(03)00212-5

Roymahapatra., G., M. Mandal., S., F. Porto., W., Samanta., T., Giri., S., Dinda., J., L. Franco., O., and K. Chattaraj., P. (2012). Pyrazine Functionalized Ag(I) and Au(I)-NHC Complexes are Potential Antibacterial Agents. *Current Medicinal Chemistry*, *19*(24), 4184–4193. https://doi.org/10.2174/092986712802430090

Sabounchei., S. J., Pourshahbaz., M., Hashemi., A., Ahmadi., M., Karamian., R., Asadbegy., M., and Khavasi., H. R. (2014). Synthesis and structural characterization of dimeric phosphine ylide Cu(I) complexes: Application in Suzuki cross-coupling reactions and biological evaluation as antibacterial agents. *Journal of Organometallic Chemistry*, *761*, 111–119. https://doi.org/10.1016/j.jorganchem.2014.03.017

Sabounchei., S. J., Shahriary., P., Salehzadeh., S., Gholiee., Y., Nematollahi., D., Chehregani., A., and Amani., A. (2014). Gold(iii) complexes of 5-methyl-5-(pyridyl)-2,4-imidazolidenedione: Synthesis, physicochemical, theoretical, antibacterial, and cytotoxicity investigation. *New Journal of Chemistry*, *38*(3), 1199–1210. https://doi.org/10.1039/c3nj01042b

Santiago., C. (2015). *Santiago , Carolina (2015) Application of plant metabolites to overcome antibiotic resistance of methicillin resistant Staphylococcus aureus (MRSA). PhD thesis , University of Nottingham* . Nottingham. Retrieved from Santiago., C. (2015). Santiago , Carolina (2015) Application of plant metabolites to overcome antibiotic resistance of methicillin resistant Staphylococcus aureus (MRSA). PhD thesis , University of Nottingham . Nottingham.

Sauer., J., Bachman., M. A., and Swanson., M. S. (2005). The phagosomal transporter A couples threonine acquisition to differentiation and replication of Legionella pneumophila in macrophages.

Savić., N. D., Milivojevic., D. R., Glišić., B. Đ., Ilic-Tomic., T., Veselinovic., J., Pavic., A., Vasiljevic., B., Nikodinovic-Runic., J., and Djuran., M. I. (2016a). A comparative antimicrobial and toxicological study of gold(iii) and silver(i) complexes with aromatic nitrogen-containing heterocycles: synergistic activity and improved selectivity index of Au(iii)/Ag(i) complexes mixture. *RSC Advances*, *6*(16), 13193–13206. https://doi.org/10.1039/C5RA26002G

Savić., N. D., Milivojevic., D. R., Glišić., B. Đ., Ilic-Tomic., T., Veselinovic., J., Pavic., A., Vasiljevic., B., Nikodinovic-Runic., J., and Djuran., M. I. (2016b). A comparative antimicrobial and toxicological study of gold(iii) and silver(i) complexes with aromatic nitrogen-containing heterocycles: synergistic activity and improved selectivity index of Au(iii)/Ag(i) complexes mixture. *RSC Advances*, *6*(16), 13193–13206. https://doi.org/10.1039/C5RA26002G

Schenone., M., Dančík., V., Wagner., B. K., and Clemons., P. A. (2013). Target identification and mechanism of action in chemical biology and drug discovery. *Nature Chemical Biology*, *9*(4), 232–240. https://doi.org/10.1038/nchembio.1199

Schillaci., D., Arizza., V., Dayton., T., Camarda., L., and Stefano., V. Di. (2008). In vitro anti-biofilm activity of Boswellia spp . oleogum resin essential oils, *47*, 433–438. https://doi.org/10.1111/j.1472-765X.2008.02469.x

Schwalbe., R., Steele-Moore., L., and Goodwin., A. C. (2007a). *Antimicrobial Susceptibility testing procols*.

Schwalbe., R., Steele-Moore., L., and Goodwin., A. C. (2007b). *Antimicrobial Susceptibility Testing Protocols. Journal of Chemical Information and Modeling* (Vol. 53). https://doi.org/10.1017/CBO9781107415324.004

Selvaganapathy., M., and Raman., N. (2016). Pharmacological Activity of a Few Transition Metal Complexes: A Short Review. *Journal of Chemical Biology & Therapeutics*, *01*(02), 1–17. https://doi.org/10.4172/2572-0406.1000108

Selvaraj., V., Nirmala Grace., A., Alagar., M., and Hamerton., I. (2010). Antimicrobial and anticancer efficacy of antineoplastic agent capped gold nanoparticles. *Journal of Biomedical Nanotechnology*, *6*(2), 129–137. https://doi.org/10.1166/jbn.2010.1115

Senn., M. M., Mccallum., N., and Berger-b., B. (2010). International Journal of Medical Microbiology Regulation of antibiotic resistance in Staphylococcus aureus, *300*, 118–129. https://doi.org/10.1016/j.ijmm.2009.08.015

Shaku., M., Ealand., C., Matlhabe., O., Lala., R., and Kana., B. D. (2020). *Peptidoglycan biosynthesis and remodeling revisited*. *Advances in Applied Microbiology* (1st ed., Vol. 112). Elsevier Inc. https://doi.org/10.1016/bs.aambs.2020.04.001

She., P., Liu., Y., Wang., Y., Tan., F., Luo., Z., and Wu., Y. (2019). Antibiofilm efficacy of the gold compound auranofin on dual species biofilms of Staphylococcus aureus and Candida sp. *Journal of Applied Microbiology*, *128*(1), 88–101. https://doi.org/10.1111/jam.14443

She., P., Zhou., L., Li., S., Liu., Y., Xu., L., Chen., L., Luo., Z., and Wu., Y. (2019). Synergistic Microbicidal Effect of Auranofin and Antibiotics Against Planktonic and Biofilm-Encased S. aureus and E. faecalis. *Frontiers in Microbiology*, *10*(OCT), 2453. https://doi.org/10.3389/fmicb.2019.02453

Shukla., S. K., and Rao., T. S. (2013). Dispersal of Bap-mediated Staphylococcus aureus biofilm by proteinase K. *The Journal of Antibiotics*, (August 2012), 55–60. https://doi.org/10.1038/ja.2012.98

Siddiqui., A. H., and Koirala., J. (2020). Methicillin Resistant Staphylococcus Aureus. StatPearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK482221/

Sim., J., Jamaludin., N. S., Khoo., C., Cheah., Y., Nadiah., S., Abdul., B., and Seng., H. (2014). In vitro antibacterial and time-kill evaluation of phosphanegold (I) dithiocarbamates , R 3 PAu [S 2 CN (iPr) CH 2 CH 2 OH] for R = Ph , Cy and Et , against a broad range of Gram-positive and Gram-negative bacteria, 225–236. https://doi.org/10.1007/s13404-014-0144-y

Singh., Naorem, Peter., U., Goswami., G., and Fekete., C. (2020). Characterization of methicillin ‐ resistant Staphylococcus aureus through genomics approach. *3 Biotech*, *10*(9), 1–19. https://doi.org/10.1007/s13205-020-02387-y

Singh., Nina, and Yeh., P. J. (2017). antibiotic resistance, *70*(11), 1033–1042. https://doi.org/10.1038/ja.2017.102.Suppressive

Sobral., R. G., Ludovice., A. M., De Lencastre., H., and Tomasz., A. (2006). Role of murF in cell wall biosynthesis: Isolation and characterization of a murF conditional mutant of Staphylococcus aureus. *Journal of Bacteriology*, *188*(7), 2543–2553. https://doi.org/10.1128/JB.188.7.2543-2553.2006

Sobral., Rita G., Jones., A. E., Des Etages., S. G., Dougherty., T. J., Peitzsch., R. M., Gaasterland., T., Ludovice., A. M., De Lencastre., H., and Tomasz., A. (2007). Extensive and genome-wide changes in the transcription profile of Staphylococcus aureus induced by modulating the transcription of the cell wall synthesis gene murF. *Journal of Bacteriology*, *189*(6), 2376–2391. https://doi.org/10.1128/JB.01439-06

Sochacki., K. A., Barns., K. J., Bucki., R., and Weisshaar., J. C. (2011). Real-time attack on single Escherichia coli cells by the human antimicrobial peptide LL-37. https://doi.org/10.1073/pnas.1101130108

Song., T., Duperthuy., M., and Wai., S. N. (2016). Sub-Optimal Treatment of Bacterial Biofilms. *Antibiotics (Basel, Switzerland)*, *5*(2). https://doi.org/10.3390/antibiotics5020023

Sreedharan., S. M., and Singh., R. (2019). Ciprofloxacin functionalized biogenic gold nanoflowers as nanoantibiotics against pathogenic bacterial strains. *International Journal of Nanomedicine*, *14*, 9905–9916. https://doi.org/10.2147/IJN.S224488

Stewart., P. S., and Costerton., J. W. (2001). Antibiotic resistance of bacteria in biofilms. *THE LANCET*, *358*, 135–138.

Stick., R. V, and Williams., S. J. (2009). *Carbohydrates : The Essential Molecules of Life* (Second). Elsevier.

Su., P. W., Yang., C. H., Yang., J. F., Su., P. Y., and Chuang., L. Y. (2015). Antibacterial activities and antibacterial mechanism of polygonum cuspidatum extracts against nosocomial drug-resistant pathogens. *Molecules*, *20*(6), 11119–11130. https://doi.org/10.3390/molecules200611119

Sy., C. L., Huang., T.-S., Chen., C. S., Chen., Y.-S., Tsai., H.-C., Wann., S.-R., Wu., K.-S., Chen., J.-K., Lee., S. S.-J., and Liu., Y.-C. (2015). Synergy of beta-lactams with vancomycin against methicillin-resistant *Staphylococcus aureus* : correlation of the disk diffusion and the checkerboard methods. *Journal of Clinical Microbiology*, *54*(December), JCM.01779-15. https://doi.org/10.1128/JCM.01779-15

Tallarida., R. J. (2006). An Overview of Drug Combination Analysis with Isobolograms. *Journal of Pharmacology and Experimental Therapeutics*, *319*(1), 1–7. https://doi.org/10.1124/jpet.106.104117

Tam., V. H., Schilling., A. N., and Nikolaou., M. (2005). Modelling time – kill studies to discern the pharmacodynamics of meropenem, (March), 699–706. https://doi.org/10.1093/jac/dki086

Tan., Y. J., Tan., Y. S., Yeo., C. I., Chew., J., and Tiekink., E. R. T. (2019). In vitro anti-bacterial and time kill evaluation of binuclear tricyclohexylphosphanesilver(I) dithiocarbamates, {Cy3PAg(S2CNRR′)}2. *Journal of Inorganic Biochemistry*, *192*(September 2018), 107–118. https://doi.org/10.1016/j.jinorgbio.2018.12.017

Teitzel., G. M., and Parsek., M. R. (2003). Heavy metal resistance of biofilm and planktonic Pseudomonas aeruginosa. *Appl. Environ. Microbiol.*, *69*(4), 2313–2320. https://doi.org/10.1128/AEM.69.4.2313

Tella, AC and Obaleye., J. (2009). Copper(II) Complexes of 4, 4-Diaminodiphenylsulphone: Synthesis, Characterization and Biological Studies. *Journal of Chemistry*.

Thangamani., S., Mohammad., H., Abushahba., M. F. N., Sobreira., T. J. P., Hedrick., V. E., Paul., L. N., and Seleem., M. N. (2016). Antibacterial activity and mechanism of action of auranofin against multi-drug resistant bacterial pathogens. *Scientific Reports*, *6*(1), 22571. https://doi.org/10.1038/srep22571

Thangamani., S., Younis., W., and Seleem., M. N. (2015). Repurposing ebselen for treatment of multidrug-resistant staphylococcal infections. *Scientific Reports*, *5*(1), 11596. https://doi.org/10.1038/srep11596

Theuretzbacher., U. (2011). Resistance drives antibacterial drug development. *Current Opinion in Pharmacology*, *11*(5), 433–438. https://doi.org/10.1016/j.coph.2011.07.008

Tiekink., E. R. T. (2002). Gold derivatives for the treatment of cancer, *42*, 225–248.

Tortora., G. J., Funke., B. R., and Case., C. L. (2018). *Microbiology: An Introduction* (13th ed.). Boston: Pearson Education.

Tremaroli., V., Fedi., S., Turner., R. J., Ceri., H., and Zannoni., D. (2008). Pseudomonas pseudoalcaligenes KF707 upon biofilm formation on a polystyrene surface acquire a strong antibiotic resistance with minor changes in their tolerance to metal cations and metalloid oxyanions. *Archives of Microbiology*. https://doi.org/10.1007/s00203-008-0360-z

Vaidya., M. Y., McBain., A. J., Butler., J. A., Banks., C. E., and Whitehead., K. A. (2017). Antimicrobial Efficacy and Synergy of Metal Ions against Enterococcus faecium, Klebsiella pneumoniae and Acinetobacter baumannii in Planktonic and Biofilm Phenotypes. *Scientific Reports*, *7*(1), 1–9. https://doi.org/10.1038/s41598-017-05976-9

Valle., J., Toledo-arana., A., Ghigo., J., Amorena., B., Penadés., J. R., and Lasa., I. (2003). SarA and not s B is essential for biofilm development by Staphylococcus aureus, *48*, 1075–1087.

van Duuren., J. B. J. H., Müsken., M., Karge., B., Tomasch., J., Wittmann., C., Häussler., S., and Brönstrup., M. (2017). Use of Single-Frequency Impedance Spectroscopy to Characterize the Growth Dynamics of Biofilm Formation in Pseudomonas aeruginosa. *Scientific Reports*, *7*(1), 5223. https://doi.org/10.1038/s41598-017-05273-5

Van Vuuren., S. F., Suliman., S., and Viljoen., A. M. (2009). The antimicrobial activity of four commercial essential oils in combination with conventional antimicrobials. *Letters in Applied Microbiology*, *48*(4), 440–446. https://doi.org/10.1111/j.1472-765X.2008.02548.x

Vergalli., J., Dumont., E., Cinquin., B., Maigre., L., Pajovic., J., Bacqué., E., Mourez., M., Réfrégiers., M., and Pagès., J. M. (2017). Fluoroquinolone structure and translocation flux across bacterial membrane. *Scientific Reports*, *7*(1), 1–8. https://doi.org/10.1038/s41598-017-08775-4

Vincent., I. M., Ehmann., D. E., Mills., S. D., Perros., M., and Barrett., M. P. (2016). Untargeted metabolomics to ascertain antibiotic modes of action. *Antimicrobial Agents and Chemotherapy*, *60*(4), 2281–2291. https://doi.org/10.1128/AAC.02109-15

Von Eiff., C., McNamara., P., Becker., K., Bates., D., Lei., X. H., Ziman., M., Bochner., B. R., Peters., G., and Proctor., R. A. (2006). Phenotype microarray profiling of Staphylococcus aureus menD and hemB mutants with the small-colony-variant phenotype. *Journal of Bacteriology*, *188*(2), 687–693. https://doi.org/10.1128/JB.188.2.687-693.2006

Walsh., C. (2003). *Antibiotics: Actions, origines, resistance*.

Weaver., L., Noyce., J. O., Michels., H. T., and Keevil., C. W. (2010). Potential action of copper surfaces on meticillin-resistant Staphylococcus aureus. *Journal of Applied Microbiology*, *109*(6), 2200–2205. https://doi.org/10.1111/j.1365-2672.2010.04852.x

Worthing., K. A., Schwendener., S., Perreten., V., Saputra., S., and Coombs., G. W. (2018). Characterization of Staphylococcal Cassette Chromosome mec pseudintermedius Infections in Australian Animals, *3*(6), 1–7.

Yang., Y., Severin., A., Chopra., R., Krishnamurthy., G., Singh., G., Hu., W., Keeney., D., Svenson., K., Petersen., P. J., Labthavikul., P., Shlaes., D. M., Rasmussen., B. A., Failli., A. A., Shumsky., J. S., Kutterer., K. M. K., Gilbert., A., and Mansour., T. S. (2006). 3 , 5-Dioxopyrazolidines , Novel Inhibitors of UDP- N - Acetylenolpyruvylglucosamine Reductase (MurB) with Activity against Gram-Positive Bacteria, *50*(2), 556–564. https://doi.org/10.1128/AAC.50.2.556

Yeo., C. I., Tan., S. L., Kwong., H. C., Edward., R. T., Yeo., C. I., Tan., S. L., Kwong., H. C., and Tiekink., E. R. T. (2020). [(Z)-N-(3-Fluorophenyl)-O-methylthiocarbamato-κS](tri- phenylphosphane-κP)gold(I): crystal structure, Hirshfeld surface analysis and computational study, (I), 1284–1290.

Yeo., C. I., Tan., Y. S., and Tiekink., E. R. T. (2020a). Crystal structure of (tricyclohexylphosphane- κ P) - [(Z) - N - (3- fl uorophenyl) - O - methylthiocarbamato- k 1 S] gold (I), C 26 H 40 AuFNOPS, (I), 1–5.

Yeo., C. I., Tan., Y. S., and Tiekink., E. R. T. (2020b). Crystal structure of (μ2-1,1′-bis(diphenylphosphino)ferrocene-κ2P,P′)-bis[(Z)N-(3-fluorophenyl)-O-methylthiocarbamato-S]digold(I) chloroform solvate, C50H42Au2F2FeN2O2P2S2, CHCl3. *Zeitschrift Für Kristallographie - New Crystal Structures*, *0*(0), aop. https://doi.org/10.1515/ncrs-2020-0386

Yeo., C. I., and Tiekink., E. R. T. (2020). Crystal structure of (μ2-1,1′-bis(diphenylphosphino)butane-κ2P,P′)-bis[(Z)-N-(3-fluorophenyl)-O-methylthiocarbamato-κS]-di-gold(I), C44H42Au2F2N2O2P2S2. *Zeitschrift Für Kristallographie - New Crystal Structures*, *0*(0), aop. https://doi.org/10.1515/ncrs-2020-0353

Zhang., Jianying, Liu., J., Ling., J., Tong., Z., Fu., Y., and Liang., M. (2016). Inactivation of glutamate racemase (MurI) eliminates virulence in Streptococcus mutans. *Microbiological Research*, *186–187*, 1–8. https://doi.org/10.1016/j.micres.2016.02.003

Zhang., Jiaqin, and Biswas., I. (2009). A Phenotypic microarray analysis of Streptococcus mutans liaS mutant, *155*(Pt 1), 61–68. https://doi.org/10.1099/mic.0.023077-0.A

Zhang., Ling, Fan., F., Palmer., L. M., Lonetto., M. A., Petit., C., Voelker., L. L., John., A. S., Bankosky., B., Rosenberg., M., and Mcdevitt., D. (2000). Regulated gene expression in Staphylococcus aureus for identifying conditional lethal phenotypes and antibiotic mode of action, *255*, 297–305.

Zhang., Lixin. (2005). Integrated approaches for discovering novel drugs from microbial natural products. *Natural Products: Drug Discovery and Therapeutic Medicine*, (6), 33–55. https://doi.org/10.1007/978-1-59259-976-9_2