

Development, Optimization, and Characterization of Antimicrobial Compound-Loaded Nanoparticles for Enhanced Delivery and Eradication of Multidrug Resistant Pathogens

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ABSTRACT

Synergizing natural antimicrobial compounds with nano particles drug delivery system provides powerful strategy to overcome multidrug resistant [MDR] pathogens. Natural antimicrobial compounds extracted from marine organisms and microbial metabolites and soil microorganisms these are main sources collected samples such as bioactive compounds, Nano carries and metallic nanoparticles like silver, zinc oxide or copper oxide integrate or penetrate bacterial cell wall through direct electrostatic contact. Recently advances in nanotechnology particularly the development of nanoparticles for drug delivery have generated significant impact in medicines and health care. And enhances drug solubility, improve the drug stability increase the targeted delivery facilitate controlled, sustained drug release. and offer provide a protective hidden-like surface immune evasion. enhance intracellular accumulation at infection sites. Isolation identification of microorganism then screening the bioactive compound extraction. Following purification and elucidation of active compounds. Improve nanocarriers will be formulated and optimized to improved the delivery of the selected antimicrobial compounds natural antimicrobial compounds will be selected based on their reported bioactivity and particularly polymeric nanoparticle such as polylactic-co-glycolic acid -based nanoparticle will be developed and optimized using appropriate formulations will be characterized particle size, polydispersity index zetapotential, morphology ,encapsulation, efficiency drug loading and invitro release profile. The physicochemical stability and an evaluation will be conducted to determine the suitability of the developed formulation. the antimicrobial efficacy of the formulations will be estimated against selected MDR pathogens using suitable microbiological techniques, such as minimum inhibitory concentration [MIC] and minimum bactericidal concentration [ABC]assays. In addition, antibiofilm activity will be assessed by Analyzing both the inhibition of biofilm formation and the disrupt biofilm and eradication using suitable experimental methods. Comparative studies involving free natural antimicrobial compounds, naked nanoparticles and compound-loaded nanoparticles will be performed to determine the impact of nanoparticles-based delivery to the observed antimicrobial effects.

Keywords: Antimicrobial nanoparticles; Multidrug-resistant pathogens; Natural antimicrobial compounds; PLGA nanoparticles; Antibiofilm activity; Drug delivery; Antimicrobial resistance.

INTRODUCTION

Antimicrobial resistance has occurred as one of the most critical global public health treats of threats modern era compromising decades of progress in the prevention and membrane disruption. It has revolutionized the field of antimicrobial therapy by enabling the development of advanced nanoscale systems proficient of overcoming the limitations of

conventional antimicrobial agents nanocarriers typically ranging from 1to 100um in size treatment of infectious diseases, the widespread and often inappropriate use of antibiotics in human medicine. Multidrug resistant bacteria resist conventional drugs via efflux pumps, β -Lactamase Enzymes and low membrane permeability nanoparticles bypass these barriers. And modulate drug release characteristics

target drug molecules to desired sites and deliver multiple drugs simultaneously due to these unique advantages they are able to improve the pharmacokinetic profile and therapeutic index. Additionally, nanomaterials exhibit multifaceted antimicrobial activities such cell 100um in size. Metallic nanoparticles are antimicrobial activity produced their broad- spectrum antimicrobial property with highly synthesized and produced multifunctional therapeutic activity. potentially increasing the bioavailability. unfortunately, biofilms have become a highly frequent problems in the clinical environment as microorganisms may adhere to and colonize the surfaces of biomedical devices. thus, in order to avoid the acquiring of nosocomial infections. according to nanoparticle optimization followed by formulation parameter such as independent variable these are the factors systematically changed during the optimization experiments and dependent variables are the characteristics measured to evaluate the quality of the prepared nanoparticles these are response parameters

Naturally Antimicrobial Compounds

Pant derived phytochemicals are major classes essential oils , alkaloids, flavonoids, tannins, terpenoids, and other natural antimicrobial agents, phytochemicals are naturally occurring biologically active secondary metabolites produced by plants primarily for their own protection against pests pathogens, environmental stress ,while not classified as essential nutrient for humans survival, they provide notable health and therapeutic properties. Main classes of phytochemicals are polyphenols is also called as phenolic compounds the largest and most widely studied groups including flavonoids such as Anthocyanins, quercetin and catechins. phenolic compounds and stilbenes they are found in berries, green tea red wine and cocoa, acting as strong antioxidants and anti-inflammatory agents. Terpenoids also called as isoprenoids the largest family of natural products over the 40,000 structures derived from five-carbon isoprene units, they give plants their distinct aromas and flavours Eg: menthol in peppermint, artemisinin in sweet wormwood and Taxol in pacific yew. Alkaloids are nitrogen containing compounds known for potent biological and pharmacological activities well-known example include morphine, codeine, caffeine and Atropine. Carotenoids ,pigments responsible for the red orange and yellow hues in fruits and vegetables such as beta-carotene, lycopene, lutein and Zeaxanthin, serving as cellular antioxidants. Organosulfur compounds such as sulfur-containing chemical found heavily in garlic, onions and cruciferous vegetables like Broccoli that support detoxification and cellular defence.

Phenolic Compounds

1.Quercetin: is naturally occurring flavonoids ,a subclass of phenolic compounds, that exhibit potential

antimicrobial and antibiofilm properties, it is found in onions, apple, berries, grapes and other plant sources.it is a promising candidate for investigating activity against multidrug-resistant (MDR) pathogens . property of quercetin produced antibacterial activity may inhibit the growth of certain bacteria and antibiofilm produced prevent the biofilm formation in selected or desired bacterial species.it is also produced antifungal activity and may exhibit activity against certain fungi. And enzyme inhibition may interface with bacterial enzymes involved in metabolism and other cellular functions. Antioxidant property produced help the neutralize free radicals.

2.Caffein acid: is occurring natural sources from coffee, fruits, vegetables, they may produced antibacterial and potential antibiofilm activity.

3.Ferulic acid: natural sources from rice bran, wheat, and cereals, such as generated antimicrobial activity and potential membrane disruption.

4.Euhenol: natural sources from clove may treated disrupts the microbial membranes and inhibits microbial growth.

5.Carvacrol: occurring from oregano and other aromatic plants, may increase membranes permeability and causes leakage of cellular contents. Terpenoids are naturally occurring bioactive compounds that exhibit antimicrobial properties and have potential applications in combating multidrug-resistant (MDR) Pathogens.

6.Betulinic acid: Most important applications from terpenoids is a pentacyclic triterpenoid belonging to the lupane family and Betulinic acid natural sources obtained from birch bark and other plant sources it has been investigated for antimicrobial activity.

7.Artemisinin: appears from sweet wormwood (*artemisia annua*) and initially known for its antimalarial activity, but it potential antibacterial applications required further investigation. Thymol, carvacrol, geraniol are produced antimicrobial activity against the MDR pathogens depends on the compound, concentration and bacterial strain.

8.Tannins are naturally occurring plant derived polyphenolic compounds that expose antimicrobial properties against bacteria, fungi and certain viruses. They are secondary metabolites found in plants, fruits, seeds, bark, leaves and roots. tannins can be broken down by hydrolysis is called as hydrolysed tannins example :tannic acid , Gallotannins, Ellagitannins, Punicalagin, Punicalin etc these combined properties are antibacterial activity and antifungal activity and antiviral activity and potential to increase the activity

of certain antibiotics against the resistant bacteria. And another one condensed tannins are also called as proanthocyanidins and consist of flavonoids units. Examples are procyanidins, propelphinidins, catechin-based oligomers are enhance the properties antibacterial activity, antifungal activity. And potential antibiofilm activity. interference with microbial enzymes and proteins.

Tannins may inhibit microorganisms through various mechanisms are cell membrane damage due to interference with microbial cell membrane, protein precipitations which are binding to microbial proteins and altering their functions. And enzyme inhibition mechanism of antimicrobial action may inhibiting enzymes required for microbial growth

ALKALOIDS

Alkaloids are naturally occurring nitrogen-containing organic compounds that exhibit various biological activities, including potential antimicrobial properties. They are found in plants some microorganisms. certain alkaloids are being investigated for their ability to inhibit bacterial growth, interface with biofilm formation, and enhance the activity of conventional antibiotics.

1.Berberine: occurring natural sources from berberis species and other plants. may produce antibacterial activity, investigated for antibiofilm and antibiotic-potentiating effects.

2.Indolmycin: obtained from certain bacteria including actinomycetes mostly present in soil collected from different locations and produce a microbial alkaloids antibiotic that inhibit bacterial protein synthesis.

3.Matrine: occurring natural sources from sophora flavescens. may produced potential antibacterial activity effects and antifungal effects in certain experimental models.

4.Harmine: obtained from Peganum harmala it was noted antibacterial activity and antifungal effects in laboratory studies.

5.sanguinarine: obtained from benzo phenanthrinidine Iso quinoline class of alkaloid. Natural sources from sanguinaria canadensis and other plants. May disrupt microbial membranes and interface with cellular proteins.

6.Carotenoids: carotenoids pigments are among the most important pigments and have many applications in various food, cosmetics, hygiene industries and biotechnology. These pigments are produced by plants and microorganisms including *Rhodotorula* spp to study the antimicrobial and antibiofilm effects of the carotenoids pigments from *Rhodotorula glutinis* on food spoilage bacteria (staphylococcus aureus and

salmonella Typhimurium) were the two food borne bacterial strains this study investigates the antimicrobial properties of *Rhodotorula* carotenoids pigments agents various food borne bacterial strains.

Microbial-derived antimicrobial agents:

these are natural antimicrobial agents from non-plant sources which are the produced by bacteria, fungi, actinomycetes, other microorganisms such as streptomycin antimicrobial agent obtained from streptomyces griseus, it Enhance the antibacterial activity. Gentamicin produced by Micromonospora purpurea, may interferes with bacterial proteins translation, and Tetracycline broad spectrum agents that binds the 30S ribosomal subunit. And Nisin is a bacteriocin produced by certain strains of Lactococcus lactis and exhibits the antibacterial activity, particularly against the Gram-positive bacteria. And Lysozyme is a naturally occurring enzyme that damages bacterial cell walls. Some Antimicrobial compounds such as Endolysins comes from bacteriophages it has been producing the break down bacterial cell walls. Marine bacteria ,sponge, algae, other microorganisms produce diverse bioactive compounds. Antimicrobial agents from Marine organisms such as brominated alkaloids obtained from marine sponges, may produce potential antimicrobial activity.

Multidrug-Resistant Pathogens: multidrug-resistant (MDR) pathogens are microorganisms including bacteria and fungi, that have developed resistance to multiple antimicrobial agents they can cause in infections that are difficult to treat using conventional antimicrobial drugs. Some bacteria are resistant to many different antibiotics they are multidrug resistant, and multidrug resistant bacteria can be difficult to treat and facilitate spread of antibiotic resistance a bacteria can have several resistance genes each providing resistance to a particular -antibiotics. the clustering of resistance genes frequently takes places on short DNA fragments is called plasmids. the development of antimicrobial resistance is associated with several mechanisms including enzymatic drug inactivation, modification of drug targets, reduced membrane permeability, active efflux pumps, and biofilms formation. These mechanisms produce pathogens to survive antimicrobial exposure and contribute to persistent infections. Multidrug-resistance generally defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories relevant to the organism.

1.Staphylococcus aureus(MRSA):It is a very common germ about one out of every three people have the germ on their skin or in their nose this organism does not cause problems for most of the people, it is a gram-positive bacteria, staphylococcus aureus was reported in1961, within the one year of methicillin introduced in 1960.(MRSA) methicillin-resistant staphylococcus

aureus is a type of bacteria that is resistant to several antibiotics, although anyone get a MRSA infection the risk increase for people with hospitalizations and skin contact with other such as in contact sports, and exposure to crowded and unhygienic places, causes sepsis or death, the symptoms of an S.aureus infection including MRSA depends on the part of the body that is infected, broken skin such as cuts, most staphylococcus aureus and MRSA skin infections red, swollen, painful, warm to the touch accompanied by a fever. And important complications are MRSA infection can cause serious problems in and outside of healthcare settings, including pneumonia (lung infections), blood stream infections, surgical site infections, sepsis may produce in the body's extreme response to an infection (if left untreated),death(if left untreated).MRSA is one of the most widely studied organisms in natural antimicrobial and nanoparticles delivery system formulations, it has been antibiofilm activity, MRSA is a specifically major resistant form of S. aureus its methicillin resistant is primarily associated with the *mecA* gene, less commonly, *mecC* which encodes an altered penicillin-binding protein called PBP2a.this protein has reduced affinity for beta-lactam antibiotics, allowing the bacterium to continue synthesizing its cell wall despite exposure to these drugs.

2.Pseudomonas aeruginosa is a gram-negative bacteria it can present in soil water, moist environment it rarely harms healthy people, but it can cause severe and life-threatening infections in people with weakened immune systems, and it can be resistant to antibiotics, making this infections difficult to treat, and also cause urinary tract,lung, blood .it can spreads contact with contaminated surfaces or equipment, and exposure in soil or water. Properties of MDR pathogen when it develop resistance to atleast three or more classes of antibiotics, nanoparticles delivery systems developed intrinsic resistance low outer membrane permeability its outer membrane less permeable than that of other bacteria, then severely restricting antibiotic entry. And efflux pump systems that actively pump out any antibiotic that manage to penetrate the cell. P. Aeruginosa is highly proficient at forming thick, sticky biofilm form that physically blocks antibiotics and immune cells.

3.Klebsiella pneumoniae :it is a gram -negative bacterium, may cause pneumonia, urinary trach infections and meningitis, most of the antimicrobial properties of different natural compounds and antibiofilm against K .pneumoniae , it is anaerobic bacteria causes severe pneumonia, particularly in ventilated patients, and klebsiella is now resistant to many antibiotics including one of the latest antibiotic-carbapenem, then Carbapenemase-resistant klebsiella pneumoniae is very difficult to treat. nano formulations design drug-loaded or metal-oxide nano formulations

and biosynthesis followed by culture preparations and metal ion reduction and biofilm formation. Clinically important to resistance to mechanisms,

4.Acinetobacter baumannii: it is a gram-negative aerobic, non-motile because lack of flagella and many biofilm forming bacteria, the process is mediated by flagella however A. baumannii this process seems to be by pili, it can be present in a soil, water, and survive long periods on dry hospital surfaces (nosocomial).pathogens produce specialized enzymes that physically break down or chemically alter the antibiotic molecule, neutralizing its therapeutic power. example superbugs like klebsiella pneumoniae or Acinetobacter baumannii produce Carbapenemases or beta-lactamases. these enzymes act like scissors, snipping apart the chemical rings of vital ,last-resort drugs like carbapenems and penicillins, treating a multidrug-resistant(MDR) Acinetobacter baumannii infection requires specialized, aggressive medical management because this pathogen is resistant to standard antibiotics, and bacteria are master adaptors, single-drug therapies often fails or trigger further resistance then combination therapy using the following specialized options, example: Sulbactam combinations at the given high dose sulbactam is cornerstone for treating A. baumannii while traditionally used to back bacterial enzymes, sulbactam uniquely acts as a direct bacterial killer against Acinetobacter.

5.mutidrug-resistant fungal pathogens are a growing global health crisis. Primarily azoles, polyenes, and echinocandins, when fungi develop reistance to one more of these classes, treatment options become severely compromised. And MDR fungal pathogens candida auris it is a critical priority pathogen these are invasive hospital-acquired infections like blood stream, wound, and ear infections with high mortality rate, many isolates are MDR the majority show resistance to fluconazole (azoles). And which are the high-priority pathogens like Nakaseomyces glabrata it also called as Candida glabrata these are naturally exhibit reduced susceptibility to azoles and repeatedly infects elderly people, it can be produced efflux pump overexpression and biofilm formation, genomic plasticity and target site alterations

Nanoparticle-based delivery systems

Nanoparticle delivery systems are engineered nanoscale carriers ranging 1-200nm designed to transport therapeutic agents improve the solubility, protect the payloads from premature degradation, and achieve controlled or site-specific release, important parameters are ;1. Physicochemical parameters *particle size and size distribution

Nanoparticles can function as drug carriers or, in certain formulations, as antimicrobial agents themselves. Important platforms include:

Polymeric nanoparticles: PLGA-based systems can encapsulate active compounds and provide controlled release.

Liposomes: Lipid-based carriers that can improve the delivery of selected antimicrobial agents.

Metallic and metal-oxide nanoparticles: Silver, zinc oxide and other materials may exhibit antimicrobial activity through mechanisms such as membrane damage and oxidative stress.

Natural-product-loaded nanocarriers: These formulations may improve the stability, delivery and local availability of phytochemicals.

The selection of a carrier should consider the physicochemical properties of the active compound, intended administration route, compatibility, toxicity and required release profile.

Development and Optimization

A systematic formulation-development approach is necessary to identify suitable nanoparticle characteristics. Critical formulation variables may include polymer concentration, drug-to-polymer ratio, stabilizer concentration, solvent composition and preparation conditions.

Design of Experiments (DoE), including factorial designs and response-surface methodologies, can be used to evaluate the effects of independent variables and their interactions. Important responses include particle size, polydispersity index, zeta potential, encapsulation efficiency, drug loading and in-vitro release.

The optimized formulation should demonstrate reproducible manufacturing characteristics, adequate physicochemical stability and acceptable biological safety

Characterization and Biological Evaluation

The developed nanoparticles should undergo comprehensive evaluation.

Particle size and polydispersity index: Assess particle dimensions and size distribution.

Zeta potential: Evaluate surface charge and potential colloidal stability.

Morphological analysis: Use suitable microscopy techniques to examine particle shape and structure.

Encapsulation efficiency and drug loading: Determine the proportion of active compound incorporated into the carrier.

In-vitro drug release: Investigate release kinetics under appropriately justified experimental conditions.

Antimicrobial activity: Determine minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC), where applicable.

Antibiofilm activity: Assess inhibition of biofilm formation and activity against established biofilms using suitable validated assays.

Safety evaluation: Investigate cytotoxicity, hemocompatibility where relevant, and other route-specific safety endpoints.

Comparisons among the free compound, blank nanoparticles and compound-loaded nanoparticles are essential to determine whether the carrier provides a measurable improvement in antimicrobial performance.

Challenges and Future Perspectives

Despite their potential, nanoparticle-based antimicrobial systems face challenges involving toxicity, manufacturing scalability, batch-to-batch reproducibility, stability, biological distribution and regulatory requirements. Laboratory antimicrobial activity does not necessarily predict clinical efficacy. Further studies should establish pharmacokinetic and pharmacodynamic relationships, in-vivo efficacy, safety margins and the potential for resistance development. Standardized experimental protocols and appropriately designed clinical investigations will be essential for translating promising formulations into practical therapeutic applications.

Strengths of the Review

This review brings together several connected aspects of nanoparticle-based antimicrobial research, including natural and microbial-derived compounds, important MDR pathogens, carrier selection, formulation optimization, physicochemical characterization and biological evaluation.

It emphasizes the need to distinguish the activity of a free compound from the effects of a blank carrier and a compound-loaded formulation. It also highlights the importance of evaluating antibiofilm activity and biological safety alongside conventional antimicrobial endpoints.

The discussion of polymeric, lipid-based and inorganic nanoparticle platforms provides a framework for selecting formulations according to the properties of the active compound and the intended application.

Limitations of the Review

This article is a narrative review and does not present original experimental findings or a quantitative synthesis of published data. The discussion is based on the references included in the manuscript, and a formal systematic search and study-selection process has not been documented.

The available evidence is not uniformly applicable to all natural compounds, nanoparticle platforms, bacterial pathogens or fungal pathogens. Differences in experimental methods, formulation characteristics and biological endpoints may limit direct comparisons between studies.

Furthermore, the review does not establish the clinical effectiveness or safety of any specific nanoparticle formulation. Additional literature verification and a more detailed evidence comparison are necessary before making formulation-specific conclusions.

CONCLUSION

Antimicrobial compound-loaded nanoparticles represent a promising research direction for improving the delivery of natural and conventional antimicrobial agents against MDR pathogens. PLGA nanoparticles and other nanocarriers may improve compound stability, regulate release and enhance antimicrobial or antibiofilm activity. A systematic approach integrating formulation optimization, physicochemical characterization, microbiological evaluation and safety assessment is necessary to establish their advantages. Future research should prioritize reproducibility, clinically relevant testing and translational feasibility.

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