World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-5, December 2021
ISSN: 2749-3644

A REVIEW ON NANOPARTICLES COMBINED ANTIBIOTICS IN SUPPRESSING BACTERIAL RESISTANCE

Rita N. N. Rammo
Biology Department, College of Science, University of Kirkuk, Kirkuk, Iraq.
Corresponding E-mail: rita.rammo@uokirkuk.edu.iq

Article history:

Received: October 20th 2021
Accepted: November 20th 2021
Published: December 30th 2021

Abstract:

Recent World Health Organization reports put much emphasis on the issue bacterial resistance to antibiotic therapy. Multi-drug resistance (MDR) h prompted researchers for alternative to monotheraputic approach introducing nanotechnology that involve in their diverse sense – materi (metals / metal oxides), synthesis (organic / phytogenic) and synergis dynamical interaction. Toxicity in host cells emerged as limitation to tl approach. Green nanotechnology with the ease of employment is hoped to less toxic but need to be researched further with emphasis on *in-vivo* arena gain acceptability. This review is intended to shed a light on MDR organisı and elimination strategies and current approaches of nanotechnologies that a utilized in the path to eradicate MDR especially the combinational therapy synthetic or green NPs with antibiotics.

Keywords: Antibiotic-resistance mechanisms, Combination therapy,Nanoparticles, Synergism, Green nanotechnolog

INTRODUCTION

The problem of multi-drug resistant organisms has become an immense issue of concern to human health that recent reports of WHO are concerned with [1]. Scientific laboratories have dealt with this issue in versatile approaches. The main concern is tailored toward eradication of bacterial resistance by the assumption of basic principles in conjunction with current emerging technologies such as nanotechnology [2] One major field of research is adapting plant natural antibacterial substances since medicinal plants are known for their ability in strengthening of immune system with prophylaxis potential in fighting infectious diseases [3]. A rational perspective need to be realized for the design of metal and plant based antimicrobials. With the expectation of green nanotechnology and relevant combinational therapy adjuvant to antibiotics be explored as alternate modern procedure in the combat against MDR organisms [4].

Other gigantic field of research is applying nano-particulate systems as therapeutic option for treating MDR bacteria [5,6]. Bulk of the work over the last two decades is dedicated in its major theme to *in-vitro* utilization of nanoparticles and their technology regarding synthesis, physicochemical properties etc. as feed input data and exploring issues such as toxicity, bio-film, stability, etc. as knowhow output reality [7,8]. Synergistic interaction between co-antibiotic regimes [9,10] and synergism efficacy of adjuvant nanoparticles with antibiotic regimes are both targeted toward lessening the danger in the confrontation to bacterial multidrug resistance [11, 12, 13]. Recent field of interest in MDR and biofilm is focused on the use of plasmid-carrying bacteria as evolutionary adaptation to antibiotic treatment [14].

The aim of this review was to look at the very recent outline of the conduct of nanoparticles when combined with antibiotic as vehicle to counteract bacterial resistance and to draw some characteristic features that shape the forthcoming research work in the mandate of living well.

MULTI-DRUG RESISTANT ORGANISMS

Mechanism:

Resistance of bacteria to antibiotic are basically divided into two types intrinsic and /or acquired resistances. The intrinsic type has to do with the morphology of a particular bacterium and depends on its biological properties for example E. coli bacteria shows intrinsic resistance to vancomycin [15]. The acquired type occur as a result of the acquisition by the bacteria to the resistance genes, mutant chromosomal DNA and combined mechanism of both. Bacterial biofilm formation also contribute to antimicrobial activity. These mechanisms are illustrated in Figure 1.

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-5, December 2021
ISSN: 2749-3644

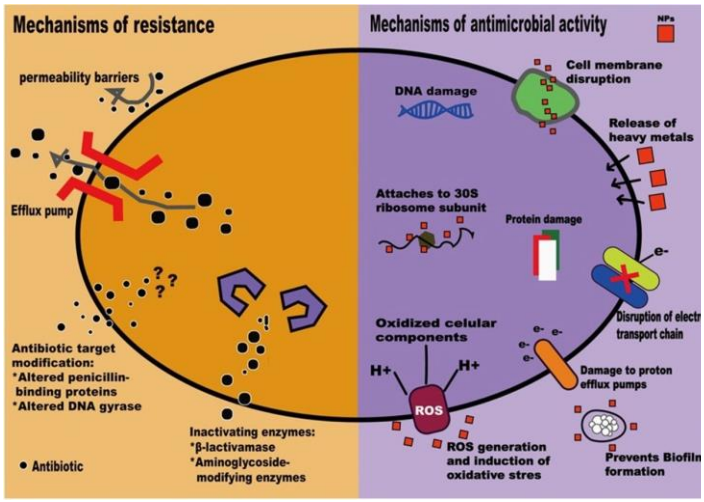

Figure 1. Multiple mechanisms of resistance(left) and antimicrobial activity(right) in bacteria.

Details of mechanism of resistance involve (a) activation of efflux pumps that remove antibiotics from bacteria and (b) inactivation enzymes which degrade the antibiotics. As to the mechanism of antimicrobial activity which include biofilms resulted from bacterial invasion are composed of complex polymeric matrixes synthesized by polysaccharides that are able to shield the embedded organism against antimicrobial agents[16]. Biofilm formation also contribute in delaying the penetration of antibiotics, genetic material exchange between biofilms and the alteration in the metabolism of bacterial cells [17].

Elimination strategies:

Many approaches are being involved in the quest for combating bacterial resistance and essentially along the following lines:

I. Traditional antibiotic combination therapy.
II. Nanoparticulate systems.
III. Natural phyto (green) compounds NPs.

The activity of antibiotic combined therapy to counteract microbial resistance has been widely used for treating infections of high mortality rates. This strategy is used when mono therapy show limitations: in potency ; in toxicity ; and in weak penetration and in turn hinder efficacy [18]. Reasons for the combinational therapy include the increase of antibiotic activity by the utilization of synergistic effect, the prevention of emerging resistance, the facilitation of antibacterial activity against microorganisms forming biofilms, the penetrational efflux of antibacterial agents into cell membrane and the inhibition of toxin and enzyme production [19]. Details of the other strategies in the following sections.

Paradigm of adjuvant nanoparticles

Recent advances in nanotechnology particularly in the field of engineering nanoparticles with suitable physicochemical properties as models for drug enhanced delivery are considered as promising solution for targeting resistant organisms [20]. Mechanisms of increased drug delivering capacity of antibacterial agents by encapsulation in nanoparticulates are: alteration in the efflux pump activity of the bacteria (Fig.1 left side) ; nanoparticles anti-biofilm formation activity (Fig.1 right side) ; and increased penetration of NPs through biofilm structure [21].

The organic route of drug delivery system of NPs include liposome, polymeric micelle, polymeric nanoparticles and solid lipid nanoparticles. These exhibit the advantage of handling either hydrophobic or hydrophilic drugs, biodegradability and low toxicity ; but lack long shelf life, poor stability at unconditioned temperatures and less effective encapsulation [22].

The metal or metal oxide NPs route of drug delivery system include the release of metal ions ready to be absorbed by cell membrane ; each type of metal ion possess different sensitivity to microorganisms depending on their oxidation states. This dependency however dose not play a key role in bacterial inhibition which implies that other factors need to explored such as the pH of lipid vesicles that could be the reason in low antimicrobial activity [23]. Therefore the contribution of metal ion release may not possibly be the prevailing mechanism of bacterial inhibition and standardized testing conditions are needed for each type of nanoparticles for absolute evaluation. The WHO guidelines define adult daily acceptable concentration for each metal ion [24]. When the consumption of metal ions is more than therapeutic dose, it may lead to adverse effect on normal cells. Therefore evaluation of toxic effect of NPs are needed in regard of slowing metal ion release by the introduction of nanocomposites with inorganic / organic doping compounds for controlled release of metal ions thereby reducing toxicity [25]. Wang *etal*. (2017) [26] attributed toxicity of NPs to the production of creative oxygen species (ROS) (see Fig.1 right side) which inhibits bacterial growth through lipid peroxidation, restricted amino acid synthesis and DNA replication.

Synergism versus toxicity

Synthesized nanoparticles are known to induce bacterial inhibition by their resistance mechanisms such as influx and biofilm. The use of NPs as an adjuvant to antibiotics in synergistic mode of interaction is to minimize the high dose effect that can carry more threat to host cells rather than the original infection caused by the bacteria itself. In this respect the procedures of chemically and biologically synthesized nanoparticles and their dosage levels together with antibiotic contribute to the rise of

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-5, December 2021
ISSN: 2749-3644

toxicological effects [27]. Thus mastering the function and mechanism of synthesized NPs with antibiotics bring about new strategies in the whelm of nano field technology in the endeavor to suppress resistance at lower dose and least toxicity. Many reviews and articles notably [28], [29], [30] and [31] are presented on synthesized nanoparticles combined with antibiotics in the synergistic interaction against biofilm formation. Excerpts of such data are given in Table 1.

Table 1. Synergy of metal / metal oxide NPs and antibiotics against biofilm formation in different bacterial species

Nanoparticle	Antibiotic	Species		Referenes
		G+	G-	
ZnO	Ceftriaxone Ceftazidime Gentamicine	Enterococus faecalis S. aureus	P. areuginosa E. coli Shigella	[26]
Ag	Amikacin Kanamycin oxytetrcycline Streptomycin	S. aureus	P. areuginosa E. coli	[27]
MgO , CaO	Rifampicin Neomycin	S. aureus	P. areuginosa	[28]
CeO2	Ciprofloxacin Levofloxacin Rifampicin	S. aureus	P. mirabilis E. coli	[29]

Green nanotechnology

Recent research work is directed on microbial and plant mixed nanoparticles in combination with antibiotics as least toxic carriers to host cells. Phyto-nanotechnologies are marked for their eco-friendly, non-toxic and single step synthetic process without the need to use toxic chemicals or sophisticated physical appliances. Basically, in plant assisted synthesis, the extract is mixed with metal solution for certain time at convenient temperature and specific pH. The features of the plant extract play the role of a stabilizing, capping, and reducing agent in the synthesis of metal nanoparticles owing to the presence of carbonyl and hydroxyl groups [3]. Parts of plant eg. root, stem, latex, leaves are used in the process as they contain components like phenols, flavinoids, proteins, vitamins which are supposed to act as a reducing agent. The ease of extraction of these biomolecules can further be benefited as capping and stabilized agent in preventing agglomeration. Moreover, the use of metabolites in the reduction process are supposed to bind to the surface of NPs thereby increase their activity [32]. The process of achieving stabilized nanoparticles from green synthesis depicted from [3] is given in Figure2.

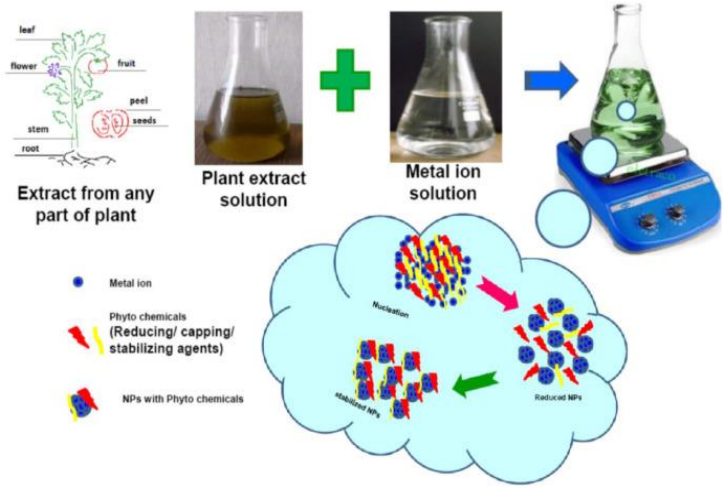

Figure 2. Green synthesis of metal and metal oxide NPs with markers of synthetic mechanism.

Bulk of research work and reviews are focused on the synthesis, inter- action mechanism and handling techniques of green synthesized metal and metal oxide nanoparticles [33, 34, 35, 36, 37].

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-5, December 2021
ISSN: 2749-3644

CONCLUSION

It is legitimate to claim that antibiotics since their discovery saved humanity from serious infectious diseases but not for long as being hindered with resistance even with new classes of antibiotics became of common practice in treatment. Monotheraputic approach thus become of limited value to confine MDR pathogens. Attention is being focused on the resistance of bacteria by the use of adjuvant therapy with antibiotics. The combinational antibiotic therapy due to their broad spectrum activity showed negative effect on natural micro-biome. Therefore researchers turned their efforts on nanotechnology to counteract MDR bacteria.

Nanoparticles with the novel physicochemical properties as bactericidal active compounds when used as adjuvant with antibiotics extended excellent *in-vitro* activity against MDR pathogens but hindered with toxicity issue to living cells. Green nanotechnological approach can be taken for further intensive investigations at the least of being toxic free and more biocompatible.

Recent *in-vivo* approach of confining MDR and biofilm issues may be dealt with adaptive antibiotic treatment facilitated by plasmid-carrying bacteria.

Acknowledgment: The author extends his appreciation to Prof. N. N. Rammo for valuable comments.

Conflict of interest: None

REFERENCES

1. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. Rev. Antimicrob. Resist. 20 (2014), 16
2. Baptista P.V. , Carvallo M.A. Nano – strategies to fight multidrugResistance bacteria – "a battle of the titans". Front. Microbiol. 9. 1441.Doi.10.3389/fmicb. 2018/01441
3. Ruddaraju L.K. , Pammi S.V.N. , Guntuku G. et al , A review on anti-bacterials to combat resistance from ancient era of plants and metals to present and future perspectives of green nano technological combinations. Asian J. Pharma. Sci. 15(1) (2020), 42-59
4. Mostafa A.A. , AlAskar A.A. , Almaary K.S. , Dawoud T.M. , Sholkam E.N.Bakri M.M. Antimicrobial activity of some plant extracts against bacterial strains causing food poisoning diseases. Saudi J. Biol. Sci. 25 (2) (2018), 361-366
5. Mba I.E. , Nweze E.I. Nanoparticles as thearaputic options for treating multi-drugresistant bacteria: research progress, challenges and prospects. World J. Micribio. & Biotechno. 37(108) (2021), 1-30
6. Lee N.Y. , Ko W.C. , Hsueh P.R. Nanoparticles in the treatment of infections caused by multidrug resistant organisms. Front. Pharmacol. 10 (2019), Article 1153
7. Munir M.U. , Ahmed M. , Usman M. , Salman S. Recent advances in nanotechnology aided materials as antibiotics substitutes. Inter. J. Nanomed. 15 (2020), 7329-7358
8. Gupta D. , Singh A. , Khan A.U. Nanoparticles as efflux pump and biofilm inhibitor to rejuvenate bactericidal effect of conventional antibiotics. Nano Resear.Lett. 12 (2017), 454
9. Rammo R.N.N. Evaluation of some antibiotics in combination activity againstisolates of *Staphyococcus aureus* and *Pseudomonas aeruginosa.* J. Al Nahrain Univer. Sci. 17(4) (2014), 174-179
10. Magihara M. , Crandon J.I. , Nicolau D.P. The efficacy and safty of antibiotic combination therapy for infections caused be G+ and G- organisms. Expert Opin. Drug Saf. 11(2) (2012), 221-233
11. Kankala R.K. , Lin N.Z. , Lee C.H. Combating antibiotic resistance through the synergistic effects of mesoporous silica –based hierarchical nanocomposites. Nanomater. 10 (2020), 597
12. Baker S. , Pasha A. , Satish S.H. Biogenic nanoparticles bearing antimicrobial activity and their synergistic effect with broad spectrum antibiotics: emerging strategy to combat drug resistant pathogens. Saudi Pharma. J. 25(1) (2017), 44-51
13. Gupta A. , Saleh N.M. , Das R. , Landis R.F. Synergistic antimicrobial therapy using nanoparticles and antibiotics for the treatment of multi-resistant bacterial infection. Nano Futures. 1(1) (2017), 015004
14. Zhang P. , Mao D. , Gao H. *et al.* Colonization of gut microbiota by plasmid carrying bacteria is facilitated by evolutionary adaptation to antibiotic treatment. ISME J. (2021)https://doi.org/10.1038/s41396-021-01771-x
15. Cold H.S. Vancomycin-resistant entercocci: mechanisms and clinical observations. Clin. Infect. Dis. 33(2) (2001), 210-219
16. Richards J.J. , Melander C. Small molecule approaches toward the non-microbial modulation of bacterial biofilm growth and maintenance. Antiinfect. Agents Med. Chem. 8(4) (2009), 295-314

World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-5, December 2021
ISSN: 2749-3644

17. Khameneh B. , Diab R. , Ghazvini K. , Bazzaz B.F. Breakthroughs in bacterialresistance mechanisms and the potential ways to control them. Microbial Pathogensis. 95 (2016), 32-42
18. Kon K. , M. Rai Antibiotic resistance mechanisms and new antimicrobial approaches. Academic Press, USA (2016)
19. Cheesman M.J. , Ilanko A. , Blonk B. , Cock I.E. Developing new antimicrobial therapies: are dynergistic combinations of plant extracts/compounds with conventional antibiotics the solution?Pharmacogn Rev, 11 (22) (2017), pp. 57-72
20. Eleraky N.K. , Allam A. , Hassan S.B. , Omer M.M. Nanomedecine fight against antibacterial resistance: an overview of recent pharmaceutical innovations. Pharmaceutics. 12(2) (2020), 42
21. Diab R. , Khameneh B. , Joubert O. , Duval R, Duval R. Insights in nanoparticle bacterium interactions: new frontiers to bypass bacterial resistance to antibiotics.Curr. Pharm. Des. 2(8) (2015), 4095-4105
22. Huh A.J., Kwon Y.J. "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J. Control Rel. 156 (2011), 128-145
23. Zhu X., A.F. Radovic-Moreno, Wu J., R. Langer, Shi J. Nano medicine in the management of microbial infection-overview and perspectives. NanoToday. (4) (2014), 478-498
24. World Health Organization (WHO) guidelines for drinking-water quality. http://www.who.int/water_sanitation_health/waterquality/guidelines/chemicals/zi-nc/en/.
25. Stankic S., Suman S., Haque F., Vidic J. Pure and multi metal oxide nanoparticles: synthesis, antibacterial and cytotoxic properties. J. Nanobiotechnology. 14 (1) (2016), 73
26. Wang L., Hu C., Shao L. The antimicrobial activity of nanoparticles:present situation and prospects for the future. Int. J.Nanomedicine. 12 (2017), 1227-1249
27. Vasanth S.B., Kuria G.A. Toxicity evaluation of silver nanoparticles synthesized by chemical and green route in different experimental models. Artif. Cells Nanomed. Biotechnol. 45 (8) (2017), 1721-1727
28. Rammo R.N.N. The role of MgO and CaO nano-particles on Staphylococcus epidermidis isolated from catheter indwelling patients.Indian J. Pub. Heal. Res. & Devlo. 10(8) (2019), 2182-2187
29. Rammo R.N.N. Resistance to biofilm formation by synergisticcombination of cerium oxide nanoparticles with antibiotics against wound/urinary catheter isolated bacteria. Pakistan J. Med. & Heal. Sci.15(4) (2021), 950-954
30. Nadeem M., Abbasi B.H. , Younas M. , Ahmad W. , Khan T. A review of the green synthesis and anti-microbial applications of gold nanoparticles.Green Chem. Lett. Rev. 10 (4) (2017), 216-227
31. Patra J.K., Baek K.H. Antibacterial activity and synergistic antibacterial potential of biosynthesized silver nanoparticles against food borne pathogenic bacteria along with its anticandidal and antioxidant effects. Front. Microbiol. 8 (2017), 167
32. Abdelghany T.M. , Aisha M.H. , Mohamed A.R. , Al Abboud A. , Alawlaqi M.M. , Magdah A.G. , *et al.* Recent advances in green synthesis of silver nanoparticles and their applications: about future directions. A review. Bionanoscience. 8 (3) (2018), 5-16
33. Abo-Shama U.H. , El-Gendy H. , Mousa W.S. Synergistic and antagonistic effects of metal nanoparticles in combination with antibiotics against resistance strains of pathogenic microorganisms. Infect. Drug Resist. 13(2020), 351-362
34. Barapatre A. , Aadil K.R. , Jha H. Synergistic antibacterial and antibiofilm activity of silver nanoparticles biosynthesized by lignin-degrading fungus. Bioresour. & Bioprocess 3 (2016), 8
35. Kotrange H. , Najda A. , Bains A. Gruszecki R. *et al.* Review: Metal and metal oxide nanoparticles as a novel antibiotic carrier for the direct delivery of antibiotics. Antibiotics Int. J. Mol. Sci. 22 (2021), 9596
36. Mohamad N.A.N. , Arham N.A. , Jai J. , Hadi A. Plant extract as reducing agent in synthesis of metallic nanoparticles: a review Adv. Mater. Res, 832 (2013), 350-355
37. Vijaya raghavan K., Ashok kumar T. Plant-mediated biosynthesis of metallic nanoparticles: a review of literature, factors affecting synthesis,characterization techniques and applications. J. Environ. Chem.Eng. 5 (5) (2017), 4866-4883