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Antibiotics at the crossroads – Do we have any therapeutic alternatives to control the emergence and spread of antimicrobial resistance?

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Abstract:

Antibiotics once regarded as magic bullets are no more considered so. Overuse of antibiotics in humans, agriculture, and animal husbandry has resulted in the emergence of a wide range of multidrug-resistant (MDR) pathogens which are difficult to treat. Antimicrobial resistance (AMR) is a serious global health problem associated with high mortality in the era of modern medicine. Moreover, in the absence of an effective antibiotic, medical and surgical interventions can highly become a risk. In recent times, the decreased incline of pharmaceutical industries toward research and development of newer effective antibiotics to fight this MDR pathogens have further fuelled the scarcity of antibiotics, thus the number of antibiotics in the pipeline is extremely limited. Hence it is high time for the development of new strategies to fight against dangerous MDR pathogens. Currently, several novel approaches explored by scientists have shown promising results pertaining to their antimicrobial activity against pathogens. In this article, the authors have summarized various novel therapeutic options explored to contain AMR with special attention to the mechanism of action, advantages, and disadvantages of different approaches.

Keywords:

Antibiotic resistance, herbal medicine, microbiome, nanoparticles, phage therapy, probiotics, quorum sensing

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Introduction

Increasingly recognized antimicrobial resistance (AMR) in the modern world is a global health concern. Without effective antibiotics, treating infections has become extremely difficult. Furthermore, medical and surgical interventions can highly become a risk.[1] Though AMR is a natural phenomenon, acceleration of development of resistance to many folds is contributed by multiple factors. Figure 1 depicts common contributing factors for the development of AMR. Overuse/misuse of antibiotics in humans, animals, and agriculture, inadequate infection control practices, increased use of invasive devices, inadequate facilities for rapid diagnosis of infections, increased national and international travel are the key contributing factors for the rapid emergence of drug-resistant pathogens.[1,2] In addition, the decreased incline of pharmaceutical industries toward research and development of newer antibiotics has led to the scarcity of newer effective antibiotics to treat infections caused by multidrug-resistant (MDR) pathogens.[3] Bacteria have developed AMR by several mechanisms. Among those are enzymatic drug inactivation/modification, altered target production, decreased drug permeability, increased efflux due to over-expression of efflux pumps, bypassing

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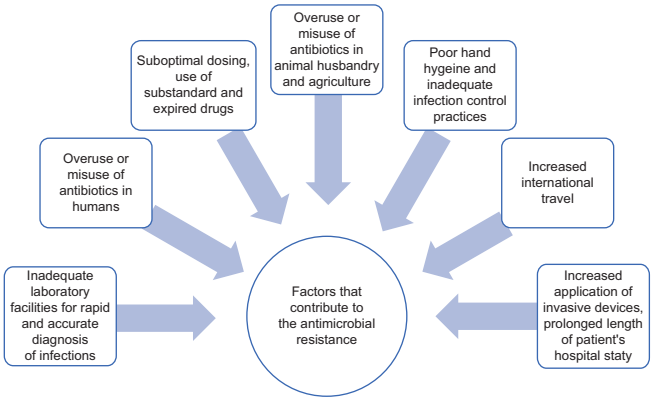

Figure 1: Contributing factors for emergence of antimicrobial resistance

of metabolic pathway/overproduction of target, target mimicry, and others.[4] Biofilm formation and quorum sensing (QS) are the more recently recognized drug-resistant mechanisms, often triggered by exposure to antibiotics.[5] Antibiotics are no more regarded as magic bullets, rapid and continuous emergence of drug resistance may sooner lead to "pre-antibiotic" era if the problem is not taken seriously.[6] This has triggered initiatives globally to develop novel and more effective strategies to combat drug resistance menace. Currently, several promising strategies, alternative to antibiotic therapy are in different stages of clinical trials, showing promising signs, few may sooner be approved for human therapy.[7] Figure 2 depicts the common novel strategies which are currently in different stages of clinical trials. The present article outlines the latest alternative approaches to antibiotic therapy to control the emergence and spread of AMR with a special focus on the mechanisms, advantages, and disadvantages of various novel approaches.

Nanoparticles

Nanomaterials have at least one dimension in the nanometer scale range (1–100 nm), as a result, there is a considerable difference in their physical and chemical properties from those of bulk materials.[8] Nanoparticles (NPs) have several distinct properties such as ultra-small size, high surface to volume ratio, enhancement of drug solubility and stability, easy way of synthesis, biocompatibility with target agents, and their modulated release that can be controlled by stimuli such as heat, temperature, and pH.[8,9] In addition, they have microbicidal properties which have led to the new hope in utilizing NPs to combat drug-resistant pathogens.[10] NPs have shown promising alternative solutions as they not only have microbicidal effects by themselves but also can act as carriers for delivering antibiotic molecules and natural antimicrobial compounds.[8] Several NPs such as Ag-NPs, Zn-NPs, Au-NPs, Al-NPs, Cu-NPs, Ce-NPs, Cd-NPs, Ti-NPs, etc. and metallic oxide

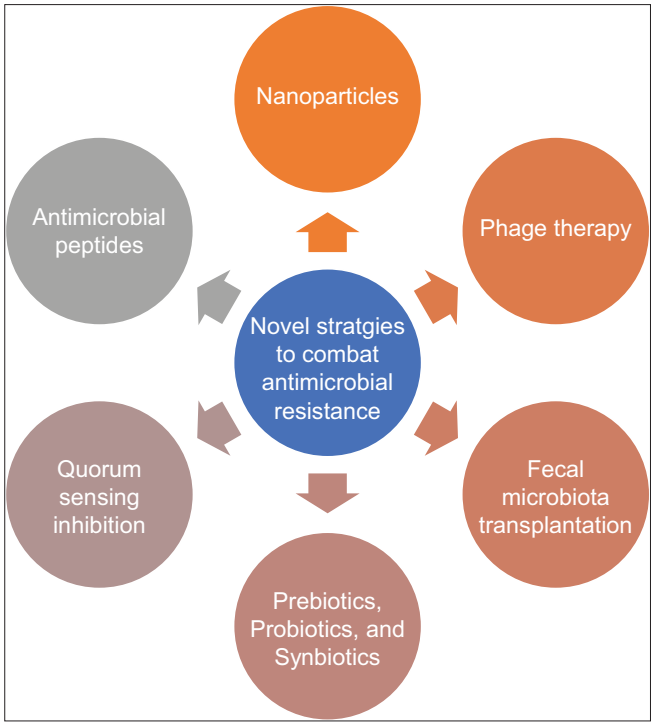

Figure 2: Novel strategies to combat drug resistance menace

nanoparticles (NPOs) Such as ZnO-NPs, CdO-NPs, CuO-NPs, TiO_2-NPs, and Au_2O_3-NPs have shown bactericidal effects.[8,11,12] NPs are of extreme use to tackle MDR pathogens, as they exert antibacterial activity through multiple mechanisms unlike antibiotics which have one specific target.[8] Induction of intracellular effects such as interaction with DNA, cell membrane, bacterial proteins, RNA, etc., direct cell wall damage, oxidative damage to cellular structures by generation of reactive oxygen species (ROS), inhibition of biofilm formation, and activation of both innate and adaptive immune responses are the well-recognized killing mechanisms generated by NPs.[13-16] Figure 3 shows the antibacterial mechanisms of NPs and NPOs. The oxidative stress, metallic ion release, and nonoxidative mechanisms are still the most recognized antibacterial mechanisms induced by NPs.[8] The production of ROS namely superoxide (O^-_2), hydroxyl radical (OH^-), hydrogen peroxide (H_2O_2), and singlet oxygen $^1[O_2]$ results in disturbed redox homeostasis resulting in oxidative stress, affecting membrane lipids and altering the structure of DNA and proteins, and thus significantly enhance bacterial death.[17] Several studies have demonstrated microbicidal effect of Ag-NPs, Au-NPs, ZnO-NPs, and TiO_2-NPs against MDR pathogens such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Methicillin-resistant Staphylococcus aureus, and Enterococcus faecalis* by oxidative stress through production ROS.[18-20] Non-oxidative killing mechanisms involve interference of NPs with cell wall and cell

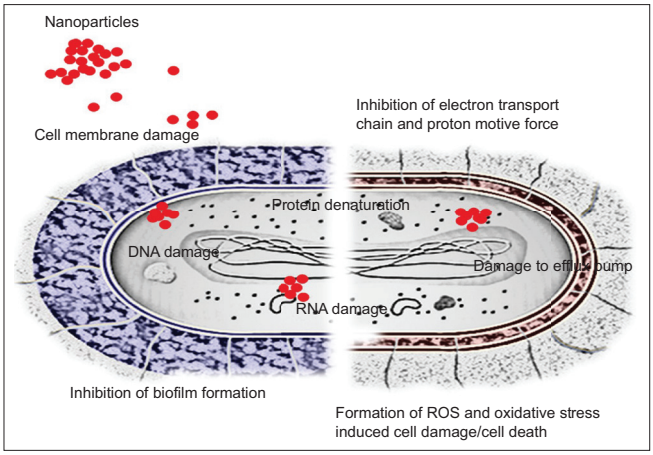

Figure 3: Antibacterial mechanisms of nanoparticles and NPOs

membrane which act as defensive barriers by protecting cell and its contents from the environmental insult.[8] A study has demonstrated the accumulation of NPs in the cell wall leads to formation of irregularly shaped pits, perforation, and disturbance in metabolic process.[21] Another study by Joost *et al*. demonstrated that treatment with TiO_2NP causes increased cell volume and thereby result in membrane leakage and cell death.[22] Numerous experimental studies have also demonstrated that NPs are capable of inhibiting biofilm formation and survival of microorganisms by disruption of cell membrane.[23-25]

Besides as broad-spectrum microbicidal agents, utilizing NPs as vectors to deliver antimicrobial agents has greatly enhanced their effectiveness.[8,9,26] The most attractive characteristic of NPs is their ability to deliver a wide range of therapeutics, either bound to their large surface area or enclosed within the structure to the site of infection effectively and safely at a controlled rate of target delivery.[27] One of the obstacles associated with antibiotic therapy is their poor membrane transport. This limitation can be overcome by using drug-loaded NPs which can enter by endocytosis, thereby facilitate effective intracellular drug delivery.[8,10] Membrane penetration can also be achieved by using certain NPs such as Au_2O_3-NPs which are capable of interacting with surface lipids.[10] Furthermore, multiple antibiotics can be loaded with NPs and delivered, thereby a highly complex antimicrobial mechanism of action can be achieved to which bacteria are unlikely to develop resistance.[28] However, there are reports suggesting the development of resistance to Ag-NPs and also, exposure to NPs may enhance microbial tolerance to these NPs.[29,30]

Apart from drug delivery, NPs can also increase the potency of the antimicrobial agent passively by facilitating prolonged drug retention at the specific infection site or actively through surface conjugation with active molecules that bind to a certain target.[8,10] Therefore, designing an effective drug delivery strategy must carefully consider the balance between the surface modification interaction strength, the rate of compound release, and the stability of the conjugate.[10,31] Several researchers have investigated the conjugation of antibiotics to NPs to overcome their potential therapeutic limitation.[10] A study has demonstrated better achievement of minimum inhibitory concentration with the use of conjugated ampicillin, kanamycin, and streptomycin with gold NPs against both Gram-positive and Gram-negative bacteria compared to the use of these free drug counterparts.[32] Another study attempted to uncover the mechanism of action of vancomycin loaded Au-NPs against vancomycin-resistant *Staphylococcus aureus*.[33] The study proposed that only when the drug is conjugated with NPs could result in nonspecific multivalent interactions and anchoring of carrier to proteins involved in cell wall synthesis.[33] Furthermore, the authors concluded that the consequences of nonspecific binding of NPs has resulted in compromised membrane stability and subsequent cell death by demonstrating pits in the cells by visualization through transmission electron microscope.[33] Few researchers also have demonstrated the use of bimetallic NPs compared to single NPs enhances the efficacy of drug many folds against several MDR pathogens and also reduces the required therapeutic dosage.[34-36] Bimetallic NPs have shown improved electronic, optical, and catalytic properties compared to monometallic NPs.[37]

Despite the great potential of NPs to prevent and treat bacterial infections, several gridlocks pertaining to the short term and long term exposure of NPs to humans needs to be explored. Some of these include biocompatibility, the interaction of NPs/nanoantibiotics with cells, tissues, and organs, potential toxicity, clearance, and metabolism, apart from economic impact as the preparation of NPs is expensive.[10,38]

Phage Therapy

Bacteriophages (BPs) are viruses that can infect and kill bacteria without affecting human cells. They are ubiquitously found in the ecosystem; soil, water, oceanic and terrestrial surfaces and known to have controlled the growth and spread of bacteria since ancient ages. Phages are tiny particles made up of protein or proteo-lipid capsids enclosing fragments of nucleic acids (either DNA or RNA, most often DNA) and are present wherever bacteria are present in the environment.[39] Phages can be said to be virulent (lytic) or temperate (lysogenic) based on their developmental life cycle.[39] The virulent phages, capable of bacterial lysis are relevant in the context of BP therapy.[39] Early evidence of antibacterial activity of phages was reported

by the English bacteriologist Frederick Twort, and by the French-Canadian microbiologist Felix d'Hérelle in 1915 and 1917, respectively.[40] In 1919, following a successful phage therapy in treating a boy who presented with bacterial dysentery, phage therapy got recognized immediately as a therapeutic option in treating bacterial infections.[41] However, subsequently, with the discovery of penicillin and other antibiotics and their worldwide marketing, the use of phages as potential therapeutic agents lost attention.[41] The increasing global health burden of infections, especially caused by MDR pathogens in the 21st century incited renewed interest in phage therapy as an additional tool to treat bacterial infections.[39] BPs have several advantages over antibiotics to treat bacterial infections. Firstly, at least one BP is available against any one type of bacteria. In this regard, they are more effective than antibiotics, though there are some antibiotics that have a wide spectrum of activity. However, there is no single antibiotic available that can kill all bacteria that exist.[42] Secondly, BPs have a narrow spectrum of activity and kill only the bacteria that they recognize. This avoids the most important problem related to antibiotic therapy i.e. destruction and elimination of normal microbiota of skin, gut, and oral cavity, easy colonization and overgrowth of pathogen bacteria, and the emergence of drug-resistant bacteria.[43] A study demonstrated bacterial specificity of BPs by administering a cocktail of nine T4-like *Escherichia coli* BPs to 15 healthy individuals. After 2 days of the administration, they could isolate the phages in the feces of all the treated individuals and there was no evidence of alteration in their microbial flora.[44] Additionally, BPs have many more advantages over antibiotics. BPs are regarded as safer, cheaper, and better tolerated since they infect and replicate only in target bacterium without affecting human cells.[45] Furthermore, BPs are easy to administer, do not require repeated doses unlike antibiotics since they can remain in the human body for up to several days.[42] Hence, generally few doses are enough to achieve optimum concentration at the site of infection. Unlike antibiotics, the effect of BPs is limited to the site of infection and are capable of reaching bacteria residing in any organ or system of the human body, which is hard to be penetrated by antibiotics.[46] A recently recognized biofilm-mediated resistance, harder to counteract by antibiotics can be easily dealt with BPs modified by modern DNA technologies. Lu and Collins demonstrated the destruction of *E. coli* biofilms by using genetically engineered BPs. The study results were encouraging as genetically engineered BPs can attack simultaneously bacteria cell and biofilm matrix and reduce biofilm count almost to zero levels.[47] Besides, Edgar *et al*. demonstrated genetically modified BPs can be useful to fight against AMR.[48] Currently, several studies on human beings have shown the benefits of topical application of BPs in treating wound infections including diabetic foot infections.[49,50] Additionally, several randomized clinical trials (RCTs) have demonstrated the positive outcome of phage therapy to treat bacterial diarrhea and respiratory infections including in cystic fibrosis patients.[51-53] However, there are certain factors that limit the use of BPs in human therapy. Firstly, the available data of phage therapy in human trials are few and are from non-randomized and placebo control studies. Secondly, identification, isolation of specific phages, and therapeutic preparation of phages for human use are complicated.[54] It involves sequencing of phage genome and deletion of gene segments that might encode for integrase, antibiotic resistance, toxin production, and others. In addition, it requires formulation and stabilization of pharmaceutical product separately for each phage, that could lead to more expenses and time-consuming. This could demotivate pharmaceutical industries to conduct extensive research and phage preparation for human therapy.[42,55] Third, the potential possibility of the development of bacterial resistance mechanisms to phages cannot be ruled out. Modification of binding receptors, secretion of substances that interfere with the adhesion of phages to bacterial surfaces, interference with injection of phage nucleic acid, phage replication, and release may make phages ineffective.[56] Fourthly, phages by themselves may contribute to the development of drug-resistant bacteria and may result in the emergence of new, more resistant bacterial pathogens. Temperate/lysogenic phages may integrate into bacterial DNA and consequently may act as potential vectors for horizontal gene transfer and diffusion of resistant genes among bacterial pathogen by a phenomenon of transduction.[57] Finally, BPs and their products are foreign antigens and therefore the immune system may induce an immune response and reduce their effectiveness.[58] To conclude, the present pieces of evidence obtained through non-randomized trials are insufficient to allow the use of phages for human therapy. Furthermore, properly designed studies specifically targeted to solve the aforementioned problems are crucial before phages can be licensed for human therapy.

Quorum Sensing Inhibition

Quorum sensing (QS) is a cell-to-cell communication mechanism employed by the microbiome and it depends on microbial population density. The formation of high-density microbial population results in the generation of a sufficient number of small signaling molecules (autoinducers) that activate the expression of countless genes that control diverse functions such as biofilm formation, virulence, drug resistance, drug tolerance, production of siderophores, proteases, and others. Both Gram-positive and Gram-negative bacteria communicate through the QS mechanism but use different signaling molecules (autoinducers). N-acyl homoserine

lacton (AHL, also designated autoinducer-1, AI-1) molecules which are synthesized by LuxI-type enzyme are predominantly used by Gram-negative bacteria while auto-inducer peptides (AIP) are predominantly used by Gram-positive bacteria.[59] Since QS is involved in a wide range of bacterial virulence mechanisms including AMR, hypothetically QS inhibition (QSI) or quorum quenching seems to be a promising strategy to fight against various types of pathogens.[60] The phenomenon of quorum quenching causes the reduction of pathogens' virulence by interrupting communication-dependent pathogenicity induction through several mechanisms.[61] First, quenching molecules inhibit the production of signaling molecules such as AIP, AHL, etc. Second, by reducing the activity of QS molecules, and lastly, by the degradation of QS molecules.[61,62] With the increasing antibiotic resistance, researchers decipher the quorum quenching approach as a potential novel strategy to combat AMR. QS Signals produced by pathogens play a key role in biofilm formation. When QS signals reach a certain threshold, bacteria will secrete adhesion molecules involved in biofilm formation which occurs through several sequential phases namely attachment, micro-colony formation, maturation, and dispersion.[63] Biofilm consists of bacterial cells and an extracellular polymeric substance composed of proteins, polysaccharides, and DNA that may interfere with the penetration of antibiotics and immune cells, thus inducing antibiotic tolerance. Besides, the biofilm with high bacterial cell density and increased QS induces selection pressure that ultimately enhances the rate of development of resistant cells through genetic mutation and horizontal gene transfer.[61,62] Quorum sensing inhibition plays a dual role on bacteria by preventing biofilm formation and expression of virulent genes.[64] However, several challenges and limitations are associated with quorum quenching such as modulation in metabolic activity, decrease in the threshold for QSI activation, biofilm formation, QSI mediated increase of virulence, and disturbance of host-microbial flora, increase in resistance against QSI, etc., are the noted challenges that need to be extensively investigated.[65]

Antimicrobial Peptides

Anti-microbial peptides (AMPs) also regarded as cationic host defense peptides are a highly diverse family of small proteins with a varying number of amino acids.[66] A wide range of AMPs are naturally found among classes of life such as animals, plants, bacteria, yeast, and also, they have been synthesized in laboratories.[67] These AMPs found to have a variety of biological activities such as antitumor, anti-inflammatory, antibacterial, antifungal, antiviral, and antimitogenic activity, in addition to their ability to act as immune modulators.[67] Several studies have demonstrated the therapeutic activity of AMPs *in-vitro* and *in-vivo* against many bacteria.[68] AMPs are proven to be effective against MDR pathogens, hence they are potential candidates for combating AMR. AMPs possess several advantages; produce microbicidal activity in the micromolecular range, rapidly kill bacteria, and have low resistance selection. Furthermore, they demonstrate antibacterial action by interfering with multiple targets; alter the cell membrane, interfere with the formation of protein and cell wall, and others.[67] Human cathelicidin peptide (LL-37) was proven to be an effective AMP against both Gram-negative and Gram-positive bacteria in previous studies.[69,70] Additionally, it showed anti-biofilm activity against *P. aeruginosa, S. aureus*, and *A. baumannii*.[69,70] Colistin is a lost resort peptide antibiotic used against many Gram-negative bacteria especially MDR pathogens in the hospitalized patients. Currently, two colistin-derived AMPs namely AA139 and SET-M33, which act similarly to colistin are in the developmental stage, and have shown good activity against MDR pathogens *in-vitro* and *in-vivo* infection models.[71]

The major disadvantage of AMPs for systemic use is their susceptibility to degradation by proteolytic enzymes present in body fluids, i.e. intestinal mucosa, saliva, blood plasma, and others. This would directly affect their stability and pharmacokinetic profile. Recently, a newer class of peptides that have high specificity and potency, termed selectively targeted AMPs ("STAMPS") have been developed.[72] These STAMPs found to have significantly increased bactericidal activity against a specific pathogen without harming the microbiota because the technology utilizes two functionally independent peptide domains combined through a small linker; one peptide domain functions as killing moiety and other functions as high-affinity binding moiety.[73] Several STAMPs developed against Gram-negative bacteria such as *P. aeruginosa* and Gram-positive bacteria such as *MRSA, E. faecalis* have shown promising outcomes.[74-76] However, more clinical research still required in the development of targeted antimicrobial therapy.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) is a procedure intended to restore the microbiome by infusing stool from a healthy donor to a recipient who has a gut microbiota imbalance.[77] FMT delivery to the gut can be done either through endoscopy, nasogastric tube, or ingestion of the capsule.[78] FMT has been described long before in 1958 but it increasingly gained importance in the last decade for the treatment of many gut disorders.[79] Currently, FMT is an accepted treatment for recurrent *Clostridium difficile* infection (rCDI), also considered for treating inflammatory bowel diseases (IBDs).[78] The efficacy and safety of FMT for treating rCDI was

proved to be good by several RCT and case series.[80] These studies demonstrated the superiority of FMT over vancomycin therapy in treating recurrent CDI with a high-recovery rate of more than 90%.[80] Fischer *et al*. revealed a high cure rate (90%) of rCDI with FMT in patients who failed maximum antibiotic therapy.[81] Another study by Moayyedi *et al*. reported FMT to be superior to vancomycin or placebo therapy.[82] It has been suggested that imbalance in normal gut microbiota is associated with the pathogenesis of IBDs and FMT is beneficial to treat IBDs.[83] However, the efficacy of FMT was higher among rCDI compared to IBD patients, suggesting many other factors contributing to flare-up of IBDs apart from imbalance of normal microbiota.[84] Two recent RCTs have demonstrated 55% response to FMT treatment with 20%–30% remission among ulcerative colitis patients.[85,86] Furthermore, reports suggest flare-up of IBD in patients treated with FMT, and thus careful follow-up of these patients treated with FMT is crucial.[87] Apart from IBD and rCDI, FMT therapy was also evaluated and considered for treating several conditions such as autoimmune diseases, neurological diseases, nonalcoholic steatohepatitis, and inflammatory bowel syndrome.[78]

Selecting a donor for stool sample collection is quite challenging. In the United States, stool banks have emerged wherein stool sample from healthy donors was collected, processed, and preserved.[78] A young age healthy volunteers were selected as donors after thorough screening through history, physical examination, serum, and fecal tests for various infectious agents such as bacteria, viruses, and parasites.[88] These developments have enabled a number of advances in FMT therapy. First, FMT therapy by using stool from healthy donors was found to be more effective, less expensive, and less time-consuming compared to patient-directed donors. Secondly, the use of multiple healthy donors' fecal samples would enhance microbial diversity enormously in recipients.[78] In line with this, an RCT study demonstrated better remission in ulcerative colitis patients treated with multi-donor FMT.[86] However, it needs more studies to confirm this finding. Currently, FMT proved to be much effective in rCDI through RCTs and case series. However, certain facts such as long-term risks are unknown. Screening of donors through history taking and investigations may not reveal all future risks and diseases that might emerge in the donor at a later stage. Therefore, high-quality large-scale control trials are needed to understand FMT efficacy, potential benefits, and potential risks.

Probiotics, Prebiotics, and Synbiotics

The gut commensal flora designated as the microbiome is gaining importance and increasingly investigated to determine its role in the prevention of infection, inflammatory diseases, neurologic and immune development, and others.[89] The gut microbiome that plays a key role in human health is influenced by various factors including antibiotic use, nutrition fiber, animal byproducts, and environmental sources such as water.[90] These factors especially antibiotics and dietary changes cause disruption of the normal commensal flora and facilitate colonization by pathogens. The pathogens carrying antimicrobial-resistant genes (ARG) may transfer to normal flora and the accumulation of all ARGs within the microbiome is labeled as resistomes.[91] Subsequently, the gut normal flora carrying resistomes can act as a nidus for the transfer of resistant genes to pathogens. Furthermore, other stressors that cause mucosal damage may facilitate the spread of these drug-resistant strains systemically through the bloodstream. With the increase in the frequency of infections due to MDR pathogens globally, the gut microbiome and resistome modification particularly by nutritional modification using prebiotics, probiotics, and synbiotics appear to be an ideal approach for a possible reduction in drug-resistant pathogenic infection.[91]

Prebiotics are certain dietary compounds selectively fermented by microbiome in the human gut to produce metabolic byproducts such as short-chain fatty acids (SCFAs), butyrate, acetate, and propionate.[92] These byproducts, particularly SCFAs improve mucosal barrier functions in the gut by multiple mechanisms; provision of energy for enterocytes, upregulation of epithelial tight junctions, promotion of mucus production, and upregulation of regulatory T-cell functions to decrease inflammation.[91] In this way, prebiotics promotes the expansion of gut commensal flora and the reduction of the pathogenic population. Prebiotics are not systemically absorbed and are generally safe with minimal side effects such as flatulence, altered stool consistency, and abdominal cramping.[93] Earlier reports have demonstrated the benefits of prebiotics in different patients: reduction in gut inflammation in patients after ileal pouch-anal anastomoses, reduction in gastrointestinal symptoms in patients after hematopoietic stem cell transplantation, and reduction of inflammation in a patient with type 2 diabetes.[94-96] However, the research related to the use of prebiotics to manipulate microbiome and resistome is still in the infancy stage compared to probiotics. Moreover, conducting RCTs is challenging since the number of factors need to be controlled such as type of diet, fiber content, and amount of consumption, etc.[91]

In contrast to prebiotics, probiotics are live bacteria or fungi which have a beneficial effect on the human host when they are consumed in adequate amounts.[97] *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*

are commonly used/experimented probiotics to prevent *Clostridium difficile* infections, traveler's diarrhea, irritable bowel syndrome, postoperative infections, decrease eczema in children or allergic rhinitis, reduce risk of hepatic encephalopathy in cirrhosis patients, and elimination of *Helicobacter pylori* infection.[91,97] Probiotics benefit through several mechanisms: competitive exclusion of pathogenic bacteria, improving intestinal barrier function, production of antimicrobial substances such as bacteriocins, SCFAs, hydrogen peroxides, etc., and by boosting the immune system by improving local mucosal cell-mediated immunity, promoting the production of antibodies, and reducing epithelial injury.[97] Probiotics have certain additional advantages over prebiotics. First, probiotics are naturally found in food items such as yogurt, cheese, etc., in addition to commercialized products. Second, probiotics synthesize certain antimicrobial substances such as bacteriocins which can cause the destruction of pathogens and prevent biofilm formation. Lastly, probiotics are live bacteria, and they can physically occupy an epithelial niche and thereby inhibit colonization of the pathogen.[91,98] So far, probiotics are better explored compared to prebiotics for manipulating microbiome. Literature review shows mixed results and so strong recommendation for use of probiotics cannot be made.[91] One of the potential risks associated with probiotics is microbial contamination and the introduction of ARGs to the microbiome making them potentially dangerous pathogens.[91] Previous studies reported lactobacillus bacteremia associated with probiotic therapy in patients with central line or IBD.[99,100]

Synbiotics are a combination of both prebiotics and probiotics. It involves the administration of both metabolic precursors (prebiotics) and live microorganisms (probiotics). *Bifidobacterium*, *Lactobacillus*, and *S. baulardii* are the commonly used probiotics, while fructose-oligosaccharide or inulin are used as prebiotics.[91] Literature regarding the use of synbiotics in combating AMR is very limited. The two available studies reported no significant impact of synbiotics in countering colonization or eradication of MDR pathogens.[101,102] In one study, unexpected colonization with candida was observed following synbiotic therapy though candida was not included in the synbiotic preparation.[101] The colonization disappeared immediately after the cessation of the therapy. The exact reason for candida overgrowth was unknown, but it was believed that overgrowth of candida was supported by synbiotic preparation.[101] Another study demonstrated that there was no significant impact of studied synbiotic in preventing MDR colonization compared to placebo.[102] In conclusion, the strategy of microbiome modification through probiotics, prebiotics, and synbiotics is in the early stage. From the available studies, the microbiome modulation approach appears to be safe and well-tolerated by the study population. However, strong conclusions to recommend the use of probiotics, prebiotics, and synbiotic as an alternative strategy to combat AMR cannot be made and it requires further exploration.

Herbal Medicine

Herbal medicine involving the use of drugs derived from plants and plant extracts has been practiced since ancient times especially in developing countries.[103] Several essential oils extracted from plants possess antimicrobial properties. Moreover, they have low cytotoxicity and side effects, degrade quickly in water and soil, easy to prepare, and less expensive which makes them low-cost, environment-friendly alternatives to antibiotics.[103,104] A wide range of plants are known to have medicinal values. However, only 10% of them have been investigated scientifically. Therefore, there is a scope for researchers to explore these plants for their potential medicinal values.[103] In recent times, herbal medicines have been extensively explored to evaluate their ability to fight MDR pathogens. Herbal medicines like allopathic drugs are known to act by several mechanisms: disruption of the cell membrane, interaction with membrane proteins such as ATPases, inhibition of essential enzyme synthesis, coagulation of cellular contents, impairment of proton-pump function with leakage of ions, and others.[103] In addition, some herbal medicines such as lemongrass oil are known to inhibit bacterial biofilm formation.[105]

Herbal medicines are considered to be useful alternatives to treat MDR pathogenic infections, and it is believed that microorganisms cannot develop resistance to herbal drugs.[106] However, recent reports suggest that certain bacteria can counter the bactericidal or bacteriostatic effect of herbal medicines.[107] Nosocomial pathogens such as *P. aeruginosa, K. pneumoniae,* and *E. coli* have shown resistance to certain herbal drugs such as turmeric, unripe banana, and lemongrass.[106] Brown and Brown have isolated MDR strains resistant to ceftriaxone and tetracycline in garlic suspensions.[108] Furthermore, drug-resistant bacteria in herbal medicines may act as a source for the transfer of resistant genes to commensals in consumers.[109] Ogunshe and Kolajo in Nigeria demonstrated the existence of drug resistance in indigenous oral flora among consumers of herbal medicine.[110] At present, studies revealing microbial resistance to herbal drugs are limited and moreover, mechanisms of development of resistance are not well understood. Therefore, it needs further extensive studies to understand the mechanisms of resistance to herbal drugs.

Conclusion

AMR in the number of human pathogens is considered one of the most serious global health concerns. Infections caused by MDR pathogens are difficult to treat, often require expensive and sometimes toxic drugs for therapy. Furthermore, infection with MDR-pathogens is associated with high mortality.[111-115] Problems related to AMR are increasing day by day and are expected to become more problematic worldwide if they are not taken seriously. Furthermore, the research toward the development of new drugs to combat AMR is becoming scarce because antibiotics are no more profitable for pharmaceutical companies due to the problem of the rapid emergence of drug resistance. Several novel approaches explored by scientists in recent times have shown promising signs to fight against AMR. However, they need to be further explored for their long-term use risk/benefits in humans, bioavailability, toxicity, and others. Let us hope these strategies would be a promising alternative treatment options to contain dangerous drug-resistant pathogens in the future.

Abbreviation

Ag-NPs- Silver nanoparticles
Al-NPs- Aluminum nanoparticles
Au-NPs - Gold nanoparticles
Au2O3-NPs - Gold oxide nanoparticles
Ce-NPs- Cerium nanoparticles
Cd-NPs - Cadmium nanoparticles
CdO-NPs- Cadmium oxide nanoparticles
CuO-NPs - Copper oxide nanoparticles
Cu-NPs- Copper nanoparticles
Mg-NPs- Magnesium nanoparticles
Ni-NPs- Nickel nanoparticles
Ti-NPs- Titanium nanoparticles
TiO2-NPs- Titanium dioxide nanoparticles
Zn-NPs- Zinc nanoparticles
ZnO-NPs - Zinc oxide nanoparticles

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Conflicts of interest

There are no conflicts of interest.

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