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REVIEW ARTICLE

Role of Nutrients and Phyto-compounds in the Modulation of Antimicrobial Resistance

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Abstract: Antimicrobial resistance is quickly spreading and has become a major public health problem worldwide. If this issue is not resolved, it may cause a shift back to the pre-antibiotics era and infectious disease will again be a serious problem, especially in developing countries. Since the discovery of antibiotics, bacterial resistance has emerged, enabling certain bacteria to withstand antibiotic effects. The emergence of antibiotic resistance is fueled by excessive and improper use of antimicrobial agents, especially in developing countries. For this reason, alternatives to or modifications of current treatment methods have been sought. Researchers are attempting to discover new strategies for dealing with antimicrobial resistance to avoid reverting to the pre-antibiotic era. From this perspective, recent studies indicate that certain compounds can act in synergy with currently used antimicrobials to enhance the potential of antimicrobial agents and thus to reduce the emergence of antimicrobial resistance. This review highlights the possible synergies of various agents that can augment antibiotic activities. Some of the agents discussed in this review include phytobiologics, phytochemicals, antioxidants, vitamins, peptides, nano-antibiotics, drug-compound interactions and other nutrients. Some of these synergies are already being used to enhance the potential of currently used antimicrobial agents. More studies need to be conducted to better understand the mechanism of action of such compounds, and based on the results, new compounds may be sought.

Keywords: Antibiotics, resistance, phyto-compounds, anti-oxidant, modulation.

1. INTRODUCTION

The discovery of the antibiotics sulfonamide (1930) and penicillin (1940s) revolutionized the treatment of infectious disease, and the scientific community believed that those therapeutic agents would eliminate all of the infectious agents that had posed potential threats to human existence throughout the world. As a result, when natural antibiotics were marketed after the 1940s, the morbidity and mortality rates linked to infectious disease significantly decreased [1, 2]. Such developments motivated the scientific community, and several other types of new antibiotics were introduced that are still on the market [2]. Later, antibiotics research slowed down and most introduced antibiotics were derived from already-available ones [1, 2]. During the last 30 years, only one new antibiotic has been discovered [3]. In the beginning, patients and physicians were unfamiliar with and unaware of the health hazards associated with the excessive, uncontrolled misuse of antibiotics. For this reason, antibiotics were over-prescribed by physicians and were easily accessible to the public at large in many countries even without a doctor's prescription. For this reason antibiotics were abused by the public, resulting in the emergence of antibiotic resistance, the most serious global health problem that is threatening the survival of *Homo sapiens* [4-7]. In this study, we review the published work on synergies conducted on antimicrobial resistance. Pubmed database was searched for literature using words "antimicrobial resistance", "antimicrobial agents", "antimicrobial synergies", "modulation of antimicrobial resistance", "phyto-compounds synergies against antimicrobial resistance" etc.

2. EMERGENCE OF ANTIMICROBIAL RESISTANCE

The emergence and severity of infections have become a menace to the entire human population, and infections are a leading cause of mortality, especially in developing countries [7, 8]. It is reported that approximately two million people acquire infections annually in the United States of America and 70% of these cases are treated with at least one type of antibiotic (9). Worldwide, approximately 25,000 people die every year due to infectious agents that are resistant to treatment with commonly used antibiotics [10]. For instance, more than 90 of the *Staphylococcus aureus* strains are resistant to penicillin, whereas the same strain is resistant to methicillin in most Asian countries [11-13]. Extended-spectrum β-

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lactamase (ESBL)-producing *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* have shown resistance to fluoroquinolones, which constitute the last line of defense after ESBLs [14]. Resistance to ciprofloxacin, a broad-spectrum second-generation fluoroquinolone antibiotic [15], is widespread and this drug is facing failure only 20 years after its introduction [16, 17]. The prevalence of multidrug resistance (MDR) in mycobacterium strains is associated with increased death rates and a relatively reduced period of time from diagnosis to death [13]. In addition, the increased recurrence of pathogens has elevated the problem multifold; for instance, *Clostridium difficile* has an approximately 25% chance of recurrence after the initial treatment course, which is followed by multiple recurrences (surpassing 50%) [18]. Such MDR strains are contaminating our food and disturbing the normal flora, which could burden both the economy and the health sector [19]. The rise and rapid prevalence of antibiotic resistance in bacterial pathogens has wiped out the human dream of a pathogen-free world and threatens to push us back to the pre-antibiotics era if intelligent precautions and strategies are not exercised [14]. Fig. (**1**) shows the mechanism by which an antimicrobial agent inactivates the bacterial cell. Our studies on antimicrobial resistance have demonstrated that bacteria isolated from meat [20, 21], water [22, 23], dairy-based foods [24-27], and healthcare workers [28] show a high resistance to commonly used antimicrobial agents. Also, we have shown that a certain specific nutrient synergy has resulted in the modulation of the antimicrobial resistance of bacteria isolated from the environment [29]. Currently, one aspect of our research is focused on the effects of such nutrient cocktails on the resistance of clinical isolates.

The traditional drug-discovery methods are facing progressive failures in combating MDR evolution [30]. There is an increasing and urgent need to search for various strategies to enhance the efficacy of already-available drugs and to discover novel anti-infective therapeutics [30]. In this regard, new methods for dealing with resistance have been sought. One of these methods involves the use of different synergistic combinations, which is one of the new trends that possess the potential to cope with new MDR pathogens. It is believed that synergism, the combination of two or more therapeutics, could be a possible way to curb MDR pathogens [31]. It is interesting that synergy can not only enhance a drug's efficacy but can also potentiate its spectrum. Such groups and/or compounds that may produce synergistic effects with antimicrobial agents include phytocompounds [32], extracts, minerals, vitamins, and nutrients [33].

To check for synergism, *in vitro* testing was carried out for a commercial drug with one or more agents of interest. There are various techniques for accurately predicting synergy; however, the checkerboard and time-kill curve methods are the two most commonly and widely used methods [13, 34]. A progressive heuristic approach is needed to boost the search for synergy, especially against the increasing MDR strains [13].

A relatively limited number of publications have dealt with this issue. Synergism could be an emerging field if modern techniques such as genomics, metabolomics, and proteomics are applied to better understand and decipher the underlying mechanisms of resistance [13]. In addition, our previous work showed that specific nutrient synergy significantly reduced the resistance of *Staphylococcus saprophyticus*, *Salmonella*, *Listeria monocytogenes*, *Yersinia enterocolitica*, and *S. aureus* [29]. In this review, data was retrieved from the literature regarding the possible synergies that exist between commercially available antimicrobial drugs with agents of interest like: phytobiologics, vitamins, antioxidants, peptides/amino acids, nano-antibiotics and drug-compound interactions with an emphasis on the best possible synergies for combating infections.

3. BIOACTIVE PHYTOCOMPOUNDS

The kingdom Plantae has always played a vital role in human history. Plants have been used for millennia in the treatment of many ailments, especially infectious diseases, due to their innate enriched antimicrobial components [35]. Plant extracts and phytochemical compounds are some of the motivating topics in the field of antibiotics [30]. Herbal medicine is still practiced in many remote areas and is considered an effective folklore remedy [31]. Some plants that are regularly consumed as part of the human diet have shown profound health-promoting properties, especially antibacterial efficacy. Recently, research has been conducted to investigate potentiating the effectiveness of antibiotics when applied with phytobiologics [31]. It is of prime importance to understand the underling mechanisms of folklore remedies used against infections. Various synergistic combinations are being evaluated both *in vitro* and *in vivo* in order to determine the best combinations against infectious diseases. The successful outcomes from these experiments will subsequently have an effect on reducing the antibiotic resistance of microorganisms. It is expected that various possible synergies will result in the development of new drugs that will soon be marketed to treat various infectious diseases. The synergistic experiments have indicated that a few phytobiologics and phytochemicals possess the potential to weaken the resistance of antibiotic-resistant bacteria against conventional drugs. The new phytotherapeutics approach is an emerging field that may substantially relieve humanity of notorious pathogens when applied either alone or in combination with other synthetic drugs. This new generation of phytopharmaceuticals could lend phytotherapy a new legitimacy and enable phytobiologics and phytochemicals to be considered for the treatment of diseases that have hitherto been treated using synthetic drugs alone [36].

3.1. Phytobiologics

Adenium obesum the methanolic extract of *Adenium obesum* enhanced the activity of oxytetracycline, whereas tetracycline activity was improved when used in synergy with spice plants derived from *Beilschmiedia cinnamomea* against clinical MDR isolates [37]. The ethanolic extract of *Turnera ulmifolia* potentiated the

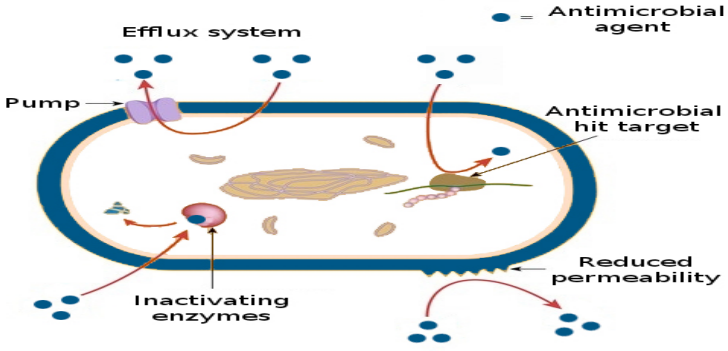

Fig. (1). Antimicrobial agent targeting bacterial cell.

efficacy of chlorpromazine against the *Staphylococcus* genus, especially methicillin-resistant *S. aureus* (MRSA) [38]. In addition, an extract from cranberry fruit enhanced the inhibition of antibiotic-resistant *S. aureus* when applied together with amoxicillin [37].

Tea leaves (both green and black) are well-known for their antibacterial activities [39]. The Chinese literature claims that the Chinese herb Xi-nan Huangqin (*Scutellaria amoena* CM Wright) has been traditionally used to cure infections [40]. In an experiment, tea leaf extracts successfully proved bacteria such as *Salmonella typhimurium*, *Shigella dysenteriae*, *Escherichia coli* and *Yersinia enterocolitica* to be more susceptible to sub-inhibitory concentrations of gentamycin, nalidixic acid, chloramphenicol, and methicillin. Remarkably, black tea extract was more effective than green tea extract. It is worth noting that the extract activity changes with the solvent and method used for the extraction of the active ingredient. For instance, the methanol extracts of green tea leaves were more potent than their counterparts' water extracts [39].

Interestingly, plant synergism is improving with advances in technology, starting with new methods of extraction and ending with the identification of a single active ingredient that is responsible for the activity. Therefore, researchers are inclined towards single active phytobiological compounds rather than total extracts, as they are more efficient [41]. Examples are listed below: Indole-3-carbinol, found naturally in plants, which has antioxidant and potential chemo-preventive therapeutic abilities that exhibit broad-spectrum antibacterial activity, as well as accelerated ampicillin activity against drug-resistant bacteria when used synergistically [42]. The oil of certain plants, eugenol, which is a bioactive component of clove oil isolated from *Eugenia aromatica*, effectively inhibited Gram-negative bacteria when used synergistically with β-lactam vancomycin [8].

Epicatechin gallate (ECG), the most abundant catechin in green tea, reduced oxacillin resistance in the case of methicillin-resistant *S. aureus*. Furthermore, Stapleton *et al.* (2004) improved ECG activity by substituting the gallate group with 3-O-acyl chains, which resulted in improved bactericidal efficacy against MRSA [43]. It was reported that another green tea component, EGCG, possesses chemo-preventive, anti-cancer, anti-inflammatory, and anti-mutagenic activities [29, 44] and de-activated *S. aureus* when combined with either ampicillin or penicillin by inhibiting the β-lactamase and penicillinase enzymes. In addition, it showed anti-cancer and anti-human immunodeficiency virus effects when combined with other nutrients and vitamins [45-49]. Moreover, it was reported that EGCG improved the antibacterial activity of ampicillin, β-lactam, and carbapenems against MRSA by directly binding to the peptidoglycan component of the cell wall, thus hindering cell wall synthesis by the bacteria [13]. Novy *et al*. (2013) reported that epigallocatechin gallate showed synergy when applied with oxytetracycline and eradicated bacteria resistant to erythromycin, methicillin, and tetracycline [32]. Moreover, synergism is helpful in reducing the usage and dosage of antibiotics, which may retard the process of antibiotic-resistance evolution [13]. Similarly, 23-methyl-6-*O*-desmethylauricepyrone and (*Z, Z*)-5-(trideca-4, 7-dienyl) resorcinol are two plant-derived compounds that hold promise in inactivating bacterial pathogens, either in synergy with erythromycin or alone [41].

Curcumin is a natural polyphenol compound isolated from the rhizome of *Curcuma longa*, which markedly reduced the MICs of the antibiotics cefaclor, cefodizime, and cefotaxime [37]. Such a synergism was not only effective against bacterial cells but against other infections as well. Candidiasis is a yeast infection that can be effectively reduced by the synergistic effect of amphotericin B with grape seed extract. This combinatorial treatment reduced the necessary concentration of amphotericin B by 75% from that used alone to achieve the same level of inhibition [13].

3.2. Phytochemicals

Synergistic remedies are already being used in Thailand for the treatment of diseases caused by *Falciparum malaria* through the combination therapy of a derivative of artemisinin with tetracycline, lumefantrine, and mefloquine [36]. Another example include the use of γ-mangostin which is a component of an extract obtained from the plant *Garcinia angostana,* and when used in the presence of ampicillin it can eradicate *Leptospira interrogans,* a spirochetes bacteria that can cause leptospirosis, one of the most widespread zoonotic diseases [50]. In addition, *Terminalia chebula* fruits contain a bioactive compound called 1, 2, 6-tri-O-galloyl-b-D-glucopyranose that can enhance the effectiveness of trimethoprim and gentamicin against MDR uropathogens [51], which are responsible for 72% of infections during pregnancy [52, 53]. Rhein, which is an anthrax quinone naturally found in rhubarb root, has demonstrated synergy with metronidazole or other polyphenols in successfully curing gingivitis, and it was observed that rhein weakened the virulence of *Porphyromonas gingivalis* by slowing down the transcription-gene-encoding pathogenicity [54].

Ethanolic extracts of Chinese traditional medicines made from *Isatis tinctoria*, *Rheum palmatum*, and *Scutellaria baicalensis* have improved the efficacy of penicillin G, ciprofloxacin, gentamycin, and ceftriaxone against MRSA which is a major problem worldwide [9, 55, 56]. Berberines are hydrophobic antibacterial agents that are produced in *Phellodendri cortex* (*Phellodendron amurense* Ruprecht) and *Coptidis rhizoma* (*Coptis chinensis* Franch). These compounds hold promise to be effective as therapeutic agents against MDR strains. Berberine has successfully inhibited the growth of MRSA, and this phytobiologically active agent significantly reduced the MIC of ampicillin and oxacillin against MRSA when used in synergy [56]. It is believed that berberine intercalates into the DNA of the pathogen, which is equipped with MDR pumps to immediately extrude it out. Berberines will be very effective if MDR pumps can be blocked. Such blocking can be achieved using another plant extract known as 5'-methoxyhydnocarpin; using the synergy of this extract and berberine together could be very effective against MDR pathogens [13].

Antibiotic-resistant *Neisseria gonorrhoeae*, another concerning pathogen, is contracted through sexual contact and causes gonorrhea. This infection is associated with bladder cancer and is the second most commonly reported infection in the United States. Recently, a synergistic combination of vitamin D and curcumin was reported to be useful in eradicating *N. gonorrhea*. It would be interesting to test the synergic combinations of this remedy with different antibiotics, as it may potentiate the efficacy of antibiotics and minimize the drug dose needed for treatment [57]. *P. aeruginosa* is an opportunistic bacterium that can cause nosocomial infections and, occasionally, death.

In a study to evaluate the potential effects of the application of phytochemicals on antibacterial activity in the presence of three standard antibiotics (ciprofloxacin, gentamicin, and streptomycin) against four bacteria, the activities of single compounds and dual combinations (streptomycin-phytochemicals) were assessed by measuring the inhibitory clearance zones [58]. It was found that all of the isothiocyanates had significant antimicrobial activities, while the phenolics were much less efficient. No antimicrobial activity was observed with phloridzin. The order of sensitivity against the test bacteria showed *P. aeruginosa* to be the most sensitive while *L. monocytogenes* was the most resistant. The results related to the dual applications revealed synergy between streptomycin and gallic acid, ferulic acid, chlorogenic acid, allyl isothiocyanate, and 2-phenylethyl isothiocyanate against Gram-negative bacteria. The results also indicated that phytochemical products, and more specifically isothiocyanates, had the potential to inhibit the *in vitro* growth of both Gram-negative and positive pathogenic bacteria. In addition, they showed synergism when applied together with less-efficient antibiotics to control bacterial growth [58].

It is surprising to note that most phytoalexins, small molecules that possess antimicrobial activities and enormous diversity, are less effective than antimicrobial agents isolated from bacteria and/or fungi. Phytoalexins such as glycosteroids, polyphenols, terpenoids, and flavonoids are less potent against MDR strains than other antimicrobial agents. However, these compounds are beneficial for human civilization. It was shown that plant-derived products adopt different mechanisms to combat MDR strains [13].

Besides infectious disease, food poisoning is of great concern in terms of both food safety and spoilage. Various bacterial pathogens are responsible for food poisoning, including *S. aureus*, which produces enterotoxin. For many years, nisin has been widely used in the food industry for food preservation. However, certain organisms have developed resistance against nisin, and its usefulness as a food preservative has been challenged. Recently, it was reported that coenzyme Q_0 can potentiate the effectiveness of nisin when they are applied together, and such an action resulted in synergy [59]. This has paved the way to finding a novel solution with the potential to help reduce spoilage problems in the food industry and to provide an alternative approach to overcoming antimicrobial drug resistance [59].

3.3. Antioxidants

Interestingly, certain plant-derived compounds are preventative and curative, as they can boost the immune system. These compounds are antioxidant in nature and can protect cells from damage [60]. Antioxidants are health promoting bioactive compounds and hold promises in treatment of serious health problems such as cancer. These compounds are widely applied to food industry to overcome oxidative food degradation. The increasing emergence of food-born antibiotic-resistant pathogens is alarmingly threating human lives and economy. The addition of antibiotics to food is no more a choice. Researchers are interested to design an effective natural bio-product that can solve the problem of oxidation and pathogen [61]. Antioxidants are important nutrients in our foods and have antibacterial activities [61, 62]. However, not all antioxidant possess antibacterial properties - as antioxidants are not polar [63]. While large-scale human studies have yet to be conducted on many antibacterial nutrients, the existing animal studies show considerable promise with these agents [60].

3.4. N-acetylcysteine (NAC)

NAC is a sulfhydryl-group-containing antioxidant and a mucolytic agent that is used in the therapy of bronchitis, and that is primarily used in the management of paracetamol overdose [64-66]. This compound is a dietary supplement commonly claimed to possess liver-protecting effects [67]. NAC inhibits cysteine utilization on the bacterial cell wall through the thiol group [66, 68, 69]. It is observed that NAC can potentiate antibiotic activities very effectively against *P. aeruginosa* when used in synergy with cefepime, ceftazidime, cefoperazone, meropenem, and tetracycline. The synergy rates were 80%. These synergies could be effectively used against *P. aeruginosa* [66]. Goswami and Jawali (2010) found that the presence of NAC (10 mM) can enhance the efficacy of β-lactams against *P. aeruginosa* [70]. The susceptibility of *P. aeruginosa* decreased moderately to ciprofloxacin and markedly to the aminoglycosides streptomycin, kanamycin, and spectinomycin due to the protection exerted by the thiol compound NAC against aminoglycoside and fluoroquinolone antibiotics [66, 71]. However, it is necessary to screen NAC synergies with all available antibiotics to optimize the best synergy combination in relation to the dose employed. NAC can antagonize certain drugs, such as tobramycin and gentamicin [72]. Until now, the MIC of NAC against *P. aeruginosa* has been 10 to 40 mg/ml. Biofilm disruption is concentration-dependent and complete disruption has been observed at 10 mg/ml NAC. Ciprofloxacin combined with NAC exhibited effective synergy against *P. aeruginosa* in biofilms. NAC's synergy with ciprofloxacin progressively decreased live biofilm-associated bacteria in comparison to the control. This combination was synergistic with NAC at 0.5 mg/ml and CIP at 1/2 MIC ($p<0.01$) [68]. NAC also possesses antibacterial properties. It was found that NAC can inhibit the growth of both Gram-positive and Gram-negative bacteria [66]. Moreover, NAC, when combined with carbenicillin or ticarcillin, increased their activity against *P. aeruginosa*. The bactericidal activity of NAC against *P. aeruginosa* and its potentiating effect with carbenicillin has been reported [66, 73].

3.5. Ambroxol

Ambroxol is an expectorant that is useful in the treatment of bronchial asthma and chronic bronchitis. Moreover, it exhibits antioxidant and anti-inflammatory properties [66, 74]. Ambroxol was evaluated for its possible synergies with different antibiotics against five clinical isolates of *P. aeruginosa*, and the synergy rates were 55%, with combinations of ambroxol with tetracycline, meropenem, cefoperazone, ceftazidime, and cefepime showing synergism; the results suggested that the combination of ambroxol with antibiotics can combat the antibiotic-resistant strains of *P. aeruginosa* [66[. It was demonstrated that ambroxol enhances the penetration of fluoroquinolone, gatifloxacin, ampicillin, and erythromycin into the targeted cells [66]. During a trial treatment carried out on 42 children, the synergism of ambroxol with antibiotics was realized [75]. In another study, it was found that ambroxol is more effective than NAC. In addition, ambroxol was an effective therapeutic agent against pneumonia when ingested with cefathiamidine in an experiment carried out on 314 children [66].

3.6. Ascorbic acid (AA)

AA has been shown for many years to exhibit antioxidant properties [76-78]. Owing to its antioxidant activity, AA is a common preservative and an important ingredient in the pharmaceutical and cosmetic industries [79, 80]. Our previous work reported that AA is immune-modulatory and can suppress HIV reverse transcriptase activity [81]. Studies have revealed the ability of AA to augment the bactericidal activity of erythromycin and sulfamethoxazole-trimethoprim, but not that of tetracycline, against *P. aeruginosa* [66]. In addition, AA can act as a β-lactamase inhibitor against *P. aeruginosa*. Furthermore, AA was reported as an efflux pump inhibitor in hemolytic *E. coli*. As a result, it can enhance the activity of different classes of antimicrobials against *E. coli* [82].

The possible synergy between antibiotics and AA against five clinical isolates of *P. aeruginosa* was evaluated and the synergy rates were 15% higher [66]. Combinations of AA with cefepime, ceftazidime, cefoperazone, meropenem, and tetracycline showed synergistic potential in combating the antibiotic resistance of *P. aeruginosa* [66]. In a different study, a group of researchers reported that AA, when applied at a concentration of 10 mg/ml, increased the susceptibility of *P. aeruginosa* to ampicillin, mediated by the inhibition of β-lactamase production [66, 76, 77, 81, 83]. Amabile-Cuevas *et al*. (2004) indicated that AA could augment the activity of tetracycline against *S. aureus* 84. Goswami *et al*. (2007) found that AA could protect *E. coli* against gentamicin and ciprofloxacin by induction of a protective phenotype for the former and antioxidant-mediated reactive oxygen species scavenging for the latter [85]. On the contrary, no effect was noted when AA was applied in the presence of penicillin, ampicillin, tetracycline, or chloramphenicol. AA significantly reduced the MIC of MDR bacteria when used in synergy with deferoxamine, cefsulodin, gentamycin, cefalothin, and chloramphenicol. Another study observed that AA is synergistically active with tetracycline, streptomycin, and chloramphenicol against *P. aeruginosa*. Future research on AA/antimicrobial interactions may find new methods to control strains of MDR *P. aeruginosa* [86].

It has been observed that high doses of AA in synergy with antibiotics can inhibit the growth of *Helicobacter pylori* [80]. Some

studies have suggested that AA may eliminate/damage the R plasmids of *Staphylococcus* that make them prone to be more susceptible to antibiotics [87]. More work is needed to potentiate the AA activity because most of these studies were carried out with high doses of AA against small numbers of bacterial cells 86. Deferoxamine can inhibit *S. aureus* growth in synergy with gentamicin, fusidic acid, cefalothin, vancomycin, and cefotaxime in the presence of AA [88]. In another study, deferoxamine activity was determined in the presence of AA against *P. mirabilis* strains, ten *E. coli* strains, and ten coagulase-negative *staphylococci* strains in lab conditions [88, 89].

The benefits of using AA together with antibiotics are considerable. High doses of AA in combination with antibiotics showed effective synergy in a trial experiment on dairy cows [90]. In humans, an astoundingly high 120,000 mg/day (nearly 2,000 times the RDA) of AA delivered intravenously has been demonstrated to accelerate the healing of burned skin in a blinded clinical trial [91]. One thousand to 3,000 mg/day (100 times the RDA) of niacin is a standard treatment for controlling cholesterol [92]. Similar doses of niacin have been demonstrated to reduce inflammation [93] and to reduce injury to the brain after a stroke [94]. In addition, we showed that AA could be a crucial vitamin for inducing apoptosis in leukemic cancer cells and that it also inhibits HIV replication [95].

3.7. Glutathione

Antioxidants such as glutathione and AA have been reported to protect *E. coli* against the antibacterial activity of fluoroquinolone and aminoglycoside groups of antibiotics [96]. The mechanism behind this protection was not fully understood and was thought to be different depending on the class of antibiotics used. For instance, unlike with ciprofloxacin, the reduced streptomycin susceptibility of *E. coli* cells is not due to antioxidant-mediated scavenging of reactive oxygen species. In the case of glutathione, it was reported that it not only reduces the antibacterial effect of certain agents, but also potentiates the antibacterial activity of β-lactam antibiotics. That study and others showed that glutathione differentially modulates the antibacterial activity of various groups of antibiotics [96]. Also, β-lactams are important antibiotics with tremendous therapeutic ability, and future studies need to be conducted to investigate the effects of glutathione on the antibacterial activity of β-lactams to help in the development of better treatment regimens for different types of infectious agents [97].

3.8. Vitamin E

Vitamin E is thought to be advantageous in ameliorating the effects of diseases such as neurological and chronic inflammation, cancer, and cardiovascular disorders. Vitamin E is an essential micronutrient in food and is composed of tocotrienols and tocopherols, possessing strong immune-modulating properties [89, 98]. A study showed that the administration of vitamin E before infection was effective at increasing the antimicrobial activity of daptomycin and tigecycline (TIG) in a mouse model of wound infection caused by MRSA [89]. The combination of vitamin E and antibiotics increases the natural killer cells' cytotoxicity [89]. These data suggest that treatment with vitamin E prior to infection and subsequent antibiotic treatment act in synergy [89].

Special cationic polycarbonates that are synthesized through organo-catalytic polymerization possess antibacterial activity that is enhanced when vitamin E is conjugated with them; the polymers have shown promising results against *Candida albicans*, *E. coli*, and *S. aureus*. Interestingly, the co-administration of these polymers with certain antibiotics, such as doxycycline, significantly ameliorates *P. aeruginosa* viability. Such results hold promise for handling microbial pathogens [99]. Vitamin E, when used in recipes with daptomycin, can synergistically elevate CD49b+ cell counts with antibacterial properties [100]. Vitamin E contains polycarbonates, which possess antibacterial activity and can inhibit *P. aeruginosa* growth. The use of vitamin E polycarbonate with different antibiotics resulted in a decrease in the MIC of the antibiotics used and an improvement of their antibacterial effects [57]. Other vitamins like A and D showed antibacterial activity in cultures against *Mycobacterium tuberculosis*, which could be used in combination therapies against MDR microbes [101].

4. OTHER ANTIBACTERIAL STRATEGIES

4.1. Peptide Synergies

Antibiotic resistance has exerted an increasing burden on the economy, which has prompted an active search for new drugs [10]. For the past few years, researchers have focused on new drug targets and subsequently new therapeutics. In this regard, antimicrobial peptides (AMPs), which are cationic peptides with less than 50 amino acids, are possible candidates of interest that can inhibit microbial growth through their mode of action against the cell membranes of bacteria [102, 103] and that do not rely on other intercellular targets [104-106]. Researchers believe that AMPs display synergy when applied with other antibiotics and can effectively inhibit bacterial pathogens. The development of resistance to virtually all current antibiotics makes the discovery of new antimicrobial compounds with novel protein targets an urgent challenge [10]. Peptide synergy with non-peptide antibiotics provides potential regimens against bacterial resistance. It is reported that antibacterial peptides, such as Ud, ΔFmscr, and ΔFm, show synergism with kanamycin and rifampin against *E. coli* [107].

4.1.1. Synthetic cationic α-helical AMPs

Synthetic cationic α-helical AMPs when applied in combination with rifampicin, inhibited the growth of *Mycobacterium bovis* BCG, *Mycobacterium smegmatis*, and *Mycobacterium tuberculosis*. Such synergism is very helpful and can delay the emergence of resistance to antibiotics [108].

4.1.2. CopA3

CopA3, a 9-mer peptide, is a derivative of the α-helical region of coprisin, a 43-mer defensin-like peptide found in dung beetles. This peptide exhibits antimicrobial activities. Both dimer and monomer forms of CopA3 are active against bacteria, with no identified hemolytic behaviors. It was reported that CopW, a cysteine-free nanopeptide of CopA3, significantly potentiated the antibacterial activity of ampicillin and that this synergy had superior antifungal efficacy [106].

4.1.3. Alafosfalin

Alafosfalin is a new phosphonopeptide that has shown profound synergy when applied with cephalexin. Alafosfalin is effective against *E. coli* and less effective against *Klebsiella*, *Serratia*, and *Citrobacter*, and it can also potentiate the activity of mecillinam and, to some extent, that of ampicillin [109, 110].

4.1.4. PMAP-36

PMAP-36 is an antibacterial peptide that can inhibit bacterial growth by damaging the bacterial membranes. PRW4, which is a truncated analog of PMAP-36, could be clinically useful in conjunction with aminoglycosides against antibiotic-resistant pathogens [110].

4.1.5. Phosphonopeptide L-Norvalyl-L-1-Aminoethylphosphonic Acid and Norcardicin-A

The combination of both the component was most potent against clinical isolates of *P. aeruginosa*, *Serratia marcescens* and indole-positive *Proteus spp*.; this synergy was observed *in vitro* and confirmed *in vivo* [111]. Certain nutrient compositions can modulate the microbial cell factory to release the antimicrobial peptides of *Lactobacillus acidophilus* that can produce antimicrobial compounds when grown on Elliker's, MRS (deMan, Rogosa, and Sharpe), and LBS (*Lactobacillus* selection) broth media [33]. Amiri *et al*. found that lysine can increase the antimicrobial activity of

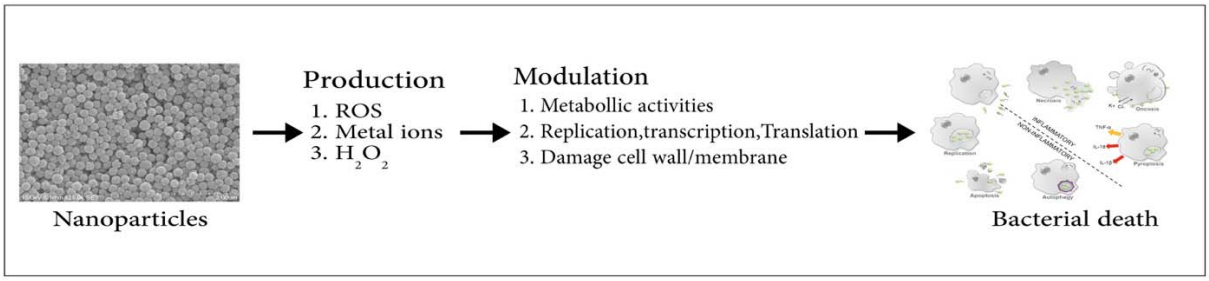

Fig. (2). Nanoparticles effects on bacterial cell death.

carbon nanotubes when used together, resulting in synergy [8]. Lysine has also shown anti-cancer activity [48].

4.2. Nano-antibiotics

Nanotechnology has projected an exciting new avenue for combating MDR bacterial pathogens [112]. Nanoparticles are developed with desired physic-chemical properties that exert antimicrobial properties alone or in combination with other antimicrobial agents [113]. Whereas, some of the nanoparticles help in delivering antimicrobial agents. For example, vancomycin has been successfully delivered inside bacterial cell through folic acid tagged chitosan nanoparticles [112]. Nanoparticles possess unique shape, size and surface area that enable them to exert antimicrobial activities through diverse mechanisms. For instance, metal oxides (TiO_2 and ZnO) inhibit bacterial growth by generating reactive oxygen species [114]. Metal nanoparticle often damage bacterial cell membrane by interacting with phosphorus and sulfur present in membrane [115]. Fig. (**2**). Shows how bacterial damage is cause by nanoparticles. This type of nanoparticles is often use in synergy with antimicrobial agent for safer delivery across cellular membrane. In addition, if used alone, the particles are enough to make porous cellular membrane and cause nutrient leakage from cellular compartment that consequently lead to cellular death [116]. Recently, a simple and inexpensive strategy was adopted for developing ZnO nanoparticles that effectively inhibited fungal and bacterial growth [117]. Moreover, some of the nanoparticles inhibit bacterial growth by inactivating vital enzymes. For instance, Ag nanoparticles release silver ions that interact with thiol groups of enzyme and causing cellular disruption [118]. Some of the nanoparticles (such as Nitric oxide releasing nanoparticles) exhibit bactericidal activities against *Acinetobacter baumannii* by irreversibly removing heme part of the proteins [119]. Some of the best known anti-microbial nanoparticles include titanium di-oxide (TiO2), iron oxide (Fe3O4), silver and zinc oxide (ZnO) [120]. Moreover, special interests are developing toward phytocompounds and nanoparticles synergies. Jamil *et al.*, (2016) successfully loaded cardamom essential oil at chitosan nanoparticles that exhibited excellent antimicrobial activities against ESBL *E. coli* and methicillin resistant *Staphylococcus aureus* [121]. Interestingly, phytocompounds and nanoparticles synergies are apparently effective and safer compared to conventional antimicrobial agents [121].

5. DRUG-COMPOUND INTERACTIONS IN SYNERGIES

Despite growing trends toward synergies development, drug-compound interactions are poorly unknown. From detailed antimicrobial evaluation, a part of drug-drug interaction is predictable. Most of the antimicrobial agent inhibit bacterial growth by targeting ribosome 50S, ribosome 30S, folic acid synthesis, DNA, cell wall synthesis and aminoglycosides. Therefore, it is understandable that phytocompounds actually enhance antimicrobial efficacy by targeting these sites. Increase antimicrobial efficacy could result from increased permeability, high bioavailability and extended release [122]. Some of the interactions in synergies could be highly complex, especially the synergy that modulate cell physiology, stimulate cellular signals that affect drug activities. For instance, a study reported *E. coli* mutant that resulted from trimethoprim and sulfonamides. These antimicrobials target dihydropteroate synthetase and dihydrofolate reductase enzymes that are involved in folic acid biosynthesis [123, 124].

In some of the synergies, compounds inhibit cellular mechanism that resists antimicrobial action. For instance, amoxicillin was successfully revived for broad spectrum activity by combing with clavulanic acid. Clavulanic acid inhibits β-lactamase that deactivate amoxicillin [122]. Moreover, it is shown that sevetral pyruvate and sugars can increase inhibition efficiency of aminoglycoside antibiotics [125]. Likewise, some metabolites (e.g. alanine) improve kanamycine activity by enhancing proton motive force that lead to higher aminoglycoside transport [126].

CONCLUSION

Antimicrobial resistance has reached alarming levels, and alternative methods should be sought. Based on this review, it seems that there possible methods of decreasing the emergence of antimicrobial resistance using the compounds discussed in this paper. In addition, future work should focus on novel compounds against which microorganisms lack the potential to develop resistance.

AUTHOR CONTRIBUTIONS

S. Harakeh and Imran Khan have equal contributions in designing and writing. E. Azhar, Soad Al Jaouni and Aleksandra Niedzweicki proof read the manuscript and substantially edited the manuscript contents. Saad B. Almasaudi helped in collecting information.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that the work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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