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Application of antimicrobial, potential hazard and mitigation plans

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\textbf{A B S T R A C T}

The tremendous rise in the consumption of antimicrobial products had aroused global concerns, especially in the midst of pandemic COVID-19. Antimicrobial resistance has been accelerated by widespread usage of antimicrobial products in response to the COVID-19 pandemic. Furthermore, the widespread use of antimicrobial products releases biohazardous substances into the environment, endangering the ecology and ecosystem. Therefore, several strategies or measurements are needed to tackle this problem. In this review, types of antimicrobial available, emerging nanotechnology in antimicrobial production and their advanced application have been discussed. The problem of antimicrobial resistance (AMR) due to antibiotic-resistant bacteria (ARB)and antimicrobial resistance genes (AMG) have become the biggest threat to public health. To deal with this problem, an in-depth discussion of the challenges faced in antimicrobial mitigations and potential alternatives was reviewed.

1. Introduction

The rapid development and evolution of microbes, as well as their ability to cause infectious diseases in humans, pose a significant global concern. Harmful microbial strains spread rapidly to the environment due to their high transmission ability and this causes the high demand and massive consumption of antimicrobial products (Rezasoltani et al., 2020). These findings showed that the rise in infectious diseases has increased the demand for antibiotics in the global industry, with antibacterial penicillin alone accounting for 23.9 percent of the entire market share in 2020 (Grant View Research, 2021). In Malaysia alone, data shows huge increment of antimicrobial consumption, as an example beta lactam inhibitor increases from 66.38% to 83.96% and cephalosporin based antibiotic from 62.11% to 86.79% in one year (2019–2020) (Tan et al., 2022).

Extensive use of antimicrobial agent showed negative impact on public health, environment and economy. Although the wide application of antimicrobial substances causes a decrease in microbe contamination to treat diseases, the release of huge amount of antimicrobial into environment is expected to accelerate the antimicrobial resistance (AMR) developed by ‘super’ microbes. Once the existing microbes develop AMR with the emerging of new resistance mechanism, it will substantially raise the difficulty to treat common infectious diseases caused by these AMR acquired microbe and become a hidden danger to public health for the next few decades (Getahun et al., 2020; World Health Organisation, 2020a). For the past 70 years, harmful infectious diseases have been treated with antimicrobial chemotherapy; however, the effectiveness of the therapies is being hampered by the development of resistance mechanisms in microorganisms to the antimicrobial drugs, and there are currently no effective alternatives. In addition, extensive literature studies proved that the use of antimicrobial agents have an impact on the functionality and composition of human gut microbiota.
which had been detailed reviewed in Pilinis et al. (2020). Moreover, the discard of antimicrobial products into the environment via wastewater and agricultural routes has been highly linked with emerging of antimicrobial resistance bacteria (ARB) and antimicrobial resistance genes (ARG) (Serwecinska, 2020).

The impact on economy can be foreseen on the fact of many countries and pharmaceutical companies throughout the world have announced plans to enhance financing for antimicrobial-related medicine or pharmaceutical development (Martin and Bowden, 2020). The outbreak of the COVID-19 pandemic is a driving force behind an even higher demand for antimicrobial products (Rezasoltani et al., 2020). Despite the rapid development of infectious disease control, the COVID-19 pandemic has made us aware that the world is still unprepared for the transmission of new diseases. Following the outbreak of the pandemic, the world is in critical demand for disinfectants and sterilizers, industry has to incorporate various techniques to attract consumers with the best efficiency of microbe removals, such as using nanomaterial in water disinfectants (Hosain et al., 2014) or the greener option of natural products as home antimicrobial disinfectants (Rutala et al., 2019). According to Statista Research Department (2021), the overall revenue of hand sanitisers in Malaysia (between 2019 and 2020) had increased dramatically from 8.35 to 14.05 million USD. AMR’s emergence was responsible for 7 million fatalities each year and the number of deaths is expected to rise to 10 million, with a massive economic loss of up to USD 100 trillion by 2050 (Murray, 2020). AMR had been highlighted on the agenda of US Centres for Disease Control and Prevention (CDC) and the World Health Organisation (WHO) (Getahun et al., 2020). It is foreseen that it can bring a heavy blow to society, the economy and the environment.

To comprehend the current issue related to the use of antimicrobial agents in connection with infectious diseases, the development of AMR, including the environmental impact of antimicrobial resistance bacteria and antimicrobial resistance genes has been critically discussed in this paper. Also covered is the progress in the production of antibacterial nanoparticles. To address the antimicrobial resistance (AMR) challenges, coordinated mitigation methods and action plans are also highlighted.

2. Sources and roles of antimicrobial agents

Antimicrobial compounds could be obtained from plants, animals, microorganisms and advanced synthetic materials (Table 1) and their function is to inhibit or destroy the growth of other microbes including bacteria, fungi, viruses, and parasites (World Health Organisation, 2020a). The use of antimicrobial agents enables the creation of an inhospitable environment to disrupt cell function and inhibit the growth of microorganisms (Armacell, 2017).

Most antimicrobial agents are derived from plant sources due to their lower production cost, high therapeutic values, and pharmacological properties. The production cost for plant-based medicine is 31% lesser compared to microbial and animal-based medicine production (Waheed et al., 2016). In addition to protect plants from infections, insects, and herbivore attacks, secondary metabolites released by plants, such as phenolic, flavonoid, terpenoids, alkaloids, tannins, and sulphur-containing compounds, also have antimicrobial effects (Guerriero et al., 2018). Thus, these bioactive compounds have been developed into antimicrobial medications to treat infections in humans, animals, and plants.

Other antimicrobial agents can be obtained from animal sources. For example, insulin (to treat diabetes) is developed from cattle and pigs (White Jr, 2014). Body secretions, fluids, and glands have been used in drug development, tiger bones, deer antlers and snake bile are also example of body parts that have been used by the Chinese as medicine. Moreover, some researchers indicated that reptiles can secrete antimicrobial peptides such as magainin which can induce pore formation and are used to treat Methicillin-resistant Staphylococcus aureus (MRSA) infection caused by Staphylococcus sp. (Ravensdale et al., 2016). Peptides secreted by South American rattlesnake (Crotalus durissus terrificus) have been developed into Crotamine, the first antimicrobial drug from venom peptide (Kerks et al., 2014). Chitosan obtained from shell of crustacean that demonstrate electrostatic interaction with predominantly anionic compounds of the microorganisms plays a primary role in the antibacterial and antiviral activity against Hepatitis C and Newcastle virus (Loutfy et al., 2020). A combination of chitosan with yeast and calcium chloride had been reported to inhibit the growth of blue mounds in pear fruit (Yu et al., 2012).

The first and widely used antimicrobial drug, penicillin, is developed from fungus Penicillium chrysogenum to suppress the growth of S. aureus(). Other examples of microbe derivatives are Cephalosporins which are produced from the fungus Acromenium as antibacterial; Streptomycin produced from bacterium Streptomyces griseus to treat TB and bacterial infections. Bacillus subtilis causes bacteremia, endocarditis, meningitis, and infections of the wounds, ears, eyes, respiratory tract, urinary tract, and gastrointestinal tract. Bacitracin is used to prevent bacterial infection on small cuts caused by Bacillus subtilis. In addition, hypovolemia medicine has been developed from polysaccharide synthesized by lactic acid bacteria, Leuconostoc mesenteroides, Streptococcus mutans and Lactobacillus brevis (Patel et al., 2012).

Antimicrobial agents act differently toward microbial (Table 1). The common mode of antimicrobial action is illustrated in Fig. 1. Antimicrobial agents bind to the plasma membrane of microbes, resulting in several malfunction effects on the plasma membrane of microorganisms. These antimicrobial agents further damage microorganism by inducing cell lysis, suppression of DNA and nucleic acid synthesis, leaking of cellular components such as cytokines and enzymes causing mitochondrial injury, and eventually cell death by necrosis (Faria et al., 2009).

3. Nanoparticles as antimicrobial drugs

Nanoparticles (NPs) ranging from 1 to 100 nm including carbon-based NPs, metal-based NPs, polymeric NPs, and lipid-based NPs have synergistic antimicrobial activities that are suitable for medical and pharmaceutical applications (Singh et al., 2018) (Fig. 2). The characteristic of NP such as mechanical, chemical, and optical properties and large surface area to volume ratio highly improves the efficacy of antibacterial activity (Panáček et al., 2018).

3.1. Carbon-based nanoparticles (CBNPs)

CBNPs such as graphene, fullerene and carbon nanotubes showed high antimicrobial activities in many studies due to their unique physicochemical properties including small particle size, electrical, magnetic, chemical, and thermal-mechanical properties (Azizi-Lalabadi et al., 2020). In short, all these three CBNPs demonstrated different carbon arrangements in different dimensions which caused different chemical and physical characteristics and a variety of mechanism modes in the antimicrobial actions (Table 2). Antimicrobial activities of CBNPs is greatly associated with their ability to destroy and disrupt the bacterial cells via different mechanisms including establishment of reactive oxidative species (ROS), chemical environment that involved electron transfer from the microbial cells, and also physical treatments that can alter the supportive growth environment (Azizi-Lalabadi et al., 2020). For instance, fullerene and their derivatives possess unique structure with numerous of hydrophilic molecules that can form conjugation with the cell wall of bacterial cell membrane which causes cell membrane disruption, DNA damage, and ultimately ceasing their metabolic activity (Fernando et al., 2018). The efficacy of CBNPs mainly depends on their contact surface modification such as the type of functional groups present on the surface and also the physicochemical reaction with the targeted microbial (Azizi-Lalabadi et al., 2020).

Graphene oxides, fullerene and carbon nanotube (CNT) are the most widely employed CBNPs in medical application with antimicrobial
| Sources         | Antimicrobial groups | Plants            | Alkaloids | Phenolic Compounds | Flavonoids | Terpenes, Terpenoids and Essential Oils | Animals | Peptides | Hormones | Microbial organisms | Active compounds | Chemical Synthesis | Medicinal Synthesis |
|-----------------|----------------------|-------------------|-----------|--------------------|-----------|----------------------------------------|---------|----------|----------|---------------------|-----------------|---------------------|-------------------|
| **Active**      | Compounds            |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| Atropine        |                      |                   |           |                    |           |                                        |         |          |          | Anthracimycin        |                 |                     |                   |
| Berberine       |                      |                   |           |                    |           |                                        |         |          |          | Bacteriocins         |                 |                     |                   |
| Caffeine        |                      |                   |           |                    |           |                                        |         |          |          | Chlorhexidine        |                 |                     |                   |
| Carpane         |                      |                   |           |                    |           |                                        |         |          |          | Chloramphenicol      |                 |                     |                   |
| Cocaine         |                      |                   |           |                    |           |                                        |         |          |          | Colistin             |                 |                     |                   |
| Glyoxaline      |                      |                   |           |                    |           |                                        |         |          |          | Collykiresorcinols   |                 |                     |                   |
| Harmame         |                      |                   |           |                    |           |                                        |         |          |          | Endolysins            |                 |                     |                   |
| Imidazoline     |                      |                   |           |                    |           |                                        |         |          |          | Eurocrystatine        |                 |                     |                   |
| Indole          |                      |                   |           |                    |           |                                        |         |          |          | Gramicidin            |                 |                     |                   |
| Isoquinoline    |                      |                   |           |                    |           |                                        |         |          |          | Halolitoralin         |                 |                     |                   |
| Lupinane        |                      |                   |           |                    |           |                                        |         |          |          | Indigoidine           |                 |                     |                   |
| Morphine        |                      |                   |           |                    |           |                                        |         |          |          | Lapaarxins            |                 |                     |                   |
| Nicotine        |                      |                   |           |                    |           |                                        |         |          |          | Laimocin              |                 |                     |                   |
| Phenanthridine  |                      |                   |           |                    |           |                                        |         |          |          | Lycinamics            |                 |                     |                   |
| Piperidine      |                      |                   |           |                    |           |                                        |         |          |          | Maribasins            |                 |                     |                   |
| Pyridine        |                      |                   |           |                    |           |                                        |         |          |          | Matamycin             |                 |                     |                   |
| Pyrrolidine     |                      |                   |           |                    |           |                                        |         |          |          | Nisin                |                 |                     |                   |
| Quinine         |                      |                   |           |                    |           |                                        |         |          |          | Phenazins             |                 |                     |                   |
| Quinazoline     |                      |                   |           |                    |           |                                        |         |          |          | Phloroglucinols       |                 |                     |                   |
| Sanguinarine    |                      |                   |           |                    |           |                                        |         |          |          | Rabelomin             |                 |                     |                   |
| Scopolamine     |                      |                   |           |                    |           |                                        |         |          |          | Reuterin             |                 |                     |                   |
| Tropan          |                      |                   |           |                    |           |                                        |         |          |          | Tauramamide           |                 |                     |                   |
| Vincamine       |                      |                   |           |                    |           |                                        |         |          |          | Unnarmincins          |                 |                     |                   |
| Yohimbine       |                      |                   |           |                    |           |                                        |         |          |          | Virginiycin           |                 |                     |                   |
| **Mode of**     | **actions**          |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Inhibition**  | of nucleic acid      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **biosynthesis**|                      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Membrane**    | **destruction**      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Membrane**    | **destruction**      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Inhibition**  | of nucleic acid      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **synthesis**   |                      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Membrane**    | **destruction**      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Membrane**    | **inhibition**       |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **Degrades**    | **cell**             |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **membrane**    |                      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| **References**  |                      |                   |           |                    |           |                                        |         |          |          |                     |                 |                     |                   |
| (Othman et al., 2019; Pavia and Plummer, 2019; Othman et al., 2019; Patra, 2012; Reghu et al., 2017) | | | | | | | | | (Othman et al., 2019; Pavia and Plummer, 2019; Othman et al., 2019; Patra, 2012; Reghu et al., 2017) | | | | (Mahazan et al., 2019; Patra, 2012; Reghu et al., 2017) | | | | (Huan et al., 2020; Kang et al., 2015) | | | | (Ghafari et al., 2019; Habbu et al., 2016; Kang et al., 2015; Keswani et al., 2019; Seal et al., 2018) | | | | (Anh et al., 2021; Bbosa et al., 2014; Fair and Tor, 2014). | | | |
functions (Fernando et al., 2018). Graphene oxide has become one of the most popular types of CBNPs, due to its ease to manufacture, low cost and widespread availability, as opposed to graphene which is more expensive and required a complex synthesis procedure (The Graphene Experts, 2021). There is evidence that carbon nanotubes are more effective antimicrobial than fullerene (Fernando et al., 2018). The CNT mode of action includes disruption of the cell membrane, morphology, and metabolic operations, which is aided by its small particle size, which allows for increased surface interaction (Azizi-Lalabadi et al., 2019).

3.2. Metal-based nanoparticles (MBNPs)

MBNPs such as silver (Ag), gold (Au), palladium (Pd), copper (Cu), and platinum (Pt) have been incorporated with antimicrobial extracts for medical application as an effective antimicrobial agent due to their reduced size and selectivity towards bacteria and pathogens (Sánchez-López et al., 2020). MBNPs exhibited a non-specific toxicity mechanism against pathogens through direct contact with the microbial cell surface, attacking the peptidoglycan cell membrane in gram positive bacteria and invasion mechanism of lipopolysaccharides cell membrane in gram negative bacteria (Shamaila et al., 2016; Slavin et al., 2017). Another study with palladium NPs exhibits high antibiofilm and antimicrobial activity against resistant clinical bacterial isolate Cronobacter sakazakii strain AMD04 (Hazarika et al., 2017).

Silver-based nanoparticles (AgNPs) are the most intensively investigated metal materials for antibacterial applications among all MBNPs (Roduru et al., 2018). AgNPs can disrupt the cell wall of microorganisms by generating reactive oxygen species (ROS) that destroy the growth mechanism of microorganisms leading to the cell death of microorganisms (Burdușel et al., 2018; Panáček et al., 2018). High antimicrobial activities of AgNPs against yeast Candida albicans and bacteria such as Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa had been reported (Garibo et al., 2020). The efficiency of AgNPs was highly related to the rate of Ag release and the total amount of Ag that is in contact with microorganisms. In addition, Ag can inhibit microbial replication through the denaturation of the DNA and RNA and nucleus disruption of microorganisms. Oxidation of metals such as silver oxide (Ag$_2$O), zinc oxide (ZnO), Silicon dioxide (SiO$_2$), titanium dioxide (TiO$_2$), and copper oxide (CuO) also show high antimicrobial properties (Dizaj et al., 2014). For instance, the application of ZnO NPs in pharmaceuticals had been widely explored and shows cell growth inhibition to a wide range of pathogens (Yusof et al., 2019).
3.3. Polymeric-based nanoparticles (PBNPs)

Plant, microbe and animal-based antimicrobial agents can be developed into polymeric nanoparticles, which provide excellent features for medication applications. Nanoparticles have multiple binding sites and small diameter, can penetrate through microbe membranes and cause cellular damage (Paladini and Pollini, 2019). The natural polymeric based nanoparticles are obtained from natural sources such as cellulose, chitosan, alginate, and starch. Chitosan exhibited antibacterial properties against Escherichia coli, Staphylococcus aureus, Shigella dysenteriae, Streptococcus mutans, Salmonella, typhimurium, Salmonella choleraesuis, and Pseudomonas aeruginosa (Cui et al., 2018; Sotelo-Boyás et al., 2017; Wassel and Khattab, 2017). When compared to the common antibiotic Ciprofloxacin, the synthesized chitosan nanogel shown strong antibacterial activity against gramme + ve (S. pyogenes) (Ahmed et al., 2020). Therefore, chitosan and sodium alginate have been developed into antibacterial hydrogel beads (Qu and Luo, 2020). Polycationic characteristics of chitosan enable interaction with anionic bacterial cell membrane resulted to cell lysis and cell leakage of cellular components (Luo and Wang, 2013). The antibacterial properties, flexibility, and recyclability of the starch hydrogel enhanced with copper nanoparticles make it a promising candidate for wound healing and filler applications (Villanueva et al., 2016). Furthermore, because the polymeric nanoparticles are biodegradable, have minimal toxicity, and have good antibacterial capabilities, these nano-layered composites have been used in the food packaging sector to increase shelf life and maintain food quality (Pandey et al., 2020). Recently, novel antimicrobial hydrogels produced by 3D-printed alginate cellulose incorporating copper show potential application in tissue engineering and regenerative medicine (Gutierrez et al., 2019). Apart from the medical application, the chitosan-alginate-AgNPs based nanocomposite is suitable as an antimicrobial filtration membrane and could be used in air conditioning systems (Venkatesan et al., 2017). There is also the potential of producing polymeric nanoparticles finishing textiles that have antibacterial properties such as cotton, wool, and bamboo for industrial textile applications (Li et al., 2017a). Generally, polymeric nanoparticles from plants are more effective and cheaper as an antimicrobial drug due to their vast availability in nature and simpler synthesis procedure compared to the animal-based antimicrobial drug (Eggers, 2019).

Synthetic polymeric-based NPs are chemically modified compounds. Synthetic PBNPs are usually present in the form of polymeric nano capsules and polymeric nanoplate in the drug delivery application either produce from the biosynthetic process such as Poly β-hydroxybutyrate (PHB) or chemosynthetic process such as Poly lactides (PLA), Polurethane, Poly (lactic-glycolic acid) (PLGA) and Polyethylene methacrylate resin (PMMA) (Christoforidis et al., 2012; Simionescu & Ivanov, 2016). Cephalosporins, carbapenems and ß-lactams are examples of synthetic polymeric-based NPs which are widely used as antibacterial agents in pharmaceutical industry (Eggers, 2019; Pereira et al., 2019).

3.4. Lipid-based nanoparticles (LBNPs)

There are many therapeutic drugs that are non-soluble in aqueous system are difficult for applications (García-Pinel et al., 2019). Nevertheless, the development of lipid-based nanoparticles with high loading capacity, thermal stability, and the ability to be mass manufactured at low cost from natural chemicals offers an ideal colloidal carriers for bioactive organic molecules and play some significant roles in antimicrobial and anti-tumours activities (Kumar, 2019). LBNPS is mainly categorised into liposomes, solid lipid nanoparticles, and nanostructured lipid carriers (Mirahadi et al., 2018). The most frequent lipid nanocarrier used in antibacterial medications is the liposome. Liposomes are mainly composed of lipids, which offer amphophilic nature with hydrophilic-head and hydrophobic-tail structure (Wang, D. et al., 2020). Liposomes can function as antimicrobial agents in both cationic or anionic form (Ng et al., 2013). In addition, liposome structure offers specific ligands that can bind with the microbial cell wall and inhibits particular microbial activities (García-Pinel et al., 2019). Nano-emulsion and oil from sage plants had been reported with high antimicrobial activities and had been widely developed as antimicrobial additives in the food industry (Yazgan, 2020).

Solid lipids nanoparticles are differentiated from liposomes with their composition of physiologial lipids that are presented in solid state. Both solid lipid nanoparticles and nanostructured lipid carriers offer similar beneficial features like site-specific targeting, exhibit low in-vivo toxicity, possess high loading capacity to load hydrophilic and

Table 2
Overview of CBNPs in the aspects of characterisation, mode of actions and other factors affecting their efficacy in antimicrobial treatment.

| Type of CBNPs | Characteristic of antimicrobial agents | Mode of antimicrobial action | Factors influence antimicrobial efficiency | Reference |
|---------------|---------------------------------------|-----------------------------|------------------------------------------|-----------|
| Graphene-based NPs | • High stability | • Cell membrane disruption | • Functional groups | (Dizaj et al., 2015; Ji et al., 2016; Jilani et al., 2018; Wang, C. et al., 2020; Yousefi et al., 2017; Zheng et al., 2018; Zhu et al., 2017) |
| 1. Graphene nanosheets | • Multidimension | • Dispersion in liquid resulting in membrane stress | • Reaction catalyst | (Ali et al., 2017; Anju et al., 2019; Azizi-Lalabadi et al., 2020; Fan et al., 2019; Mocan et al., 2017; Rajabathar et al., 2020) |
| 2. Graphene oxide | • Large surface area to volume | • Aggregation of microbial cells with graphene | • Particle size | |
| 3. Graphene oxide with metals | • Sharp edge of thick nanowalls | • Isolation of microbial cell from growth microenvironment | • Particle length | |
| 4. Reduce graphene oxide | • Synergic effect with other antimicrobial agent | • Exhibit strong toxicity against microorganisms | • Surface charge | |
| 5. Graphene oxide quantum dots | | | • Functional groups | |
| 6. Graphene oxide metal hybrids | | | • Reacton catalyst | |
| Carbon Nanotubes (CNT) | • High stability | • Aggregation in liquid medium | • Particle size | (Ali et al., 2017; Anju et al., 2019; Azizi-Lalabadi et al., 2020) |
| 1. Single walled CNT | • Large surface area to volume | • Adhesion and abortion of microbial’s cell membrane | • Buffer types | |
| 2. Multi-walled CNT | • High adsorption ability | • Aggregation of microbial cells with CNT | | |
| 3. Functionalize CNT | • Photodynamic therapy | • Accelerate electron transfer resulting ROS stress | | |
| 4. CNT metal hybrids | | • Chemical attachment of protein and polymers | | |
| Fullerene-based NPs | • High stability | • Cell membrane disruption | • Surface charge | Fernando et al. (2018) |
| 1. Fullerene | • Large surface area to volume | • Induction of ROS stress | • Functional group | |
| 2. Fullerene oxide | • Various shape | | • Particle size | |
hydrophobic molecules (Fahmy, 2018). In sum, all LBNPs types demonstrated great potential to overcome the antimicrobial resistance in addition to function as nanocarrier in the delivery system for antimicrobial drugs. To enhance their efficiency, the LBNPs technology is always incorporated into different forms such as hydrogel with a three dimensional hydrophilic polymeric network, that widely applied in industry bio-adsorbent, tissue engineering, drug and nutrient delivery, cancer diagnosis, enzyme immobilization and separation system (Qu and Lao, 2020). Calcium-algin and activated charcoal hydrogel beads had been reported to exhibit strong bactericidal effects against wide range of microorganisms such as Escherichia coli, Proteus mirabilis, Enterococcus faecalis, Pseudomonas aeruginosa, and Staphylococcus aureus (Osmokrovic et al., 2018). In addition, Ag NPs derived hydrogel beads are in conformity to showed high antimicrobial properties against Pseudomonas aeruginosa and Enterococcus faecalis (Piras et al., 2020).

4. Applications of antimicrobial agents

The primary factor in wound healing is the administration of anti-bacterial medications. One significant complication that might cause a burn patient to die after suffering an injury is wound infection (Argirova et al., 2017). The chlorinated chitosan film inhibits Methicillin-resistant Staphylococcus aureus suitable for wound healing applications (Qu et al., 2018). Polyhexamethylene biguanine (PHMB) and Chlorhexidine (CHX) are biguanide antimicrobial agents that have been applied in wound treatment (Punjataewakupt et al., 2019). Moreover, microbial transmission could occur via cross-contamination that brings by indirect contact either from clinical textiles or equipment such as patient apparel, blankets and bed sheet (Argirova et al., 2017). Therefore, extensive research has been conducted in recent decades using natural materials such as alginate (Li et al., 2017a), chitosan (Morin-Grini et al., 2019), and neem (Patel and Desai, 2014) in the development of medical textiles.

Antimicrobial agents play crucial role in food industry to maintain the quality of food, preserving the freshness of food, reducing the food waste and most importantly minimized food-borne microbial transmission. The addition of a preservative could prevent food spoiling caused by microbes. However, some chemical preservatives such as potassium sorbate, sodium benzoate, nitrate and nitrite are potentially contributed health problems such as stomach cancer (Dhiman and Aggarwal, 2019). Therefore, alternative from plants as natural preservatives in food such as Silene vulgaris (Boukhira et al., 2017), Lonicerajaponica and Magnolia obovate (Lee et al., 2018) have piqued attention. Purified essential oils from oil plants have been proven to show high antimicrobial properties, including thyme Thymus vulgaris (Gonçalves et al., 2017), and star anise Illicium verum (Dwivedy et al., 2018). Essential oils contained high aromatic hydrocarbons inhibiting growth of microbes such as Bacillus cereus, E. coli, Listeria monocytogenes, Salmonella typhimurium, and S. aureus (Samarth et al., 2017).

The food quality and preservation period can be also enhanced with the introduction of food packaging material with high antimicrobial properties. Example is chitosan film which contain positive amino acid groups that can interact with negative cell membranes of microorganims thus prevent the foods degradation (Gazon and Vazquez, 2020). Additions of essential oil such as lemongrass and clove have been incorporated into food packaging for antibacterial purposes (Ali et al., 2015; Mulla et al., 2017). The plant extracts with antimicrobial activity can be added into food to where it had been summarized in Table 3. Antimicrobial agents are also widely use in food and agricultural sectors as therapeutic, prophylaxis purposes and growth promoters, this has account for 195% and 332% increase in the production of swine and poultry for the past 30 years (Philippine Statistics Authority, 2019). These improvement is accounted for global consumption of antimicrobial in agricultural industry, approximately 63,151 tons in 2010 and this number is estimated to increase by 67%–105,596 tons by 2030 (Ibrahim et al., 2020).

Antimicrobial agents offered protection in many other industrial processes and public facilities, such as food processing facilities, water treatment systems, air conditional services and other critical operations (Heydarifard et al., 2017; Dominguez et al., 2019). Filters in air conditioners and wastewater systems, for example, limit the spread of Legionella pneumophila which can grow and thrive in the cooling system of an air conditioner to prevent legionnaires disease (Al-Abdallal et al., 2019). The introduction of antimicrobial features in the cooling tower of the air conditioner in the home or office is critically important as it is prone to microbial growth (Zhang et al., 2013). Other than that, antimicrobial agents such as MgO nanoparticles have been applied into coatings and painting to prevent microbe growth on the surface of instant walls, flooring and metal (Steinerová et al., 2020). The stability of the antimicrobial paint can be improved by adding a silica nanoposphere to immobilise the nanoparticles. Fibre-based textiles are conducive to microbial growth, due to its large surface area and high water absorption properties that offer good shelter for microbial growth (Morais et al., 2016). The growth of microbial on textile has number of negative consequences, including the appearance of unwanted stains, discoloration, and a loss of mechanical strength in the textile materials, as well as unpleasant odours and an increased risk of user infection. This is now solved by chitosan polysaccharides composite (Shahidul and Butola, 2019), silver-graphene coated textile composite (Noor et al., 2019), cotton textile treated with ammonium salt from rosin acid (Li et al., 2020), nano-emulsion for antibacterial textile manufacture (Gottamare et al., 2018), lignin polysaccharide from sugarcane bagasse in textile production (Suthornvarabhas et al., 2017).

In summary, antimicrobial agents offered many advantageous features for public health protection and food security. The increasing use of antimicrobials, on the other hand, is contributing to the establishment of antimicrobial resistance (AMR), in which more and more serious diseases have become untreatable due to drug resistance (Fofanah et al., 2020). Infectious resistant microbes are expected to kill 2.4 million people worldwide in the next 30 years, costing 3.5 billion dollars in medical care (Hofer, 2019).

5. Effect of antimicrobial resistance to the environment

There are many novel discoveries of antimicrobial agents against different pathogenic microorganisms, some are highly important, which mean very essential to human illness with limited alternatives (Table 4). Those microbes or pathogens, on the other hand, could develop resistance to antimicrobial drugs by natural selection or by obtaining antimicrobial resistance plasmids from other resistant bacteria, a process known as horizontal gene transfer (Zeineldin et al., 2019). Example of resistance affecting human health is the production of β-lactamases that inactivate β-lactam that actually existed for millions of years (Aminov, 2009). Bacteria plasmid are self-replicative DNA entities contain 20% of the commonly shared bacteria genes which is spreadable through horizontal gene transfer to transmit the resistance genes (Lorenzo-Díaz et al., 2017). Antimicrobial resistant bacterial can be found in any environment, eg gut microbiota is established at body site at an early age, a study shows that bacterial harbouring β-lactamases that inactivate β-lactam is 14.3% in a day old baby and could increase 41.5% by day 60 (Kothari et al., 2013). The antimicrobial and non-resistance species coexist in natural condition but triggered by external factors such as the existence of heavy metals in the environment and climate changes (Reverter et al., 2020; Singer et al., 2016). Some of the bacteria and their resistance mechanisms are shown in Table 5. The transmission of genetic materials between microorganisms occurred through 3 main routes: 1) Transformation, 2) transduction and 3) conjugation (Fig. 3) (Holmes et al., 2016). Non-resistance bacteria can use these strategies to acquire mutations or genes that let them to survive. Microbes with resistance genes released from humans and other animals as well as the ARG can move from terrestrial soil to aquatic environments due to the transmissibility of resistance genes.
### Table 3
Application of antimicrobials in food industry.

| Processed vegetables/ Fruits | Product | Application | Antimicrobial Agents | Result | References |
|----------------------------|---------|-------------|----------------------|--------|------------|
| Cabbage                    | Coating and packaging | Acetic, lactic, malic acids, dimethyl acrylamide, anthocyanin, chitin nanocrystal | Inhibited *E. Coli*, *Salmonella typhimurium*, and *L. monocytogenes* | (Alpaslan et al., 2018; Wu et al., 2020) |
| Apple                      | Coating film | Chitosan, polyphenols | Antimicrobial effect on several gram positive bacteria such as *Listeria monocytogenes* | Riaz et al. (2018) |
| Lettuce                    | Sanitizers | Propionic, acetic, lactic, malic, citric acid | Antibacterial effects against *E. coli*, *S. typhimurium*, and *L. monocytogenes* | (Park et al., 2011; Poinenidou et al., 2016) |
| Tomatoes                   | Coating and packaging | Garlic oil poly-vinyl alcohol, chitosan, isocatic acid Sodium alginate | Low microbial growth | Szabo et al. (2020) |
| Kiwifruits                 | Coating and packaging | Thyme, olive essential oil, olive flounder, roselle calyx extract Citral, linalool, B-Pinene | Exhibited bactericidal activity against *S. aureus*, *Y. enterocolitica*, *L. monocytogenes*, *E. faecalis* and *S. carnosus* | Lima-Ruiz-Cabello et al. (2016) |
| Strawberry                 | Edible coating | Thymol, calcium chloride, ethyl lauroyl arginate, pomegranate, nattymycin, nisin, carvacrol, roselle calyx extract | Inhibited heterotrophic bacterial Fena and moulds, yeasts colony, Reduced total aerobic mesophilic bacteria and Enterobacteria | (Amal et al., 2015; Duran et al., 2016; Li et al., 2021) |
| Jalapeno Peppers           | Sanitizers | Sodium hypochlorite, pereioxicetic acid, acidified sodium chloride, carvacrol, roselle calyx extract | Maintained microbiological and overall quality >17 days | (Rangel-Vargas et al., 2017; Ruiz-Cruz et al., 2010) |
| Orange Based Soft Drink    | Mild heat treatment | Oregum Vulgur L. Virens essential oil | Inhibited growth of *Saccharomyces cerevisiae* | Belletti et al. (2010) |
| Ready-To-Eat Salads        | Packaging | Origanum Vulgur L. Virens essential oil | Exhibited bactericidal activity against *S. aureus*, *Y. enterocolitica*, *L. monocytogenes*, *E. faecalis* and *S. carnosus* | Lima-Ruiz-Cabello et al. (2016) |
| Spinach                    | Packaging | Thyme essential oil, olive flounder bone gelatin, lactic acid and orceano | Reduced population of *E. coli* and *S. Typhi* | (Beak et al., 2017; Issa et al., 2017; Poinenidou et al., 2016) |
| Dairy-Based Product        | Burrata Cheese Packaging | Lysozyme and EDTA | Prolong shelf life | Conte et al. (2011) |
| Ricotta Cheese             | Edible coating | Galactomannans incorporating nisin, citrus essential oil, red cabbage extract | Inhibited growth of *L. monocytogenes* | (Bi et al., 2015; Fancello et al., 2020; Martins et al., 2010) |
| Mini Red Babybel® Cheese   | Films | Sodium caseinate | Reduction of *L. innocua* counts | Cao et al. (2011) |
| Fresh Kashar Cheese        | Biopolymer, edible coating | Natamycin, ginger and orange essential oil, alginate and zein | Eliminate *Aspergillus niger* | (Kavas and Kavas, 2016a; Kavas et al., 2016b; Čik et al., 2020) |
| Salooi Cheese              | Films | Natamycin | Decrease moulds/yeasts counts | Fajardo et al. (2010) |
| Yogurt                     | Additives | Anise volatile oil, oleoresin, natamycin, zinc oxide | Effective in controlling growth of *S. Thermophilus* and *lactobacillus bulgaricus* | (El-Sayed et al., 2021; Anari et al., 2022; Singh et al., 2011) |
| Feta Cheese                | Additives | Oregano and Thyme essential oils | Reduced aerobic, anaerobic, *Enterobacteriaceae*, yeast-mould, *B. cereus* and *S. aureus* counts | Govaris et al. (2011) |
| Meat                       | Films | Mentha Piperita, Bunium Pervicium, Sage nanocellulose essential oil, pomegranate, tisopro alcohol | -Effecive antibacterial activity against *S. aureus*, *Enterobacteriaceae* and *Pseudomonas* | (Ahmed and Ismail, 2010; Eman-Djomeh et al., 2015; Kapetanakou et al., 2020) |
| Ground and minced Beef     | Films | Mentha Piperita, Bunium Pervicium, Sage nanocellulose essential oil, pomegranate, tisopro alcohol | Decreased natural microflora, total microbial content down to 50% | (Fratianne et al., 2010; Konuk Takma and Korel, 2015; Mulla et al., 2017) |
| Chicken Meat               | Dipping | Thyme, balm, black cumin and clove essential oils | Decreased Monocytogenes population | (Mastromatteo et al., 2010) |
| Ostrich Patties            | Packaging | Lysozyme, Nisin, EDTA | Reduced total aerobic mesophilic bacteria and *E. coli* | (Hecer and Guldas, 2011; Khlafalla et al., 2016a, 2016b) |
| Broiler Wings              | Dipping | Chlorine Dioxide, Lactic Acid, Fumaric Acid, rosemary and sunmap extract, nisin | Reduced Monocytogenes population | (Mastromatteo et al., 2010) |
| Poultry                    | Coating | Nisinplin, Guardian, essential oils, cotrimoxazole, neomycin | - Reduced aerobic mesophilic bacteria and *E. coli* | (Hecer and Guldas, 2011; Khlafalla et al., 2016a, 2016b) |
| Sausages                   | Packaging, coating | Lemon Alkott, Thymol, thyme, whey protein, Cymobegon extract | Decreased Monocytogenes population | (Mastromatteo et al., 2011) |
| Mortadella                 | Additives | Orange Dietary Fibre, Rosemary and Thyme Essential Oil | No Enterobacteria or psychotropic bacteria were found | Bfoeira et al., 2020; Kalkan and Ergrik, 2019 |
| Lamb                       | Packaging, Films | Thyme, olive, orceano Essential Oils, Carrageenan | - Extended shelf life >25 days, reduced microbial populations | (Kabagbas et al., 2013; Martiny et al., 2020; Pabast et al., 2018) |
| Chicken Tenderloin         | Films | Thyme Essential Oil | Inactivation of *Escherichia coli* | Lee et al. (2016) |
| Fish                       | Packaging | Oregano, thyme, Essential Oil, sodium alginate, chitosan | High antimicrobial activity against *L. monocytogenes* and *E. coli* | (Andrevaris and Rerazi, 2011; Meral et al., 2019; Razi et al., 2020) |
| Hot Smoked Rainbow Trout   | Packaging | Thyme Oil, Garlic Oil | Reduced population of *S. putrefaciens*, *Enterobacteriaceae*, and *Pseudomonas* spp. | Erkan (2012) | (continued on next page)
As mentioned before, emergence of ARG are mainly due to high prescription of antimicrobial medicine to human and animal population (Center of Disease Dynamic, 2020). Improper disposal of pharmaceutical products and expired medicine (including the antibiotics) and biosolids (remaining residue after sewage treatment) pose the risk of the releasing antibiotic resistance genes (ARGs) and contaminate soil and water source (Anwar et al., 2020). Release of antimicrobial agents from different facilities provide survival pressure continuously on various microorganisms facilitate the evolution process. Faecal bacteria from human digestive system also release through sewage containing various type of bacteria and undigested medication such as antibiotics making the effluent became reservoir for antibiotic resistance development (GwenzI et al., 2020). A case study on human stools was conducted by Bich et al. (2019) showed the presence of antimicrobial resistance genes such as quinolone resistance genes (qnrS) and mobile colistin resistance genes (mcr-1 and mcr-3) in more than 90% of the sample population. Similarly, the untreated wastewater effluent from agriculture farmland could contain ARGs and release to the environment (Cheong et al., 2020). Antibiotics were given to livestock on a regular basis, which resulted in the accumulation of drug residues in the animals and dairy products (Ronquillo and Hernandez, 2017). In facts, the therapeutic use of antimicrobials prescribed for animal husbandry is significantly greater than for humans (Van et al., 2020). AMR reservoirs found in animal dung may have an impact on the soil microbiota. As reported by Han et al. (2018), the number and abundance of ARGs in animal manure are significantly higher than those in untreated soil. The cultivation of vegetables with animal manure soils that contain resistant antimicrobial might be a potential route for ARGs dispersal into food chain (Qian et al., 2018). Chemicals synthesis antimicrobial such as aluminum, lead, manganese and copper used in crop protection, causing the natural selection pressure on soil bacteria communities and the spreading of ARGs (Knapp et al., 2017). Pesticides such as bactericides and fungicides that are commonly used in agriculture could persist in soil and become a potential AMR reservoir. Aspergillus fumigatus is one of the fungi that caused aspergillosis in human that showed resistant to the triazole medication (Miller et al., 2022). According to Rybak et al. (2019), gene mutation cyp51A is the potential cause that contributes to the fungus resistance to the drug.

Similar to animal husbandry, bacterial infection often happen in cultured fish leads to frequent use of antimicrobial agents, eventually result in the development of antimicrobial resistance bacteria in aquaculture (Preena et al., 2020). Open cage aquaculture farm with free flow of water from the surrounding farm that contaminated with antibiotic become a potential reservoir of ARGs and disperse to the surrounding water (Muziasari et al., 2016). The first reported antimicrobial resistance bacteria was Aeromonas salmonicida by Snieszko and Bullock (1957). Since then ARGs are detected in the fish intestine, including sulphonamide, trimethoprim, tetracycline, aminoglycoside and chloramphenicol resistance genes (Muziasari et al., 2016). Similar ARGs were found in the fish farm sediments showing that the fish excretion also contributes to the enrichment of the resistance genes in the farm and pose a risk in the spreading of ARGs to the aquatic environment. According to Szymańska et al. (2019), ARGs originating from human and animal bodies have been discovered in the environment without antimicrobial drug pollution. Animals that tends to migrate from one place to another also contributes to the spreading of ARGs even there is no anthropogenic activities that caused the antimicrobial drugs pollution. It was found that 84% of the wild seabirds that often travel across different water zone for food, disseminating ARGs (Edwbank et al., 2021). According to Piva et al. (2020), it was found that honey bee from different experimental sites contain the same type of bacterial population with resistance against amoxicillin, further expose wildlife to the risk of infection and also become the effective intermediate vectors due to their high mobility.

6. Mitigation and action plans against AMR

To combat AMR, the 68th World Health Assembly adopted a Global Action Plan on Antimicrobial Resistance campaign in May 2015 (World Health Organisation, 2015). Minimizing antibiotic dependency and reducing antimicrobial resistance contamination in the environment is a key component of the National Action Plan, and it necessitates ongoing, coordinated, and complementary initiatives by individuals and organisations all over the world (Ying et al., 2017; Topp et al., 2017). Top antibiotic consumers such as China, the Netherlands, and Brazil have set a goal to reduce antibiotic use by 2020 (Topp et al., 2017). This resulted in a considerable fall in antibiotic consumption by China, the world’s largest consumer, from 162,000 tonnes in 2014 to 57 percent in 2018 (Zhang et al., 2015). Nonetheless, antibiotics given to animals in China were found to have released roughly 53,800 tonnes into the environment after being discarded in wastewater (Zhang et al., 2015). Moreover, wastewater management in low-income countries is particularly challenging and given that 14% of people globally carry E. coli in their faeces that produce extended spectrum ß-lactamase (ESBL) enzymes that resistance to penicillin, cephalosporins, cephamycin, and to some extent carbapenems, making such a challenge to control the spread of antimicrobial resistance (Karanika et al., 2016; World Health Organisation, 2020b). An overall plan of actions to encounter the threats of AMR had been summarized in Fig. 4.

To our surprise, the antimicrobial resistance effect is reported to be
| Classes          | Sub-class   | Antibiotics                  | Treatment                                                                 | References                                                                 |
|------------------|-------------|------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Beta-lactam      | Penicillin  | Ampicillin                   | Bacterial meningitis, Gastrointestinal infections                         | (Akhavan et al., 2020; Arumugham and Cascella, 2020; Peechakara et al., 2021; Yip and Gerriets, 2021) |
|                  |             |                              | Genitourinary infections, Neonatal Group B Streptococcal infection prophylaxis, Prophylaxis in surgery, Respiratory tract infection, Septicemia and Endocarditis |
|                  | Amoxicillin |                              | Acute bacterial rhinosinusitis, Community-acquired pneumonia, Ear, nose, and throat infections, Erysipelas, Genitourinary tract infection, Group A Streptococcus pharyngitis, *Helicobacter pylori* infection, Infectious endocarditis prophylaxis, Lower respiratory tract infections, Lyme disease, Periodontitis, Pharyngitis, Post-exposure prophylaxis for anthrax inhalation, Skin and skin structure infection, tonsillitis |
|                  |             |                              |                                                                            | (Akhavan et al., 2020; Arumugham and Cascella, 2020; Peechakara et al., 2021; Yip and Gerriets, 2021) |
|                  |             | Dicloxacillin, Nafcillin, Oxacillin, Methicillin | MSSA skin and soft tissue infection                                         |
|                  | Penicillin G|                              | Meningitis, Penicillin susceptible *Streptococcus pneumonia*                |                                                                            |
|                  | Penicillin V|                              | Endocarditis, *Neisseria meningitides* infection, Skin and soft tissue infection, Streptococcal pharyngitis, Syphilis |
|                  |             |                              |                                                                            |                                                                            |
|                  | First generation cephalosporins | Cefadroxil | MSSA skin and soft tissue infection                                         |
|                  |             | Cefazolin, Cephalaxin, Cefuroxime | Perioperative surgical prophylaxis                                          |
|                  | Second generation cephalosporins | Cefotaxime | Cefotetan-gynaecologic infections                                           |
|                  |             | Cefoxitin | Perioperative surgical prophylaxis                                          |
|                  |             | Cefotetan | Upper respiratory tract infections (sinusitis, otitis media)                |
|                  |             | Cefaclor, Cefpodoxim |                                                                            |
|                  | Third generation cephalosporins | Cefotaxime | Bone and joint infections                                                   |
|                  |             | Ceftriaxone | Central nervous system infections                                            |
|                  |             | Cefoperazone, Cefixime | Chancroid                                                                  |
|                  |             | Cefdinir, Cefditoren | Genitourinary-tract infections                                              |
|                  |             | Cefibuten | Gram-negative meningitis, Gram-negative osteomyelitis, Pseudomonas pneumonia, Severe Lyme disease, Skin and soft tissue infection, Streptococcal endocarditis, UTI |
|                  |             | Cefprozil |                                                                            |
|                  | Anti-pseudomonal Cephalosporins | Cefazidime | Complicated intra-abdominal infection                                       |
|                  |             | Cefazidime/ avibactam | Complicated UTI                                                             |
|                  |             | Cefepime | Meningitis                                                                 |
|                  |             | Cefotaxime/tazobactam | Nosocomial infectious-pneumonia                                              |
|                  | MRSA cephalosporins | Cefaroline | Community-acquired pneumonia                                                |
|                  |             | Cefotibiprole | Hospital-acquired pneumonia, Skin and soft tissue infection                 |
|                  | Carbapenems | Imipenem/ cilastatin | Intra-abdominal infection                                                   |
|                  |             | Meropenem | Meningitis                                                                 |
|                  |             | Doripenem | Nosocomial infection, UTI                                                   |
|                  | Monobactams | Aztreonam | Nosocomial infection, UTI                                                   |
| Tetracyclines    | Minocycline | Acne, *Actinomycosis, Amebianias, Anaplasmosis, Brucellosis, Chlamydial infections, Ehrlichiosis, Legionnaire’s disease, Leptospiriosis, Lyme disease (early stage), Melioidosis, Nocardiosis, Pelvic inflammatory disease, Rickettsia infections, Syphilis | (Nazarian and Akhondi, 2020; Patel & Parmar, 2021) |
|                  | Doxycycline | Acne, Chlamydia, Gonorrhoea, Lyme disease, Malaria, Pelvic inflammatory disease, Skin infections, syphilis |
| Aminoglycosides  | Gentamycin | Bacterial septicaemia, Bacterial endocarditis, Enterococcal bacteremia, Gastrointestinal tract infections, Meningitis, Soft tissue infection, UTI | (Block and Blanchard, 2020; Chaves and Tadi, 2020; Reyhanoglu and Reddivari, 2020; Sizar et al., 2021; Veirup and Kyriakopoulos, 2021; Waters and Tadi, 2021) |
|                  | Tobramycin | Central nervous system infection, Complicated UTI                          |
|                  | Neomycin | Hepatic coma, Surgical prophylaxis                                          |
|                  | Streptomycin | Drug-resistance *Mycobacterium tuberculosis* infection, Pulmonary tuberculosis |
|                  | Amikacin | Bacterial Endophthalmitis, Gram-negative bacteremia and sepsis, Meningitis, Pneumonia, UTI |
| Oxazolidinone    | Linezolid | Anthrax, bacterial pneumonia, bone and joint infection, brain abscess, febrile neuroepidemiology, infectious arthritis,陈痢菌, *MRS* infections, orthopaedic device-related infection, osteomyelitis, sepsis, skin and skin structure infections, subdural empyema, vancomycin-resistant enterococcal infection, ventriculitis | Aruzzo & Preus (2020) |
| Macrolides       | Clarithromycin | *Helicobacter pylori* infection |

(continued on next page)
ARGs and mobile genetic elements (MGEs) as a mean to reduce the strategies to concentrate on the molecular level due to the nature of agriculture, natural and built habitats, and antibiotic manufacturing uptake of mobile genetic elements in the environment, particularly in stability that can confer such resistance which can further help to and animals (Holmes et al., 2016). The evolution of antibiotic resistance not reversible; antimicrobial resistance in several bacteria was myste-
to the environment to decrease selection pressure for plasmid survival and the likelihood for gene transfer and selection (San Millan, 2018). Another option is to include additional treatment to remove possible

| Classes     | Resistance Bacteria       | Antibiotics          | Treatment References                                      | References |
|-------------|---------------------------|----------------------|----------------------------------------------------------|------------|
|             | Coagulase negative Staphylococcus | Tetracycline         | Biofilm formation reduces the effects of antimicrobial agents | Silva et al. (2022) |
|             | Staphylococci and Enterobacteriaceae | Beta-lactam          | Destruct β-lactam rings, antibiotics unable to bind to the penicillin-binding protein, inhibit cell wall synthesis | (Bbosa et al., 2014a) |
|             | Mycobacterium spp         | Aminoglycosides      | Modify 16s rRNA to reduce binding of aminoglycosides and inhibit protein synthesis | Yokubynas & Iyer (2016) |
|             | Enterobacter aerogenes, Klebsiella pneumonia, and Pseudomonas aeruginosa | Beta-lactam          | Porin channel formation is decreased through which β-lactam crosses the outer membrane to reach the penicillin-binding protein of gram-negative protein | Yokubynas & Iyer (2016) |
|             | Vancomycin resistant enterococci (VRE) | Glycopeptides        | Remodelling of bacteria cell wall molecular structure, decrease vancomycin binding to inhibit cell wall synthesis | (Bbosa et al., 2014a) |
|             | Mycobacterium spp         | Macrolides           | Modify 16s rRNA to reduce binding of aminoglycoside and inhibit protein synthesis | Yokubynas & Iyer (2016) |
|             | Gram-negative bacteria and staphylococci | Quinolones (Fluoroquinolones) | Antibiotic pump out of cell/cellular membrane, prevent ribosomes bind to antibiotics | (Bbosa et al., 2014a) |
|             | Most Gram-positive and Gram-negative bacteria | Tetracycline         | The resistance gene (tet) activate a protein that modifies the bacterial membrane and prevents transport of tetracycline into the cell | Yokubynas & Iyer (2016) |

not reversible; antimicrobial resistance in several bacteria was myster-
iously unchanged after antimicrobial pressure was removed in humans and animals (Holmes et al., 2016). The evolution of antibiotic resistance should be studied extensively by identifying the key factors for plasmid stability that can confer such resistance which can further help to mitigate the issue (Wein et al., 2019). It is also advisable for mitigation strategies to concentrate on the molecular level due to the nature of ARGs and mobile genetic elements (MGEs) as a mean to reduce the uptake of mobile genetic elements in the environment, particularly in agriculture, natural and built habitats, and antibiotic manufacturing plant effluents (Zhang et al., 2018). This can be accomplished by designing a deletion system which can turn off the ARGs prior disposal to the environment to decrease selection pressure for plasmid survival and the likelihood for gene transfer and selection (San Millan, 2018). Another option is to include additional treatment to remove possible ARGs as part of disinfection processes in wastewater treatment plants, similar to how chlorination and ozonation are now applied (Vikesland et al., 2017). While having an efficient disposal system is recommended, certain wastes remain poorly regulated in public hospital in rural area and developing countries (Hassali and Shakeel, 2020). Despite active plans or guidelines being listed by the policymakers, the effort is futile if public behaviour remains discouraged.

While the mitigation takes a village for the program to work, the biggest challenge goes back to public behaviour and current lifestyle. A recent study in Tanzania on the distribution of ARBs in households from three ethnic groups in Tanzania found that livelihood factors are more strongly associated with AMR prevalence than antibiotic usage (Subbiah et al., 2020). So and Ramachandran (2020) argued that a powerful civil society can have a powerful voice in directing the course of AMR plan (So and Ramachandran, 2020). As a public, they can help lower the
demand by having a good lifestyle and decrease the need for treatment. For instance, the need to use antibiotics such as in *Clostridioides difficile* infection can be minimized by improving lifestyles and only resort to highly important cases by administering the right antibiotic at the right time at the right dose (Guh and Kutty, 2018). Thus, a rapid diagnostic kit for accurate detection is vital to administer specific drugs effectively and eliminate non-specific medication that could potentially widen the resistance. Besides, through enhanced public and policy-maker recognition of other health issues, excessive promotions of antibiotics in developing countries should be stopped (So and Ramachandran, 2020).

On the global scale, the heads of the Food and Agriculture Organization of the United Nations (FAO), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO) recently launched the new One Health Global Leaders Group on Antimicrobial Resistance comprises of heads of government, government ministers, leaders from private sector and civil society to catalyse global attention and action to preserve antimicrobial medicines and avert the disastrous consequences of antimicrobial resistance (World Health Organisation, 2020c). Besides, tight regulation by governmental policy and agency can mould the course into a more natural approach. For example, rising colistin resistance cases have been reported. Colistin, a last-resort antibiotic for hospital-acquired infection, is utilised as a growth promoter in a number of nations, including Japan, China, Brazil, and India. While the ban on colistin has been successful, the constant vigilance must be maintained as other gene variants might replace mcr-1, causative agent for colistin resistance (Wang et al., 2018). The ban on antibiotics has spurred companies to develop additives that promote growth without the risk of increasing antimicrobial resistance and the EU has adopted legislation to restrict the preventive use of antibiotics (Murugaiyan et al., 2022).

Due to the AMR, the world is in desperate need of a new class of antibiotics with novel mode of action to circumvent the resistance observed in certain types of bacteria and this calls for active participation from the manufacturer or pharmaceutical company to develop and formulate newer classes of antibiotics. The latest class of antibiotics was marketed in the 1980s and ever since then no new class has been discovered (Aminov, 2010). Innovation to develop new antibiotics may take several years to be fruitful and most of the research and development (R&D) cost for developing new antibiotics account for exploratory

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**Fig. 3.** Horizontal transfer mediated the development of antimicrobial resistance.

**Fig. 4.** Plans for reducing and combating antimicrobial resistance.
phases by screening a wide range of molecules from natural resources such as plants and microorganisms. For this, the pharmaceutical industry has taken initiative to tackle AMR by forming partnership with companies of the same field to launch AMR Action Fund to support small biotech companies until implementation of new reform of market-based policy is made (Morgan et al., 2020). Countries such as the UK and Sweden recently pioneered a pilot program to delay purchase of antibiotics and guarantee access to crucial antibiotics, at a fixed payment upfront, to ensure viability for the pharmaceutical companies to develop and supply antibiotics when needed (UK Government, 2020).

There are several issues that entangle pharmaceutical industry in developing new antibiotics. Production pipeline problems and high costing to develop new drugs has driven pharmaceutical giants to back out from drug development and shift their focus into more profitable ventures such as cancer drug discovery or into recent global pandemic (Plackett, 2020). Apart from high costs, low approval ratings from 1980 to 2014, and an unbalanced cost-benefit ratio, the road to find and develop new antibiotic medications has become protracted and perilous (Sun et al., 2017; Ventola, 2015). To tackle this, the economics of the antibiotics market needs to be restructured and governments may be required to pay more for a single drug (Plackett, 2020). Alternative resources can also be exploited to propel antibiotic discovery journey forward such as synthesized nano-polymers that can be used as antibiotics (Agnihotri and Dhiman, 2017). Coupled with recent advances in big data and artificial intelligence (AI), drug discovery companies manage to shorten the long pre-clinical stage and selectively screen for small molecules with high potentials from readily available big data. Currently, DSP-1181 registered by British pharmaceutical company is the only drug from such an avenue that is used to treat obsessive compulsive disorder (Burki, 2020), but the same approach can also be applied to identify new antibiotics.

Previously, antimicrobial agents such as lomefloxin and ofloxacin were often used in poultry in China to promote animal growth but it was then banned due to the national rules and regulations (Krishnasamy et al., 2015). Recently, nutraceutical animal feed was getting attention as it provides an antimicrobial-free poultry to the market. According to Morgan (2017), nutraceuticals such as plant extracts, pre- and probiotics have been used as an alternative to antimicrobial agents to provide good gastrointestinal environment and to minimize the chances of enteric infections. Unlike antimicrobial agents that could help in reducing various pathogen in the animals’ gut, nutraceutical products promoting the healthy gut environment by maintaining the pH value and protective mucin in the gut (Khan and Iqbal, 2016). A good probiotics refers to the microorganisms that have capability to survive in intestinal environment and able to boost the immune system against some pathogens when administered with right amount (Pan and Yu, 2014; Plaza-Diaz et al., 2019). Probiotics such as *Lactobacillus* and *Bifidobacterium* with are able to attached to the host intestinal wall through pattern recognition receptors, inducing signalling pathway and results in a probiotic-host interaction (Ma and Suzuki, 2018). It could trigger the production of mucus to prevent apoptosis. According to Vazquez et al. (2015), natural plant extracts contains bioactive compounds such as alkaloid, terpenes and flavonoid that could be added to the feeds due to their suppression mechanisms against the pathogenic microbial organisms.

Health expenditure of GDP related to COVID-19 has been predicted to rise by 2.2% and pharmaceutical giants are racing to develop and secure an effective vaccine that could save millions of lives (Qin et al., 2021). Unfortunately, the same urgency cannot be shared with slower moving health crises like AMR. Diseases caused by drug-resistant infection are predicted to rise to 10 million a year by 2050 if no action is taken (World Health Organisation, 2020c). Although the number of death caused by AMR is relatively small taking account of recent death tolls caused by the pandemic alone, yet a synchronized and thorough assessment while determining the value of antibiotics to not just include benefits vs costs, but also population level benefits such as reduced transmission, reduction in resistance rates and enable of other applications could really bring a harmonious effort from wide range of networks to remove AMR threat from the society (Morgan et al., 2020).

### 7. Conclusion

The considerable rise on the consumption of antimicrobial-based material, leading to many problems to the society and environment. Antimicrobial drug resistance has exacerbated disease control concerns, posing a serious threat to public health. This call for the urgent need to mitigate the AMR caused by contaminations of antimicrobial drug unintentionally release into environment. Clearly, efforts to keep the environment free of antimicrobial resistance are unattainable, but they can be minimized by multidisciplinary collaboration between regulatory agencies, pharmaceutical companies, and academics.

### Authors contributions

**Shing Ching Khoo**: Writing – original draft, data visualization, formatting. **Meng Shien Goh**: Writing – original draft, data visualization, formatting. **Amirah Alias**: Writing-editing. **Vijitra Luang-in**: Writing-editing. **Kah Wei Chin**: Writing-editing. **Tiong Hui Ling Michelle**: Writing-editing. **Nyuk Ling Ma**: Conceptualization, Supervision, Writing – review & editing. **Christian Sonne**: Conceptualization, Supervision, Writing – review & editing.

### Justification of the involvement in human or animal subjects research

This study do not dealing with any research or studies on human subjects or experimental animals.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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