

## Mechanism of Antimicrobial Resistance and Red Ginger as the Solution for Source of Natural Antioxidant: A Brief Review

Ni Kadek Yunita Sari<sup>1\*</sup>, Anak Agung Ayu Putri Permatasari<sup>1</sup>, Sri Puji Astuti Wahyuningsih<sup>2</sup>, Almando Geraldi<sup>2</sup>, Putu Angga Wiradana<sup>1</sup>, I Gede Widhiantara<sup>1</sup>, Novaria Sari Dewi Panjaitan<sup>3</sup> and Ni Nyoman Ari Mardianti<sup>1</sup>

1. Study Program of Biology, Faculty of Health, Science and Technology, Universitas Dhyana Pura.Jl. Raya Padang Luwih, Badung 80351, Bali, Indonesia
2. Department of Biology, Faculty of Science and Technology, Universitas Airlangga, Surabaya 60115, Indonesia
3. Center for Biomedical Research, Research Organization for Health, National Research and Innovation Agency, Cibinong Science Center, Cibinong - Bogor Indonesia

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\*Corresponding author  
Ni Kadek Yunita Sari

Email:  
yunitasari@undhirabali.ac.id

### ABSTRACT

In this review, we describe the known mechanisms of antimicrobial resistance which was increasing in this era, due to the misuse of antimicrobial agents such as antibiotics, or genetic and phenotypic mechanisms. The special concerns addressed by designated researchers in their study and WHO in their observations and reports, regarding the types or strains of bacteria with antimicrobial resistances, were described. In addition, the predicted mechanisms that promote the development and occurrence of antimicrobial resistance, such as bacterial biofilm formation, horizontal gene transfer, genetic mutations, free DNA which contains antimicrobial resistance genes, and plasmids transfer through transformation or conjugation from bacterial cell to cell were well described. In addition, we also tried to describe the use of *Z. officinale*. The antimicrobial capabilities of this herbal plant are attributed to its capacity to create many secondary metabolites with rather complicated structures that have antibacterial and antioxidant characteristics. *Z. officinale* had been used for many kinds of disease treatment traditionally. And along the way, the advance techniques of research in chemistry and biology fields had found out the composition and bioactive compounds. The common online databases such as PubMed, Semantic Scholar, Crossref, Medline, Scopus, and Web of Science (WoS) were utilized in this review to conduct literature searches. According to the recent progress of antimicrobial cases observed, the efforts to strengthen the surveillance, and general health systems, tightened the antimicrobial medicine distribution rules, and education for the public are indeed needed.

**Key words:** Antimicrobial resistance, gene transfer, biofilm formation, bacterial infection, *Zingiber officinale*

### INTRODUCTION

Diseases induced by microbial infections are very hazardous to human health and biosecurity worldwide (Lin & Sun, 2022). The World Health Organization defines "Good-Health" as "the development of physical and mental well-being that is not impaired by illnesses or other disorders" (Arumugam *et al.*, 2014). Antibiotic discovery has been highlighted for its utility since antibiotic

itself may enhance human health and expand human life expectancy, as well as being a key medical milestone of the twentieth century (Luo *et al.*, 2019; Salas-Ambrosio *et al.*, 2021). The mechanisms of antibacterial activity of some antibiotics had been reported, which involved the inhibition of essential biological processes of bacteria such as the bacterial cell wall production, protein synthesis, and DNA replication

(Kapoor *et al.*, 2017). However, the capacities of bacterial cells to adapt to and resist the prospective antibiotic treatment, such as the possible changes in the binding receptor, are considered as limited factors depending on the particular antibiotic action (Peterson & Kaur, 2018).

Antimicrobial resistance (AMR) in many bacterial pathogens is a severe concern to world health and a significant one in terms of morbidities (Dhingra *et al.*, 2020). Comprehensive knowledge of the molecular processes underlying the formation of AMR is required in order to develop novel therapeutic techniques to prevent AMR associated with bacterial infections (Kok *et al.*, 2022). Pathogenic bacteria may survive the antibiotic exposure through a variety of genetic and phenotypic AMR pathways (Kassinger & van Hoek, 2021). This genetic pathway may be linked to long-term alterations in antimicrobial sensitivity, such as the acquisition of cellular genetic elements and chromosomal gene mutations that lead to antibiotic resistance (Blair *et al.*, 2015). Furthermore, the phenotypic mechanism is linked to a brief reduction in antibiotic sensitivity, which may be homogeneous (as in tolerance) or heterogeneous (as in heteroresistance) (Lázár & Kishony, 2019; Westblade *et al.*, 2020). Another phenotypic process that might decrease antibiotic efficacy is bacterial biofilm formation, which can be viewed as the capacity of bacteria to form bacterial aggregates protected by a polymer matrix (Crabbé *et al.*, 2019). Understanding the metabolic pathways that support the AMR mechanism may be exploited to selectively change metabolic activity during antibiotic treatment in order to re-sensitize the bacteria cells to antibiotics (Meylan *et al.*, 2018).

Because of the influence on the AMR issue, focus is progressively moving to the utilization of bioactive components derived from plant species used as herbal remedies, which may provide both antibacterial and antioxidant sources that have an impact on human health (Cheesman *et al.*, 2017; Gupta & Birdi, 2017; Harikumar & Krishanan, 2022). The antimicrobial capabilities of this herbal plant are attributed to its capacity to create many secondary metabolites with rather complicated structures that have antibacterial and antioxidant characteristics (Chassagne *et al.*, 2021). Oxidative stress, which is defined by the appearance of an imbalance between the development of reactive species and antioxidant defence activity, may intensify in the presence of numerous degenerative

disorders and infectious diseases that are caused mostly by microbes (Widhiantara *et al.*, 2021). Antioxidants derived from *Cyperus rotundus* plant extracts, for examples, have a synergistic impact on ampicillin-resistant *S aureus* via the disintegration of peptidoglycan and cytoplasmic membranes (Angiolella *et al.*, 2018). Plant-derived bioactive chemicals are now receiving a lot of attention because to their potential medicinal and nutritional advantages as functional foods (Zeng *et al.*, 2012).

The use of medicinal plants practically by traditional practitioners remains a framework in various health care endeavors, particularly in rural parts of tropical nations such as Indonesia (Adeyemi *et al.*, 2012). The World Health Organization also confirms that approximately 74% of the 119 pharmaceutical drugs derived from plants currently used in modern medicine which is directly related to their traditional use as medicinal plants, is urging large pharmaceutical companies to conduct more extensive research to determine the potential value of plant materials. Herbs, spices, and oils have long been recognized to include chemical elements such as tannins, alkaloids, and terpenes, which are potential sources of novel compounds with varied health impacts including as AMR preventive options (Manach *et al.*, 2004).

*Zingiber officinale* (Zingiberaceae) rhizome is extensively used as a spice in cooking and as a component in traditional medicine. Turmeric, cardamom, and galangal are other members of this plant family (Hopkins *et al.*, 2013; Sulaiman *et al.*, 2014; Wahabi *et al.*, 2010). Ginger cultivation began in Asia and was extended along the commerce system to East Africa and the Caribbean (Sulaiman *et al.*, 2014). This plant may have the benefit of lowering the risk of medication resistance development. The residue of these natural substances in meat, on the other hand, is safe for human consumption and has few detrimental health implications. Ginger is also reported to be an important antioxidant that may help to minimize the development of free radicals. On the other hand, ginger also has the potential to be employed as an insecticide, antibacterial, anticancer, antidiabetic, and other bioactivities due to its antioxidant characteristics and protective functions. Ginger rhizome has recently been shown to boost growth performance in experimental animals while reducing serious negative effects from dosing.

The antibacterial property of spices, especially ginger rhizome, is induced by the presence of certain phytochemicals or essential oils. The type and contents of the plant, the quantity employed, the type of target microbe, the composition of the meal, the pH value, and the ambient temperature are the primary parameters that impact the antibacterial activities of traditional plant materials. Several investigations on the bioactivity properties of ginger rhizome and its combination with other plants had been published. However, little is known about the potentials of ginger rhizomes as AMR prevention treatments, the specific mechanism of its antimicrobial activity, and the antioxidant agents contained in it (Goel *et al.*, 2021). This review intends to highlight the existing knowledge on AMR, with an emphasis on bacterial species in the food chain, including animal, environmental, and human sources, as well as the potential of ginger rhizome as an AMR prevention solution and antioxidant agent (Gemedda *et al.*, 2021).

### **General mechanism of antimicrobial resistance (AMR)**

Most microorganisms have transformed an essential ability to continue growing in order to withstand the challenges of their environment by acquiring resistance to antimicrobial drugs used to treat infectious disorders today (Fair & Tor, 2014). AMR, also known as medication resistance, occurs when microbial agents such as bacteria, viruses, fungi, and parasites are able to modify their behaviors, proving traditional treatments ineffective for the treatment of infectious disorders. Several studies have connected greater levels of AMR to the use of pharmaceutical compounds that are not controlled by relevant agencies in certain countries, which has resulted in an increase in the prevalence of AMR in society (Annunziato, 2019).

Important cellular modifications associated with AMR in which metabolic control play an important role through (i) cellular energy generation, (ii) cell envelope remodeling, and (iii) cell-to-cell contacts in biofilms (Kok *et al.*, 2022). However, in general, AMR in bacteria may occur via four major mechanisms: (i) target alteration, (ii) drug inactivation, and (iii) drug transport and (iv) inactivation of drug agent (Figure 1) (Reygaert, 2018; York, 2021). However, owing to outer membrane structural differences, *etc.*, there are differences on mechanisms employed by Gram-negative and Gram-positive bacteria for AMR

capabilities range. Gram-negative bacteria use three main mechanisms to induce resistance, whereas Gram-positive bacteria have fewer drug absorption restrictions because they lack a broad lipopolysaccharide (LPS) membrane and the ability to use certain types of drug-binding mechanisms to achieve resistance (Reygaert, 2018; Chancey *et al.*, 2012).

The employment of generic efflux pumps is directed to transport antimicrobials out of cells, inactivate enzymes, and decrease permeability qualities that reduces medication penetration into bacteria (Birgand *et al.*, 2020; Blair *et al.*, 2015). The discovered processes involve enzymes, encoded by bacterial plasmids, could change the medicinal work of actions (Peterson & Kaur, 2018). Bacteria may highlight the metabolic pathways outlined at the beginning of this paragraph to change drug targets and avoid the binding to the target enzymes, which resulted in lowering the inhibitory impact of antibiotics (Lakoh *et al.*, 2020; Martínez & Rojo, 2011; Ray *et al.*, 2017) (Figure 1).

### **Main factors of antimicrobial resistance (AMR)**

Antimicrobial abuse and unrestricted medicine distribution have been widely documented (Batista *et al.*, 2020). AMR can be accumulated through genetic mutations, which are then passed on to the next generation via "vertical gene transfer" or the mechanism of "horizontal gene transfer/HGT," transformation (taking of DNA from the surrounding environment by competent cells), transduction (genetic transfer via viral vectors), and conjugation (DNA transfer via direct cell-cell contact) (Alawi *et al.*, 2022). Interestingly, study results to now have indicated that AMR is more prevalent in clinical infections, but their transmission in the natural environment has also emerged.

*Mobile genetic elements* (MGE) such as plasmids are one of the mechanisms that cause gene transfer in bacteria cells. There are currently no certain rules in place to manage the antimicrobial resistance transmitted by plasmid-mediated AMR circulating in the environment. Plasmids play a vital role in the transmission of AMR because they function as vehicles or vectors in distributing resistance of antimicrobial agents from one environment to another. This propagation of antimicrobial resistance genes may then be linked to numerous cellular genetic components that can also gain virulence genes from an infectious bacteria (Firoozeh *et al.*, 2022).

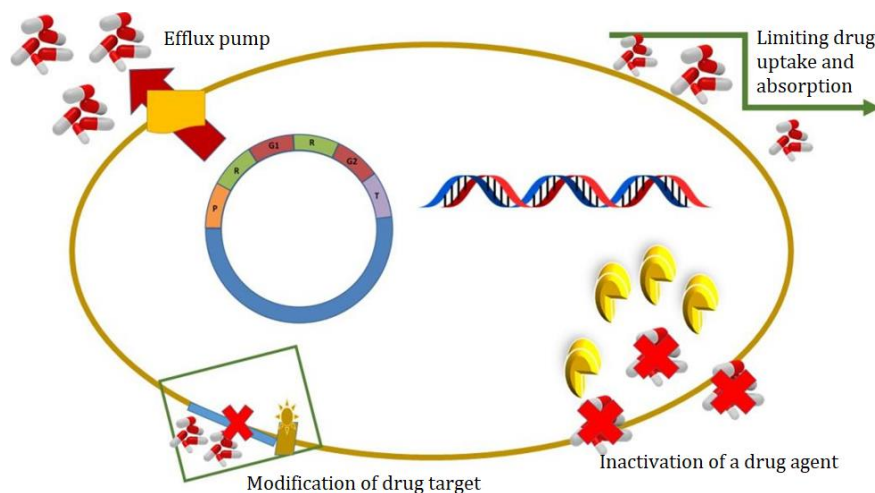


Figure 1. General mechanism of antimicrobial resistance (AMR) to drug substances. Figure are processed personally and adapted from C Reygaert, (2018).

Table I. The pathogens listed according to their antimicrobial resistance patterns based on the World Health Organization priority pathogens list (adopted and remade from Mogasale *et al.* (2021)).

Priority	Pathogens	Reported antimicrobial resistances
Critical priority	1. <i>Acinetobacter baumannii</i>	- Carbapenem resistance
	2. <i>Pseudomonas aeruginosa</i>	- 3 <sup>rd</sup> generation cephalosporin resistance
	3. <i>Enterobacteriaceae</i> species	
High priority	4. <i>Enterococcus faecium</i>	- Vancomycin resistance
	5. <i>Staphylococcus aureus</i>	- Methicillin resistance in <i>S aureus</i> (MRSA)
	6. <i>Salmonella</i> species	- Fluoroquinolone-resistance
Medium priority	7. <i>Streptococcus pneumoniae</i>	- Penicillin resistance
	8. <i>Shigella</i> species	- Fluoroquinolone resistance

The findings and descriptions from a recent review study demonstrated a positive and negative association between antibiotic resistance and virulence, as shown by the prevalence of Uropathogenic *E. coli* (UPEC) (Firoozeh *et al.*, 2022).

The absence of sanitation, biosecurity, and regulatory controls in numerous industries that use antibiotics to manage illness also contribute to give a significant impact on the advent of AMR. AMR residues which, for example, present in meat and livestock sector secretions, may exert selection pressure and generate multidrug-resistant bacteria in the animal environment (Moffo *et al.*, 2022). Poor environmental sanitation also hastens the spread of AMR, particularly in underdeveloped countries. *E. coli* is a microflora of the human gastrointestinal system and is one of the most widely investigated species. Previous study found that a dominant clone of *E. coli* was recovered from

the feces of thirty children from six semi-rural villages near Quito, Ecuador, which up to three isolates of the ST 131 clone harbored the broad-spectrum lactamase (ESBL) gene, which causes AMR (Calderón *et al.*, 2022).

#### Antimicrobial resistance (AMR) issues

Because of the risk it presents to the treatment efficacy of an ever-increasing array of infectious organisms irresponsive to standard medications, antimicrobial resistance (AMR) has emerged as one of the most important public health and environmental challenges of the twenty-first century (Nelson *et al.*, 2019). The World Health Organization (WHO) has long acknowledged the need of more consistent and coordinated worldwide efforts to combat AMR. This began in 2001, when WHO devised a framework to manage and prevent the spread of antibiotic resistant bacteria via the "Global Strategy for Containment of

Antimicrobial Resistance". Furthermore, in 2012, WHO re-released "The Evolving Threat of Antimicrobial Resistance - Options for Action", which proposes a combination of interventions such as strengthening health systems and surveillance, increasing antimicrobial use in hospitals and communities, infection prevention and control, encouraging drug development and new vaccines, and political commitment. In addition, in 2021, WHO will undertake a "World Antimicrobial Awareness Week" campaign, inviting "One Health" stakeholders, policymakers, health care professionals, and the general public to maintain their commitment to raising awareness about the issue of AMR. The pathogens with antimicrobial resistance patterns, posing the greatest threat to human health (Table I), according to the priority list by World Health Organization (WHO) (Mancuso *et al.*, 2021; Mogasale *et al.*, 2021).

Antimicrobial abuse and overuse in animals, human, and plants are the primary causes of the emergence of illnesses resistant to commercial treatments (Manyi-Loh *et al.*, 2018). Since end of 2019, the world was shocked by COVID-19 due to SARS-CoV2 infection. Because COVID-19 is caused by a virus (not a bacterial infection), antibiotics are not indicated to treat COVID-19 infection (Knight *et al.*, 2021; Monnet & Harbarth, 2020). However, not few individuals, forcing themselves based on limited proper health education and knowledge, used commercial antibiotics for COVID-19 treatment. Improper diagnostic and prescription techniques, as well as individuals who fail to adhere to treatment regimens, all contribute to AMR (Ayukekong *et al.*, 2017). As previously stated, a lack of understanding about clean water sanitation and poor sanitation in the health, livestock, agricultural, and community settings, as well as insufficient infection prevention and control measures, could promote the growth of different drug-resistant illnesses (WHO, 2021). The elements involved in the spread of AMR in diverse industries such as livestock and agriculture, the environment, and human antibiotic overuse are described below.

### **Antimicrobials resistance rates in animal husbandry**

The widespread rise of multi-drug resistance bacteria had been primarily linked to the overuse and misuse of antibiotics in agriculture and veterinary medicine. Surprisingly, the global use of antibiotics for cattle health in order to increase

output surpassed the use of pharmaceuticals in individuals. Data showed that the usage of antimicrobial drugs in the livestock industry is closely connected to the prevalence of resistant bacteria in food-producing animals (FPA) (Baron *et al.*, 2014; Chantziaras *et al.*, 2014). Fresh animal dung and manure have been identified as a primary cause of AMR. Living (resistant) bacteria, free bacterial DNA, and antimicrobial resistance genes (ARG) are transmitted through the air as dust particles (Figure 2) (Dohmen *et al.*, 2017; Laube *et al.*, 2013; McEachran *et al.*, 2015; von Salviati *et al.*, 2015).

Feces containing AMR genes or DNA may pollute farms, manure dumps, agricultural land, and the surrounding environment by runoff and aerosolization (Huijbers *et al.*, 2019; Liu *et al.*, 2018). Molecular microbiology sequencing study revealed that these ARGs are part of the airborne dust microbiome from various urban and rural locations (Yang *et al.*, 2018). Surprisingly, agricultural dust contains more diverse and extensive resistome (Li *et al.*, 2018; Luiken *et al.*, 2020).

We have reviewed many situations involving the identification of antibiotic usage and the occurrence of resistance in diverse farms around the world. The previous study examined 947 farm dust samples collected from 174 poultry farms and 159 pig farms in nine European nations. The researchers discovered that the antimicrobial resistance genes had spread via the dust of European pig and poultry farms, and that its relative abundance, as indicated by 16S rRNA, was comparable to animal waste, with the greatest amounts seen in pig farms. This discovery is intriguing since cattle pasture dust may function as a reservoir for ARGs which could be passed to other species, including humans (Luiken *et al.*, 2022).

The role of antibiotic use in the establishment of AMR in dairy farm in the British Isles has previously been examined by identifying livestock management parameters and isolating significant bacterial species from the livestock environment (McLaughlin *et al.*, 2022; Murphy *et al.*, 2018). In this particular research, the capacity of bacteria as antimicrobial resistance agents was measured using the MIC value, which is the lowest concentration of antimicrobial necessary to prevent the development of particular pathogenic germs (Michael *et al.*, 2020). Several management elements have been found as being linked with enhanced cleanliness and lower MIC values in *Enterococcus spp.* and *E. coli* throughout dairy farms in the British Isles.

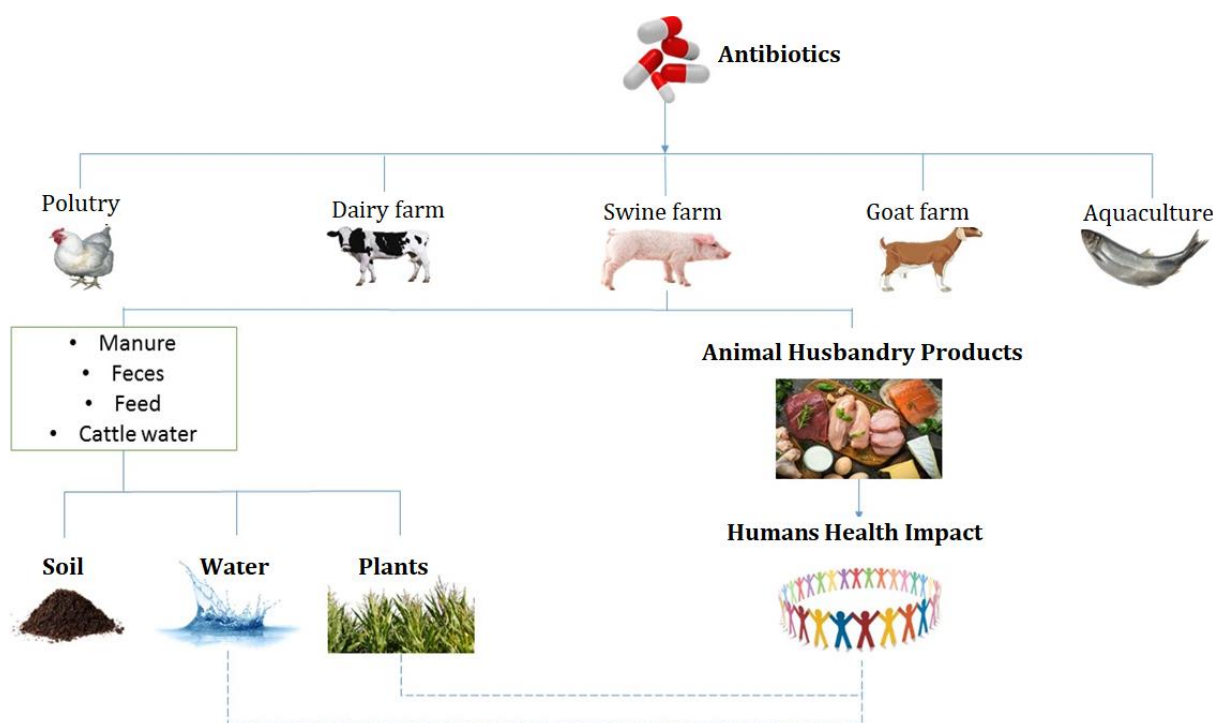


Figure 2. The possible transmission channel for AMR resulting from antibiotic induction in different animal commodities is through feces accumulating in meat products and the environment. Direct transmission is shown by solid lines, whereas indirect or prospective transmission to human health is indicated by dashed lines.

Feed and waste management, booth matting, nipple control during milking, milking frequency, cow management, and the entrance of additional animals onto the farm are among these issues (McLaughlin *et al.*, 2022). It has been discovered that livestock manure serves as a substantial reservoir of antimicrobial chemicals, resistant microorganisms, and antibiotic resistance genes (Heuer *et al.*, 2011). The feed storage area demands special consideration since it may both assist environmental factors and promote AMR to arise and spread in livestock regions (Lanyon *et al.*, 2021). The scientists also noticed that the percentage of bacteria with higher AMR features during storage as a consequence of horizontal gene transfer and selection of resistant genes led to the rise in MICs in these farms (McLaughlin *et al.*, 2022). Resistance in *Enterococci* bacteria is caused by the use of  $\beta$ -lactams, high fluoroquinolones, and high MIC values, thus breeders and veterinarians should be more cautious when using this class of antimicrobials, particularly fluoroquinolones and third and fourth generation cephalosporin medicines (McLaughlin *et al.*, 2022).

However, in addition to concentrating on the prevalence of AMR on poultry and ruminant farms, research on aquaculture was also performed. Previous study had found that the distribution and AMR susceptibility of *V. parahaemolyticus* isolated from water and animal samples (fish and shrimp) in big Korean ponds suggested the possibility of AMR occurrences. According to the reports, 34.7 % of the strains in the whole sample were shown to be more susceptible to AMR from summer to autumn. Furthermore, 90.0 % of the *V. parahaemolyticus* isolates were positive for 13 of the 15 antimicrobials resistance tests tested, particularly colistin and ampicillin. The urgency of the danger of rising AMR might also emerge as a result of Koreans' habit of eating raw seafood, so that decision-making by relevant agencies to examine the quality of the aquaculture environment is still done in a sustainable way (Mok *et al.*, 2021).

Aquaculture is a significant route for AMR to propagate into the environment. *V. parahaemolyticus*, which is now being studied, contains the *Photorhabdus* toxin (Pir), which has been found to be a virulence gene in this organism.

Although most strains of *V. parahaemolyticus* do not cause zoonotic disease in humans, growing use of antimicrobials for the treatment of aquatic animals, particularly shrimp ponds, may cause a rise in AMR. The effects of antimicrobial susceptibility, plasmid-mediated quinolone resistance gene (PMQR), *pirAB*-like virulence gene, and DNA gyrase A (*gyrA*) subtype on the virulence profile of *V. parahaemolyticus* were studied on Pacific white shrimp (*Litopenaeus vannamei*) in farmed water in seven Thai regions (Rortana *et al.*, 2018). According to the findings, 65 of the 66 isolates tested positive for ampicillin resistance, and three tested positive for a multidrug-resistant (MDR) pattern in *gyrA* subtype-IV. The researchers also thought that this isolate was derived from the same clone, but that resistance evolved in the aquatic environment (Rortana *et al.*, 2018).

#### **Antimicrobials resistance rates in the environment**

AMR hazards to animal and human health need multi-sectoral monitoring using a "One Health" strategy (Chua *et al.*, 2021; Collignon & McEwen, 2019; White & Hughes, 2019). However, the present monitoring program continues to concentrate largely on livestock and culture findings from clinical sickness in people reported at each health institution, with minimal emphasis on a broader environmental aspect (Anjum *et al.*, 2021; Hirabayashi *et al.*, 2021; Unemo *et al.*, 2021). This is relevant because indicators for AMR monitoring in the environment may explain not only the quantity of AMR in the environment, but also how anthropogenic activities originating from these human activities have a potential risk of transmission (Huijbers *et al.*, 2019; Singer *et al.*, 2016). As a result, AMR monitoring must also include assessing environmental indicators (Anjum *et al.*, 2021).

In this particular study, the data of AMR detection in the environment discovered in diverse literatures was well-described. Antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARBs) are readily released and spread throughout the aquatic environment (Keen & Montforts, 2011). ARGs have been detected in municipal and health wastewater, wastewater treatment facilities, surface water, groundwater, and drinking water (Zhang *et al.*, 2009). The presence of AMR bacteria in recreational areas, drinking water, air, and seafood sources such as shellfish gives major influence and impact on

human health issues which of few have been discussed (Huijbers *et al.*, 2015).

Epidemiological investigations of water-based infectious pathogens may help track trends in risk of transmission at the community level (Batterman *et al.*, 2009; Daughton, 2020). Estimates of the amount of SARS-CoV2 virus RNA copies from wastewater in Australia, for example, have been published and used to estimate the number of persons infected with COVID-19 in these water locations. As a result, an epidemiological investigation of AMR based on aquatic environments may serve as an early warning system for monitoring AMR on human clinical infections (Ahmed *et al.*, 2020). The *Enterobacteriaceae* and *Pseudomonadaceae* isolates were revealed to be the dominating families among the environment and animals in tests utilizing the disk diffusion technique on samples of wild animals undergoing rehabilitation and in the Wildlife Rehabilitation Center (WRC) environment. The *Enterobacteriaceae* isolates exhibited the greatest abundance and up to 20 drug resistance profiles, with 8 isolates resistant to more than 9 antibiotics, including imipenem. Furthermore, 11 resistant isolates from the *Pseudomonadaceae* family were found, including carbapenems and quinolones (Baros Jorquera *et al.*, 2021).

Microplastics are becoming as important and effective carriers of ARGs in marine, freshwater, wastewater, and urban riverine ecosystems. According to the reported findings, AMR interacts with microplastics by generating synthetic plastids, which serve as a suitable environment for biofilm development, facilitating ARG transmission through horizontal gene transfer and increasing AMR risk (Kaur *et al.*, 2022). Plastics in the environment are increasingly being exploited as a site for the creation of microbial biofilms, and, more significantly, may house human infections (Galafassi *et al.*, 2021; Wang *et al.*, 2021; Zhang *et al.*, 2021).

The plastisphere's shelter environment has been shown to promote the survival, persistence, and spread of human infections in the environment (Keswani *et al.*, 2016). Natural organic materials, on the other hand, such as seaweed and seagrass, have the ability to transport bacteria at low tide and borne at high tide, including pathogenic species from coastal locations (Pham *et al.*, 2021). Several types of pathogenic bacteria were detected on PET, PP, and PE in aquatic environments, including *Vibrio* spp. (Zhang *et al.*, 2021), faecal indicator



organisms (FIOs) *E. coli* and intestinal enterococci (IE) (Kelly *et al.*, 2021; Metcalf *et al.*, 2022; Rodrigues *et al.*, 2019) were used as parameters basic water quality monitoring to control and categorize water intended for public recreational requirements (Quilliam *et al.*, 2019).

The focus on heavy metal pollution from numerous sources raises concerns, particularly among public health experts, due to its long-term stability. Interestingly, bacteria were shown to be resistant to these chemical components, and the genes encoding the trait could be localized form plasmids containing more than the AMR producing genes (Yu *et al.*, 2017). Heavy metal contents in 305 pig manure samples were correlated to phenotypic resistance of *E. coli* to 29 antimicrobial medications. According to the findings of this investigation, copper and zinc may promote *E.coli* AMR in pig microflora (Hölzel *et al.*, 2012).

#### **Antimicrobials resistance rates in the environment**

AMR may decrease the efficacy of treatment and preventive efforts for many common infectious illnesses, resulting in increased significant morbidity and mortality, as well as higher hospital costs. Until date, AMR instances have been of particular concern to nations with low and middle incomes since they are linked with a relatively high burden of infectious illnesses. Supporting health resources to aid diagnosis, such as labs and health professionals, on the other hand, is still quite limited in comparison to the number of instances of infectious illnesses that arise.

Several studies show that the occurrence of AMR in people varies according to the environment and the kind of infectious agent. A recent Ethiopian literature review research included 19 investigations examining the prevalence of AMR in people, the majority of which occurred in metropolitan locations such as Addis Ababa, Jimma, and Hawassa. This research is notable since it cites specific causes of infection such as operation site infection, urinary tract infection, otitis media or diarrhea, and blood flow (Arega *et al.*, 2018; Nigussie & Amsalu, 2017; Tadesse *et al.*, 2018). An investigation of the incidence of antimicrobial medication distribution points at Yangon Children's Hospital and Yangon General Hospital in Yangon, Myanmar discovered that 1,255/63.4 % had been administered as much as 2,108 antimicrobial pills. The study's findings suggest that there is still a considerable risk of AMR in the hospital, suggesting that attempts to promote the

advantages of antimicrobial treatment must be closely controlled (Oo *et al.*, 2022).

The number of patients and the rate of isolation of third-generation cephalosporin-resistant *K. pneumoniae* improved in the Nosocomial Infection Surveillance program in Japan between 2019 and 2020 (Hirabayashi *et al.*, 2021). In Bosnia and Herzegovina, 108 isolates of *Brucella melitensis* from 209 patients in five health institutions were utilized in a study of Brucellosis cases produced by *Brucella melitensis* in humans. 111 (53.1%) of the total patients in the study were positive for *B. melitensis*, and 108 isolates were tested; 91 (84.3%) were resistant to trimethoprim-sulfamethoxazole in Brucella broth (BB) medium, and almost all isolates (>90%) were resistant to azithromycin in BB and cation-adjusted Mueller-Hinton broth (CAMHB) medium (Arapović *et al.*, 2022). To discover -lactamase, AMR trends of *Haemophilus influenza* isolates obtained from children's hospitals in Mainland China were studied using disc diffusion and disc cefinase procedures. As a consequence, 13,810 *H. influenza* isolates were entered between 2017 and 2019, with 63.32 percent of all strains producing -lactamase, 8.22 percent producing -lactamase negative and ampicillin resistance (BLNAR), and sulfamethoxazole resistance following 70.98% reduction in trimethoprim (Zhou *et al.*, 2021).

#### ***Zingiber officinale***

##### **Bioactive compounds present in *Zingiber officinale***

*Z. officinale* which is well known as ginger had been proven and reported to contain phytochemicals such as phenols, flavonoids, terpenoids, and other phytochemicals responsible for its use and pharmacological activities (Fahmi *et al.*, 2019; Jan *et al.*, 2022). *Z. officinale* was also reported to contain the antioxidant compounds which mostly consists of phenol derivatives such as shogaols and gingerols (Asamenew *et al.*, 2019). The antioxidant compounds contained in *Z. officinale* makes this type of ginger known as a healthy dietary food components which have the health protecting factors. The strong antioxidant activity of ginger essential oil product had been tested by DPPH and FRAP methods. Many reports had been reported various effects and useful activity of ginger and its extract. Those effects were due to its bioactive compounds, such as butanol, 3-methyl butanol, hexanal, 3,7-dimethyl-1,3,7-octatriene, camphene, 2,3-bis[methylene]bicyclo [3.2.1]octane,  $\beta$ -mycrene,  $\alpha$ -phellandrene,



limonene,  $\rho$ -cineole, 3,7-dimethyl-1,6-octadiene-3-ol, hydrate camphene, borneol,  $\alpha$ -terpineol, geranyl isobutyrate, zingiberene, farnasene, nerolidol, pentadecanoic acid, 9,12-octadecadienal, and 9,12,15-octadecatrienal (El-Ghorab *et al.*, 2010). Despite of its bioactive phenolic compound, ginger also contains various type of nutrient compounds such as protein, total lipid (fat), carbohydrate (sugars), fibers, Calcium (Ca), Vitamin C (ascorbic acid), Vitamin B-6, Vitamin B-12, Vitamin A, Vitamin D, phosphorus, potassium, magnesium, zinc, iron, niacin, depends on the condition, treatment, and extraction method applied to the ginger. Due to its bioactive compound, the ginger extracts were implemented and utilized in many kinds of use, such as diseases treatment; used in cream and gel, headache treatment, anti-mimetic, expectorant, antibacterial treatment, even for increasing the appetite (Konmun *et al.*, 2017).

#### **Antioxidant effects**

Antioxidant properties from *Z. officinale* has been tested on various models and proven effective that information provided (Table II). Due to the antioxidant activity of *Z. officinale*, it was believed to prolong healthy lifespan. Based on the experimental results reported globally, the antioxidant activity of *Z. officinale* was due to its richness in the bioactive compounds. Single compound purified from *Z. officinale* was predicted to have low antioxidant activity while the combination of several or many bioactive compounds were reported to have high antioxidant activity tested by various methods (Table II).

#### **Antimicrobial resistance preventive of *Z. officinale***

Many reports had reported the antimicrobial activity of various bioactive compounds found in ginger and its extract. By using disc diffusion method, the antimicrobial activity ginger essential oil was tested and proven against *B. cereus*, *S. aureus*, *E. coli*, *S. Typhimurium* (Gopi *et al.*, 2019) and *R. solanacearum* (Zhang *et al.*, 2022). Bacterial biofilm was known and reported to boost the resistance of bacteria against commonly used antimicrobial agents (Asma *et al.*, 2022; Flores-Vargas *et al.*, 2021; Panjaitan *et al.*, 2019; Sharma *et al.*, 2019). The antimicrobial activity of *Z. officinale* had also been tested via microdilution method against the biofilm of *S. mutans* and *S. sanguinis*, well studied pathogens that cause dental carries (Babaeekhou & Ghane, 2021). In addition, the

ginger essential oil was also reported to have antifungal activity tested on fungus culture (Romoli *et al.*, 2022). Ginger was even produced in transparent film from ginger nanocellulose fibers manufactured for food container. According to the data reported, the film made from ginger nanocellulose fibers has antimicrobial activity which could be reduced by overheating (Asma *et al.*, 2022; Li *et al.*, 2012). Due to its antibacterial activity, ginger in essential oil form was also tested in polysaccharide-based hydrogel used for burn wound healing in increasing the antibacterial activity of the hydrogel (Wang *et al.*, 2021; Wang *et al.*, 2022). The aqueous extract of *Z. officinale* showed high inhibition against *S. aureus* and *P. aeruginosa* and was better than the control drug streptomycin (Sulaiman *et al.*, 2014).

Surprisingly, certain antioxidant capabilities of natural substances may also create Reactive oxygen and nitrogen species (RONS) as a functional mechanism in avoiding pathogenic bacterial infections. This natural antibiotic has the ability to affect the pathogen's central metabolism and/or iron homeostasis, resulting in the formation of intracellular hydrogen peroxide. This combination of RONS-containing antibacterial drugs may operate synergistically against a variety of harmful microorganisms. Quinones, for example, are secondary metabolites that have antioxidant and antibacterial action against *Enterococcus* sp., *Streptococcus* sp., *S. sp.*, or *Moraxella catarrhalis* (Iorio *et al.*, 2017; Liang *et al.*, 2016) and methicillin-resistant *S. aureus* (Liang *et al.*, 2016). Compounds generated from plant secondary metabolites have antibacterial action, which explains their potential to cause oxidative alterations in bacteria, which may further limit harmful bacterium survival (Chi *et al.*, 2019). The potent antioxidant content of traditional plants such as red ginger may activate levels of reactive oxygen species (ROS) in the host, hence eradicating pathogen-mediated bacterial illnesses (Li *et al.*, 2021) (Table III).

#### ***Zingiber officinale* as a biofilm formation preventive**

Bacteria that can survive in biofilms have an extremely high adaptive resistance pattern to antibiotics and disinfectants. The issue of adaptive antibiotic resistance, which is developing internationally, functions as a barrier for treating acute and chronic illnesses caused by biofilm (Li & Lee, 2017).

Table II. The antioxidant activity of *Z. officinale* depends on its bioactive effective compound which has been studied and tested in previous studies.

Model	The effective compound	The mechanisms involved	References
Phospholipid liposomes	Thymol, carvacrol, 6-Gingerol, zingerone, and hydrotyrosol	The effective compounds inhibited and decreased peroxidation of phospholipid liposomes by Fe <sup>3+</sup> /Ascorbate.	(Aeschbach <i>et al.</i> , 1994)
LPS-activated J774.1 mouse macrophages	6-Gingerol	6-Gingerol protection by inhibiting NO synthesis in LPS-activated J774.1 macrophage and protection against peroxynitrite-mediated oxidation.	(Ippoushi <i>et al.</i> , 2003)
Streptozotocin-induced diabetic rat	Ginger ethanolic extract	Neuroprotective effect of ginger was proven to accelerate the brain antioxidant defense mechanism and decrease the oxidative stress markers; superoxide dismutase, glutathione reductase, and glutathione peroxidase, in the mitochondrial fractions of cerebral cortex from streptozotocin-induced diabetic rat.	(Shanmugam <i>et al.</i> , 2011)
Alcohol-induced renal damaged Wistar strain albino rat	Ginger ethanolic extract	Treatment of ginger ethanolic extract on alcohol treated rats increased significantly the levels of superoxide dismutase, ascorbic acid, glutathione, and uric acid.	(Shanmugam <i>et al.</i> , 2010)
	Total phenolic content of ginger leaves and rhizomes extract	Savenger effect of ginger extract inhibited the deoxyribose degradation by OH <sup>-</sup> , and inhibited the scavenging effects from 2,2-dyphenil-1-pyrcril hydrozyl radical (DPPH).	(Stoilova <i>et al.</i> , 2007)
	Polysaccharides extracted from ginger	Polysaccharide extracted with acid solution showed significant inhibitory effects on superoxide radical, hydroxyl and DPPH radical, in addition to its reducing power and strong iron(II) chelation activity.	(Chen <i>et al.</i> , 2020)
	<i>In Vitro</i>	Aqueous extract of ginger	The aqueous extract of ginger had a significantly higher inhibitory effect on both Fe <sup>2+</sup> -induced lipid peroxidation in the rat brain homogenates.
Alcohol induced liver damaged in rats	1% of dietary ginger powder	Treatment of ginger provided protective role against the ethanol induced hepatotoxicity, by reversing the levels of the superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase and glutathione content while increasing the levels of malondialdehyde (MDA) in the hepatic tissue.	(Mallikarjuna <i>et al.</i> , 2008)
Streptozotocin-induced diabetic rat	Ginger powder 5% as daily food intake	Ginger powder given to the treated rat as daily intake significantly improve the markers of diabetic neuropathy.	(Abdulrazaq <i>et al.</i> , 2012)

Table III. The antimicrobial activity of bioactive compounds and total extracts of *Z. officinale* tested on several bacterial and other microbial infections based on *in vitro* or *in vivo* studies.

Samples / Infected model	The effective compound	Antimicrobial activity tested against microbes	References
The oral swabs collected from the infected patients	Alkaloid, saponin, tannins, flavonoids, terpenoids, cardiac glycoside, and quinines.	<i>S. mutans</i> , <i>Enterococcus faecalis</i> , <i>Staphylococcus spp.</i> , and <i>Lactobacillus spp.</i>	(Ahmed <i>et al.</i> , 2022)
IC <sub>50</sub> of <i>Z. officinale</i> extract on Intracellular parasites infection	Hydroalcoholic extract of <i>Z. officinale</i>	Promastogotes and asmatigotes <i>Leishmania major</i> and <i>Leishmania tropica</i>	(Saki <i>et al.</i> , 2022)
Molecular docking following the Lipinski's rule of five confirmed the antibacterial mechanism of lariciresinol in <i>Salmonella typhimurium</i>	Methanolic and ethyl acetate extract of <i>Z. officinale</i> , especially for lariciresinol.	<i>Salmonella typhimurium</i>	(Mehta <i>et al.</i> , 2022)
<i>In vitro</i> anti-chikungunya activity was performed in Vero cell-line with maximum non toxic dosage a of <i>Z. officinale</i> extract.	Total aqueous extract of <i>Z. officinale</i>	Antiviral activity against Chikungunya virus	(Kaushik <i>et al.</i> , 2020)
Treatment for protecting naïve fish from <i>I. multifiliis</i> infection.	10-gingerol, 6-dehydroshogaol, and 6-dehydro-10-gingerol	Anti parasitic against <i>Ichthyophthirius multifiliis</i>	(Fu <i>et al.</i> , 2019)
The extract of <i>Z. officinale</i> affects strongly the membrane permeability of the pathogen and decreased the bacterial growth significantly.	Total extract of <i>Z. officinale</i> rhizomes.	Multi-drug resistance <i>Pseudomonas aeruginosa</i> and inhibiting the biofilm formation of <i>P. aeruginosa</i> .	(Chakotiya <i>et al.</i> , 2017)
<i>E. faecalis</i> infection in larvae <i>Galleria mellonella</i>	Different kinds of <i>Z. officinale</i> extracts	<i>Enterococcus faecalis</i>	(Maekawa <i>et al.</i> , 2015)
Aqueous extract of <i>Z. officinale</i> demonstrated antibacterial activity against <i>S. aureus</i> and <i>P. aeruginosa</i> , with a rise in the inhibition zone with increasing extract concentration.	Saponins dan flavonoids	The size of the inhibitory zone influenced antibacterial efficacy against <i>S. aureus</i> and <i>P. aeruginosa</i> .	(Sulaiman <i>et al.</i> , 2014)
<i>Z. officinale</i> essential oil is effective against 18 Gram-negative bacteria. Calculating MIC values for multidrug resistance <i>in vitro</i>	Geranial, neral, 1,8-cineole, camphere, β-phellandrene, and α-curcumene	<i>Z. officinale</i> essential oil is effective against 18 types of Gram-negative bacteria. <i>In vitro</i> multidrug resistance with MIC values ranging from 0.28 mg/ml to 1.09 mg/ml	(Vaz <i>et al.</i> , 2022)
Clinical experiments employing the GENMOD, Friedman, and Wilcoxon test techniques were used to use <i>Z. officinale</i> essential oil as a mouthwash to decrease the development of biofilms on teeth.	Essential oil	Mouthwash with <i>Z. officinale</i> essential oil inhibited <i>Streptococcus mutans</i> growth and efficiently reduced dental biofilm and gingival bleeding.	(Bauer Faria <i>et al.</i> , 2021)

On the other hand, as explained in this research, antibiotic abuse contributes significantly to the development of drug resistance, which may accelerate disorders caused with bacterial infections. Traditional natural compounds, such as *Z. officinale*, have been discovered and demonstrated to be efficient in suppressing or killing antibiotic-resistant bacteria in many in vitro, in vivo, and clinical experiments. These natural substances suppress the growth of bacteria and biofilms as one of their modes of action. The plant *Z. officinale*, for example, has a role in traditional medicinal herbs that have been handed down from generation to generation for use in the treatment and prevention of bacterial diseases. Natural products' anti-biofilm action is heavily reliant on factors such as (i) inhibiting polymer matrix formation, (ii) suppressing cell adhesion and adhesion, (iii) interfering the ECM creation, and (iv) reducing virulence factor gene expression. Especially compared to conventional antibiotics, *Z. officinale* extract revealed to be a highly potent antibacterial category against *S. aureus* and *Streptococcus pyogenes* (Betoni *et al.*, 2006). The alkylated gingerol content of *Z. officinale* ethanolic and *n*-hexane extracts is known to exhibit antitumorogenic, anti-inflammatory, and antiapoptotic capabilities, as well as prevent the development of resistance-causing biofilms (Ali *et al.*, 2008; Park *et al.*, 2008).

Especially with the use of conventional antibiotics, extracts of *Z. officinale* may lower the virulence factors of pathogenic bacteria while treating biofilms (Clatworthy *et al.*, 2007; Davies, 2003). The mechanism of action of *Z. officinale* in reducing biofilm development is that when tested with SDS, this extract is able to promote the separation of biofilms from the surface. Interestingly, this innovation can be applied in a variety of industrial fields, including the biomedical field, the pharmaceutical industry, and, of course, traditional health care provider facilities, to reduce the biofilm that forms on water treatment membrane filters or water/oil pipes (Kappachery *et al.*, 2010). Experiments confirmed that the 6-gingerol content of *Z. officinale* extract reduced biofilm formation via decreased expression of virulence genes such as exoprotease, rhamnolipid, and pyocyanin, as well as the molecular mechanism that causes repression of the quorum sensing (QS) gene (Kim *et al.*, 2015).

#### **Safety**

*Z. officinale* has been produced and consumed as not only traditional medicine and

spices for flavoring the food but also edible products, such as syrups, candy (crystallized ginger), dried powder, which showed that the safety to consume its products (Crichton *et al.*, 2022). There are also *Z. officinale* pomace products, which interestingly are the polysaccharides rich in bioactive compounds extracted from *Z. officinale* (Yousefi *et al.*, 2022). The dried ginger itself could be utilized for manufacturing of ginger oil (which could be used also as essential oil), ginger oleoresins, ginger powder (which could be used in food and drinks) and herbs as herbal medicine used. Special case for pregnant women, ginger consumption in various versions was still being debated. While being compared to the spontaneous abortion case in pregnant women, there was no obvious danger and even considered as a useful treatment option for women suffering from morning sickness. According to the experimental data, *Z. officinale* is relatively considered safe to be used with notice in some condition, especially for use in early pregnancy (Laekeman *et al.*, 2021, Mendes da Silva *et al.*, 2022)

#### **CONCLUSION**

How to describe and determine the antimicrobial resistance which happened progressively is still unclear, especially for the mechanisms involved in the progression and development of the resistance itself. Especially in underdeveloped countries, the burden of antimicrobial resistance is increasing over decades, which certainly affects the use of medications for treatment. For long term observation, the antimicrobial resistance also affects the economy condition of a country, since the complicated treatments in handling the resistance caused the economic burden. On the other hand, the uses of *Z. officinale* as a treatment option for bacterial or microbial infections has been described according to the data that found by many previous studies. Many studies had elaborated the antimicrobial activity from either aqueous or organic solvent extracts from *Z. officinale*, the traditional plant which contains abundant of organic compounds (Akullo *et al.*, 2022, Gunasena *et al.*, 2022). The antioxidant compounds found in *Z. officinale* leveraged the antimicrobial activity as many studies had proven as discussed above. The mechanisms of few biological uses of *Z. officinale*, based on the progression of molecular microbiology and cellular biology research, had been described. However, detail mechanisms or site of work of each bioactive compound of this

traditional plant are still considered unraveled. Therefore, future works regarding on how those bioactive in *Z. officinale* are actively functioning in the human cells or tissues or body are still recommended.

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