

Review Article

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Overcoming Antibiotic Resistance

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ABSTRACT

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The main focus of this review article is to need for “an alternative to antibiotic usage in Agriculture and medicine”. Antibiotics, a group of chemicals, either derived from, or naturally produced that along with their synthetic analogues can kill microorganisms at low concentrations. Non-judicious use of these drugs leads to the development of resistance, untreatable and complicated emerging infections demanding search for an alternative. In spite of new antibiotic and hybrid antibiotic development, natural antibiotics looks to be a promising option. Resistance to antibiotic degradation can lead to the ineffective breakdown of wastes and biomedical wastes because of evolutionary developments. Understanding of the breakdown of antibiotic resistance by use of natural antibiotics when interpreted with metabolic adaptations, biochemical pathways and thermodynamic changes will be of help to understand the problems in medicine and agriculture including development of new microbial species and suggest appropriate measures as the targeted therapeutic intervention in medicine. The work suggests on elucidation and enumeration of the pathways for antibiotic resistance transmission and identification of the prime causes of microbial evolution in environment resulting out from generation of antibiotic resistance. The present work hypothesizes on bioprospecting of natural substances with antimicrobial action to eradicate the problem of antibiotic resistance and suggests the use of natural antibiotics that can change the process of changed metabolic adaptations.

Introduction

A class of synthetic chemicals or microbial derived chemicals used to fight microbial infections is called as antibiotics. These are designed to act primarily against bacteria and fungi, and are available as counter drugs at pharmaceutical stores upon physician recommendation (Felson, 2021). These act

by killing *microbiota* or inhibiting their replication and growth in both beneficial and harmful microbes. However, indiscriminate and continuous intake leads to the development of drug resistance (Felson, 2021). Medicine recommends usage of antibiotics only against the identified and tested applications (Felson, 2021). Applications of these ranges from agriculture to medicine apart from the regular

laboratory bench work including occurrence of antibiotic resistance genes (ARGs) in dairy manures (Manyi-Loh *et al.*, 2018; Wang *et al.*, 2022).

Route of administration of these can be through: oral, topical applications, or intravenous. Some of these can be of broad- spectrum, wherein these target a large number of different bacteria, or can be of narrow- spectrum wherein these targets only specific bacteria (Felson, 2021).

In agriculture, animal husbandries are fed with antibiotics to prevent disease and increase animal growth, but overuse leads to the development of resistance bacteria that passes through food chain to humans (Klobucista, 2019). In contrast to these synthetic chemicals, there are naturally available plant extracts, vegetables, fruits, essential oils and foods with antibiotic properties or can kill or inhibit microbial growth, and these are called as ‘natural antibiotics’ (Brusie, 2023). Suggested use for intake of natural antibiotics is when person(s) turn allergic to the intake of synthetic antibiotics.

The concept of natural antibiotics comes from the sayings of Hippocrates, “let food be thy medicine and medicine be thy food” (Netmeds, 2022). However, prescription antibiotics need to be considered as the first line of therapy. These natural products fit into the definition of being antibiotics as being chemical compounds derived from or produced by living organisms that can inhibit the life process of microbes at small concentrations (Bhattacharya, 2020; Dixit *et al.*, 2021; Sharma *et al.*, 2015). Chances for side effects are very less with natural antibiotics (Sinha, 2023).

Drug resistance leads to more period of hospitalization and possibly death of patients. Approximately, seven hundred thousand people are estimated to die every year due to drug resistance illness and without containment facilities the death toll can go up to ten million a year by 2050 (Klobucista, 2019). Severity of the generation of antibiotic resistance bacteria is leading to 700,000 deaths across the globe (Hudson, 2021).

Antimicrobial resistance might impact global economy leading to \$ 1 trillion to \$ 3 trillion as output loss by 2030 (World Bank, 2017). These suggest use of natural antibiotics.

Cellular metabolism is modulated by many food and dietary components (Bhattacharya, 2023a; Bhattacharya, 2023b). Regular and excessive usage of antibiotics can modulate metabolism leading to the development of harmful effects. Herein, use of natural antibiotics can lead to a change in the process of changed metabolic adaptations, cellular signaling processes and eradicate the problem of antibiotic resistance development.

However, in-depth understanding of the mechanisms in alteration of metabolic pathways by antibiotics, or correction of the metabolic pathway by natural antibiotics needs the involvement of thermodynamics knowledge apart from the molecular mechanisms. Breakdown of the antibiotics in nature by the process of decomposition is a methodology to remove the traces from environment (Bhattacharya, 2023c; Turul *et al.*, 2023; Biswas *et al.*, 2023; Bhattacharya, 2015). However, this always may not be a guaranteed mechanism because of evolutionary developments apart from other reasons. Knowledge of thermodynamics can highlight the reasons behind success or failure in breakdown of the antibiotic in nature. This also may help to understand the process of evolution of micro-organisms.

The present work in brief discusses on the role of antibiotics in agriculture, and medicine apart from the posed problems due to the development of resistance (Datta *et al.*, 2018; Chowdhury and Uddin, 2022). Detailed discussion on the units are beyond the scope of this review. However, individual units can be further researched upon through the indexed references. The present work suggests the use of natural antibiotics that can change the process of changed metabolic adaptations, and eradicate the problem of development of antibiotic resistance. Resistance to antibiotic degradation will lead to the ineffective

breakdown of biomedical waste. Elucidation and enumeration of the pathways for antibiotic resistance transmission events apart from identification of the prime cause of microbial evolution in environment is the prime and essential part of knowledge to understand and curb the development mechanism of antibiotic resistance.

The understanding of the breakdown of antibiotic resistance by use of natural antibiotics when interpreted with metabolic adaptations, biochemical pathways and thermodynamic changes will be of help to understand the problems in medicine and agriculture including development of new microbial species and suggest appropriate measures as the targeted therapeutic intervention in medicine. Furthermore, bioprospecting of natural substances with antimicrobial action will help to limit or remove the problem of antibiotic resistance development.

Generation of antibiotic resistance

Bacteria as an example of microbial group that gains antibiotic resistance can obtain it by either of the two methods: genetic mutation, or horizontal gene transfer. Administration of drug leads to the induction of changes at the molecular level of an organism. However, if the bacteria survive and reproduces rather being killed in the presence of such drugs, it undergoes mutation. In horizontal gene transfer (HGT), bacterium acquires gene either from the environment, or directly from another bacterium or phage. The HGT as a process can accumulate ARGs in same cell and lead to the development of ARBs (Hudson, 2021; Woodford *et al.*, 2007; Burmeister, 2015; Lerminiaux and Cameron, 2019).

Increase in efflux of the antimicrobials from the cell leads to prevention of the accumulation of antimicrobial agents within the microorganism (Kapoor, 2017; Allen *et al.*, 2010).

Microorganisms' uses enzyme to inactivate the antibiotics and are primarily of three types: There

are three main enzymes that inactivate antibiotics such as β -lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyl transferases (AACs) (Mims *et al.*, 2004).

Mode of action of antibiotics

The recognized modes of action for antibiotics are grouped according to their principle mechanism of action. Lists of these are: Cell wall synthesis inhibitor, Membrane function inhibitor, Protein synthesis inhibitor, Nucleic acid synthesis inhibitor, ATP synthesis inhibitor and anti-metabolite (Rollins *et al.*, 2000; Moore, 2021). In summary, these antibiotics can either work as bacteriostatic or bactericidal (Davis, 2022).

Thermodynamics in antibiotic action

Thermodynamics play a key role to understand the mechanism of action of antibiotics. As an example, in a complex interaction formed by glycopeptide antibiotics, restriction of movement of mobile acyl-D-Ala-D-Ala moiety led to an entropic penalty directing restriction of molecular level movements in the complex (Rekharsky *et al.*, 2006). Furthermore, aminoglycoside phosphotransferase-3'-IIIa phosphorylates many aminoglycoside antibiotics by phosphorylation, leading to antibiotic ineffectiveness (Miller, 2011). Understanding of the thermodynamics of antibiotic functions can lead to their implementation in pharmaceutical applications (Szaruga *et al.*, 2021; Schenckbecher 2019).

Many of the antimicrobial agents are cyclic peptides with a rigid binding site that binds a lipid component and targets antimicrobial agents only to bacteria, but not the host cells (Epand *et al.*, 2016). Amino acid as enzymes acts also in the offering microbial antibiotic resistance. However, amino acids are also used to develop antimicrobial peptides (Idrees *et al.*, 2020). Techniques have been developed over the time as *in vivo* methods to study the antibacterial mechanism of antimicrobial peptides (AMPs) (Schäfer and Wenzel, 2020). Membrane disruptive peptides or peptidomimetics

based therapeutics, wherein peptides derived from any natural source are proving themselves as anti-cancerous and antimicrobial in nature (Lin *et al.*, 2021). Additionally, structural changes in the bacterium lipopolysaccharide moiety lead to the development of resistance against Polymyxin B, a cationic antimicrobial cationic peptides (CAMP) (Howe *et al.*, 2007).

Role of antibiotics

Antibiotics in agriculture

Adoption of intensive farming to meet the growing needs of animal protein directs administration of antibiotics in livestock feed. This results in the generation of antibiotic residues in animal products and generation of antibiotic resistance (Manyi-Loh *et al.*, 2018). Despite this creation of drug resistance fears, adoption of antibiotics in farming is expected to rise (Rears, 2023). Primarily, in horticulture and agriculture antibiotics are used to control bacterial diseases of high-value fruit, vegetable and ornamental plants. Samples of streptomycin-resistance genes in plant associated bacteria like *Erwinia amylovora*, *Pseudomonas spp.*, *Xanthomonas campestris* are with transfer-proficient elements and similar to those isolated from humans, animals and soil. However, the genetic uniqueness was seen in the plasmids of streptomycin resistance genes in human and plant pathogens (McManus *et al.*, 2002). This raises the possibility of transfer of resistance to human and animal pathogens and generation of environmental persistence effect (Taylor *et al.*, 2020). Antibiotic resistance in phytopathogenic bacteria is understood to be due to horizontal gene transfer from epiphytic commensal microbiota (Sundin *et al.*, 2018). Antibiotic enriched cow-manure derived amendments upon application to soil increases the number of antibiotic rich genes (ARG) and mobile genetic elements (MGE) (Jauregi *et al.*, 2021). In summary, misuse and overuse of antibiotics in agriculture leads to the generation of antibiotic resistant bacteria (ARB) including agricultural soils that can lead to untreatable infections, and is creating a worldwide challenge for

food systems and public health Mayo Clinic (2023); Manyi-Loh *et al.*, (2018); Hiltunen *et al.*, (2017). Antibiotic residues also has been traced in animal wastes (Epps and Blaney, 2016).

Antibiotics in compost preparation

Compost as a process refers to the controlled decay of organic materials for fertilizer preparation. Composting reduces ARGs, potential for spread of antibiotic resistance to spread and resistome risk, but does not limit ARGs or their mobility prior to land application (Keenum *et al.*, 2021). One reason to start the problem is with addition of manure and manure derived amendments with manure sourced from antibiotic fed livestock (Chen *et al.*, 2019). The possible way to break down this antibiotic transmission chain is to break down before these reach field (Chakravorty, 2016). Antibiotic if added as a raw material along with other organics for composting (both aerobic and anaerobic) can variably influence post composting bacterial and fungal community structure and has been observed in experiment with Doxycycline (DOX) and Gatifloxacin (GAT) (Wang *et al.*, 2022). However, composting is a suggested way to reduce formation of antibiotic resistant bacteria and reduce ARGs in manure compost (Xie *et al.*, 2018). A properly treated and handled compost is safer than a raw manure.

The suggestive of USDA's National organic program standards directs a period of 120 day interval between the time of applying raw manure for crops having edible parts in actual contact with soil (carrots and potatoes, for example) and 90 day time gap for crops with edible parts not in actual contact with soil (beans, corn and peas, for example) (Beecher, 2015). Antibiotics if not fully broken down in composting, reduce nitrogen transformation in the compost (Schueler *et al.*, 2021). Antibiotic residues and ARBs in manures can be reduced by either of the two ways: with spread and distribution of manure on fields, antibiotic gradually leaches to water source which can be fed to the livestock, or use of manure solids as bedding for livestock. The

purpose remains as ingestion of such antibiotic residues and ARBs will be broken down or turned to ineffective chemical within the animal gut during the animal digestion process (Hein, 2019). Furthermore, inoculation of biochar with *Bacillus subtilis* led to the reduction of ARGs and MGEs in composting (Wu *et al.*, 2022). Composting with human excreta also led to the reduction of ARGs (Werner *et al.*, 2022).

Antibiotics in medicine

The main use of antibiotics in medicine is to treat certain illness but these do not cure everything and unwanted consumption leads to development of resistance. Many people resort to self-medication with antibiotic intake in situations of ill health.

This represents not only inadequate adherence to the use of policies on antibiotic intake but also this showcases negligence of one towards one's own health (Kassa *et al.*, 2022; Virmani *et al.*, 2017). This practice also leads to treatment failures (Elmahi *et al.*, 2022), apart from the way to look for the development of new antibiotics (Schneider, 2021).

Antibiotics in laboratory experimentation

Laboratories use antibiotics in advanced biology experiments as selective markers. Furthermore, antibiotics are used to determine antimicrobial susceptibility testing (AST) (Bayot *et al.*, 2022; Amsterdam, 1988). The AST is essential to identify effective dosage and define a therapy profile for treatment and recovery from infections (Khan *et al.*, 2019).

Even though there can be adoption of different selection regimes leading to the generation of high-level antibiotic resistance in drug gradients, the adaptive laboratory evolution led to merging of genotypes and phenotypes (Jahn *et al.*, 2017). However, laboratory-based methods to detect resistance can help to elucidate resistance or susceptibility of an isolate against any therapeutic candidates (Yalew, 2020).

Antibiotic resistance genes

The development of antibiotic resistance leads to development of antibiotic resistance genes (ARGs). Hospital waste water is one of the prime source for development of antibiotic resistance genes Zhang *et al.*, (2020) apart from the livestock wastes (He *et al.*, 2020). Such discharges act as source for the development of environmental hotspots for ARGs and ARBs (Kunhikannan *et al.*, 2021; Chowdhury and Uddin, 2022; Serwecińska, 2020). Antibiotic resistance genes related to tetracycline and β -lactam antibiotics were also traced in waste water discharges at Almendares river (Graham *et al.*, 2010). The ARGs can be traced to nine major class of antibiotics, namely, tetracyclines (*tet*), sulfonamides (*sul*), β -lactam (*bla*), macrolide-lincosamid-streptogramin-B (MLSB) (*erm*), aminoglycosides (*aac*), FCA (fluoroquinolone, florfenicol, chloramphenicol, amphenicol) (*fca*), quinolone (*QnrA*), multidrug (*mdr*) (He *et al.*, 2020; Martinez, 2012). Municipal solid waste transfer stations has reported release of airborne ARGs (Li *et al.*, 2022). Hospital effluent from an Indian hospital at Mumbai reported the presence of carbapenemases and integron borne ARGs with the dominance of *Acinetobacter* spp. (Marathe *et al.*, 2019) and presence of *Morganella morgani* and *Bacillus cereus* as ARBs from Mizoram, India (Hauhnar *et al.*, 2018).

Furthermore, hospital waste water from Iran observed the presence of ARGs from *Escherchia coli* and *Pseudomonas* spp. (Asghari *et al.*, 2021). Study of an Indian origin waste water sample analysis revealed the predominance of ARGs against aminoglycoside, macrolide, carbapenem, trimethoprim, and sulfonamide antibiotics (Talat *et al.*, 2023). Livestock manure also has been observed to spread ARGs through mobile genetic elements (MGEs) (Checcucci *et al.*, 2020). Environmentally sinker waste water systems also harbor ARGs (Mutuku *et al.*, 2022). Additionally, ARGs has been traced in antarctic soils also (Goethem *et al.*, 2018). However, ARGs can also be traced at the natural environments (Allen *et al.*, 2010).

Natural antibiotics

The emergence of antibiotic resistance has led to the search and development of new antibiotics. Herein, natural products or derivatives from natural products like phenols, polyphenols, terpenoids, essential oils, alkaloids, lectins, polypeptides, etc. if can inhibit microorganisms at low concentrations with less or no side effects are considered to be an antibiotic and are called as 'natural antibiotics' (Sinha, 2023). A more detailed information on list of natural compounds to fight against antibiotic resistance can be found in the work of Alvarez-Martinez *et al.*, (2020).

Table 1 discusses in brief and exemplarily benefits of natural antibiotics. These natural antibiotics can impact on the transfer of resistance mechanism and or overcome or modulate resistance by altering usage Isaacson *et al.*, (2002).

Future Directions

Research works can be directed on elucidation of metabolic adaptations during the antibiotic driven evolutionary trajectories (Zampieri, 2017). Knowledge of thermodynamics can lead to the identification of potential inhibitors as drug candidates against the problem of resistance development (Zhi *et al.*, 2013). Antibiotic residues in environment creates persistence effect. Researchers have used polymers of intrinsic microporosity to remove traces of antibiotic from water (Alnajrani *et al.*, 2020). Further work with conductive materials has shown that these materials in composting can attenuate ARGs, bioavailability of antibiotics and effect the process of horizontal gene transfer and microbial community structure formation. However, properties and dosage of these materials influence their role (Nnorom *et al.*, 2023).

Similarities in configuron relaxation happening at the glass-liquid transition may be similar to the formation of humus, or processes in composting (Ojovan, 2008; Science. JRank, 2023). Municipal solid waste systems can also lead to the

development of ARGs and ARBs (Anand *et al.*, 2021). The environmental effects of antibiotic resistance genes can be directed for control under aerobic solid composting system (Huan *et al.*, 2021).

Phylogenetic insights onto the evolution of ARGs and ARBs can be a component to understand the mechanism of microbial evolution (Aminov and Mackie, 2007). Metagenomic approaches will be of help to elucidate presence of ARGs (Schmieder and Edwards 2012). Bioprospecting of natural antibiotics can lead the development of antibiotic alternatives.

Development of antibiotic resistance is one of the global threats. This affects any person irrespective of geographical location and age. Resistance leads to longer hospital stay, more cost, death threats and emergence of pan-drug resistant microorganisms (Hutt, 2016; Larsson and Flach, 2022). Biomedical waste at Tiruchirapalli, India lead to the identification of predominant flora as *Escherichia coli*, *S. aureus*, and *P. aeruginosa* (Gajalakshmi and Raja, 2019). The risk extends from tuberculosis to sexually transmitted diseases, urinary tract infections apart from making routine hospital inspections difficult.

In conclusion, development of new and hybrid antibiotics can hold the risk situation for a while because misuse of antibiotic administration needs to be stopped at the foremost (Domalaon *et al.*, 2018). Though antibiotics are in the process of discovery and development, the resistance problem cannot be stopped but managed only (Ventola, 2015). The problem of antibiotic resistance will lead to an era of bad microbes and no drugs (Ross, 2017). This suggests immediate attention to contain antibiotic resistance in the environment (Sinha 2019). The problem extends from medicine to agriculture, and practices apart from the laboratory bench works. Thus, there is a requirement to look for an alternative, and use of natural antibiotics is a promising option to overcome the resistance effect and opt the same for therapeutics not only in medicine, but also in agriculture.

Table.1 Natural antibiotics and their benefits

Natural Antibiotics	Benefits	References
Garlic	Inhibits <i>Salmonella</i> and <i>E. coli</i> , <i>Candida albicans</i> and MRSA	Brusie (2023); Malka (2021); Sinha (2023)
Honey	Kills methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	
Ginger	Anti-bacterial, lowers blood sugar levels and fight seasickness	
Echinacea	Inhibits <i>Streptococcus pyogenes</i>	
Goldenseal	Inhibits MRSA, fights bacterial diarrhea and urinary tract infections	
Clove	Antibacterial and kills <i>E. coli</i>	
Oregano	Antioxidant and antifungal, acts against sinus infections	
Myrrh extract	Antagonistic to <i>E. coli</i> , <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Candida albicans</i> , <i>Klebsiella pneumoniae</i>	
Thyme oil	Antibacterial	
Turmeric	Antagonist to MRSA and <i>E.coli</i>	
Lemongrass	Antibacterial skin infections	

Author contributions

Sumit Biswas and Partha Pratim Mandal worked as undergraduate students in this project. Sumit Biswas presented part of the work at FOSET, Kolkata. Susinjan Bhattacharya and Soma Mukherjee conceived and designed research. Susinjan Bhattacharya wrote the manuscript, analyzed and edited. Soma Mukherjee reviewed and edited manuscript. All authors have read and approved the manuscript.

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Data Availability

No new data were generated or analyzed in support of this research.

Declarations

Ethical approval

The article does not contain any studies involving human participants or animals performed by any of the authors.

Conflict of interest

The authors declare no competing interests.

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