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ARTICLE

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SELECTED TRADITIONAL REMEDIES AND THEIR ROLE IN THE MANAGEMENT OF ANTIMICROBIAL RESISTANCE

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Antimicrobial resistance is among the top ten public health threats. Most hospital isolates of priority pathogens, listed by WHO, including Acinetobacter, Escherichia, Klebsiella, Mycobacterium, Salmonella, Shigella from West Bengal showed resistance to almost all common antibiotics. This article will highlight the antimicrobial potential of a few traditionally used household spices, food and medicinal plants and their bioactive phytochemicals to counter drug-resistance by preventing resistant developing processes. However, their purity, safety, efficacy, and integration with modern medicine requires extensive study.

Introduction

Microbes, the microscopic members of earth, can strike upon or invade animals including human anywhere anytime. The human body is constantly assaulted by numerous microbes including acellular viruses, unicellular bacteria, uni- to multi-cellular fungi, and protozoa to way inside (Sarkar *et al*., 2024). However, most microbes are harmless, or easy to fight off, while several are merciless killers (Chattopadhyay *et al*., 1999; Lopez-Roldan *et al*., 2013). Merely, a century ago no one had heard about streptococcal toxic shock syndrome (STSS), soil-borne infection by *Variovorax durovernensis (*Payne *et al*., 2024*)*, Lyme disease, AIDS, Sin-Nombre, Kaposi's Sarcoma, Hepatitis viruses; Ebola, and SARS-Corona Viruses. The discovery of antibiotics and their widespread use had transformed the dreaded bubonic plague, meningitis, pneumonia, syphilis, and tuberculosis (TB) into mere inconvenience. However, by late 1970 the scientific community was overwhelmed by their victory against infectious diseases (Singh *et al*., 2021). The discovery of vaccines helps to control a number of dreaded bacterial diseases including diphtheria, *Haemophilus influenzae* type-B, Meningococcal meningitis, *Streptococcus pneumoniae*, Tetanus, Pertussis and the spread of Tuberculosis; along with viral diseases including polio, chickenpox, smallpox, flu, hepatitis A-B, Papilloma virus, Measles, Mumps, Rubella, Rotavirus, and Respiratory Syncytial virus (Swedish Council on Health Technology Assessment. 2009). However, the re-emergence of TB, malaria, yellow fever, and the advent of HIV/AIDS, Ebola, Hanta and SARS Coronaviruses shattered the vaunted pride of modern medicine. Faced with Dengue, AIDS, COVID-19, and ever-increasing antibiotic-resistant pathogens, the scientific and medical community realized its gradual retreat in the battle against germs. Even extensive research with a strict vigil is unable to stop the recent COVID-19 pandemic, as well as drug-resistant infections caused by multi-drug resistant (MDR) *Mycobacterium tuberculosis*, *Streptococcus pyogenes*, methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL

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producing bacteria, vancomycin-resistant bacteria, MDR-*Salmonella enterica* Serovar Typhi, drug-resistant Malaria etc. (Meyer *et al*., 2011; Chattopadhyay *et al*., 1999; Urban-Chmiel *et al*., 2022; Mandal, 2011). Germs once confined to a certain region have now picked up rides to all over the globe, making the world a *global village*, due to industrialized trade and commercial travel. While the injudicious use of antibiotics in all walk of life generates antibiotic-resistant "superbugs which make the life-saving drugs useless (Christaki *et al*., 2020). These information's not only creates panic among people, but may make the age of antibiotic into an age of anxiety (Chattopadhyay *et al*., 1999).

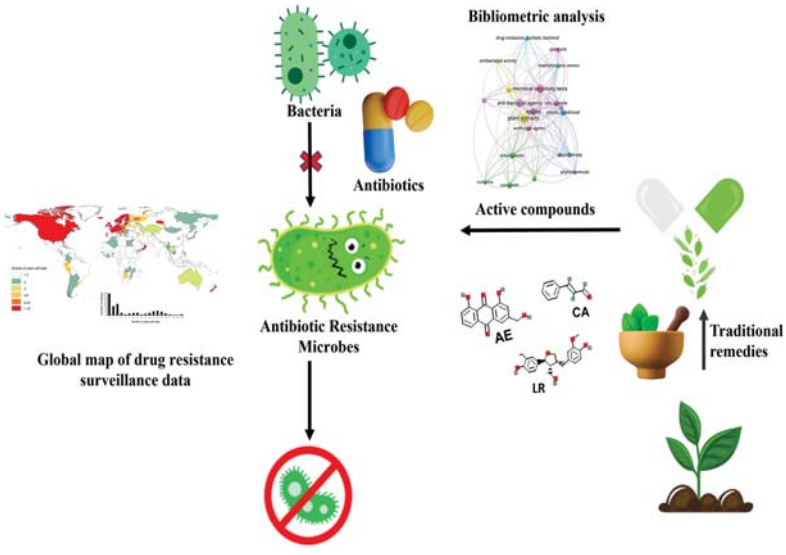
Antimicrobial resistance (AMR) is the ability of microbes including virus, bacteria, fungi, and parasites to survive and grow in presence of an antibiotic/ antimicrobial agent that used to kill or stop their growth. Resistant microbes not only make the treatment ineffective by withstanding the effect of antimicrobial agents, but lead to persistent infection with increased risk of spread. AMR is the resistance developed by the microbes to the drugs used to treat those infections; while *Antibiotic resistance* is the resistance of the infection causing microbes over the antibiotics. Since the dawn of human colonization mankind depend on plant kingdom not only for food, but also for clothes, shelter, and healthcare, including microbial diseases (Chattopadhyay *et al*., 2009). Global studies indicated a growing interest of health and pharmaceutical industries in harnessing nature-based remedies including spices, food and medicinal plants as a source of antimicrobial molecules to counter drug-resistant microbes (Khatri *et al*., 2016). Ethnomedicinal surveys and phytochemical screening reports are used as indicative information for finding new therapeutic leads (Abdallah *et al*., 2023). Thousands of medicinal plants are reported to have antibacterial activity and many against drug-resistant pathogenic, food-borne or microbes that cause spoilage around the globe (Sarangi *et al*., 2024). Thus, this article will portray the antimicrobial resistant profile of some common priority pathogens, isolated from the patients admitted to a tertiary Infectious Diseases Hospital, Kolkata, West Bengal, during 2020-2023; along with their sensitivity profile against respective antibiotics as well as towards selected spices, food, medicinal plants, and plant-derived phyto-antimicrobials, studied around the world, to highlight their ability to counter bacterial drug-resistance. This effort will encourage researchers and drug-developers to focus on selected natural resources in mitigating the huge problem of AMR.

Methodology

The information presented in this article was gathered via searching and retrieving scientific reports and publications from diverse databases, including search engines Science Direct, Scopus, Web of Science (WoS), and Google Scholar. The key terms included are medicinal plants, ethnomedicines, spices and food plants, plant extract, antimicrobials, phyto-antimicrobials, phytomedicine, nutraceuticals, polyphenols. The extracted data from research articles were analysed. Text-mining program with VOS-viewer, a tool for visualizing authors, publications, references, and location similarities for bibliometric analysis (Van Eck & Waltman, 2010; http://www.vosviewer.com/; Leiden University, Netherlands). VOS-viewer generates a map (Fig. 1) where each node represents a specific term, while the distance between nodes indicates similarity, and the thickness of connecting lines reflects the strength of their relationships. Plants are not only an excellent source of naturally occurring phytomolecules that serve as food, nutrient, and medicine, but the history of their use dates back even before the discovery of their chemical nature. Contemporary literature indicated that plant-derived bioactive molecules are future-sustainable promising antimicrobials. The bibliographic analysis presented in Fig. 1 indicated that global health may benefit from the green circular economy. An item's colour indicates its origin cluster, while the lines connecting items represent their relationships. The distance between two items reflects the strength of their association based on keyword links.

Current Status of Traditional Remedies Against MDR

Emerging antibiotic resistance results in failure of treatment of an infection with the existing drug(s), which then complicate the treatment and develop chronic Illness, with increased expenditures, and loss of manpower. Bacteria, being a single cell machinery, can easily adapt to the starving conditions, abiotic stress, antibiotics or antimicrobial drugs, and the host immune defense due to its ability to evolve rapidly. Intense inappropriate use of antimicrobials/ antibiotics by the society can led to the development of MDR-strains. Phytochemicals are found to complement antimicrobials/antibiotics due to their varied chemical nature and bioactivities that can target microbial physiological, metabolic, and genetic machinery. Four major groups of phytochemicals, including alkaloids, coumarins, phenols, and terpenes are found to have inhibitory potential against MDR microbes by interacting with the bacterial membrane proteins, efflux pumps, biofilms, and



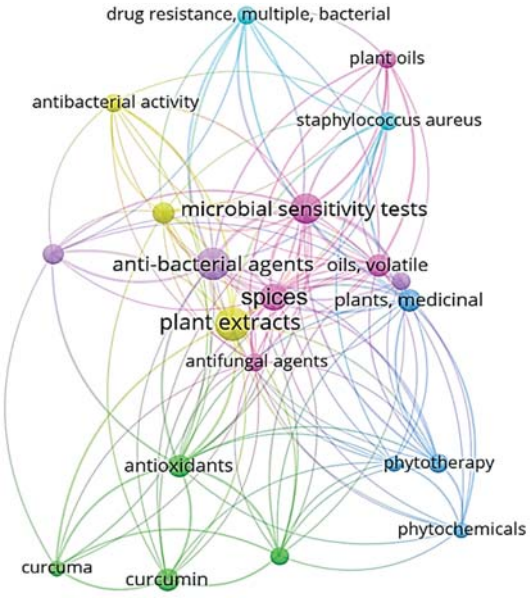


Fig. 1: Bibliometric Analysis of the Current Research on Antimicrobial Effects of Plant-derived Bioactive Compounds.

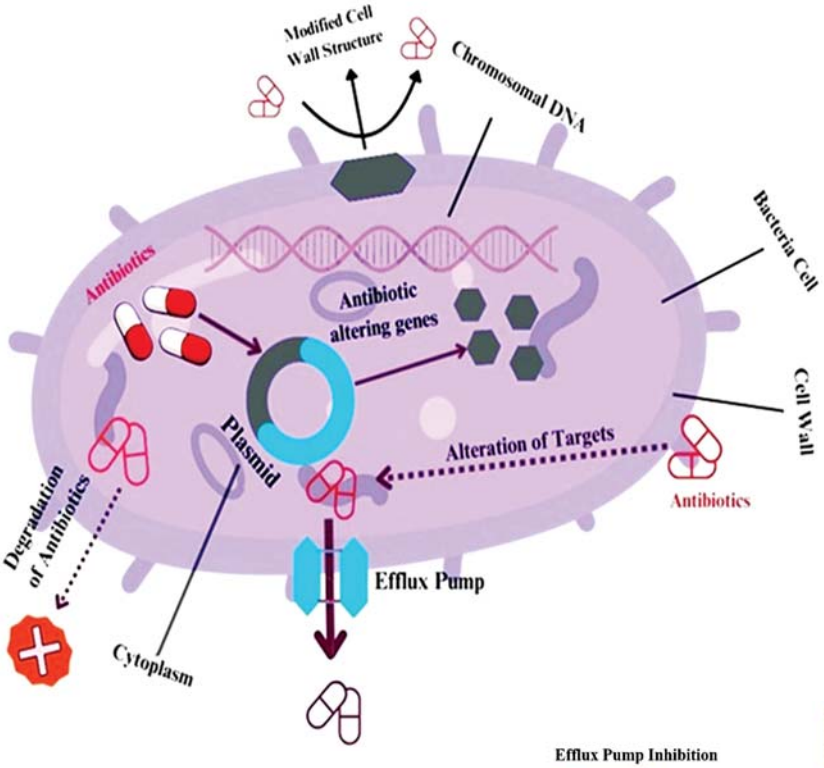


Fig. 2. Major Mechanisms of Bacterial Resistance Against Antibiotics.

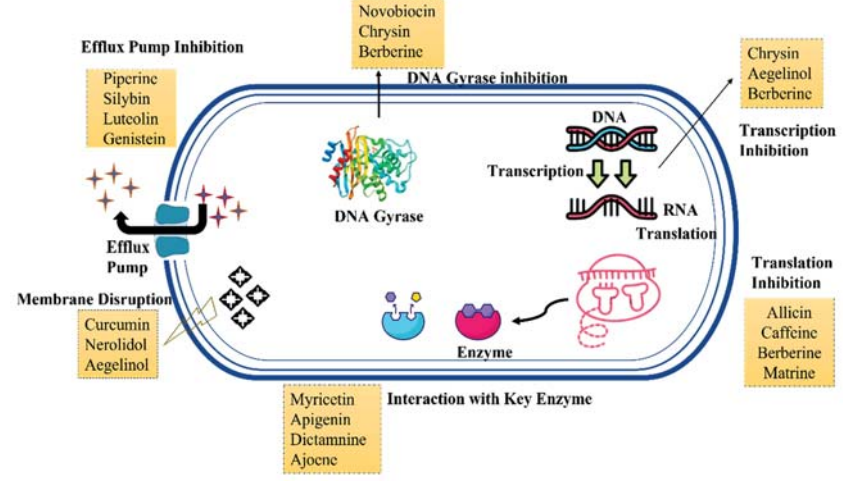


Fig. 3: Promising Phytochemicals to Combat Bacteria Resistant.

cell-to-cell communication (Suganya *et al*., 2022), that help bacteria to develop drug resistance. Plant extracts contain complex phytochemicals; thus, it is quite difficult for the bacteria to resist phytochemicals.

Origin of Antibiotic Resistance: Bacterial penicillinase was discovered even before the discovery and use of penicillin by Alexander Fleming in 1928. Resistant strains that deactivated the antibiotics emerged mainly as a result of the extensive use of antibiotics. It was found that chemically acclimatize penicillin can stop its cleavage by the enzyme penicillinases/â-lactamases (Kong *et al*., 2010). The antibiotic streptomycin was introduced in 1944 for the treatment of TB (TB Alliance, 2019), but streptomycin-resistant *M tuberculosis* was developed during treatment. Even the use of streptomycin and isoniazid, or anti-TB drug cocktail as routine therapy failed to stop the development of rapid resistance and MDR globally. In the last three decades *M. tb* developed extremely drug-resistant (XDR) form against all front-line antibiotic's amikacin, ciprofloxacin cycloserine, ethionamide, ofloxacin, and para-amino salicylate to become totally drug-resistant (Dheda *et al*., 2014). Till date it was not evidenced that MDR-*Mtb* is developed through horizontal gene transfer (HGT), indicating that AMR in *M. tuberculosis* might be through spontaneous mutation (Klopper *et al*., 2013).

Evolution of Microbial Drug Resistance: Causes and Mechanisms: In the bioorganic evolutionary tree, microbes evolve, survive, reproduce, and spread quickly and efficiently to adapt their environments for survival. When a bacterium is exposed to or treated with an agent to stop its growth the microbe tries to survive through genetic changes (Fig. 2). Thus, the development of resistance is a genetically controlled instinct of living organisms, from tiny microbes to the highest evolved human being. Antimicrobials are widely prescribed in human, but about 50% of these prescriptions are deemed unnecessary (Bassetti *et al.*, 2022). The inappropriate use, overuse, or misuse of antimicrobial drugs is a key factor contributing to the rise of antimicrobial resistance. Societal lack of awareness about the dangers of misuse and overuse, and the implications of drug-resistance plays critical role in perpetuating practices that drive resistance. The societal significance of AMR is multifactorial, necessitating community awareness and education

Table 1: **Major Mechanisms of Antimicrobial Resistance**

Types	Mechanism	Reference
Efflux pumps	Help to expel drugs/antibiotics from bacterial cell, first reported for tetracyclines in 1970's, now found in a diverse Gram-negative MDR bacteria.	Gaurav *et al*., 2023
Outer membrane (OM) *permeability*	OM of Gram-negative bacteria is a strong barrier to drugs, which may pass in two ways: via a lipid-mediated pathway for hydrophobic drugs or by diffusion via porins for hydrophilic molecules. Bacteria uses both to enhance their resistance to antibiotics via modifications of OM permeability.	Delcour, 2009
Reduced uptake	Membrane permeability of resistant bacteria reduce either by increasing efflux or decreasing the uptake. The decreased uptake was notices in beta-lactam resistance Gram-ve bacteria, as â-lactams penetrate the periplasm to bind the targeted penicillin-binding proteins of cytoplasmic membrane.	Reygaert. 2018
Enzymatic inactivation of antibiotics	Clinically resistant bacteria express some enzymes that can modify or inactivate the antibiotics; these enzymes are changed to react with the antibiotic and thereby neutralize its ability to kill the microbes.	Schaenzer and Wright. 2020
Target alternation	Antibiotic target-site alteration is a frequent mechanism of resistance; it occurs to evade the antibiotic's effect by interfering with its target site. To do this, bacteria have developed a variety of strategies, including target protection (preventing the antibiotic from reaching its receptor) and changes via mutation of the target site, resulting in a lower sensitivity to the drug	Munita and Arias., 2016
Mutation	Spontaneous alteration of DNA sequence like a single base-pair change can alter the expression of one or more amino acids, that alter or change the enzyme or cell structure resulting in resistance to the targeted antibiotic	Woodford and Ellington., 2007
Plasmid-mediated	Plasmid mediated antibiotic resistance genes can be moved between bacteria of the same or different species by conjugation, leading to the spread of MDR bacteria. Resistance caused by MDR plasmids severely limits the treatment options for Gram-negative bacterial infection	Schultsz and Geerlings, 2012
Biofilm formation	Bacteria stick to damaged tissue or medical devices often form a slimy coat of polysaccharides and peptide matrix or biofilm that confer resistance to antibiotics	Stewart and Costerton, 2001

empowering individuals to make informed choices about antibiotic use, and to encourage stewardship by understanding of its causes and effects (Salam *et al*., 2023; Frid-Nielsen *et al*., 2019). An immediate consequence of AMR includes (i) the growing number of treatment failures and deaths from resistant infections, (ii) a substantial strain on healthcare systems, (iii) the depletion of resources, and (iv) compromised patient care due to prolonged hospital stays, increased costs, and need for intensive and costly interventions (Dadgostar, 2019). The use of antimicrobials in food and livestock industries fuels resistant bacteria that enter the food chain, endangering human health. The rise of untreatable, pan-resistant bacteria requires urgent global action through international cooperation, surveillance, and capacity-building to prevent a potential global health crisis caused by AMR (Chinemerem *et al*., 2022; Singh *et al*., 2024; Coque *et al*., 2023; Samtiya *et al*., 2022). Communities can help to mitigate resistance through proper hygiene, vaccination, and judicious antibiotic use. The important mechanisms of bacterial resistance development are depicted in Table 1.

Some bacterial communication depends on its population density using tiny signaling molecules that stimulate the expression of several genes to regulate antibiotic resistance and a variety of activities. This is found in *Pseudomonas aeruginosa* when moves to a new niche and exposed to antibiotics (Hernando-Amado *et al*., 2019).

A microbe is either killed or survives when exposed to an antimicrobial agent, although microbial cells harbour some genes that can overcome the effect of drugs for their survival. Usually, those genes do not express until the organism is repeatedly or continuously exposed to an antimicrobial agent in sub-inhibitory concentrations, which induce the specific gene(s) to express. Thus, the survived bacterium, from drug exposure, will replicate and their drug-resistant progeny will become dominant in that microbial population. Thus, the evolution of resistance is a natural phenomenon, occurs due to erroneous replication or exchange of resistant traits between them. Bacteria develop their resistance by a number of ways, either through structural alteration, modifying physiological action, or by genetic changes. The major mechanisms are presented in Fig. 2.

Additionally, there are other factors including (i) *Societal Pressures*: the use and misuse of antimicrobials create a selective pressure for resistant organisms; while societal pressures accelerate resistance (Laxminarayan *et al*., 2013). (ii) *Inappropriate Use*: inappropriate use of antimicrobials by self-medication or healthcare providers during viral infection or undiagnosed illness help to select resistant microbes, (iii) *Inadequate Diagnostics*: when an infection is treated by a broad-spectrum antibiotics or antimicrobial without identifying the bacterium and its sensitivity, create selective pressure and accelerate AMR, (iv) *Hospital Use*: critically ill patients those who are more susceptible to infections require antimicrobials, but often administered heavier or repeated use of antibiotics select resistant microbes. The use of antibiotics by close contact of sick patients may create an environment for the spread of resistant microbes (Levy, 2002). (v) *Agricultural, diary, and pisciculture Use*: the use of antibiotics to agricultural, diary and fish feed promotes drug-resistance. More than 50% of antibiotics are used for food, and agriculture

Table 2. WHO New Bacterial Priority Pathogen List (BPPL) for 2024

Critical Group	High Group	Medium Group
Acinetobacter baumannii carbapenem- resistant	***Salmonella Typhi*** fluoroquinolone- resistant	**Group A *Streptococci*** Macrolide- resistant
Enterobacterales third-generation cephalosporin-resistant	***Shigella spp.*** Fluoroquinolone-resistant	***Streptococcus pneumoniae*** Macrolide- resistant
Enterobacterales carbapenem- resistant	***Enterococcus faecium*** vancomycin-resistant	***Haemophilus influenzae*** Ampicillin- resistant
Mycobacterium tuberculosis Rifampicin- resistant	***Pseudomonas aeruginosa*** Carbapenem- resistant	**Group B *Streptococci*** Penicillin- resistant
	Non-typhoidal S*almonella* Fluoroquinolone- resistant	
	Neisseria gonorrhoeae 3rd generation cephalosporin, and fluoroquinolone-resistant	
	Staphylococcus aureus Methicillin-resistant	

Table 3. Resistogram of Bacterial Isolates (priority pathogen) from a Tertiary Care Hospital During 2020-2023

Antibiotics[1]	*E. coli*	*Klebsiella Spp*	*Enterobacter Spp*	*Citrobacter Spp*	*Acinetobacter baumannii complex*	*Pseudomonas Spp*	*Shigella Spp*	*Salmonella Spp*	*MRSA*	*Enterococcus Spp.*
AMP	-	-	-	-	-	-	26%	7%	-	88%
PIT	56%	75%	35%	46%	88%	34%	-	-	-	-
SF	-	-	-	-	-	-	24%	-	-	-
CTR	-	-	-	-	-	-	-	12%	-	-
CTX	76%	82%	43%	48%	-	-	-	-	-	-
CPM	-	-	-	-	91%	64%	-	-	-	-
MRP	29%	46%	27%	24%	86%	47%	-	-	-	-
AK	26%	35%	21%	24%	84%	65%	-	-	-	-
CIP	89%	89%	38%	57%	-	68%	19%	28%	89%	-
LE	83%	78%	43%	48%	88%	57%	12%	15%	-	-
COT	55%	66%	54%	31%	-	-	-	-	-	-
FO	7%	28%	35%	11%	-	-	-	-	-	-
NIT	11%	36%	38%	18%	-	-	-	-	-	-
CL	4%	10%	8%	2%	6%	4%	-	-	-	-
VA	-	-	-	-	-	-	-	-	0%	27%
LZ	-	-	-	-	-	-	-	-	5%	6%
TEI	-	-	-	-	-	-	-	-	1%	22%
AZT	-	-	-	-	-	-	-	9%	-	-

[1] AMP: Ampicillin (10 µg); PIT: Piperacillin + Tazobactam (100/10 µg g); SF: Cefixime (30 µg); CTR: Ceftriaxone (30 µg); CTX: Cefotaxime (30 µg); CPM: Cefepime (30 µg); MRP: Meropenem (10 µg); AK: Amikacin (30 µg); CIP: Ciprofloxacin (5 µg); LE: Levofloxacin (5 µg); COT: Co-trimoxazole (25 µg); FO: Fosfomycin (200 µg); NIT: Nitrofurantoin (300 µg); CL: Colistin; VA: Vancomycin; LZ: Linezolid (30 µg); TEI: Teicoplanin (30 µg); AZT: Azithromycin (15 µg)

industry, without knowing the threat of drug-resistant microbes in food, and animals. The poor infection control, inadequate sanitary conditions and inappropriate food-handling also help in the rapid spread of AMR. The World Health Organization (WHO) on May 17, 2024 released the new Bacterial Priority Pathogen List (BPPL) for 2024 (Table 2), the second report on priority pathogens, after the first global priority list of 12 Antibiotic-resistant pathogenic bacteria in 2017 (Asokan *et al*., 2019).

To combat the drug-resistant menace, that pose the greatest threat to public health, require strategies including extensive research, development, national and international coordination to combat AMR. Thes list of bacteria presented in Table 2 is a useful reminder of the danger caused by the bacteria that are already developing resistance or becoming resistant to antibiotics. As per our hospital AMR data presented in Table 3, *Escherichia coli* shows resistance to Ciprofloxacin (>80%), 3rd generation cephalosporins (>70%), BL-BLI (>50%), Amikacin and Meropenem (>25%); while the resistance of *Klebsiella* species is >75% to most of the antibiotics. About 25% *Salmonella* Typhi and 12% *Shigella* isolates are resistant to fluoroquinolones; 80% *Acinetobacter* spp are resistant to cephalosporins, BL-BLI and carbapenems. Colistin is the lone antibiotic with >90% sensitivity.

Globally, antibiotic resistance kills an estimated 700,000 people each year (Mancuso *et al*., 2021), and some experts predict that number could rise to 10 million by "The low 2050 if efforts are not made to curtail resistance or develop new antibiotics. The once-robust fruit has been plucked, and the development pipeline for antibiotics now yields nothing more than a trickle of effective molecules, despite the critical need for these drugs (Dutescu and Hillier 2021). Compared to hundreds of cancer medications, roughly 40 novel antibiotics were in clinical development for the US market as of September 2016 (Willyard, 2017). The drug-resistant, including multi-drug resistant (MDR) profile of the bacteria, isolated in the Microbiology Department of a tertiary care hospital Kolkata is presented in Table 3.

Table 4. List of Selected Spices and Medicinal Plants and their Active Compounds Against WHO Priority Pathogens and their Origin

Plants	Compound	Bacterial Isolates	Multiple antibiotic resistance STATUS (MAR)[1]	MIC (mg/ml)	Mode of Action	Reference
Cinnamomum zeylanicum Cinnamon Family: *Lauraceae*	Cinnamaldehyde dimethyl acetal, α-copaene Cinnamic aldehyde Eugenol	*P. aeruginosa* *Klebsiella pneumoniae* *Salmonella enteritidis*	CTR FO PB CL	MIC 0.0562-0.225 µg/mL MBC 0.1125-0.225 µg/mL	Anti-efflux activity by lowering the efflux-associated gene *MexA* and *MexB.* Decreased the expression of the genes (treC, fimA, and mrkA) linked to biofilms in *Klebsiella pneumoniae*.	Al-Bayati and Mohammed, 2009 Abdelatti *et al*., 2023 Mahrous *et al*., 2023 Alibi *et al*., 2023 Karuppiah and Rajaram 2012
Allium sativum (Garlic) Family: *Alliaceae*	Diallyl Disulfide, Ajoenes Allicin, Ally methyl sulfide (AMS)	*E. coli* *Enterobacter sp.* *P. aeruginosa* *Metronidazole*-resistant *H. pylori* *S. aureus MRSA*	AMP, AMC, CAZ, G, OFX, PEN, C, Cd, AK, TE S, TE, Nv, C, VAN, E, AMC, NX, CIP AMP, AMC, CAZ, G, OFX, PEN, C	65.50 µg 110.80 µg 58.50 µg (ZOI= 19.45 mm)	Organosulfurs damage bacterial membrane integrity by forming disulphide linkages with free sulfhydryl groups of enzymes. Phenol, flavonoids, and sulphur compounds like S-ally-(L)-cysteine (SAC, hydrophilic) are hydrophobic and have strong radical scavenging properties.	Ankri and Mirelman, 1999 Bhatwalkar *et al*., 2021 Li *et al*., 2015 Sarangi *et al*., 2024 Karuppiah and Rajaram 2012
Zingiber officeinale (Ginger) Rhizome Family: *Zingiberaceae*	Lariciresinol, Gingerol and shogaol	*E. coli* *Enterobacter sp.* *P. aeruginosa* *MDR AcrAB-TolC* *Salmonella enterica serovar Typhimurium*	AMP, AMC, CAZ, G, OFX, PEN, C, Cd, AK, Ch, TE S, T, Nv, C, Va, E, M, AMP, AMC, Na, NX, K, CIP AMP, AMC, CAZ, G, OFX, PEN, C Na, E, VAN, TE, OFX, Nx, CAZ, C, AK	75.60 µg 185.50 µg 67.00 µg	Inhibit efflux pump	Karuppiah and Rajaram 2012
Piper nigrum L. (Black pepper) Pet Ether Extract Family: *Piperaceae*	Piperine	*S. epidermidis* *K. pneumoniae* *P. aeruginosa* *Staphylococcus aureus* *Salmonella typhi.*	CAZ, TGC, LE, CIP, Ak, G, IPM	0.625 mg/ml	Damage cell wall and cell membrane, decrease enzyme activity and destroy cell morphology.	Pérez *et al*. 1994

Plants	Compound	Bacterial Isolates	Multiple antibiotic resistance STATUS (MAR)[1]	MIC (mg/ml)	Mode of Action	Reference
Curcuma longa L. (Turmeric) Family: *Zingiberaceae*	α-Phellandrene 4-Hydroxybenz aldehyde	*Escherichia coli* *P. aeruginosa* *Streptococcus agalactiae* *Helicobacter pylori*		5µg/mL	Decrease FtsZ proto-filaments bundling. Reduce macromolecular leakage, NFκB activation	Khatri *et al.*, 2023
Solanum lycopersicum (Tomato) Family: *Solanaceae*	Tomato-derived antimicrobial peptides (tdAMPs) Apoplastic heme-binding protein 2 (SlHBP2)	*Salmonella Typhi* Uropathogenic *E. coli CI5* *Pseudomonas syringae* (Pst)		MIC 16µg/mL MBC 32µg/mL Concentration range 3-25 µg /mL (Pst)	Affinity for bacterial membranes is higher	Farvardin *et al.*, 2023.
Aloe vera (L.) Burm Family: *Asphodelaceae*	Aloe-emodin	*Mycobacterium tuberculosis* (H37Rv) *Staphylococcus aureus* *Pseudomonas aeruginosa*	CIP, G, TMP, CIP, E		Target mycobacterial cell wall lipid production	Rens *et al.*, 2018
Tagets erecta L. (Marigold) Family: Asteraceae		*K. pneumoniae* *Pseudomonas aeruginosa,* *Salmonella typhi,* and *Staphylococcus aureus*		39 µg/mL		Khouchlaa *et al.*, 2023
Mallotus peltata Bark Family: *Euphorbiaceoe*	β-Sitosterol Ursolic acid Acetyl-Bergenin Tannin	*Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus faecalis, Bacillus subtilis, Escherichia coli and Proteus mirabilis*		MIC ranges from 128 to 2000µg/ml	Chattopadhyay *et al.*, 2002;	
Odina wodier Roxb Bark Family: *Anacardiaceae*	Chlorogenic acid	*Staphylococcus aureus* *Bacillus subtilis*	C, OFX, NOR, Q, CIP All sensitive	256 µg/mL	Effect in alteration of structure	Ojha *et al.*, 2013
Shorea robusta Family: Dipterocarpaceae	Coumarins, flavonoids, Triterpenes, Resveratrol, Bergenin, Ursolic acid	*Salmonella enterica* Serovar Typhi	A, AMC, C, CIP, NA, NOR, OFX, SXT, T	MIC: 256-450µg/ml MBC: ≤512-1024 µg/ml		Chattopadhyay *et al.*, 2018; Kumar et al., 2019

[7]Antibiotics: AMP (Ampicillin-10µg), AMC (Amoxicillin-30µg), AK (Amikacin 30 µg), FOX (Cefoxitin 30 µg), CEP (Cephalothin-30µg), C (Chloramphenicol-30 µg), CIP (Ciprofloxacin-5 µg), CAZ (Ceftazidime), CTR (Ceftriaxone-30 µg), CD (Clindamycin-2 µg), CL (Colistin), ERY (Erythromycin-15 µg), G (Gentamycin-10 µg), KAN (Kanamycin-30 µg), MEC (Methicillin-5 µg), NV (Novobiocin-30 µg), NA (Nalidixic acid-30 µg), NOR (Norfloxacin-10 µg), OFX (Ofloxacin-5 µg), PEN (Penicillin G-10 Units), PB (Polymixin B), S (Streptomycin-10 µg), TE (Tetracyclin-30 µg), TGC (Tigecycline), TMP (Trimethoprim), VAN (Vancomycin-30 µg). ZOI: Zone of inhibition.

Some Essential Indian Spices and AMR

Infectious diseases caused by pathogenic and food poisoning microbes are integral part of human health. Most current antimicrobial agents, used to extend shelf-life, food safety and to counter pathogens, are now useless due to microbial resistance. Thus, spices, known for preservation of foods including clove, cinnamon, cumin, oregano, thyme etc having strong activity against *Staphylococcus aureus*, MRSA, *Pseudomonas aeruginosa*, *Vibrio parahaemolyticus* etc. are now investigated as new and safe antimicrobial agents (Liu *et al.,* 2017). Food-borne bacteria not only spoil food, but cause foodborne diseases and multidrug resistant variants including *Staphylococcus aureus*, *Escherichia coli,* and *Pseudomonas aeruginosa* (Miladi *et al*., 2016). Organic acids, benzoic and sorbic, used as preservatives to increase safety and stability by controlling microbes result in microbial resistance (Silva and Domingues, 2017). Moreover, most chemical preservatives unable to eliminate many pathogenic bacteria like *Listeria monocytogenes* or delay the growth of spoilage microbes (Tajkarimi *et al*., 2010). Natural products, are accepted due to better human tolerance and chemical diversity (Atanasov *et al*., 2021), and the antimicrobial activities of natural products are studied and applied in food industry. Traditionally, Indian food includes several spices, and most kitchen includes a minimum 6-8 spices, depending on family choice. The list of common Indian spices having antimicrobial potential is presented in Table 4.

Essential Indian Spices, Food, and Selected Medicinal Plants

Growing evidence in the last few decades revealed that plants including food, medicine and spices, contain diverse secondary metabolites with antimicrobial activities that protect plants against infections and stress of the environment and biota (Nabavi *et al*., 2015). Among those metabolites' alkaloids, lectins, polyacetylenes, polypeptides, polyphenols, and terpenoids have significant antimicrobial activities; and are mostly safe for food products (Simoes *et al*., 2009). Usually, most traditionally used plants including spices, food and medicinal plant extracts, phytochemicals and nutraceuticals kill of bacteria by: (i) increase membrane permeability of Gram-negative bacteria; (ii) disrupting bacterial membrane structure and function; (iii) alter bacterial cell wall or membrane; (iv)interfere with bacterial metabolism; (v) disrupt biofilm; (vi) prevent Quorum sensing and (vii) modulate host cell immunity. However, out of diverse chemical groups, four major group of phytochemicals including alkaloids, coumarins, phenols, and terpenes showed strong inhibitory activities against MDR-bacteria via disruption of biofilms, and cell-to-cell communication, as well interacting with the membrane proteins, and bacterial efflux pumps (Suganya *et al*., 2022). Antimicrobial edible and medicinal plants like garlic *Allium sativum* L., tea *Camellia sinensis* L., thyme *Thymus vulgaris* L., turmeric *Curcuma longa* L., berries of Rosaceae family, and spices like *Cinnamomum* species (Nabavi *et al*., 2015; Marchese *et al*., 2014) are known for their antibacterial potentials. The exploration of traditional medicines (TM) for new antimicrobials offers several advantages (Cox and Balick, 1994; Prance, 2007), including (i) a more targeted approach, compared to random testing of plants (Quave *et al*., 2008); (ii) ethnobotanical data on use of plant parts, method of preparation, application, key ingredients, restrictions, harvest timing, storage, and treatment duration provide essential information for isolating bioactive compounds and designing studies (Miller and Su, 2011); (iii) herbarium records of plant specimens also help in identifying bioactive compounds and support biodiversity, climate, and taxonomic studies; while (iv) ancient ethnobotanical texts, like Bald's Leech Book, offer valuable drug discovery clues, as shown by its successful treatment of *Staphylococcus aureus* infections (Harrison *et al*., 2015).

Here we will address the antibacterial strength and limitations of only a few recent studies on some common plant species.

Aloe Vera: Aloe vera or *Aloe barbadensis* Miller (Asphodelaceae/Liliaceae) is a perennial xerophytic succulent shrub well known for its medicinal properties, including strong antibacterial and inflammatory activity. Aloe vera's gel and latex contain chromones aloesin, saponins, lupeol, salicylate, cinnamomic acid, phenolics and several anthraquinones including aloin and emodin having antiviral, antibacterial, analgesic activities (Surjushe *et al*., 2008). Alo emodin can break down bacterial cell wall, interfere with protein synthesis, and inhibit replication of diverse pathogenic wild and drug-resistant Gram-positive and Gram-negative bacteria (Arbab *et al*., 2021). It has been reported that the Aloe vera gel can significantly diminish or eradicate the growth of various drug-resistance bacteria, including *Salmonella* Typhi, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* (Jokhio, 2022). Aloe vera sap at 5% and 80% concentration can kill both wild-type and drug-resistant *S. aureus* and *E. coli*, respectively (Azahra *et al*., 2019). While Aloe vera ethanol extract and aloe vera gel have strong *in vitro* activity against MRSA (Chacón *et al*., 2019; Kumar *et al*., 2024).

Black Pepper: Black pepper or *Piper nigrum* of Piperaceae is a well-known culinary spice, having strong antibacterial potential, attributed to its bioactive alkaloid piperine, and essential oils against a wide range of Gram-positive and Gram-negative bacterial isolates (Feitosa *et al*., 2023). Piperine, has been shown to disrupt bacterial cell membranes, inhibit biofilm formation, and interfere with protein synthesis, resulting in bacterial death. The antimicrobial properties of black pepper is shown to enhanced by its EOs, containing caryophyllene and limonene (Zou *et al*., 2015). Piperine and black pepper EO demonstrated strong activity against several Gram-positive bacteria tested, with zone of inhibition ranging from 8.23-18.1 mm and 3.14-10.43 mm, respectively (Hikal, 2018). Another study revealed that black pepper EO (BPEO) inhibit *Escherichia coli* at MIC of 1.0 µl/mL, and the zone diameter of 17.12-26.13 mm (Zhang *et al*., 2017). Moreover, BPEO and piperine have strong antibacterial activity against MRSA, with inhibition zones from 8.23-18.1 mm, while piperine demonstrated maximum inhibition of MRSA at 0.5%, indicating its potential as a potent antibacterial agent (Abdallah, 2018).

Cinnamon: Cinnamon, an aromatic condiment used as spice, obtained from the inner bark of *Cinnamomum* tree. The most preferred cinnamon is the Ceylon variety *Cinnamomum zeylanicum*; syn. *C.* verum, followed by the Chinese *C. cassia*, Indonesian *C. burmanni* and Vietnamese *C. loureiori* (Abeysinghe *et al*., 2020). Both *C. zeylanicum* and *C. cassia* are used as spice and traditional medicine, with variable chemical composition, bioactivities and benefits (Ali *et al*., 2021; Unlu *et al*., 2010). Chemically, the major component of Cinnamons is its volatile essential oils (EOs) including cinnamic acid, cinnamate, coumarin, protocatechuic acid, polyphenols (Muhammad *et al*., 2021; Sebai *et al*., 2019), cinnamaldehyde, cinnamyl acetate and eugenol, (Trifan *et al*., 2021; Jayawardena & Smith, 2010), along with calcium, iron, manganese, and dietary fiber (Chericoni *et al*., 2005; Hariri & Ghiasvand, 2016). The nutritional, and medicinal properties, includes antibacterial, anti-inflammatory, antioxidant, and antitumor (Jafarizadeh-Malmiri *et al*., 2022; Bertacchi *et al*., 2021; de Silva & Esham, 2020) create its global demand. While significant antimicrobial and antioxidant activities of cinnamaldehyde, cinnamate, and cinnamic acid make cinnamon a natural food preservative for the poultry and food industry and increase the shelf life of food products (Ali *et al*., 2021; Suriyagoda *et al*., 2021). Now, this spice is focused on eco-friendly, sustainable farming, clean label, and counter antibiotic resistance. A recent review suggests the use of Cinnamon EOs as an antimicrobial ingredient of edible coating, adhesive patches and biodegradative films to prevent foodborne and spoilage microbes (Lucas-González *et al*., 2023). The cinnamon EO showed antibacterial activity against both wild and drug-resistant pathogenic and spoilage bacteria including Gram-positive *Entercoccus faecalis Micrococcus luteus, Staphylococcus. aureus, Streptococcus sp., Listeria monocytogenes* as well as against food-borne Gram-negative *Escherichia coli, Pseudomonas aeruginosa, Shigella dysenteries,* and *Salmonella* Typhimurium. by inhibiting biofilm formation, cell division, motility, quorum-sensing, ATPase, and altering membrane porins and lipid profile of cell membrane (Vasconcelos *et al*., 2018). Due to lipophilic nature, conjugated double bond and chain-length phenylpropenes of cinnamon EO also had antifungal activity also (Xie *et al*., 2017). However, the MIC and MBC of EO varies due to oil type, variety, extraction method and dose. The EO from leaves had higher MIC against *E. coli* O157:H7, and *Listeria monocytogenes* with least MBC (Cava-Roda *et al*., 2021); while MIC against *E.coli* differ (El-Zehery *et al*., 2022; Khanoonkon *et al*., 2022). Cinnamon EO was found to be more effective against Gram-positive bacteria, as found with *L. monocytogenes* having lower MIC than *E. coli* (Cava-Roda *et al*., 2021; El-Zehery *et al*., 2022). While other studies revealed that *E. coli* is more sensitive than *S. aureus* (Khanoonkon *et al*., 2022; Mohammadi *et al*., 2020), but its higher efficiency against *S. aureus* is also reported (Khazaei *et al*., 2021). The cinnamon bark EO tested against 50 clinical isolates of *Mycoplasma hominis* isolated from the cervical swabs of randomly selected women, responsible for bacterial vaginosis, pelvic inflammation, and pyelonephritis, revealed that its main constituents were cinnamaldehyde (97% *w*/*w*), have strong bactericidal activity, with MIC ranging from 250 to 1000 µg/mL (Sleha *et al*., 2014). Moreover, EO of cinnamon showed strong antibacterial activity targeting bacterial Efflux pump of extensive and pan-resistance *Pseudomonas aeruginosa* isolates of Human and Animal origin (Abdelatti *et al*., 2023), indicating its importance in the management of AMR.

Curcumin: Curcumin, a yellow pigment of turmeric, has been demonstrated antibacterial activity against MRD-*Acinetobacter baumannii* in multiple studies. Curcumin directly interacts with bacterial DNA, inducing oxidative stress, DNA damage, and apoptotic cell death (Adamczak *et al*., 2020). Moreover, curcumin coupled with epigallocatechin-3-gallate (EGCG) has a synergistic effect against MDR *A. baumannii* (Odo *et al*., 2023). This activity could be attributed to curcumin that disrupt bacterial outer membrane. Curcumin can be effective against MDR bacteria, such as *Klebsiella pneumoniae*. However, its antibacterial efficacy differs in different bacteria. Curcumin

is effective against four clinical isolates of *K. pneumoniae* at a concentration's of 2000 µg/mL; but 3000 µg/mL for one isolate (Karami-Zarandi *et al*., 2022; Adamczak *et al*., 2020). Crude turmeric paste inhibited the growth of *Staphylococcus aureus* at 10% but *Escherichia coli* was inhibited at 30% when added to nutrient agar; while aqueous extract can kill *S. aureus* at MIC of 800 ìg/ml and *E. coli* at 2000 ìg/ml. The *in vitro* MIC of curcumin was 125-250 g/mL against MRSA (Teow *et al*., 2016; Mun *et al*., 2013).

Garlic: Garlic or *Allium sativum* (Alliaceae) is one of the oldest vegetables cultivated by human for taste, smell and medicinal use. Garlic had excellent antimicrobial activities against multidrug-resistant isolates of bacteria, particularly against *Acinetobacter baumannii* at 5-10 mg/mL, and its susceptibility increases with concentration of garlic extract (Ramos *et al*., 2018; Abouelfetouh and Moussa, 2012). Garlic extract has bactericidal or bacteriostatic effect to inhibit the growth of a broad range of bacteria, including MDR strains. The susceptibility of fresh garlic extract was comparable to gentamycin, as the fresh garlic extract showed increased antibacterial potential in combination with gentamycin and or ciprofloxacin, which can inhibit drug sensitive and MDR-isolates showing synergistic or added effect indicating the potential use of these combinations in inhibiting drug-resistant pathogens, using garlic as a supplement in antibiotic therapy, to increase the effectiveness of those antibiotics (Magryœ *et al*., 2021). Chloroform extract of garlic demonstrated bactericidal activity against multiantibiotic-resistant *Acinetobacter* isolates (Rao and Naik, 2023). Interestingly, garlic has been shown to reduce the production and activity of toxins A and B of *Clostridium difficile*, essential for its pathogenicity. The garlic cloves powder significantly reduces the activity of these toxins, to mitigate the *Clostridium difficile* infections (Roshan *et al*., 2017). Allicin, the main ingredient of garlic and one of its oxygenated sulphur molecules showed antibacterial activity against a variety of microbes including *Escherichia coli*, MDR-enterotoxigenic *E. coli.* Moreover, garlic powder is effective against *Salmonella enteritidis*, MRSA, and *E. coli* O-157 (Circella *et al*., 2022). One study showed that 1% solution of fresh garlic powder can eliminate O-157 in 6h, and garlic powder from fresh garlic is more efficient than powder from old garlic. Studies have also demonstrated the antibacterial effectivity of garlic extract and its organosulfur compounds against drug-sensitive, drug-resistant, and exceptionally drug-resistant (XDR) strains of *Mycobacterium tuberculosis* (TB). The direct antibacterial activity of garlic to TB bacilli is not very strong, but it induces host macrophages to release pro-inflammatory cytokines and a protective Th1 response (Dwivedi *et al*., 2019). A study on *M. tuberculosis* revealed that the ethanolic extract of garlic had a minimum bactericidal concentration (MBC) of 7.5 ppm and a minimum inhibitory concentration (MIC) of 3.25 ppm; while ropB and rrs were the most productive genes in *Mtb.* Garlic clove contain several compounds including Diallyl sulfide, Diallyl disulfide, Diallyl trisulfide, Allyl methyl disulfide, Allyl methyl trisulfide (Fazeli-Nasab *et al*., 2021).

Ginger: **Gingerol**, a phenolic compound isolated from ginger (*Zingiber officinale*, Zingiberaceae) interact with bacterial cell walls to cause cellular damage in bacteria. Gingerol is shown to have anti-TB activity against drug-resistant, dormant, and starving strains of *Mycobacterium tuberculosis* (Mtb). In addition, gingerol can induce pro-inflammatory protective cytokines in the spleen of infected animals, along with the inhibition of Mycobacterial growth in *Mtb* infected mice (Bhaskar *et al*., 2020). Additionally, gingerol can stimulate Th1 and Th17 immune responses (Baldin *et al*., 2019). Two phytochemicals of ginger Enone-A and Shogaol demonstrated bactericidal effects against *Staphylococcus aureus*, MRSA, *E. coli*, and Extended Spectrum Beta Lactamase *E. coli* (ESBLEC) by interacting with active site with higher dock scores than anti-TB antibiotics (Corpuz *et al*., 2021). Another study demonstrated that ethanolic extract of ginger rhizome at 250-500 mg/ml have significant l activity against MRSA. The ethanolic ginger extract (EGE) was sensitive to MRSA at MIC of 400 mg/ml along with other bacteria (Rahman *et al*., 2020). Wang *et al* reported that ginger essential oil (GEO) at an MIC of 2.0 mg/mL and at of 4.0 mg/mL kill *Escherichia coli*, with a zone diameter of 12.3 mm (Wang *et al*., 2020). While at 50 mg/mL, ethanol extracts and GEO exhibit strong antibacterial activity against *Streptococcus pyogenes* at MIC and MBC of 1 mg/ml (Edo *et al*., 2024).

Tomato: *Solanum lycopersicum*, or tomatoes (Solanaceae), are known for its active compounds lycopene, phenolics, and saponins that contribute to significant antibacterial activity. These substances can damage bacterial cell membranes, inhibit metabolic pathways, and cause oxidative stress, thereby inhibit the growth of different bacteria (Aktepe *et al*., 2024). Although tomatoes antibacterial effect was weak than traditional antibiotics, but it showed promise, especially against Gram-positive *Staphylococcus aureus* (Mekky *et al*., 2024). The fruit, and leaves of tomatoes have demonstrated encouraging antibacterial activity against a variety of pathogenic bacteria. Several compounds, including four antimicrobial peptides, glycoalkaloids (tomatine), phenolics (chlorogenic acid, caffeic acid), and other secondary metabolites were

isolated from various parts are thought to be responsible for its antibacterial effect (Wang *et al*., 2024). Tomato seed oil at 20 µL/disc had potential antibacterial activity against several bacteria, including *Staphylococcus aureus*, *Escherichia coli*, *Acinetobacter baumannii*, and *Enterococcus faecalis*, at concentrations of 0.1 to 5.0 mg/mL (Ma *et al*., 2014). Interestingly, tomato-derived antimicrobial peptides tdAMP-1 and tdAMP-2 have strong activity against drug-resistant, acapsular, and hypervirulent strains of *Salmonella* Typhi, as well as *E. coli* and other enterobacteria. A recent study showed that, tomato juice containing tdAMP-1 and tdAMP-2 when incubated with *S. Typhi* for 24 h, the bacteria was completely eradicated (Kwon *et al*., 2024; Pereira Batista *et al*., 2019).

Marigold: Marigold or *Tagetes erecta* L. (*Asteraceae*), an ornamental plant, is also known for its potent antibacterial activity, owing to its high concentration of bioactive flavonoids, saponins, triterpenoids, essential oils, and thiophenes (Wu *et al*., 2023). These compounds shown to have strong antibacterial properties against a wide range of pathogenic bacteria, including Gram-positive and Gram-negative isolates. Thiophenes, in particular, are known for their ability to disrupt bacterial cell membranes and inhibit essential enzymes, resulting in bacterial cell death. The ethanol extract of marigold flowers inhibits *Staphylococcus aureus* with inhibition zones of 8.59±0.047, 9.23±0.026, and 10.23±0.044, respectively (Cahyaningrum and Widyantari, 2023). Trinh *et al*. demonstrated that flavonoids in marigold have antibacterial properties against several pathogens including *K. pneumoniae*, with a maximum zone of inhibition of 29.50 mm. Another study showed that leaf extract of Mexican marigold has antibacterial activity against *K. pneumoniae* and other bacteria that cause airborne disease and skin infections. The petroleum ether extract of dried pot marigold *Calendula officinalis* leaves had the strongest antibacterial activity against *K. pneumoniae* (Do Rosário Palma *et al*., 2023). The remarkable antimicrobial properties, low to non-toxic nature, specified phytochemicals produced by nature with mass affordability made this plant a potential antimicrobial and antiseptic agents in clinical and industrial applications against a range of pathogenic bacteria, including MDR strains. Some of its phytochemicals has approved by the Food and Drug Administration, following clinical evaluations. The effectiveness of various phytochemicals in treating drug-resistant, particularly MDR bacterial infections is presented in Fig. 3.

Many plant-based therapies are thought to work synergistically, but detecting synergy in complex plant extracts remains challenging due to limited techniques and understanding of how multiple compounds target various biological systems. Despite this, plant extracts with synergistic activity offer a valuable opportunity to combat drug-resistant pathogens. Chemically complex extracts may also be more effective than monotherapies, as microbes find it harder to develop resistance to multifaceted attacks. Harrison *et al*. (2015) showed that the combination of curcumin (CCM) and epigallocatechin gallate (EGCG) had significant synergy against *Acinetobacter baumannii*. (Ganiae *et al*., 2022) While CCM alone had an MIC of >256 µg/mL and the same for EGCG ranged from 128-1024 µg/mL. Interestingly, the addition of EGCG reduced CCM's MIC by 3- to 7-fold, with the lowest observed MIC for CCM being 4 µg/mL. In checkerboard assays, synergy was noted in 5 out of 9 isolates, with an additive effect in the others. The combination demonstrated bactericidal activity, with 4- to 5-log reduction in bacterial counts after 24 hours, outperforming the individual effects of either polyphenol compounds (Harrison *et al*., 2015). Till date more than 76 studies reported *in vitro* synergistic effects of pure drugs with natural products against bacteria, 60 as antibacterial adjuvants mostly with aminoglycosides or beta-lactams against MRSA obtained from 22 plant species and 33 phytocompounds (Nitsch-Velásquez, 2020; Ayaz *et al*., 2019). A recent review on synergistic effects of phytometabolites with antimicrobial drugs against biofilms produced by *Staphylococcus aureus* and *Pseudomonas aeruginosa* indicated that the combined action at lower doses can alter or inhibit acquired resistance mechanism and reduce undesirable effects (Bonincontro *et al*., 2023).

Another study by Atta *et al*. (2023) demonstrated synergistic antimicrobial effects between cefixime and four plant extracts against resistant clinical isolates of *S. aureus*. Cinnamic acid, gallic acid, and quercetin, inhibited both Gram-positive (4) and Gram-negative (13) isolates. Methanol extracts of *Curcuma amada*, *Momordica charantia*, and *Terminalia chebula* inhibited *S. aureus*, while ethyl-acetate extracts of *Curcuma amada* and methanol extracts of *Nigella sativa* were effective against Gram-negative isolates. The synergistic activity, confirmed through reduced bacterial growth and protein content, was time and concentration-dependent, suggesting that plant can serve as effective adjuvants to cefixime in combating AMR (Atta *et al*., 2023). These findings highlight the effectiveness of synergistic phytocompounds in overcoming microbial resistance compared to single compounds. However, a deeper knowledge of plant-antimicrobial combinations and their possible targets is needed to develop next-gen novel antimicrobials and/or improve current antimicrobials to fight drug-resistant infections.

Discussion and Conclusion

Nowadays world is facing a silent pandemic of anti-microbial resistance as the available antibiotics are getting increasingly ineffective and the pipelines of new antibiotics dry up. So, there is a critical need of new weapon to fight against those virulent microbes. AMR is not only a most critical challenge, but also threatening to reverse the decades of scientific progress in treatment of infectious diseases, as 'Antibiotics' is still a powerful tool to safeguard global health. In India the overuse and misuse of antibiotics in every walk of life including human healthcare, agriculture, food, livestock, and veterinary industries, mostly due to lack of socio-professional integrity and honesty, led to a rapid rise in resistant bacteria, demanding immediate action to tackle the alarming situation.

Phytochemicals of plants are known to complement antimicrobials due to their enormous chemical diversity and varied bioactivities, by targeting the physiological, metabolic, and genetic machinery of pathogenic microbes using three RD's: right drug, right drug and right direction. Global studies revealed that four major group of phytochemicals including alkaloids, coumarins, polyphenols, and terpenoids significantly inhibit pathogenic MDR-bacteria by targeting the bacterial efflux pumps, membrane proteins, cell-to-cell communication, and biofilm formation, the mechanisms that help bacteria to develop drug-resistance.

Plants, since its origin, have survived all types of stresses (Borges *et al*., 2016), including drought, temperature swings, sunshine; lack of oxygen, salt, and nutrients, as well as attack of pests, insects, nematodes, fungus, bacteria, viruses and anthropogenic activities like pollution, pesticide etc (Iriti & Faoro, 2009; Suzuki *et al*., 2014; Rausher, 2001). To withstand stresses, plant has modified their cell wall, produce antipathogen-proteins, and lytic enzymes (War *et al*., 2012), along with a wide-range of bio-dynamic secondary metabolites (Borges *et al*., 2016) to provide non-specific defense against virus, bacteria, fungi, parasite; having anti-inflammatory, antioxidant and immunomodulating properties (Dehghan *et al*., 2016; Gonzalez-Lamothe *et al*., 2009); and as nutritional constituents (Lahiri *et al*., 2019). The role of plants in infectious diseases is well documented (Chattopadhyay *et al*., 2018) with better safety, availability, biodegradability, sustainability, patient tolerance (Mahizan *et al*., 2019). Moreover, extract or phytocompounds can target microbial drug-resistant mechanisms, alone or in combination with antimicrobials (Chattopadhyay *et al*., 2018; Mahizan *et al*., 2019). Thus, plant kingdom can play a key role in drug-discovery process, as it: (i) provide enormous scaffold diversity with structural complexity, (ii) structurally optimized through evolution, (iii) have higher molecular mass, (iv) contain large number of tetravalent carbon atom to form single covalent bond with other atoms, (v) have fewer halogen and nitrogen atoms, (vi) higher number of H-bond donor and acceptors, (vii) lower calculated octanol-water partition coefficient with higher hydrophilicity, (viii) greater molecular rigidity that help in protein-protein interaction, (ix) provide major source of orally used drugs, and (x) help to understand their safety and efficacy by its use in traditional medicine (Atanasov *et al*., 2021), making it quite difficult for the bacteria to develop resistance over phytochemicals, compared to the known chemistry of most antibiotics. A recent study highlighting the emergence and spread of partial artemisinin resistance in East and Horn of Africa is a significant concern, as artemisinin-based combination therapy has been effective against *Plasmodium falciparum*, and current treatment guidelines are inadequate in addressing this issue (Assefa *et al*., 2024). Therefore, researchers have to adopt a more critical and vigilant approach, implementing robust national programs for the future. Additionally, it is essential to recognize that plant can produce diverse classes of phytochemicals to survive in various climatic conditions, and the interaction of these chemicals with animal systems as nutrients, nutraceuticals, and phytopharmaceuticals also varies. Traditional medicine (TM) also has several drawbacks including (i) questionable quality, as poor quality control can impact toxicity; (ii) safety risks from improper processing, adulteration and contamination with harmful substances; (iii) side effects like dizziness, headaches, and nausea; (iv) interactions with other medications that may reduce the effectiveness or increase side effects; (v) limited scientific evidence for efficacy; (vi) slower healing compared to emergency treatments; (vii) selection of remedies by inadequately trained practitioners; and (viii) lack of accuracy and reproducibility in traditional preparation methods, affecting consistency and safety. Additionally, the use of TM to combat AMR require to identify the effective extract and or phytopharmaceuticals from complex plant extracts, isolation of antimicrobial compounds, and potential adverse effect such as asthma and allergy, if any. Researchers need to keep in mind that the plants produce phytochemicals of diverse classes for their survival in different climatic conditions; while the interactions of those phytochemicals with animal systems, as nutrients, nutraceuticals, or pharmaceuticals, can also differ. Additionally, current diagnostic techniques for clinical antimicrobial resistance are limited (Hassall *et al*., 2024), with inadequate understanding how plant extracts

or phytomolecules, alone or in combination, interact with microbial resistance mechanisms for developing effective therapeutics to combat AMR using plant-derived substances.

Thus, it is reasonable to hope that future research to mitigate AMR will be of multi-fold, in which natural resources of spices, food and medicinal plants will play a key role.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper

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Abbreviations

AIDS: Acquired immunodeficiency syndrome

AMR: Antimicrobial resistance

BL-BLI: β-lactam/β-lactamase inhibitor

DIZ: diameter of inhibition zone

EGCG: Epigallocatechin gallate

EOs: Essential oils

HIV: Human immunodeficiency virus

HSV: Herpes simplex virus

MBC: minimum bactericidal concentration

MDR: Multi-Drug Resistant

MDR-*Mtb:* Multidrug resistant *Mycobacterium tuberculosis*

MIC: minimal inhibitory concentration

MRSA: Methicillin-resistant *Staphylococcus aureus*

NFêB: Nuclear Factor kappa B

SARS-Corona Virus-2: Severe acute respiratory syndrome coronavirus 2

Th1 and Th17: T helper type 1 and T helper 17

treC: T-cell receptor excision circles

UTI: Urinary tract infection

VRE: Vancomycin-resistant enterococci

WHO: The World Health Organization

XDR: Extremely drug-resistant

ZOI: Zone of Inhibition ❒

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