



A Review On Natural Products To Overcome Antimicrobial Resistance[Amr]

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ABSTRACT:

Antimicrobial resistance (AMR) is a critical issue in health care in terms of mortality, quality of services, and financial damage. In the battle against AMR, it is crucial to recognize the impacts of all four domains, namely, mankind, livestock, agriculture, and the ecosystem. Many sociocultural and financial practices that are widespread in the world have made resistance management extremely complicated. Several pathways, including hospital effluent, agricultural waste, and wastewater treatment facilities, have been identified as potential routes for the spread of resistant bacteria and their resistance genes in soil and surrounding ecosystems. The overuse of uncontrolled antibiotics and improper treatment and recycled wastewater are among the contributors to AMR. Health-care organizations have begun to address AMR, although they are currently in the early stages. In this review, we provide a brief overview of AMR development processes, the worldwide burden and drivers of AMR, current knowledge gaps, monitoring methodologies, and global mitigation measures in the development and spread of AMR in the environment.

KEYWORDS:Antimicrobial resistance, combating antimicrobial resistance, food animals, National action plan on antimicrobial resistance, one health concept.

INTRODUCTION:

AMR poses a significant public health threat in the modern era. As antibiotics lose their effectiveness due to the development of drug resistance, the treatment of infections become increasingly challenging, and in some cases impossible.^[1] Researches from the “CENTRE FOR DISEASE CONTROL& PREVENTION” (CDC) ,WHO and public health institutions around the world continue to assert that remedial actions must be implemented globally to address the spread of AMR . According to the CDC, more than 2 million AMR infections occur annually in the united states resulting in an estimated 29,000 deaths. The medical cost for AMR treatment is over \$4.7 billion.

For example, in the European union it is estimated that more than 6,70,000 infections are caused by AMR each year and about 33,000deaths as a result of it.^[2]

An assessment of 2019 global data found that an estimated 4.95 million deaths were associated with bacterial AMR, including 1.27 million deaths attributed to bacterial AMR during the global COVID-19 pandemic,

AMR rates have continued to rise in the period from March to October 2020. Nearly 80% of hospitalized patients for COVID-19 received antibiotics, which contributed to this AMR trend.

About half of the drug registered by FDA between 1981 and 2019 were natural products, or derivatives which was roughly double the share of all synthetic drugs. Among these drugs, natural products continue to be an important source for the discovery and development of anti-infective drug candidates. Around 42.3% of all anti-infective agents are derived from natural products, their derivatives and natural products mimics. Natural products are characterized by a great diversity of scaffolds and high structural complexity. Among plant-derived natural products, alkaloids, phenolic derivatives, terpenoids are promising sources of anti-bacterial lead compounds that can help to fill the drug development pipeline.



HOW ANTI-MICROBIAL RESISTANT GERMS SPREAD AROUND THE WORLD?

Modern travel of people, animals can easily spread. More than one billion people are on the move globally.^[3] This includes 410 million travelers arriving in the U.S through more than 300 points of entry each year.

Some examples of how antimicrobial-resistant germs can spread-

- Person-to-person during activities like handshaking, working out.
- Between people and animals, including pets and petting zoos.
- Some germs may be common in certain parts of the world, but less common in others.^[4] When people travel internationally, they can get infections from other people, animals, contaminated food or water through receiving medical care.
- New forms of resistance can emerge and spread quickly, especially resistance shared among germs through mobile genetic elements.
- Antimicrobial-resistance germs can share their resistance genes with other germs, making the infections they cause more difficult, or even impossible.

HOW ANTIMICROBIAL-RESISTANCE GERMS SPREAD IN THE COMMUNITY:

Germs including antimicrobial-resistance germs, live and spread within communities (between people, animals and food) through common activities and sometimes makes people sick.

- Person-to-person during everyday activities.^[5]
- From food to people and between people and animals without appropriate hand hygiene.
- People can also get an infection when traveling, then spread these germs when they return.

- Community-associated infections can happen to healthy people who have not had a recent interaction with health care (healthcare associated germs tend to impact sicker,more vulnerable people while they receive care.)

HOW TO PREVENT SPREAD OF AMR:

Germs will inevitably find ways to resist antibiotics and antifungals,which is why aggressive action is needed now to keep new resistance from developing and to prevent the resistance that already exists from spreading.[⁶]Global efforts can contribute to solutions that protect people from this threat,including-

- Improving quality and consistency of infection control nation wide.
- Detecting and responding to AR early,containing it before it becomes common.
- Enhancing and developing products that improve hygiene,prevent infections and keep germs from spreading.
- Increasing education and awareness around infection prevention and control.
- An antimicrobial-resistant threat somewhere can quickly become a threat anywhere,when infection prevention and control capacity is strengthened in a country,the world benefits.

WHAT INITIATIVES HAVE BEEN TAKEN TO PREVENT AMR ?

- **National Programme on AMR containment:** Launched in 2012. Under this programme, AMR Surveillance Network has been strengthened by establishing labs in State Medical College.
- **National Action Plan on AMR:** It focuses on One Health approach and was launched in April 2017 with the aim of involving various stakeholder ministries/departments.
- **AMR Surveillance and Research Network (AMRSN):** It was launched in 2013, to generate evidence and capture trends and patterns of drug resistant infections in the country.
- **AMR Research & International Collaboration:** Indian Council of Medical Research (ICMR) has taken initiatives to develop new drugs /medicines through international collaborations in order to strengthen medical research in AMR.
- ICMR along with the Research Council of Norway (RCN) initiated a joint call for research in antimicrobial resistance in 2017.
- ICMR along with the Federal Ministry of Education and Research (BMBF), Germany has a joint Indo-German collaboration for research on AMR.
- **Antibiotic Stewardship Program:** ICMR has initiated Antibiotic Stewardship Program (AMSP) on a pilot project across India to control misuse and overuse of antibiotics in hospital wards and ICUs.
- DCGI had banned 40 Fixed Dose Combinations (FDCs) which were found inappropriate.

WORLD ANTIMICROBIAL AWARENESS WEEK

The World Antibacterial Awareness Week (WAAW), also known as World Antimicrobial Awareness Week, is an annual event conducted by the World Health Organization (WHO). Every year in November, initiatives are taken in many countries around the world to increase awareness of global antimicrobial resistance and to encourage best practices among the general public, health workers, and policymakers to avoid the further emergence and spread of drug-resistant infections.[⁶]The first-ever public campaign was done in Europe but as the campaigns continued to grow and spread, more countries kept joining the initiative. Even this year, the world antimicrobial awareness week has been celebrated all over the world with the theme 'Spread Awareness, Stop Resistance'.

PLANT DERIVED NATURAL PRODUCTS WITH ANTIMICROBIAL AGENTS:

ALKALOIDS:

Alkaloids have been used in botanical medicine for over >3500 years, with the *Eberspapyrus* (1500 BCE) mentioning the first recorded medical use of the opium poppy. They are a diverse class of natural products originally documented as basic, organic nitrate containing secondary metabolites produced by plants, microbes and animals. The class is broadened to now include most nitrogen containing natural products to low mol.wt or their derivatives. The most prevalent class are indole alkaloids with other classes including tropane, quinoline, isoquinoline, pyridine, pyrrolidine and steroidal alkaloids.[7] Many plant alkaloids and their derivatives are still prescribed today for a variety of medical reasons such as severe pain (oxycodone, morphine, fentanyl), as anti malarial (quinine), to treat hypo tension (ephedrine) or used recreationally (caffeine, nicotine, cocaine). Medical chemists often explore the inclusion of nitrogen into the parent compound due to its remarkable ability to improve the pharmacological profile of new drug derivatives. Several plant natural products alkaloids or their derivatives with anti bacterial activity are described below-

AMIDE ALKALOIDS:

Piperine and piperlongumine are amide alkaloids found in many species of piper. Piper beetle in the piperaceae family has been used extensively in Ayurvedic medicine in many applications with some examples being as an anti helminthic, astringent and to treat diarrhea.[8] Several different species of piper are used throughout Peru, Brazil, Panama and Mexico for treating a variety of ailments such as toothaches, dysentery, coughs, wound healing and more addition to these traditional uses, Piperine has multiple biological uses and has been found to have anti tumor, anti fungal, analgesic and anti depressant properties.

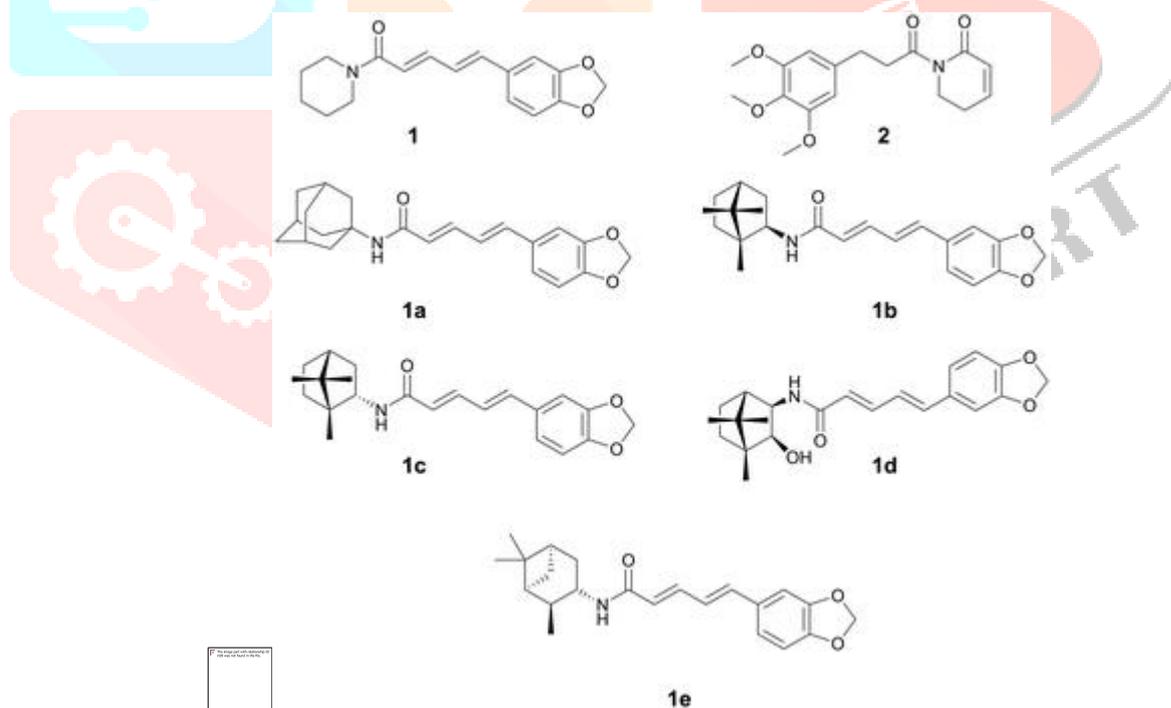


Fig. 1 Amide alkaloids and derivatives with antimicrobial activity.

PHENOLICS:

The oldest historical record of plant phenolic compounds used as medicine comes from the *Eberspapyrus* (1500 BCE), where ancient Sumerians and Egyptians recorded the uses of what is now known as treating pain and fever.[9] Thousands of years later, salicin and salicylic acid were isolated and later derivative to acetyl salicylic acid. Better known by its generic name, Aspirin it has since become the most used drug in the world, providing one of the ultimate examples of ethanobotanical records guiding the discovery of a new drug. There are over 8000 known plant phenolic compounds, making it the largest class of plant secondary metabolites.[10] They are seemingly ubiquitously expressed in plants and play many roles, from defense and

signaling to pigment biosynthesis and regulation growth. Phenolics are classified as having at least one hydroxyl group directly bonded to a mono or poly cyclic aromatic hydrocarbon and are biosynthesized through shikimate or phenyl propanoid pathway. The phenolic compounds highlighted below are those that exhibit antibacterial properties.

LIGNANS:

Lignans are a structurally diverse group of phenols characterized by beta, beta linkage of phenyl propane units. They act as antioxidants and defense molecules against pathogenic fungi and bacteria.^[11] The lignans are bioactive, non-nutrient, non-caloric phenolic plant compounds. Their basic chemical structure consists of two phenyl propane units linked by a C-C bond between the central atoms of the respective side chains (position 8 or beta), also called beta-beta bond. Lignans are present in plants both as aglycosides (without sugars) and as glycosides (with sugars).

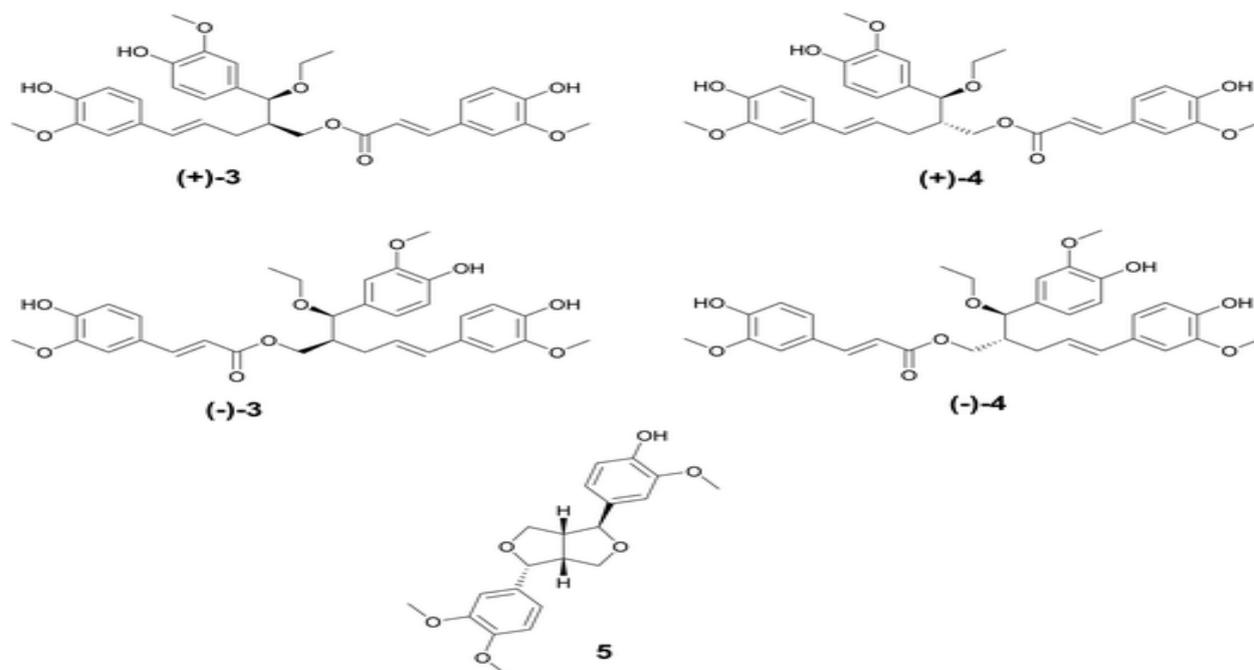


Fig. 2 Lignans with antimicrobial activity.

ANTHRAQUINONES:

Quinones are composed of aromatic rings with two ketone substitutions in the structure, and this chemical class can be divided into sub-categories of benzoquinone, naphthoquinone, and anthraquinone. Among them, anthraquinones are found throughout nature and have been isolated from fungi, plants, and bacteria.^[12] Anthraquinones contain an anthracene skeleton with keto groups on the 9 and 10 positions of the tricyclic ring. They display a wide range of bioactivities such as anticancer, anti-arthritic, and laxative properties. Compound 6 is an anthraquinone derivative that was isolated from the stem of *Stereospermum fimbriatum* DC. The antibacterial mechanism of action is unknown, but it has been noted for other anthraquinones against gram (+ve) bacteria, that as carbon number increases, so does the antibacterial activity. This trend suggests that lipophilicity and the ability to permeate/disrupt the bacterial membrane is one of the major factors in the antibacterial activity of anthraquinones against gram (+ve) bacteria.

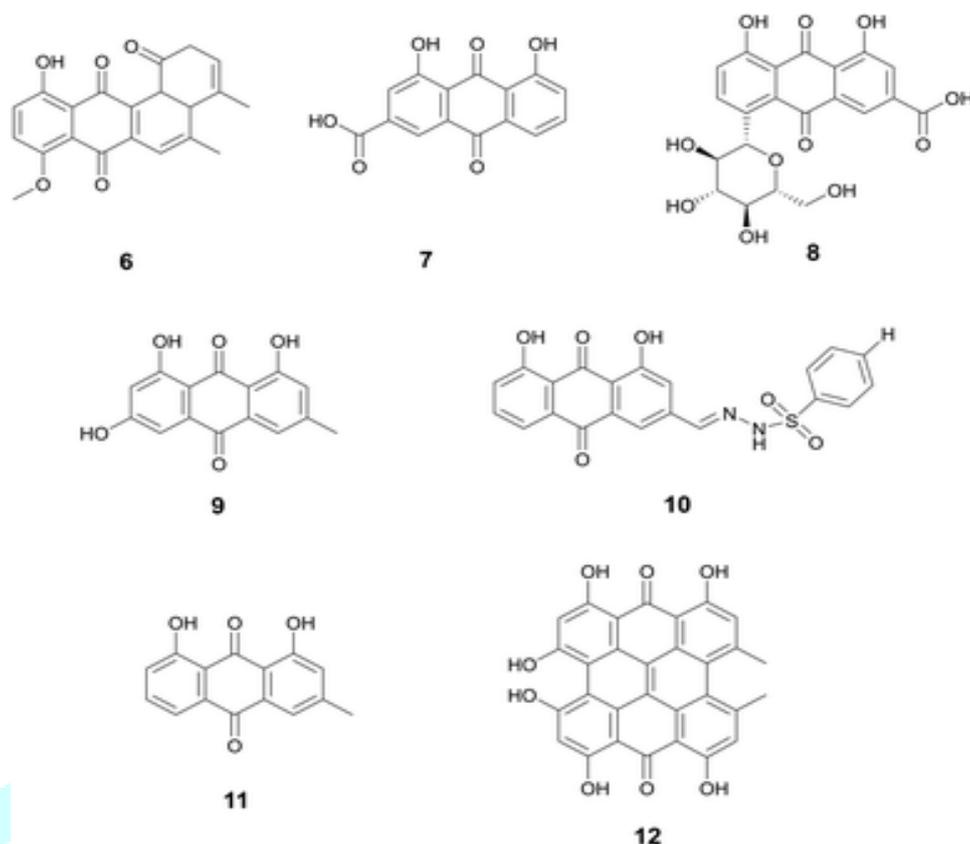


Fig. 3 Anthraquinones and derivatives with antimicrobial activity.

COUMARINS:

Coumarin is a fragrant organic chemical compound in the benzopyrone chemical class, which is a colorless crystalline substance in its standard state. The coumarins occur as secondary metabolites in the seeds, roots and leaves of many plants.^[13] Coumarins are also used as some dye lasers, and as a sensitizer in older photovoltaic technologies. It naturally occurs in different families such as Umbelliferae, Rutaceae, Leguminosae. Many coumarin derivatives like dicumarol, warfarin and acenocoumarol act as anti-coagulant and vitamin-K antagonist. It has a sweet odor, and has been used in perfumes. Coumarin was synthesized by the Perkin reaction. Coumarin can occur either free or combined with the sugar glucose. It is banned as a food additive in the United States due to the concerns of its hepatotoxicity.

FLAVONOIDS:

Flavonoids are polyphenolic compounds possessing 15 carbon atoms; two benzene rings joined by a linear three-carbon chain having the carbon skeleton of 15 carbons in a C₆-C₃-C₆ arrangement as two benzene/phenyl rings and a pyran ring.^[14] Flavonoids were discovered in 1938 when a Hungarian scientist, Albert Szent-Györgyi, used the term vitamin-P to describe them. Flavonoids constitute one of the most characteristic classes of compounds in higher plants. Many flavonoids are easily recognized as flower pigments in most angiosperm families. Flavonoids are phenolic compounds widely present in plants and foods of plant origin. Over 4000 flavonoids have been identified, most of them occur in fruits, vegetables and beverages (tea, coffee, beer, wine and fruit drinks.) The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species (ROS).

TERPENOIDS:

Terpenoids are a class of organic compounds comprised of an isoprene unit, have been used in medicine for thousands of years. Terpenoids also form a group of naturally occurring compounds, the majority of which occur in plants, a few of them have also been obtained from other sources. Terpenoids are volatile substances which give plants and flowers their fragrance. They occur widely in the leaves and fruits of higher plants, conifers, citrus and eucalyptus.^[15] The simpler mono and sesqui-terpenes are the chief constituents of the essential oils obtained from tissues of certain plants and trees. The di- and tri-terpenoids are not steam-volatile. Terpenoids are the hydrocarbons of plant origin of the general formula (C₅H₈)_n as well as their oxygenated, hydrogenated and dehydrogenated derivatives. Terpenoids are colorless liquids, soluble in organic solvents and

inorganic in water, most of the terpenoids are optically active, volatile in nature, boiling point is 150-180 C.^[16] They are unsaturated compounds. They undergo addition reaction with hydrogen, halogen, halogen acids to form addition products. They undergo polymerization and dehydrogenation in the ring. On thermal decomposition, terpenoids give isoprene as one of the products.

EX: Limonene, citral, eugenol.

MECHANISM OF ACTION OF AMR:

The exposure of bacteria to subinhibitory concentrations of antibiotic drugs is one of the primary causes of antimicrobial resistance (AMR), which is mainly caused by the improper use of antibiotics in clinical and agricultural settings. Antibiotic-resistant bacteria use a variety of mechanisms, such as antibiotic inactivation by enzyme breakdown or a change in the enzymatic scaffold; the expression of efflux pumps maintains intracellular antibiotic concentrations below inhibitory levels; alterations to the antibiotic's intended target; and modifications of the cell membrane's permeability. Enzymatic degradation or modification of the antibiotic scaffold is one resistance mechanism that renders the drug ineffective. The classic examples of these enzymes are the β -lactamases and TetX antibiotic-modifying enzymes. Antibiotic resistance can also be developed by protecting, modifying, or overexpressing the intended target. Altering the cell-wall PBP to overcome β -lactam antibiotic activity is the best-known example: VRE use this strategy by enzymatically modifying the peptidoglycan, which reduces the target's affinity for vancomycin. In addition, two other resistance mechanisms include the use of efflux pumps or changes in membrane permeability to prevent the antibiotics from entering the bacterial cells. Bacteria produce either a multidrug efflux pump or an antibiotic-specific exporter, such as tetracycline efflux pumps, to keep antibiotic concentrations within the cell at subinhibitory levels. On the contrary, few bacteria decrease porin expression or produce a more selective porin variant to prevent antibiotics from entering the cell by lowering membrane or wall permeability. Some bacteria can develop extensive resistance by using many complementary mechanisms. Clinical isolates of *Enterobacter cloacae* develop high-level resistance to carbapenems as a result of a porin mutation that reduces carbapenem absorption and increases the synthesis of a chromosomal β -lactamase.

METHODS OF MONITORING AMR:

Various methods have been extensively utilized for the monitoring of AMR in the environment. Some of these methods i.e., culture based, molecular based, and nanotechnology based are discussed in the following-

1) Culture based methods:

The microbe culture medium (solid/semisolid/broth) in which microbes are grown and quantified in research experiments has traditionally been considered the gold-standard methodology for the detection of antimicrobial resistant bacteria. Culture based techniques are inexpensive, relatively precise and convenient. ^[17] Antimicrobial resistant microorganisms can be effectively obtained from samples by incorporating antimicrobials of interest in the growth medium for selection, and if analogous experiments are performed lacking antimicrobials, the fraction of a microbial species that appears to be tolerant can be assessed. For certain antibiotics, such as colistin, the broth microdilution minimum inhibitory concentration (MIC) test is still considered the gold standard for determining sensitivity.

Although this method of AMR surveillance is widely adopted, it has enormous constraints. Many pathogens encountered in the habitat cannot be cultivated under laboratory conditions, false-negative results can arise from samples contaminated with high concentrations of chemicals, and the cultivation phase can be time-consuming, demanding prolonged incubation, numerous steps, and validation assays.^[18] The methodology adopted to preserve the specimens, as well as the preservation period, could have a significant impact on the rescue and enumeration of specific entities. Undoubtedly, the major drawback of these techniques is the relatively limited productivity.

Various culture-based automation technologies have been introduced to accelerate lab cultivation and assessment.^[19] For example, the VITEK system (bioMérieux), the microscan-walkaway system (Beckman Coulter), the BD Phoenix (Becton, Dickinson and Company) and the Biolog Microbial Identification (Biolog Inc). These technologies work by testing cultivated organisms in miniature growth chambers filled with various chemicals; any growth or change in colors will be detected and through an algorithm, the strain and

its phenotypic characteristics can be obtained. The result is reported as ID at the species level accompanied by its anti-biotic sensitivity profile (AST). Usually these systems require a pure isolate and an incubation period of upto 48 hours, and it costs more than the gold-standard biochemical phenotypic testing.

2)Molecular based method:

To genetically analyze pathogenic and commensal microbial populations, molecular methodologies were implemented.^[20] These have been utilized to recognize and monitor antimicrobial-resistant genes. Known ARGs, molecular variables used for the classification of genus and species such as 16s rRNA, along with mobile genetic elements such as intergrons (In), are notable examples of targets.

The nucleic acid amplification test (NAAT) is based on the polymerase chain reaction (PCR) that can assess the existence or omission of a targeted gene. In any given sample, ARGs of interest can be detected using specific DNA probes in a conventional PCR experiment. Quantitative PCR (qPCR) provides real-time results and precise statistical outcomes with response rates that are faster than conventional PCR. Using qPCR is a useful technology to investigate the effectiveness of actions on AMR. Epic PCR is the third method with high throughput that allows analysis of entire populations in a strategy that integrates 16s and ARG of each cell, allowing tolerance to be attributed to a particular microbe.^[21] The most advanced probe-based PCR method for studying the presence of ARGs of interest in a defined sample in metagenomics, in which a whole sample of DNA collected from an ecological sample can be thoroughly analyzed.^[22] This methodology has often been used to recognize genes in a variety of feces samples from people and livestock, including sewage and wastewater effluent, medical debris and human and animal guts.

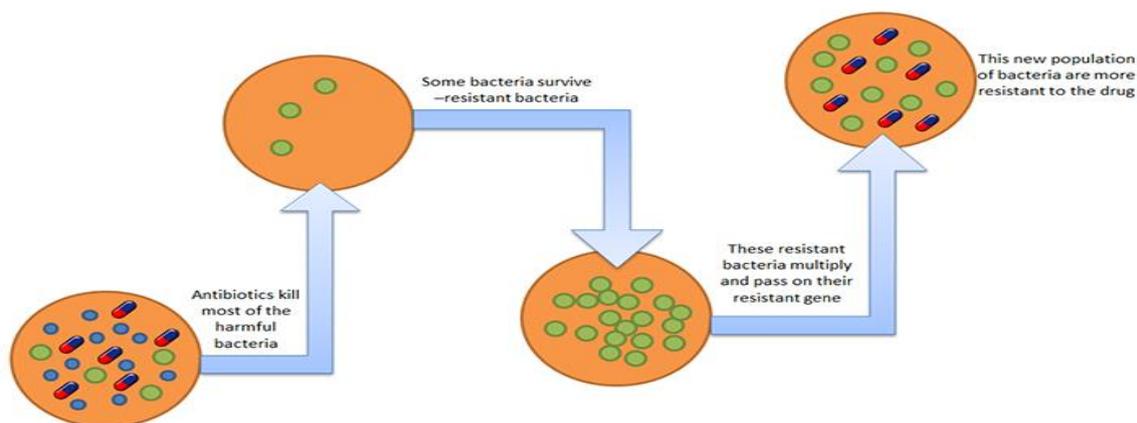
Molecular techniques based on PCR are rapid compared to culture based approaches, and thus can uncover various ARGs, even in bacteria that were challenging to cultivate in laboratories. However, it has been recognized that the gene is usually not synonymous with tolerance, as demonstrated by diagnostic labs, since genes are not always expressed. Currently, many commercial automated PCR based technologies for bacterial identification (ID) and ARGs are available and widely adopted. These come in cartridges that are preloaded with DNA probes for detection of 16s and many ARGs.^[23] The tests are rapid (2-6hr) and the samples are loaded directly without the need to isolate and purify the bacteria. These automated systems are expensive, usually not aimed at food and environmental samples, and require continuous updates from the factory to cover new ARGs. Examples of these technologies are GeneXpert (cephid) and AMPLICOR (ROCH), both of which depend on multiplex qPCR technology.

The most precise and accurate molecular tool for studying a specific organism and its ARGs to date is the utilization of whole-genome sequencing (WGS). Here, the whole DNA of an organism can be screened, along with ARGs, their copy numbers, mutations, and novel resistance genes. The most used platforms for WGS worldwide are Illumina, Nanopore Minion, and PacBio HiFi technology. WGS requires highly skilled technicians, expensive settings, and knowledge in data processing and manipulation.^[24] The use of WGS is not considered the first step in active AMR surveillance, but can provide significant information about the source of ARGs and their dynamics, hence they are better suited for use in academic settings or national public health authorities.

3)Mass spectrometry:

Recently, protein profiling of organisms using mass spectroscopy techniques has been implemented for bacterial identification. Specifically matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-ToF MS) is a recent molecular technique that evaluates AMR in microbial specimens. Identifying bacteria with MALDI-ToF is rapid, very accurate, and can process larger volumes than regular molecular techniques.^[25] Unfortunately, it requires an isolated bacterium and access to a specialized database, and the initial setup investment is costly. However, many advances have been made in the detection of ARGs using MALDI-ToF instruments, and the machine has been adopted by many hospitals around the world. The two major brands of MALDI-ToF technology in microbial identification are MALDI Biotyper and VITEKMS.

How Does Antimicrobial Resistance Occur?



CURRENT KNOWLEDGE GAPS IN UNDERSTANDING AMR :

There are still deficits in the literature on the interrelationship between antimicrobial administration in food-producing animals, susceptibility in the biosphere, possible detrimental consequences on people and livestock welfare, and certain associated environmentally related complications as part of the One Health approach. The evaluation of AMR threats in the community from antimicrobial administration in veterinary health care to people and livestock welfare appears to be problematic due to the heterogeneity of the problem and the lack of relevant data on the processes and routes associated with the genomic, biochemical, and community levels.^[26] Furthermore, there is a considerable information barrier on the influence that reception habitat exerts on the fate of AMR, multidrug-resistant bacteria, and ARGs. To adequately analyze the implications of AMR in the environment, it could be preferable if the relative input of the environment versus the influence of different factors had been evaluated with reference to the situation of AMR.

In contrast to country funding for research, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) is implementing a collaborative strategy in the European Council with the objective of integrating regional research initiatives to better combat the threat of AMR. Network mapping describes countless resources and propagation mechanisms, all of which are presumably driven by the ever-increasing incidence of AMR in therapeutic, animal, and ecological contexts.^[26] In addition, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) offers financial support to companies that are developing novel and potentially effective solutions to antibiotic resistance. However, more research is required to obtain new insights into the fundamental mechanisms of resistance, gene transfer, and bacterial evolution. This involves an active examination of the function of persistence and host–pathogen interactions, as well as their contribution to antimicrobial resistance. Exploring topics such as these may lead to the discovery of novel therapeutic and diagnostic targets. Furthermore, to adequately understand and address the nascent hazard of AMR, it seems that there is a significant need for political will to carry out novel projects, expand tools, and evaluate risk-analysis strategies.

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