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Microbiome-Modulating Natural Products: A Promising Strategy to Address Antibiotic Resistance

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ABSTRACT:

Antibiotic resistance has emerged due to the extensive, and at times irrational, use of antibiotics. Advances in genetics, biochemistry and chemical engineering in the past decades have unveiled this treasure trove of natural products (also called natural medicines) and allowed for their use against a variety of microbial infections to extend life and health, of all the diseases diagnosed, infectious diseases are of major concern due to the role of antibiotics in their prevention and cure. Since the discovery of the first antibiotic, penicillin different classes of antibiotics have been isolated and utilized in the clinic leading to remarkable achievement in the treatment of human and animal pathogens. The use of antibiotics, however, has not been restricted only to combat infectious diseases. They have also been used as drugs to treat tumors, viral infections, protozoa infections, trypanosomiasis and wounds. Microbiome-regulating natural products leverage the complexity of microbial communities, particularly the mammalian microbiome, in order to confer health benefits even without requiring direct activity against any potential human pathogens. These interventions can range from focusing on enhancing the presence of beneficial microbes – even to a certain defined community composition, to even targeting the vital growth and/or metabolic processes of disease-causing pathogens.

1. Introduction

On a conceptual level, research efforts striving to develop microbiome-modulating natural products (MMNPs) should pursue for the dynamic manipulation of host-associated microbial assemblages to achieve desired clinical effects (Alghamdi et al., 2024). Semi-synthetic and synthetic antibiotics have been produced by making small changes of an existing compound to evade resistant bacteria. Novel antibiotics, however, can also be easily metabolized and detoxified by enzymes through bioinformatic techniques. MMNPs represent a genuine departure from the mostly static models of traditional antibiotics. Natural products harness the accumulated effect of interactions within a complex ecosystem rather than representing the synergism of petri-dish-like drug reactions. Exquisite dynamic control or modulation, rather than merely change, of complex dynamics is necessarily a part of rational strategies to use MMNPs. Some of the most effective prescription medicines are those that do not block key proteins but, paradoxically, modulate them. Some theories of ecological networks suggest that it may be easier to control complex ecosystems than to understand all their working parts. If true, modulation of ecosystems (or parts of them) may prove more tractable over the longer term than expected.

Natural products play an indispensable role in microbial life, mediating ecological interactions such as competition and cooperation (Ramírez-Rendon et al., 2022). This has been fruitful to humans, as evidenced by the astonishing variety of biologically active compounds that have been identified and developed for use as drugs. The indispensability of such compounds is held in stark contrast with the threat posed by the looming antibiotic resistance crisis, which is widely believed to be fueled as much by the absence of pharmaceutical R&D investment as by evolutionary processes and anthropogenic biological disturbances. In light of current global public health demands, there is pressing interest in innovative strategies to develop antimicrobials and therapies that combat infectious diseases (Chawla et al., 2022).

1.1. Background and Significance

At this point, we also need to accept that an optimal solution can not be known since the gut microbiota are very diverse, functionally redundant, and host dependent. Therefore, generalizations should not be made, these biological constraints have to be measured. Secondly, the more characterization of prebiotic, probiotic, postbiotic, and FMT the more generalized approaches can be made to alter the microbiome. This may also allow for some degree of personalization based on the individual's intestinal microbial flora. Other strategies are also conceivable, one of which is the application of microbial viruses. These viruses, also known as bacteriophages, often show a high level of specificity towards their bacterial victim. Two types of phages, i.e., virulent phages and temperate phages, may be modified and used as therapeutic agents.

Alternatives are important in this scenario, both to cope against drug resistance and to limit the use of synthetic antimicrobials that may cause a serious health problem. Natural products have shown encouraging results as an option because of their wide range and diverse targeted biological activity, minimal side effects, and at the same time prevention of resistance development (Qadri et al., 2022). They provide potential in addition to becoming an alternative. In an attempt to discover novel antimicrobial agents from natural products, many researchers have recently demonstrated a rise in antibacterial and antifungal activities of natural compounds or their derivatives.

Antimicrobial resistance is a major public health problem and has become a global burden. The misuse and overuse of other healthcare facilities, including certain antibiotics, are mostly

responsible for the steady rise in antibiotic resistance(Yang et al., 2021). Furthermore, the development of newer compounds to counteract these issues has declined drastically. In 2014, the World Economic Forum has estimated that antibiotic resistance costs the world up to $100 trillion, along with 10 million lives/year since 2050. Many scientists believe that if the situation continues to worsen at the current rate, the problem of antibiotic resistance will get out of control by 2050(Matzaras et al., 2022).

1.2. Rationale for the Review

It is noteworthy that most living organisms associated with complex ecosystems in soil, marine environment, plant roots and guts of organisms are known to secrete natural substances. In human beings, the vast number and diverse allele of microbial species produce a range of bioactive molecules, which exert a multitude of effects on their habitat, and their host organisms. This interplay helps in maintaining a balanced environmental state, including equipping the host with the ability to fend off incoming pathogenic microbes. These microbe-derived natural products—termed secondary metabolites or bioactive compounds due to their low nutritional value—have potential as part of the human body's defense system and provide many functions, including signaling, quorum sensing, host protection, chelation of metals, and regulatory processes that direct the actions of commensals or modulate host-cell responses.

Antibiotic resistance has emerged due to the extensive, and at times irrational, use of antibiotics (Ramírez-Rendon et al., 2022). Plants and microbes have the capacity to produce diverse compounds, collectively called second- ary metabolites, which contribute significantly to human health and wellbeing (Qadri et al., 2022). With the advent of time, microorganisms have adapted to the adverse and frequently selective conditions prevalent in the medical, agricultural and veterinary fields. They have developed and acquired genes to evade the effect of antibiotics, rendering many antibiotics useless. Clinical microbiologists have found that the bacteria adapt resistance to multiple antibacterial drugs leading to chronic and untreatable infections which are thought to be the major cause of increasing mortality and morbidity in developing and developed regions(Ternent et al., 2014). If the situation continues to worsen, and no proper alternative strategies are adopted, it is thought that the global burden of antimicrobial resistance (AMR) will reach 10 million deaths and cost US $100 trillion by 2050. In this context, the discovery of new drugs is extremely desirable. In the extant era, natural products are an underexploited resource for the discovery of antimicrobials.

2. The Human Microbiome

Human microbiome is estimated to consist of 100-fold more genes than the human genome, with a high and diverse potential for secondary metabolism, meaning generation of small molecules with potential bioactivity. The human microbiota can transform environmental chemicals and drugs, which may also impact host health. Microbial communities can also produce metabolites with potential beneficial and curative effects. For example, gut bacteria can convert diet-derived tryptophan to the bioactive metabolite indole-3-aldehyde, activate intestinal AhR signaling, and subsequently impact ILC3 immunomodulatory capacity. Microbial deconjugation of food-derived phenolic glucuronides and hepatic metabolites can impact host health and metabolism. The capability to metabolize plant-derived polyphenols could provide interesting starting matter for the discovery natural products with great therapeutic potential. Understanding and uncovering the metabolic capabilities of both pathogenic bacteria and human colonizers could open new approaches for fighting infections and dysbiosis or enhancing beneficial activites.

Most of the human microbiota resides in the gut. The gut microbiota is a complex and dynamic community consisting of bacteria, viruses, fungi, and protozoa, and contain around 100 trillion cells. It performs numerous beneficial functions such as digestion and fermentation of food, production of essential vitamins and nutrients, and modulate immune system by helping conversion of T-cell to immunoglobulin A. The composition and abundance of gut microbiota are influenced by age, gender, diet, environment, lifestyle, and co-habitation with other humans. Despite inter- and intra-individual variabilities, few core species are generally present in most of the healthy individuals. The core phyla are Bacteroidetes and Firmicutes, along with some low-abundance phyla like Actinobacteria, Tenericutes, and Proteobacteria.

The human body is an ecosystem of interconnected microbial communities in which a large majority of microorganisms are usually symbiotic, such as commensals or mutualistic residents (W. Keith & G. Pamer, 2019). Disruption of the balance host resident microbes, i.e., when one type of microbes outgrows, will have significant metabolic and immunomodulatory effects (Matzaras et al., 2022). A German microbiologist Joshua Lederberg used the term 'microbiome' to describe the microbial communities and genes they host. The 21st century has seen considerable attention on human microbiome, owing to a tremendous development of -omic and metagenomic technologies (Alghamdi et al., 2024).

2.1. Definition and Composition

There is a growing understanding of how broad-spectrum antibiotics can have unwanted side effects on the normal commensal microbes, and result in the development of drug-resistant bacteria that have more effective BGCs, either within pathogenic or commensal bacterial species. Thus, an opportunity exists to functionally exploit this natural resource of members of the human microbiota's natural goods that respond to antibiotics or modulate the immune system. The human microbiome shows promise in additional applications, including disease mapping, drug development, self-regulated drug delivery, and cancer treatment.

The human microbiome has emerged as a rich source of untapped next-generation antibiotics. The development of our microbiome commences at birth and continues in an age-dependant manner. Based on an individual's diet, genetics, metabolites, and immune status, the microbiome landscape and composition change drastically in both numbers and types of organisms. The human microbiome can be used for personalized medicine, such as stratification of individuals based on their microbial ecosystems for the purpose of enhancing the effectiveness of tailored treatments.

The human microbiome is a crucial aspect of human health, contributing to various physiological and immune processes (Penders et al., 2013). The microbial inhabitants within ourselves can be explored for the discovery and identification of alternative medicines, including antibiotics and modulators of the immune response, to combat drug-resistant pathogens (Shim, 2022). Meta-omic studies have revealed that the microbiome harbors a broad spectrum of biosynthetic gene clusters (BGCs) for the production of natural products, including polyketides, nonribosomal peptides, prenylated polyketides, and ribosomally synthesized and post-translationally modified peptides (Prifti & Zucker, 2013).

2.2. Role in Health and Disease

In the GIT, several metagenomic conditions are essential in the diagnosis and prognosis of human illnesses. Metagenomics has revealed certain alterations in various ecological and genetic components which are ultimately associated with various human health conditions. Balanced function and composition of microbial communities may sustain the human health which is essential for the metagenomic equation. Due to genetic and environmental factors, the gut metagenome does not remain stable over time. Initially, the gut microbial community

in the human fetus is dictated by the genetic factors. Maternal and neonatal factors are the contributing factors which influence the composition and metabolic potential of the human gut metagenome. After birth, gestational age at the time of delivery, as well as mode of delivery and feeding have a substantial impact on its evolution. Factors such as high obesity risk, predisposition to extreme weight gain, and diseases in obesity and metabolic syndrome, adenovirus infection, cancer, cow's milk allergy, asthma, and multiple sclerosis (MS) may trigger alterations in the composition and metabolic potential of the human gut metagenome in terms of functions and pathways. The host states such as disease of the host, assessment for diagnostic purposes, support for treatments, and prevention of diseases are influenced by alterations in the human microbiota, metagenome, metabolomics, and enzymatic activities. Moreover, microbiota modulation strategy is therapeutic. Substantial evidence suggests that increasing the amount of diverse community can be therapeutic.

Role in Health and Disease The role of the human microbiota in promoting health has been extensively studied. Although the composition of the microbiome is difficult to define, the two major phyla in the human gastrointestinal (GI) tract are Bacteroidetes and Firmicutes. Commensal microbes provide the host with required vitamins, ferment non-digestible dietary carbohydrates into short-chain fatty acids (SCFAs), prevent colonization by opportunistic pathogens, and aid in maintaining the intestinal epithelial barrier. Many immune mechanisms, including the regulation of Tregs and B cell activation, were also promoted by commensal bacteria. However, during unhealthy situations, alterations in the diet or physiology affect the balance between the host and the microbiota. Disruption of homeostatic interactions between the host and the microbiota cause several diseases such as inflammatory bowel disease (IBD), chronic kidney disease (CKD), cardiovascular disease (CVD), obesity, type 2 diabetes (T2D), Alzheimer's disease (AD), ageing, autoimmunity, and cancers. This imbalance or dysbiosis has been favourably associated with lowered diversity when considering the fecal microbiota.
Introduction The human microbiome, made up of various microorganisms such as bacteria, fungi, and viruses, influences different facets of host physiology including digestion, immunity, and metabolism (Fei Wong & Santiago, 2017). This organ system not only plays a vital role in maintaining health, but it can also act as a reservoir for antibiotic resistance determinants that can be transferred to clinically significant pathogens (Ramírez-Rendon et al., 2022). In addition, disruptions in the microbiome can lead to dysbiosis that can result in infections from antibiotic-resistant bacterial pathogens, several examples of which are known (Prifti & Zucker, 2013). There are numerous studies involving the human microbiome, indicating its association with various fatal diseases, including cancers, allergies, asthma, and other dysfunctions of the immune system. Early detection of illness is feasible with the help of new inputs from metagenomics.

3. Antibiotic Resistance: Current Challenges

Moreover, other complementary and alternative interventions are available to address and relieve infections such as phytotherapy. Herbal therapy is a well-established health practice which targets the drug of phytoconstituents extracted from the medicinal herb. Due to their broad range of bionetwork and antimicrobial mechanisms, plants have been used as invaluable sources to find individual and combined treatments for anti-infectious products (Matzaras et al., 2022).
To this end, valuable human microbiota, probiotics and health supplements are usually prescribed after antibiotic therapy. Reported scientific evidence has shown a number of TCMM (traditional Chinese and Western Medicine Medicine) and indispensable medicines derived from other sources to be side-resistant. For example: SilverNanoparticles (AgNPs),

gold and other compounds of the Antimicrobial Medicines. Their mechanism(s) of action could be perfect to fix the project before it is actually polished to save more factors and reduce the risk of the "killer-by-sample" adverse response to antibiotics (Shim, 2022).
The increase in antibiotic-resistant bacterial pathogens is a concern worldwide, and leads to significant human and economic losses. The problematic resistance to therapy is partially due to the extensive use of antibiotics in the clinics, animal farming and other industries. As a result, the number of conventional antibiotics in the pipeline to address this challenge has dramatically declined. Therefore, alternative measures for the prevention and control of infectious diseases are largely needed (J. Cheesman et al., 2017).

3.1. Mechanisms of Antibiotic Resistance

Several pathogens are resistant to more than one antibiotic, a condition which referred to as Multi drug resistance (MDR). These resistant bacteria make the treatment more difficult by necessitating a stronger and more potent antibiotic to be administered to a person with MDR. (ref.) Some specific pathogens are unable to resist any single antibiotic that can be used against them. This situation has been defined as liable to all antibiotics susceptible pathogens or extensively drug resistant pathogens. In addition, a particular type of resistant pathogen is bacteria that resist nearly all currently available treatments.
The horizontal gene transfer (HGT) significantly contribute to the widespread dissemination of resistance factors among bacterial pathogens. HGT is a genetic transfer process via 3 different ways in which distinct bacterial cells can directly share or take up the novel genetic material among closely or distantly related bacteria. Moreover, changes in genetic materials can lead to rapid evolution and antibiotic resistance, thus evolving new mechanisms that are favoured by strong selection pressure from the environment. As a result, bacteria have developed novel defence systems and sophisticated machineries to manage the environmental threats like antibiotics. One such example is multidrug resistance (MDR), which simply implies that the organism responded to a range of pharmaceutical compounds that differ substantially from their likely physiological functions (M. Mira et al., 2014). The most common approach to bacteria to achieve MDR is to use efflux pumps that recognize and actively push a wide variety of different molecules outside the cell.
Antibiotics have been used to treat patients with a variety of bacterial infections and have shown a significant contribution in decreasing the burden of infectious diseases (Alghamdi et al., 2024). However, the misuse, overuse of antibiotics, and the lack of new antibiotic development have nourished the uncontrolled rise of antimicrobial resistance (AMR) worldwide. Over time, bacteria have developed various mechanisms to resist the action of antibiotics, including the common ones such as drug inactivation, target modification, efflux pumps blocking, drug evisceration, and lack of cell wall penetration. Moreover, the high genetic flexibility and transfer capacity in a range of methods have played pivotal role in the widespread dissemination of resistance factors among bacterial populations (I. Shabatina et al., 2023).

3.2. Global Impact and Public Health Concerns

Hundreds of thousands of neonatal deaths are associated with infections caused by resistant bacteria due to suboptimal conditions for neonatal care facilities in low-income countries. A comprehensive estimate on the superbugs-related fatalities in adult and children identified that the annual toll of superbugs at 1.27 million in the Indian population rises to 4.15 million fatality by 2050 and remain the highest related to that of other countries, as stated by experts of the U.K and Denmark in 2020 based on the data 2017. The number of annual deaths rises to put an additional huge burden on the healthcare system to 10 million since India had 1.393 billion people in 2020.

In addition to human health concerns, antibiotic-resistant bacteria are a serious threat to global food security leading to substantial losses to agriculture resources and create an economic burden. According to the Global Review on AMR 2021 report, almost 1/3rd of the total antibiotic users are followed by the agriculture sectors from the E.U. and the U.K. as reported by the data received in 2021. Despite the ban of human antibiotics on the animals in the E.U. (since 2006) and to the U.K. (since 2016) except under special circumstances, it is still not clear that what amount of antibiotics are really crawled into the ecological niches through food wastages, water pollutions, and other environmental factors. Moreover, approximately 70% of the antibiotics are being washed out as effluents in India of their total production, out of which 45% are from the agriculture sector. There is no such equivalent data available till 2021 by the WHO on this issue, although using antibiotics also in crops production in the U.S., Europe, Canada, and Australia.

Antibiotic resistance has emerged as a significant global health problem leading to treatment failures of common bacterial infections (El-Ansary et al., 2022). The spread of resistant strains between communities and hospital-acquired infections further aggravates the crisis, making treatment expensive and, at times, impossible. Complicated and multi-drug resistant infections are "almost impossible to manage" with the currently available countermeasures (Vera et al., 2021). Owing to the overuse and misuse of antibiotics in human and animals, the bacterium acquired the ability to evade not only the drugs meant for them but also the drugs meant to treat similar infections. The consequence of this includes superinfections, inappropriate and delayed treatments that resulted in severe health-related problems (J. Cheesman et al., 2017).

4. Natural Products as Microbiome Modulators

It is these dynamic changes in the composition and functionality of the microbiome that raise the question whether these can be steered, beyond probiotic intervention under conditions of disturbance or deficiency of beneficial bacteria. This process, referred to as 'structural modulation of the microbiome', can, for instance, involve the in vivo selection of beneficial bacteria from complex ecosystems by using carefully selected nutrients. Even complex extracts, for instance from vegetable matrices, which are known to contain a variety of bioactive compounds (i.e., lettuces), have been shown to structurally modulate the gut microbiome in pigs. Furthermore, other beneficial effects, such as a decreased load of P. acnes, linked with acne development in humans, have been reported in connection to Lactococcus extracts. In addition to metabolites produced as by-products of fermentation, another, rapidly emerging research topic is the potential modulatory role of natural, non-digestible compounds from marine resources whether structurally similar or greatly different from carbohydrates. These compounds can be metabolized by the intestinal microbiota.

In the domain of microbiome research and the relevance of microbiomes for various fitness parameters of the host across phyla, insecurity research is rapidly expanding (Matzaras et al., 2022). The human gut microbiome is composed of a variety of anaerobic and facultative anaerobic bacteria and facilitates the decomposition and processing of complex carbohydrates, the demise of microorganisms, as well as the supply of vitamins to the host and the defense against pathogens. Beneficial commensal bacteria also actively protect the host from invasive pathogenic species. The gut microbiome shows major differences between individual hosts, both in terms of the abundance and diversity of bacterial species, even though functional properties, such as metabolic pathway usage, show major similarities. Notably, the gut microbiome can shift between these states relatively quickly, for example following dietary changes, antibiotic consumption, or a course of infection with a gastrointestinal pathogen (Soo Xi Yap et al., 2014). Moreover, compositionally simplistic

conditions may still contain novelty species or bacteria with novel functions, so that even low-diversity distillations may have various functional properties (Amaning Danquah et al., 2022).

4.1. Definition and Examples

Narrow-spectrum antibiotics are antimicrobial agents targeting a specific subset of microorganisms. For example, fidaxomicin is an antibiotic that is primarily active against Clostridium difficile or fidaxomicin and the combination of nerincin and polymyxin E are inactive against most resident and transient commensal gut bacteria. In practice, it is quite difficult to design or screen for narrow-spectrum antibiotics but can sometimes overcome this limitation by developing derivatives of broad spectrum antibiotics with reduced ability to inhibit a commensal bacterial target [ref:
According to the World Health Organization (WHO), bacterial resistance is a global crisis and a decrease in the susceptibility of bacteria to antibiotics is observed in virtually all important bacterial pathogens (Böttcher & Gersbach, 2020). Bacterial resistance increases morbidity, mortality, duration of hospitalization and consequently, healthcare expenses. While there are numerous factors that contribute to resistance to a different degree, a key driver of resistance is the overuse of broad-spectrum antibiotics which has resulted in their widespread release into the environment and subsequent 'leakage' into commensal and environmental microbiomes, including the human gut, likely selecting for resistance among their members (Amaning Danquah et al., 2022). In contrast, a significant advantage of narrow-spectrum antibiotics is the potential for these antibiotics to have less selective effect on commensal microbiomes, resulting in slower emergence of resistance among their members.

4.2. Mechanisms of Action

Microbiome-derived antimicrobial peptides present a potential therapeutic solution for treating Pseudomonas aeruginosa infections. In a recent study, Suchard and coworkers have carefully analyzed around 95,000 sequences of ribosomally synthesized and post-translationally modified peptides (RiPP) from the human microbiome to identify gene cluster families encoding 479 unique RiPP. Screening known antibiotics against 56 cysteine-rich RiPP identified twelve inhibitors of P. aeruginosa. Detailed analyses identified origin of five known antibiotics. The antimicrobial peptide responsible for all this action displayed no sequence homology to any known antibiotic and was home-drafted unpicked with any known or detected mechanism. This research highlights this class of new antimicrobials and the microbiome-resting resources available for identification and exploitation for developing new drugs to treat infections. Furthermore, since the organisms that produce the discovered antibiotics also have genes conferring immunity to those drugs, the genes specific to the new antibiotics and immunity can be used more securely than with toxic antibiotics currently employed in commodity settings and animal agricultural fields.
Antibiotics have been important for the treatment of bacterial infections and microbial diseases (Iskandar et al., 2022). However, their overuse and misuse have initiated the global health threat of antibiotic resistance (Shim, 2022). Antibiotic resistance has developed in response to widespread use of conventional antibiotics thereby reducing their efficacy and making the treatment difficult (Kong et al., 2022). To add to the growing problem, the sustainable pipeline of new antibiotics, especially those effective against Gram-negative pathogens, has been drying up over the last few decades. This situation demanded an urgent requirement of new antibacterial agents that could be employed to treat the currently resistant microbial strains.

5. Evidence of Natural Products in Combating Antibiotic Resistance

With the encouragement of anti-resistance drugs and the development of resistance to some probiotics, natural products having a low propensity to produce anti-resistant bacteria or bacteriophages have perhaps the most relevance for alterations in the microbiota. It has been demonstrated that some natural materials can enhance the resistance of typical antibiotics for resistant pathogens. Through various potential mechanisms, bacterial resistance arises and combines intrinsic and acquired resistance. As an influential conference report, some natural materials have been shown to act against bacterial resistance in the form of one kind of acquired resistance determinant (e.g., one integron). This is an essential pattern for the evolution of resistance in an ecological area, even though there may be alternative mechanisms to produce resistant bacteria and exchange integrons. Indirect resistance is likely to contribute to growth yield benefits within one particular place after the anti-resistance bacterial growth is suppressed.

The worldwide emergence of bacterial resistance to antibiotics has become a major public health issue (Böttcher & Gersbach, 2020). An estimated 2.8 million drug-resistant infections occur annually in the US and Europe, accounting for approximately 54,000 deaths per year (Chindelevitch et al., 2022). The rise of MDR pathogens has generally discouraged efforts to combat infectious diseases, which for the most part are based on previous generations of drug discoveries. Most pharmaceutical companies have quit the antibiotics sector, while the numbers of public candidates are still extremely limited (Kong et al., 2022). The development of non-antibiotic strategies is to decrease or prevent the transfer of resistance. Some natural products can be beneficial for bacterium-symbiotic consortia to improve the health status of the host. In this aspect, the most commonly reported natural products include polysaccharides and phenolic compounds. Additionally, genetic material for anti-resistance, minority populations, and bacteriocins can be important commodities as biomaterial for microecological and symbiotic consortia.

5.1. In vitro and In vivo Studies

The candidature of A. indica for its efficacy against antibiotic resistivity has been further established by the histopathological studies conducted in mice mode of infection. The toxicological studies in healthy Sprague Dogley rats conducted by the authors also indicate the nontoxic nature of the A. indica leaves extract upto its 2000 mg/kg b. wt. dose. The emergence of infection causing microbes showing resistivity against routine drugs, is hitting the scientists and the global community; severely. Since it is happening on a global scale and at an accelerated pace, it is arguable that they should be considered as a global issue to be managed with a holistic approach. Moreover, antibiotic resistance is altered through gene expression. These resistant heap loads of gene become dead when the compounds act upon various genes of resistant organisms; the chances of gene transfer to another bacteria decreases consider). A. indica leaves extract alone or in synergism with antibiotics; the gene transfer decreases. These findings indicate the possibility that A. indica leaves extract and some natural compounds, under sub-inhibitory concentration could be utilized for reduction in dose and analysis of interval of antibiotics; thereby delaying the emergence of antibiotic resistance in future and a valuable candidate as microbiome modulator.

The efficacy of microbiome-modulating natural products, such as probiotics, prebiotics, and synbiotics, has already been demonstrated in vitro and in vivo both in mitigation of pathogen overgrowth and with antibiotics resistance gene harboring human pathogenic GI bacteria, both under in vitro and in vivo conditions (Rueda-Robles et al., 2022). Within Indian

scenario, the pathogenic E. coli obtained from healthy adult individuals, poultry birds, farm animals and diagnostic mycological culture samples were found to exhibit resistance to ciprofloxacin, a second-generation fluroquinolone, which is an antimicrobial category often utilised in poultry industry (Matzaras et al., 2022). The incidence of third generation cephalosporin-resistant E. coli in FAEC of farm animals increased from 53.20% in 2007 to 81.18% in 2016 in India (Kong et al., 2022). The plant-based natural compounds like appleacetogenin, 1'-acetoxychavicolacetate (laurel lactam) and microbiota modulators like probiotics/ prebiotics, and polyphenol rich Acalypha indica leaves extract at subinhibitory concentration, were demonstrated to potentiate the efficacy of probiotic, Ampicillin and levofloxacin when tested against both β-lactam and fluroquinolone resistance gene harboring ciprofloxacin resistant E. coli isolates, under in vitro conditions.

5.2. Clinical Trials and Translational Research

Recent studies have shown that natural products modulate the microbiome and provide plausible solutions for resistance and our dependence on antibiotics, but translational research and clinical trials are crucial to explore the potential of these products thoroughly so that they can contribute effectively to the fight against antibiotic resistance.(H. Elmaidomy et al., 2022) For instance, it has been discovered that the human commensals can produce novel antibiotics that inhibit pathogen colonization and offer promising therapeutic options for infection., Micorunting Sabromin and lactobacillic acid, with an emphasis on translational research including the animal model and subsequent mechanisms of action, a phase I clinical trial. BB-12 is a main seasoning or beverage in natural food, a widely used kind of probiotic molecule. A specific method for boosting the synthesis of bacteriocin was found using lactoococcus lactis. A promising option as a feed or as an oral care probotic could be found in the future but it should be helpful to investigate the medical application of these very useful discoveries as human or veterinary probiotics.

Clinical trials and translational research plays an important role in the development of antibiotics but with severe risk of resistance, researchers now have started their focus towards developing a next generation of antibiotics called microbiome-modulating natural products (MMNPs) which can be used for harnessing the antimicrobial activity of human commensals.(Shim, 2022) MMNPs have diverse chemical structures and influence the target bacteria that are different from traditional antibiotics.(Amaning Danquah et al., 2022) Some of them still have efficacy against antibiotic resistant bacteria. Moreover, in focus of today's world and their research is effectiveness in clinical trials. For instance, a commensal S. hominis, formed lantipeptide thuricin CD fund to have the same efficacy against skin infection S. aureus in human clinical trial as the positive control gentamicin that is synthetic peptide antibiotic.

6. Challenges and Future Directions

Antibiotic resistance efficacy of the herb-derived lenses, pharmaceuticals, vitamins, caffeine, or flavonoids is well-documented against key nosocomial pathogens like nosocomia (MDR), vancomycin-resistant enterococci (VRE), ampicillin (ampC) β-lactamase producers, gut flora members Citrobacter freundii, and MBL-producing gut commensal strains like Mirabilis morganii, Raoultella ornithinolytica, Enterobacter hormaechei including MD-Ra Klebsiella aerogenes (Kong et al., 2022). The compound(s), 4-amino-3-[4-phenoxy-3-(trifluoromethyl) phenyl]- 1H- pyrazole-1-yl]-2-oxo butanoic acid (PubChem CID: 86254799) (e-value 0.0, and 22 antimicrobial 16S rRNA gene sequences), feruloylamide glycosides, cortisol succinate, kojic acid, uridine (e-score 1.9, with 17 antimicrobial 16S rRNA gene sequences), and epigallocatechin-gallate, adenosine, ubiquinone, and ibuprophen (e-score 0.8 contains 36

antimicrobial 16S rRNA gene sequences) shown low e-value and maximum antimicrobial 16S rRNA gene sequences.

Introduction of Microbiome-Modulating Natural Products: A Promising Strategy to Address Antibiotic Resistance The engaging complexity of microbial communities (microbiomes) has intrigued microbiologists for centuries steered by unresolved questions, what are the primary determinants of microbial community structure, and function? The response to both the question remains an elusive subject. Integration of high-throughput sequencing and bioinformatic approaches has expanded our perspectives on microbiomes by investigating predatory interactions, symbioses, distributional patterns, and drug resistance environmental genes (Matzaras et al., 2022). For instance, these methods have unveiled that about 99% of natural microbes are not cultured in the laboratory, leading to the "great plate count anomaly" resulting in the untapped microbial resources of antibiotics production. The unchequered rapid explosion of commensal, commensal-pathogenic, and pathogenic microbes increase food, environmental biofilms, and hospital-associated biofilm resistances to any known antibiotics, disinfectants, and metals (Shim, 2022). At this juncture, market imperative for new and potently natural and semisynthetic antibiotics driven primarily by gut and other human microbiomes are unequivocally emphatic.

6.1. Regulatory Hurdles and Standardization Issues

Advanced technologies and study of microbial communities in general and the human microbiota specifically, have demonstrated that the evolutionary relationship between host and microbiota is underpinning the importance of microbiota health for the health of the host (Matzaras et al., 2022). The development of strategies successful at addressing chronic diseases will have to consider the well-being of both the host and its microbiota. The key to success of these strategies is to modulate the microbiota in a way that will enhance host health. The interaction of antibiotics with the microbiota led to a cascade of efforts to develop new antibiotics that would spare the microbiota. While these efforts were of limited success, it became obvious that even broader, more ambitious approaches are needed beyond sparing the microbiota. Additional option under development includes, microbiome restoration strategies and a few new molecules such as narrow spectrum virulence factor inhibitors with minimal effects on commensals. The appeal of these strategies is that in principle, they would deliver a focused action against the pathogens, sparing both the host and the microbiota. Their development is fraught with additional regulatory and pharmacological challenges.

Natural products have always played a crucial role in the discovery and development of new antimicrobial agents (Qadri et al., 2022). These natural products have served as lead compounds for the discovery of semi-synthetic and synthetic derivatives, and have also contributed to the discovery of novel targets or mechanisms of action (Ahmad Bhat et al., 2021). A significant percentage of compounds obtained from natural sources, especially plants and fungi, have been derived from their ability to interact in productive ways with microbes. This fertile interaction has resulted in natural products, which serve in a defensive role for the producer, as a result of their biological activity against pathogens and/or herbivores. Natural products from microorganisms such as bacteria and fungi, have been particularly amenable to this strategy.

6.2. Novel Approaches and Emerging Trends

There are signs that the problem is starting to be recognized and tackled effectively. At the foremost of strategies to address resistance is using conserved cellular targets and inhibitory mechanisms. As of 2021, most known agents targeting such cellular processes have been discovered, leading to much disinterest from industry in discovery programs that are heavily reliant on the exploitation of conserved mechanisms. Nonetheless, many other classes of

agents are available, and currently are used as therapeutics. In response to the challenges posed by a lack of new therapeutic agents, researchers have started to explore unconventional, enzymatic, metabolic, structural, or mechanistically non-conserved targets. Until 30 years ago, natural products were the only compounds with antimicrobial properties available to mankind. When synthetic antibiotics were developed, however, natural product-based discovery of such agents faced severe competition from screening collections of non-natural, synthetic molecules, which had the advantage of being less complex and more diverse.

INTRODUCTION Antibiotic resistance, simply defined as the loss of bacterial sensitivity to antibiotics, is recognized as a major global threat to public health and modern medicine (Raza et al., 2021). It is a natural consequence of the Darwinian evolutionary process that allows microorganisms like bacteria, fungi, and viruses to adapt to pressures in their environment. However, the use, misuse, and overuse of antibiotics in healthcare and agriculture over the past decades has dramatically accelerated the process of resistance development, leading to the current crisis. It has been estimated that at least 2.8 million people are infected with resistant bacteria and other pathogens every year in the United States and Europe, and more than 30,000 people die as a direct result of these infections (Amaning Danquah et al., 2022). Based on current trends, this number could grow to 10 million by 2050 world¬wide, making antimicrobial resistance a leading cause of death (Ternent et al., 2014).

7. Conclusion

Natural products derived from plants, animals, invertebrates, fungi, and microorganisms have been utilized for centuries by many cultures as alternative and complementary sources of chemodiverse chemical entities for treatment of a myriad of human diseases owing to their vast structural complexity and striking biodiversity. As living systems continue to generate unique molecular diversity and structural novelty, natural products remain the primary source of new and potent drug leads in multiple therapeutic areas including infectious diseases. Among them microorganisms represent a precious taxonomic group that has already offered the lion’s share of antibiotic compounds currently employed in managing bacterioses, fungal and viral infections. Microorganisms (especially certain members of the Actinobacteria and Proteobacteria phyla) have been the source of half of all new structural antibiotic classes developed over the last few decades. A big advantage of discovering antibiotics from natural products is the fact that they likely target multiple pathways. As such, the odds that a bacterium will develop resistance to the agents are quite low.

The rise in antimicrobial resistance (AMR) is making tackling infectious diseases an increasingly difficult public health challenge. Indeed, the AMR has become a real threat for a host of important human pathogenic bacteria and is recognized as one of the principal public health burdens worldwide (Soo Xi Yap et al., 2014)|(Kong et al., 2022). In addition, AMR is further complicated by a pronounced pipeline drought in the discovery and development of novel antibiotics capable to counteract the dissemination of multi-drug resistant bacteria (Amaning Danquah et al., 2022). Consequently, innovative preventive approaches and/or alternative pharmacological interventions are urgently required to protect susceptible individuals from a plethora of infectious diseases and consequently curb AMR. Natural products represent an impactful source of biologically validated antimicrobial agents.

7.1. Summary of Key Findings

Understanding the architecture and the regulation of how these different microbial communities are constructed and shaped by different environmental factors, including natural product metabolites, is a giant leap in microbial ecology and could have potentially

significant ill-health consequences for both livestock animals, crops, and humans (Vega-Bautista et al., 2019). The active roles and regulation of the resident microbial populations within such systems could also allow the development of novel therapeutics for livestock production, with the microbiota providing the available 'drug' treatments that could specifically 'seek-and-destroy' or suppress the growth and infections caused by those disease-causing pathogens which are unsuitable targets for direct antibiotic therapy either due to intrinsic resistance or significant human health implications of their control. Entrepreneurial spirit has focused the application, particularly in human health, on manipulating these dominant, defined resident microbial populations to enhance beneficial roles, with new therapeutic outcomes focussing microbiome-modulating treatments on dietary and other lifestyle interventions that specifically alter to the human gut microbiota.

Natural products, having been the sources for the majority of antibiotics used in human and veterinary medicine, continue to be a potential inspiration for the identification of new therapeutics in the post-antibiotic era (Chawla et al., 2022). In this context, microbiome-regulating natural products are also being explored as an alternative approach towards addressing the issue of unchecked antibiotic resistance, which also avoids the pitfalls of targeting and selecting for resistance among individual pathogenic strains, and therefore may represent a relatively sustainable solution (Matzaras et al., 2022). Such microbiome-regulating natural products leverage the complexity of microbial communities, particularly the mammalian microbiome, in order to confer health benefits even without requiring direct activity against any potential human pathogens. These interventions can range from focussing on enhancing the presence of beneficial microbes – even to a certain defined community composition, to even targeting the vital growth and/or metabolic processes of disease-causing pathogens.

7.2. Implications for Future Research and Clinical Practice

Numerous techniques have been assessed to promote colonization by symbionts. Using potent probiotics with direct-bactericidal capacities would offer some advantages, including possible rapid effect and no need to pick a new strain for each patient, therefore streamlining manufacturing although benefits should not be overstated, considering short-term survival of probiotics at most. The main advantage of techniques promoting colonization by commensals in situ would potentially be a more durable result with the potential to affect more than one species, as recommendable to prevent pre- and post-exposure colonization, since pathogen genetic make-up could differ between colonizing and environmental cells. Researchers tend to promote probiotics over techniques promoting commensals concentration, if only because probiotics are more widely commercially available. The use of Lactobacillus and Bifidobacterium has historically characterized the array probiotics, largely due to their status as traditional yoghurt and cheese fermentators. As most research has focused on them, they have been more readily authorized as probiotics.

Several obstacles and research gaps exist that require addressing. Most importantly, it is crucial to identify when to intervene (Matzaras et al., 2022). Several characteristics of bacterial colonization could play a role, such as the time required for an innocent bacterium to start interfering with pathogen action or bacterial capacity to interfere with the pathogen course (Alghamdi et al., 2024). Beyond temporal consideration, more knowledge is required concerning the impact of environmental pressure on the colonization process, including hospitalization former antibiotic exposure, viral infection, or preexisting microbial population. Finally, single strains are generally tested in clinical trials. However, up to 500–1000 bacterial species can occupy the GI tract, around 1.5 kg of matter rich in microbial cells and their products. Comprehensive studies are thus needed to comprehend how interplays between multiple inhabiting microbes can affect diseases and treatments, including the ability

of one organism to negate pathogen interference by another organism, assuming pathogen colonization remains an event mainly limited by resource competition.

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