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A systematic review on natural products with antimicrobial potential against WHO's priority pathogens

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Abstract

Background Antimicrobial resistance (AMR) is a critical global issue, with bacteria increasingly resistant to traditional antibiotics, resulting in more treatment failures and higher mortality rates. Resistance can be defined microbiologically or clinically and arises through genetic mutations or acquired traits. In response to this growing threat, the World Health Organization (WHO) established a priority list of antibiotic-resistant bacteria in 2016 to guide the research and development of new antimicrobial agents. The COVID-19 pandemic has further exacerbated AMR, underscoring the urgent need for new antibiotics. Natural products continue to be a valuable source of antibacterial compounds and play a significant role in developing new antimicrobial treatments.

Method This study employed a systematic review methodology, conducting comprehensive searches across PUBMED/MEDLINE, WEB OF SCIENCE, and SCOPUS databases, adhering to modified PRISMA-ScR reporting guidelines. A research librarian assisted in developing the search strategy, with searches executed on May 5, 2024, without restrictions on publication dates.

Study selection process Titles and abstracts were screened using Rayyan and Endnote. Inclusion criteria focused on original studies examining the antimicrobial effects of natural products against antibiotic-resistant pathogens, including risk estimates with 95% confidence intervals. The review identified significant effects of natural products on 12 families of antibiotic-resistant bacteria as reported by the World Health Organization (WHO). These findings underscore the potential of natural compounds as therapeutic agents in combating antimicrobial resistance.

Results A total of 4371 articles published between 2014 and 2024 were initially identified, from which 290 articles were selected for detailed review based on their relevance to the study period. All included studies were clinical trials. The analysis indicated that most of the research on dietary plants was conducted in countries within the Middle East, South America, and Africa. Among the pathogens investigated, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, and *Staphylococcus aureus* emerged as the most frequently studied due to their involvement in a wide range of infectious diseases. The findings revealed that alkaloids, flavonoids, phenols, saponins, tannins, and terpenoids were the principal classes of plant-derived compounds exhibiting antioxidant activity

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against bacterial strains. These bioactive compounds were extracted using a variety of solvents, including ethanol, methanol, aqueous solutions, benzoate, ethyl acetate, n-butanol, and methanolic preparations obtained from different plant parts such as leaves, bark, flowers, and roots. Notably, flavonoids represented 24.8% of the antioxidant product derivatives examined. The overall results underscore the significant therapeutic potential of regional medicinal plants in combating pathogens resistant to chemical drugs. Their antioxidant and cytotoxic properties may enhance the efficacy of existing antibiotic classes and contribute to reversing antimicrobial resistance.

Conclusion Based on the findings of this review, the diverse effects and therapeutic efficacy of herbal compounds in managing antibiotic resistance were extensively examined. Consequently, in light of the demonstrated antimicrobial activities of these plant-derived compounds, further investigation into their potential as alternative agents to counteract antibiotic resistance has become increasingly essential.

Keywords Natural product, Antibacterial agents, Anti-Infective Agents, Antimicrobial, MDR, Multidrug resistant, Plant extracts

Introduction

Antimicrobial resistance presents a pressing global challenge, as bacterial pathogens increasingly become resistant to traditional antibiotics which were widely used against bacterial infections as a standard treatment before the development of microbial resistance, leading to a rise in treatment failures and mortality rates [1]. Antimicrobial resistance can be defined both microbiologically and clinically. Microbiologically, resistance is characterized as a genetically acquired or mutated trait. The development of antibiotic resistance arises from various mechanisms, including conjugation, transduction, and transformation. Clinically, resistance refers to a level of antimicrobial activity associated with a high likelihood of treatment failure [2, 3]. In recognition of the significance of antibiotic resistance, the World Health Organization (WHO) established a priority list of antibiotic-resistant bacteria in 2016 to drive focused research efforts in this field [4]. The WHO Bacterial Priority Pathogens List for 2024 is categorized into three groups: Critical, High, and Medium. The Critical group includes *Acinetobacter baumannii* (carbapenem resistant), *Enterobacterales* (third-generation cephalosporin resistant), and *Enterobacterales* (carbapenem resistant). The High group comprises *Salmonella Typhi* (fluoroquinolone resistant), *Shigella* spp. (fluoroquinolone resistant), *Enterococcus faecium* (vancomycin resistant), *Pseudomonas aeruginosa* (carbapenem resistant), *Non-typhoidal Salmonella* (fluoroquinolone resistant), *Neisseria gonorrhoeae* (third-generation cephalosporin and/or fluoroquinolone resistant), and *Staphylococcus aureus* (methicillin resistant). The Medium group includes *Group A Streptococci* (macrolide resistant), *Streptococcus pneumoniae* (macrolide resistant), *Haemophilus influenzae* (ampicillin resistant), and *Group B Streptococci* (penicillin resistant). Additionally, *Mycobacterium tuberculosis* (rifampicin resistant) has been added to the list, although it is not classified under any of the previously mentioned groups [5]. This priority list aims to enhance global coordination of research and development strategies for discovering new agents against resistant bacteria and serves as a crucial guide for researchers seeking to develop novel antimicrobial agents to combat these resilient pathogens [6].

Antimicrobial resistance (AMR) poses a significant challenge to health systems today, with rates of resistance surging following the COVID-19 pandemic. This increase has led to substantial constraints in antibiotic treatment options [7]. Creating new antibiotics is highly challenging due to the complexity of the science and the time-consuming, costly development process. The other key obstacles include limited understanding of bacterial permeability, reliance on in vitro methods that fail to simulate host environments, and the intricate nature of bacterial systems. These issues collectively hinder modern, reductionist approaches to antibiotic discovery highlighting the urgent need for new antibiotic therapies [8–10]. Historically, natural products have provided a rich source of antibacterial compounds and have played a crucial role in the development of antimicrobial medications [11]. These natural products can serve as potent therapeutic agents against pathogenic bacteria [12, 13]. Additionally, the antimicrobial effects of these plant-derived compounds can sometimes be enhanced through strategies such as combining them with non-antimicrobial substances. This approach may lead to synergistic interactions that amplify their effectiveness and broaden their application potential [14].

This systematic review aims to identify potential candidates with antimicrobial properties from natural products and evaluate their effectiveness against the World Health Organization's (WHO) priority list of antibiotic-resistant pathogens. By bridging the gap between traditional and novel antimicrobial sources, this study seeks to contribute to ongoing efforts to combat antibiotic resistance and enhance treatment options for infectious diseases.

Method

Search techniques and databases

Given our goal to assess the efficacy of potential natural products against antibiotic-resistant "priority pathogens" [15] systematic review was conducted through a comprehensive search of the PUBMED/MEDLINE, WEB OF SCIENCE, and SCOPUS databases, using relevant keywords until May 5, 2024. Primary search terms and MeSH phrases included ("natural product*" OR "natural compound*") AND (antibacteri* OR antimicrobial*) AND (MDR OR "multi-drug resistant *") and their combinations. The search terms and Boolean operators were customized to fit the specific requirements and functionalities of each database. Detailed retrieval terms and search strategies are provided in the supplementary material. Additionally, reference lists of the selected articles were reviewed to identify further relevant publications.

Study selection and inclusion criteria

Two independent reviewers examined the titles and abstracts of the chosen studies to determine if they met the inclusion criteria. Studies were included if they fulfilled the following four requirements: 1- the study had to be an original; 2- the exposure could be related to antimicrobial effect of natural products; 3- the outcome could be the antimicrobial effects of these products against pathogens; and 4- the studies should be written in English. Any questions regarding article inclusion were then forwarded to the third writer for resolution. To make sure inclusion criteria were consistently followed, a third reviewer independently examined a subset (5%) of study titles and abstracts for eligibility.

Data extraction and quality assessment

Using a standardized data extraction form, researchers gathered the following information from selected studies: authors, year of publication, study design, location, sample size, recruiting site, study design, data collection method, languages, and results. These data were then organized into a customized Microsoft Excel template. To accurately represent the effectiveness of these products, the findings were further summarized into a set of relevant categories.

The quality of the included research was assessed using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials. This quality assessment aimed to evaluate the methodological rigor and potential bias in the studies. The findings from this assessment were considered when interpreting the results (Table S1).

Out of 4371 publications, after removing duplicates, we identified 290 studies as applicable (Fig. 1). Conference abstracts, review articles, and non-empirical studies (such as personal accounts) were excluded.

Results

At the outset of our study, we identified a comprehensive dataset comprising 4371 articles published between 2014 and 2024. This extensive collection offered a robust foundation for our analysis. Following the removal of duplicate records and a thorough screening of titles and abstracts, a total of 290 full-text articles were deemed relevant and selected for data extraction (Fig. 1). Based on the studies reviewed, the distribution of habitats for plants containing compounds with antimicrobial properties is as follows: Saudi Arabia (n = 4), Sudan (n = 1), Nigeria (n = 14), Cameroon (n = 18), India (n = 58), Germany (n = 3), Egypt (n = 13), Iran (n = 7), Iraq (n = 3), Ethiopia (n = 9), Morocco (n = 3), Philippines (n = 2), Algeria (n = 2), South Africa (n = 7), Croatia (n = 1), Brazil (n = 19), Ghana (n = 6), Palestine (n = 1), Italy (n = 2), Thailand (n = 7), Pakistan (n = 9), Vietnam (n = 3), China (n = 12), Mozambique (n = 2), Burkina Faso (n = 2), Bangladesh (n = 3), Portugal (n = 3), Zimbabwe (n = 1), Kenya (n = 1), Tanzania (n = 1), Mexico (n = 9), Rwanda (n = 2), Kashmir Himalaya (n = 1), Indonesia (n = 5), the United Kingdom (n = 3), the United States (n = 4), Romania (n = 1), Malaysia (n = 2), France (n = 1), United Arab Emirates (n = 1), Japan (n = 1), Turkey (n = 1), Afghanistan (n = 1), Somalia (n = 1), Madagascar (n = 2), Spain (n = 1), Greece (n = 1), and Sri Lanka (n = 1). Additionally, some studies did not specify the habitats of certain plants. Included studies focused on evaluating the efficacy of herbal medicines in managing and treating diseases and pathogens that exhibit resistance to standard pharmaceutical treatments. Meanwhile, India, accounting for 20% of the research efforts, has emerged as a significant contributor to exploring the potential of herbal and medicinal plants in combating drug-resistant pathogens.

In this literature review *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Salmonella Typhimurium*, *Enterobacter aerogenes*, and *Acinetobacter baumannii* are the common bacteria have reviewed. In our study, we discovered a variety of phytochemicals prevalent in regional plants, including flavonoids, tannins, phenols, terpenoids, alkaloids, and steroids. Among these, flavonoids were found to be the most abundant, constituting 24/82% of the identified phytochemicals. Tannins and phenols were also notably common, making up 19/44% of the phytochemical composition in these plants. Methanol extract, ethanol extract and fractions, microdilution method, acetone extract, ethyl acetate, and n-butanol are the more frequent extract methods for phytochemicals preparation in these studies. Based on the data obtained

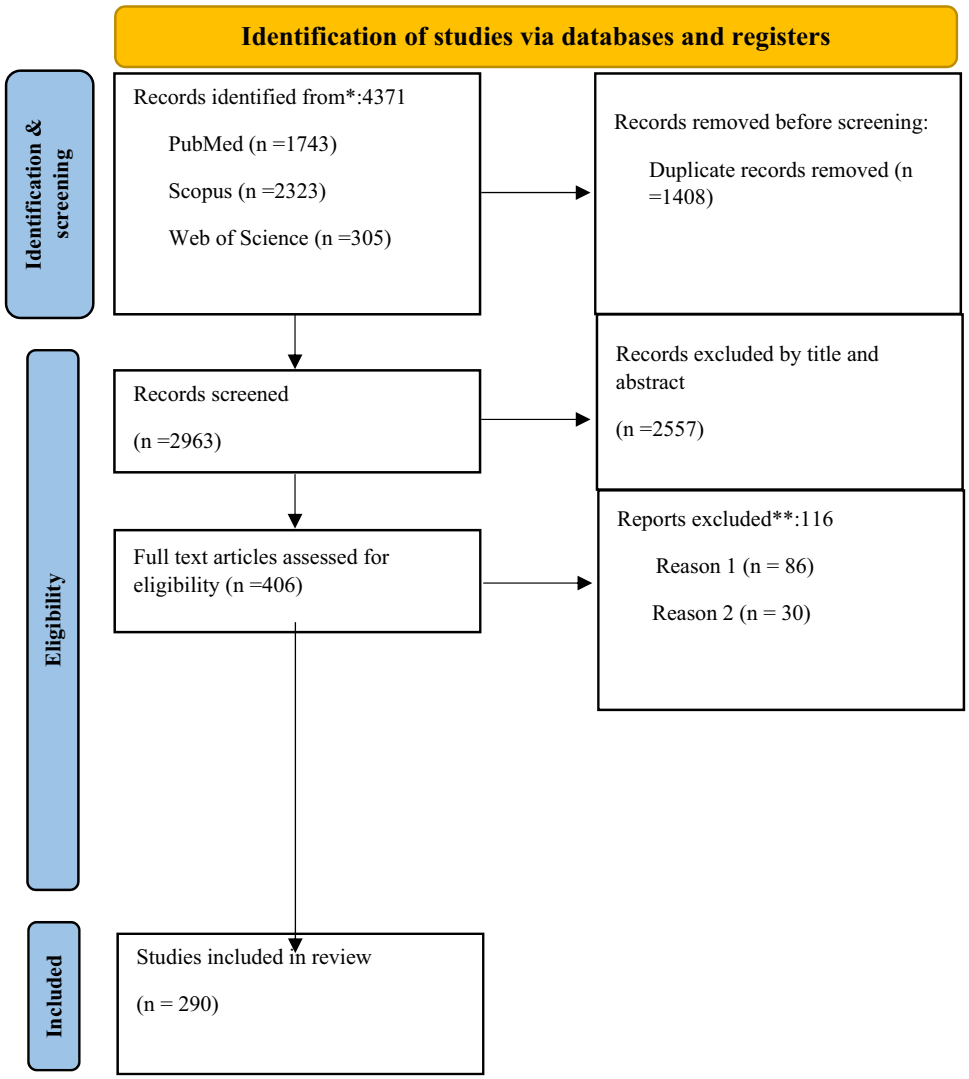

Fig. 1 PRISMA 2020 flow diagram for systematic literature review

from the studied articles, the mean minimum inhibitory concentration (MIC) of the naturally extracted compounds was approximately 0.2 µg/ml and the minimum bactericidal concentration (MBC) of these extracts was less than 64 µg/ml. Current studies indicate that multiple phytochemicals are present in various parts of plants, exhibiting antimicrobial, anti-inflammatory, and antioxidant effects that play a significant role in addressing drug resistance. These compounds can reduce bacterial resistance to antibiotics, lower the MIC values of antibacterial drugs, inhibit bacterial growth, enhance the effectiveness of different antibiotic classes, reverse resistance mechanisms, decrease inflammatory factors such as IL-6 and C-reactive protein, modulate antibiotic resistance in multidrug-resistant pathogens, and demonstrate synergistic effects when combined with applied antibiotics (Table S2).

Discussion

Antibiotic resistance is emerging as a major global health concern as the variety of critical conditions caused by multidrug-resistant pathogens is rapidly growing each day. Addressing this challenge requires discovery of novel antibiotics and antimicrobial substances. Therefore,

research in this field has been a top priority over the past 20 years. With a clear understanding of resistance mechanisms, various strategies have been adopted. Natural products, along with compounds derived from them and their associated endophytes, have played a crucial role in the fight against microbial infections since the mid-twentieth century. The unique triad of structural diversity, safety, and non-toxic qualities in these natural substances makes them particularly noteworthy and drives interest in studying them [16].

The dilemma of antibiotic resistance is becoming increasingly critical in developing countries. Higher consumption of medications due to relatively easy access has led to disproportionately higher incidence of inappropriate antibiotic use which ends with significant elevated levels of resistance in these countries. India is one of the countries with the highest infectious disease burden globally, which aligns with our findings, showing that India has made the most significant contribution to studying this issue [17]. Following India, the most significant contributors to this research were Brazil, Cameroon, Nigeria, Egypt, and China. In addition to the previously mentioned countries, several others have made moderate contributions to this research area, though to a lesser extent. These countries are spread across four continents: Africa (Ethiopia, Ghana, South Africa, and Morocco), Asia (Pakistan, Indonesia, Thailand, Iran, Bangladesh, and Vietnam), North America (Mexico and the United States), and Europe (Germany, UK, and Portugal). These four continents also encompass several countries that made lesser contributions to this area. Figure 2 illustrates the frequency distribution of countries in terms of plant-derived compounds with antimicrobial properties.

Our findings highlight *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* as the most frequently examined and researched pathogens. *Staphylococcus (S.) aureus*, a harmless component of humankind's normal flora, can transform into a threatening pathogen [18]. Like *Staphylococcus aureus*, *E. coli* is naturally found in the gut flora and is generally vulnerable to many antimicrobial agents. Through horizontal gene transfer, *E. coli* can gain a significant capacity to acquire resistance [19]. The multidrug-resistant phenotype of these bacteria is one of the most challenging pathogens to treat in the history of antibiotics, leading to immune system failure and posing numerous dangers [18, 19]. *Morchella conica*, or black morel, and *Morchella esculenta*, or sponge morel, are edible mushrooms from the *Morchellaceae* family, prized for their culinary value. A 2022 study demonstrated that fungal extracts inhibit the growth of methicillin-resistant *Staphylococcus aureus* (MRSA), highlighting their potential as antibacterial agents, with their compounds possibly serving as drug candidates [20].

In contrast, *Pseudomonas aeruginosa* emerges as an opportunistic pathogen primarily affecting immunocompromised individuals [21]. While the pathogen is evolving into one of the most critical antibiotic-resistant agents, its eradication is becoming a challenge [21]. Even though many of these three pathogens can pose severe

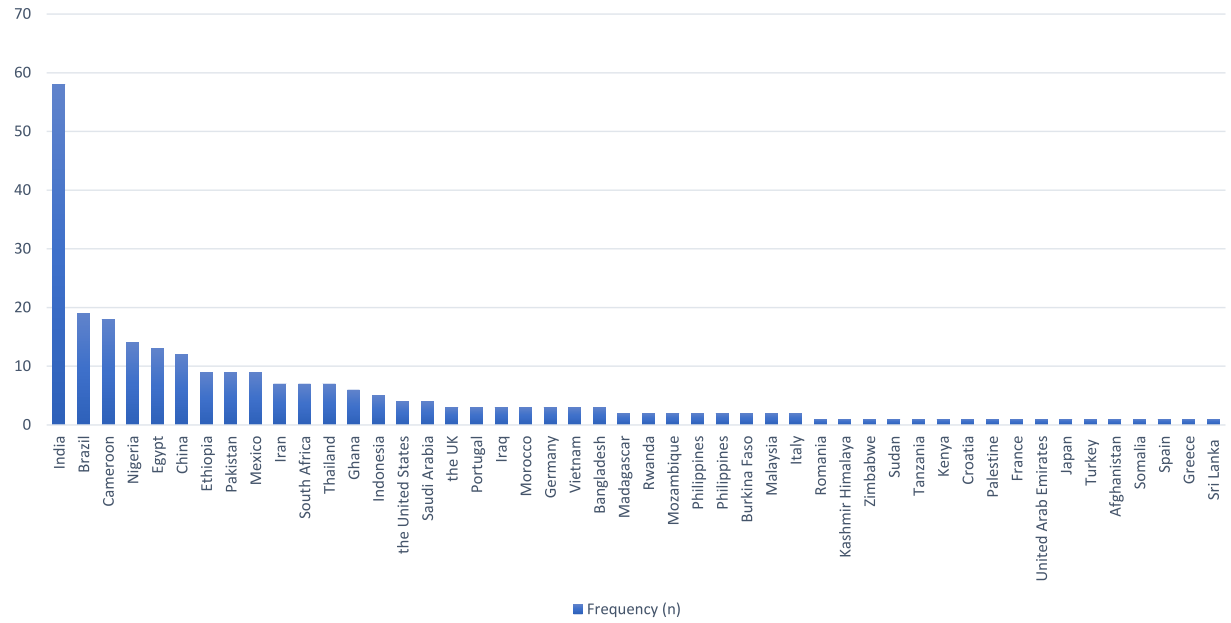

Fig. 2 Distribution of Countries Contributing to the Plant-derived Compounds

threats to public health, the polymicrobial nature of some infections is also noteworthy [22]. Although the exact mechanism stays unclear and not fully understood, the cooperation of *Pseudomonas aeruginosa* and *Staphylococcus aureus* and their interaction can lead to heightening both their pathogenicity and antibiotic resistance in many cases [22]. These three organisms and their combinations can pose significant risks and cause various challenges.

Our findings showed that following the top three pathogens, the most frequently studied agents were *Bacillus subtilis*, *Klebsiella pneumoniae*, *Salmonella Typhimurium*, *Enterobacter aerogenes*, and *Acinetobacter baumannii*. We can categorize these bacteria using three different perspectives.

Bacillus species, as the first group to comprehend, present a complex dilemma. On one hand, their immune-boosting properties leads to their utilization in probiotic dietary supplements [23]. However, in contrast, there is an increasing concern about their potential to transfer antibiotic resistance genes [23]. This concern is heightened by the discovery that Bacillus strains in commercial probiotic products are resistant to multiple antibiotics [23]. In conclusion, this agent can be either beneficial or risky to public health, depending on the circumstances.

The next group that can cause hospital-acquired infections is *Klebsiella pneumoniae*, *Enterobacter aerogenes*, and *Acinetobacter baumannii*. *Klebsiella pneumoniae* and *Enterobacter aerogenes* are the agents responsible for a significant portion of hospital-acquired infections with the former being the cause for one-third Gram-negative infections in hospitalized patients [24, 25]. Unlike *Enterobacter aerogenes*, *Klebsiella pneumoniae* is commonly found on the mucosal surfaces of healthy individuals [25]. But resistant strains of this agent acquire this quality through elements like plasmids and transposons [25]. Moreover, the resistant phenotypes of *Enterobacter aerogenes* demonstrate a significant ability to adapt and rapidly develop resistance to β-lactam antibiotics during treatment [24]. *Acinetobacter baumannii,* as the final agent of this cluster, is a Gram-negative ESKAPE microorganism linked with high mortality rates, mostly causing nosocomial infections [26]. MDR phenotypes of this agent mostly pose a severe risk to immunocompromised and critically ill patients and are linked to prolonged hospital stays, the use of catheters, and mechanical ventilation therapy [26]. A study in Pakistan found that extracts from *Morchella conica* and *Morchella esculenta*, two fungal species, have the potential to inhibit the growth of *Acinetobacter baumannii* (carbapenem resistant) [27]. The aforementioned data highlight the need for careful regulation of antibiotic use in hospitals to prevent the rise and spread of resistance.

Lastly, *Salmonella Typhimurium*, not a nosocomial agent nor an immune-boosting agent but a major cause of foodborne illnesses, is a prominent strain that affects both humans and animals worldwide [28]. The rising antibiotic resistance in this pathogen is a significant global issue and a clear understanding of antibiotic resistance patterns is crucial for its cure [28]. Figure 3 illustrates how often each of these agents were being studied.

When considering the causes that has led us to the dilemma of antibiotic resistance and the urgent need for finding alternatives, it is crucial to recognize two factors that have brought us to this point. The synergism of significant decline in production line for antibiotics since the late 1960 s and the lengthy approval time for antibiotics are the main two notes that need to be highlighted [29]. In this point the circumstances in which we find ourselves arise and we have increasing need for

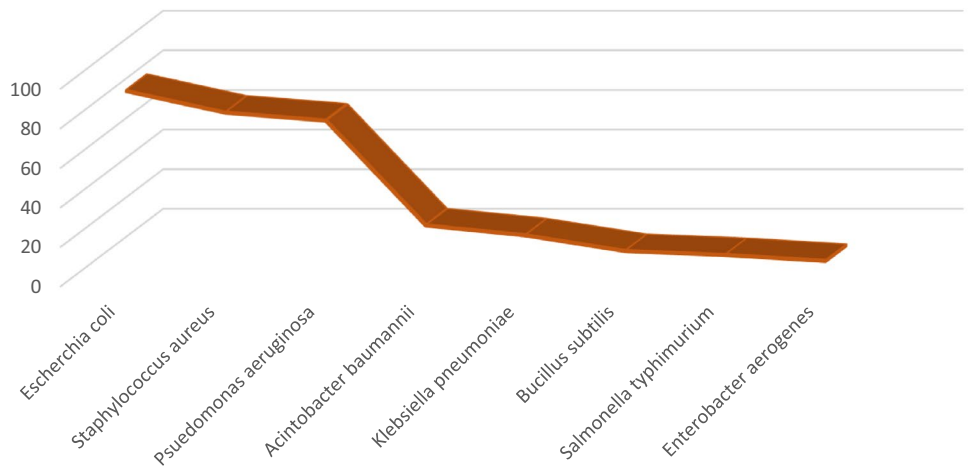

Fig. 3 Frequency of Study for Each Pathogen Agent

alternatives to antibiotics, to prevent and treat infection, including available botanicals that are naturally beneficial, which can be used as an alternative to antibiotics or complement antibiotics [29]. Figure 4 depicts these key points.

From ancient times to the present, medicinal plants have been used for medicinal purposes and utilized as antimicrobial agents the main reason for this is their availability; medicinal plants have historically been preferred options for treating infectious diseases. Phytochemicals, or metabolic compounds of plants, are secondary metabolites that possess antimicrobial properties and are defined by their structural and functional diversity which makes them useful in opposing pathogenic microbes. Phytochemicals can kill bacteria directly, induce disruptions to important cellular functions, and enhance existing antibiotics to treat infections by circumventing microbial resistance. Therefore, phytochemicals are promising candidates for new antimicrobial therapy development [30].

Antimicrobial subtypes of phytochemicals encompass a wide range of substances, including various phenolic compounds, alkaloids, saponins, iridoids and secoiridoids, polyacetylenes, glucosinolates, terpenoids, sulfinates, limonoids (tetranortriterpenoids), and anthranoids. These substances can all act as effective aids against bacteria, fungi, and viruses [31]. Our results indicated that flavonoids were the most prevalent phytochemical in the studies, making up 24/82% of the identified phytochemicals, followed by tannins and phenols, which accounted for 19/44% of the composition (Fig. 5).

Flavonoids are crucial compounds with antimicrobial properties. According to a study conducted by Ababutain IM and colleagues on *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*, it was determined that the extract of *Vitex agnus-castus* exhibits antimicrobial effects [32]. Furthermore, another study conducted on the extract of *Punica granatum* revealed that flavonoid compounds possess antimicrobial properties against the mentioned bacteria, which are part of the WHO's list of priority pathogens [33]. These plant compounds are effective against bacteria through mechanisms such as the inhibition of bacterial growth, disruption of the cell wall, and inhibition of enzyme activity [34].

Another group of effective plant compounds is tannins. According to a study, tannins derived from *Cerana indica* propolis exhibit antimicrobial properties against various bacteria, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*, all of which are classified as priority pathogens by the WHO [35]. According to a study conducted by Nair A and colleagues, tannins exert their antibacterial effects through mechanisms such as damaging bacterial membranes and hindering biofilm production [36].

Based on a study conducted in 2022 by Akinduti and colleagues on the leaf extracts of *Moringa oleifera*, *Vernonia amygdalina*, *Azadirachta indica*, and *Acalypha wilkesiana*, it was determined that certain phenolic compounds are effective in combating MDR *Staphylococcus aureus* bacteria in skin and soft tissue infections [37]. Additionally, another study conducted by Alenazy and colleagues on the extract of *Trigonella foenumgraecum* revealed that phenolic compounds not only exhibit antimicrobial effects against *Staphylococcus aureus* but also demonstrate such effects on *Escherichia coli* [38]. Based on numerous studies, phenolic compounds can exert effects on bacteria through various mechanisms, including outer cellular layer morphology damage, adhesion binding, and membrane infraction [39, 40].

Terpenoids are another significant group of compounds with antimicrobial properties. According to a

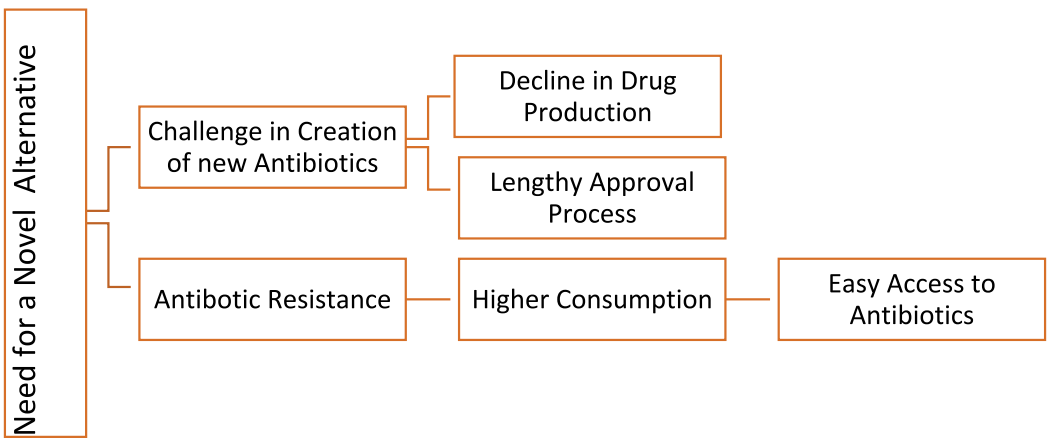

Fig. 4 The causes for the urgent need for novel alternatives

Fig. 5 Frequency of Phytochemicals Prevalent in Regional Plants. *Please note that in this chart, the remaining types of plant-based compounds are reported collectively. As a result, their cumulative percentage appears higher compared to flavonoids

study conducted on the extract of *Dodonaea viscosa*, these compounds have shown effectiveness against various bacteria, including *Escherichia coli*, *Salmonella typhi*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Serratia marcescens*, *Klebsiella pneumoniae*, and *Staphylococcus spp* [41, 42]. According to a 2022 study conducted by KJSDO Dias and colleagues, terpenes have been identified as significant efflux pump inhibitors. This finding highlights their potential role in drug development aimed at combating antibacterial resistance [43].

Alkaloids are compounds produced by various plants. According to a study conducted on *Sophora alopecuroides*, these compounds have been shown to be effective against resistant *Escherichia coli* through mechanisms such as synergistic interaction with ciprofloxacin, inhibition of efflux pumps, and reduction of oxidative stress response [44]. This compound is also effective against other bacteria, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, and *Pseudomonas aeruginosa* [45]. According to various studies, other plant-derived compounds such as saponins, which are extracted from a type of *Cerana indica* propolis, exhibit antimicrobial effects against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* [35]. In addition to the compounds discussed earlier, other plant-derived substances such as steroids, glucosinolates, aromatic alcohols, aromatic acids, and cinnamic acid have also been shown to possess antimicrobial properties against the microbial agents listed by the WHO as priority pathogens [46–48].

Building upon the insights presented and the supplementary data provided in Table S2, it becomes abundantly clear that an array of plant-derived compounds have been identified for their remarkable efficacy against diverse bacterial pathogens, including those flagged as priority by the WHO. These compounds leverage multifaceted mechanisms to target microbial agents, underscoring their immense potential as foundational elements in the design of novel pharmaceutical interventions. By integrating these natural compounds into drug development, we can confront the growing challenge of antimicrobial resistance, thereby mitigating its impact and alleviating the global burden of infectious diseases. The implications of such advancements not only pave the way toward reducing microbial resistance but also align seamlessly with the overarching goals of this study, fostering transformative progress in combating microbial diseases [13].

The next objective of this study was to address the prevalent types of extraction methods utilized in studies. The definition of extraction refers to a process in which specific compounds are isolated or obtained from a source material [49]. Type of a phytochemical extraction method is based on and named after the used solvent in the process [49]. These methods are categorized by their solvents into two main groups. Solvents such as

ethanol, glycerol, fatty oils, ionic liquids, acetic acid, isopropanol, supercritical CO_2, deep eutectic solvents, and natural deep eutectic solvents are clustered under the label of green solvents, referring to their recyclable, nontoxic and bio gradable nature [49]. The second group of solvents consists of other types of organic solvents such as acetone, chloroform, butanol, methanol, ethyl acetate, methyl acetate, benzene, hexane, cyclohexane, and more [49]. Our study showed that the most used methods for preparing phytochemical extracts in these studies were methanol extract, ethanol extract, acetone extract, ethyl acetate extract, n-butanol extract, and methanolic extract. Among these, ethanol was the only widely used green solvent. Figure 6 provides a categorization of these methods.

In order to discuss the next objective, we must define two terms. While MBC is a representation of the lowest concentration of an antimicrobial substance required to inhibit the visible growth of a microorganism after an overnight incubation period, MBC refers to the lowest concentration of the former substance but to prevent the growth of an organism when it is subculture onto media without antibiotics [50].

Our study showed that the studied herbal extractions presented a mean MIC of 0.02 µg/ml. This result, analyzed by the aforementioned definition, indicates a potent antimicrobial effect. Furthermore, the MBC, ranging from 0 to less than 64 µg/ml, shows the concentration at which the extract can completely eliminate the microbial agents. The combination of these MIC and MBC values suggest that the herbal extracts are highly effective even at very low concentrations, which is promising for developing alternative antimicrobial therapies. The wide range of the MBC highlights variability in bactericidal effectiveness, potentially due to differences in bacterial strains or extract composition. Overall, the data underscore the potential of these herbal extracts as strong candidates for antimicrobial agents, particularly in combating multidrug-resistant pathogens, where traditional antibiotics may fail. Further research could optimize their use in clinical settings.

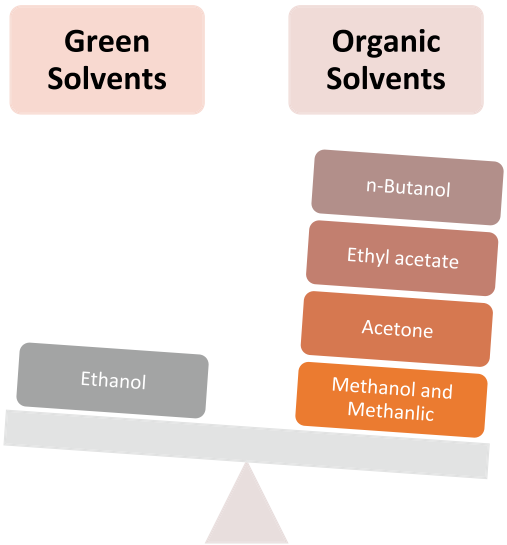

Fig. 6 Categorization of Frequently Used Extraction Methods

The efforts to investigate and scrutinize the antimicrobial properties of medicinal plants has been a main focus in the past decade since we are witnessing the globally rapid rise of drug-resistant pathogens [51]. The high and increasing virulence of these agents, fused with the abating effectiveness of currently available antibiotics, intensifies the issue [51]. Plant-based products, rich sources of chemical entities bringing fewer side effects, offer a variety of antimicrobial potentials and have emerged as an increasingly important area of focus in the pharmaceutical industry [51]. Our findings demonstrated the antimicrobial properties and potentials of many natural products against several high-priority antibiotic-resistant pathogens listed by the WHO. Although these products demonstrate antimicrobial activity independently, pairing crude extracts with antibiotics may offer an effective approach to addressing bacterial resistance. Phytochemicals also have a significant potential to amplify antibiotics' bacteriostatic or bactericidal effects [52]. Therefore, a synergistic approach can also shed light on the issue of antibiotic resistance [52]. Further research into the extraction and antimicrobial potential of these plant-based medicines is crucial in addressing the challenge of antibiotic resistance.

Limitations

While this study provides valuable insights into the antimicrobial properties of natural products against antibiotic-resistant pathogens, several limitations should be acknowledged. First, the reliance on published clinical trials may cause bias in outcomes as most of the published clinical trials have had positive outcomes. Second, the search strategy was specified to three major databases, possibly overlooking relevant studies from other sources, including gray literature. Additionally, excluding studies published in languages other than English further limits the scope of the review. To enhance the inclusivity of future research, it would be beneficial to incorporate a broader range of databases, include studies in multiple languages, and consider gray literature.

Conclusion

In conclusion, the data in this study illustrate a whole image of the promise that plant-based products hold in combating the escalating antibiotic resistance. The phytochemical properties of natural plants, particularly when grouped with the antimicrobial potential of available antibiotics, pave the way toward a potent strategy to address the antibiotic resistance issue. The results demonstrated the effectiveness of herbal extracts at low concentrations, highlighting their potential as viable antimicrobial agents. Future research exploring the optimization of the extraction methods and process and the synergistic effects between phytochemicals and conventional antibiotics can be of great use. Thorough investigations focusing on the specific mechanisms through which these combinations enhance antimicrobial efficacy and expanding to include a greater spectrum of antibiotic-resistant pathogens will be crucial for developing novel therapeutic approaches. As the global health threat of antibiotic resistance continues to grow, the exploration of plant-based antimicrobial therapies could play a critical role in developing sustainable and effective treatments.

Supplementary Information

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Additional file 1)

Additional file 2

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Some parts of this manuscript have been edited for grammar and vocabulary using artificial intelligence (AI).

Author contributions
S.S. and E.M. made substantial contributions to the conception and substantively revised it. P.M., S.Y. and M.M.R wrote the main manuscript and made contribution to acquisition, analysis and interpretation of data. S.D., S.Z., F.F. and S.G. made contribution to acquisition and analysis of data and wrote main manuscript. A.A, A.T., A.G. and F.A. made contribution to design of study and acquisition of data. S.J. made contribution to analysis and interpretation of data and substantively revised the work. All the authors have approved the submitted version and any substantially modified version that involves the author's contribution to the study. Also, they have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Declarations

Ethics approval and consent to participate
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Competing interests
The authors declare no competing interests.

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