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Searching for new agents against Enterobacteriaceae from nature: approaches, potential plant species, isolated compounds, and their respective properties

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Abstract The rising trend of antibiotic-resistant infections around the world and the low antimicrobials development pipeline volume are necessitating continued efforts in the search for novel treatment options. The prominent success from fungi and bacteria as sources of antibiotics has long motivated widespread efforts in the search for antibacterial compounds from other natural sources including plants. This review aimed at appraising the approaches and outcomes from studies commissioned to evaluate the antibacterial activities of crude plant extracts and phytochemicals. Notably, the existing traditional practices provided the greatest motivation in screening for antibacterial properties of plants, whereby the need to validate ethnomedically reported potentials formed a crucial objective. Moreover, choices of experimental techniques to address different objectives were largely dependent on the prevailing access to resources, facilities, and technical skills. The lack of streamlined guidelines dedicated to testing of crude plant extracts have resulted into broad methodological variations and lack of a standardized classification system for antibacterial activities exhibited by plant extracts. Furthermore, libraries of 128 extracts from different plant species and 122 phytochemicals substantially active against the *Escherichia coli* and *Klebsiella pneumoniae* were assembled. This enabled the elucidation of existing patterns between the Minimum Inhibitory Concentrations (MICs) and studied plant families, plant tissues, extractants, phytochemical classes, as well as the rules of drug-likeness, penetration and accumulation. The insights provided in this review will potentially impart the ongoing efforts with improved experimental designs, inspire ideas for further studies and contribute to successful hunting for new antibacterial chemical scaffolds via in silico approaches.

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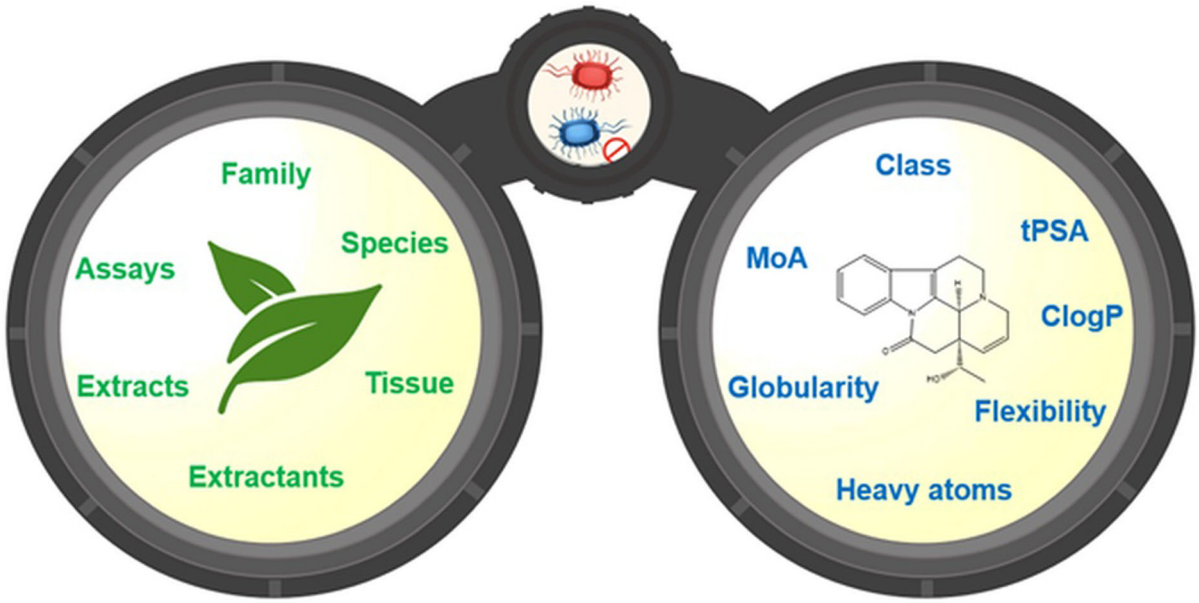
Graphical abstract



Keywords Biochemoinformatics · Compounds library · Crude extract · *Escherichia coli* · Isolation · *Klebsiella pneumoniae*

Introduction

The ever-increasing rates of antimicrobial-resistant infections warrant continuous efforts in the search for new treatment options. Among others, nature is a potential source of novel effective antimicrobial agents. Numerous bacteria and fungi species have already contributed to the existing arsenal of antibiotics. However, the natural development of Antimicrobial Resistance (AMR) among bacteria, augmented with factors like misuse of antibiotics and extensive utilization of antibiotics in agriculture, has rendered most antibiotics less useful (Anand et al. 2019; Hoffman 2020; Murray et al. 2022).

Antibiotic-resistant infections due to gram-negative bacteria are generally more difficult to treat, hence posing a more serious public health threat. The World Health Organization (WHO) categorizes carbapenem-resistant and third generation cephalosporins-resistant Enterobacteriaceae as pathogens of critical priority against which new antibiotics are urgently needed. This is mainly due to their global spread of resistance, high healthcare burden, low treatability, and low pipeline volume among other factors (*Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis*, 2017; WHO 2021).

Although plants are yet to contribute to any of the antibiotics currently available on the market, studies on the antibacterial properties of plant extracts and the isolation of antibacterial compounds are extremely common. As a result, the literature on reports of plant extracts or isolated compounds with a diverse range of antibacterial activities is increasingly rich. The outcomes of such studies are partly meant to inform further efforts in isolation, biological screening, syntheses, and optimization of biological and pharmacokinetic activities among others. However, these follow-up approaches are usually occluded by various factors, which include: difficulty in the screening of the bulky literature for plant species with targeted activities, the limited geographical distribution of potential plant species, and low reproducibility of previous findings due to numerous factors (Masota et al. 2021).

Moreover, plants host a great potential to deliver compounds with a high degree of diversity and chemical novelty which lower changes for the rapid development of cross-resistance while increasing the likelihood to hit new bacterial targets and modes of action. Reports on antibacterial plant extracts and the responsible phytochemicals are therefore crucial to the entire community of researchers in the discovery and development of antibiotics. In addition to advocating for the development of traditional ways of treating bacterial infections, a rich diversity of antibacterial phytochemicals can potentially inspire further approaches in screening, designing, and syntheses of novel antibiotics (Anand et al. 2019; Katz and Baltz 2016; Newman and Cragg 2016).

To this end, the availability of concrete information on plants with high potential for delivering active antibacterial compounds is key. Additionally, the creation and updating of specialized libraries of phytochemicals with experimentally proven antibacterial potentials are essential for bridging the gap between initial crude extracts screening or isolation studies and further stages down the line of antibiotics development.

Furthermore, such studies must be conducted following the most reliable approaches to avoid high failure rates in subsequent studies. Variations of phytochemical profiles due to geographical, ecological, and climatic differences are inevitable. In return, more efforts should be placed on streamlining and adhering to the standard and up-to-date experimental approaches, to ensure increased reliability of the resulting data.

This review aimed at addressing the key gaps in the areas of: (i) scarcity in up to date collective evaluation of what is known across practices, limitations, and findings from studies investigating antibacterial potential of crude plant extracts and phytochemicals, (ii) lacking detailed accounts focused on closely related bacteria hence providing lesser confounded profiling of evaluated natural products, and (iii) limited availability of biochemoinformatic profiling phytochemicals to grant a better understanding of their contribution towards the search for novel antibacterial agents.

Here we highlight different aspects and approaches in the screening of plant extracts for antibacterial activities, specifically against the gram-negative *Escherichia coli* and *Klebsiella pneumoniae*. Highlights are provided on common motivations and objectives in studying of plants for their antibacterial potentials, the nature and essence of traditional practices around the studied plant species, as well as selected aspects in the preparation of crude extracts and testing of their antibacterial activities. Furthermore, the accounts on recently isolated compounds with high activity against the two bacteria, including their chemical and drug-likeness characterization and relevant statistical analyses are included. Despite the differences in scope and methodological approaches this review is not the first one addressing this topic. By building upon and providing updates on other existing reviews, this review, can serve as a valuable resource among researchers and developers working on nature-derived antibiotics, allowing effective utilization of resources, avoiding the potential pitfalls, and inspiring various experimental aspects.

Methods

Peer-reviewed research articles from studies on antibacterial plant extracts were obtained from Google scholar, PubMed, and Web of Science scholarly databases using the search string: (antibacterial OR antimicrobial) AND (plant OR crude OR extract*) AND ("*Escherichia coli*" OR "*Klebsiella pneumonia**") AND ("broth" AND ("microdilution" OR "macro dilution")). Further filters were placed to remove studies which involved essential or volatile oils, algae, lichen, propolis, as well as nanoparticle formulations of crude plant extracts. The search included articles published between January 2010 and December 2021 in English language and no limitations on the types of journals were put in place.

Retrieved articles were further screened for relevance using their titles, abstracts and the main bodies in that order. All articles reporting the antibacterial activities of essential or volatile oils and that exclusively used disc or well diffusion to determine the Minimum Inhibitory Concentrations (MICs) were thereafter excluded. Only articles which reported the use of broth microdilution or macro dilution assays and with the crude extracts showing MIC values of $\leq$ 128 µg/mL against *E. coli* and/or *K. pneumoniae* were included.

Concerning isolated compounds, an independent search was done on the same set of scholarly databases

using the search string: (*isolat* OR characteriz*) AND (compound* OR agent* OR phytochemical*) AND (antibacterial OR antimicrobial) AND plant AND ("Escherichia coli" OR "Klebsiella pneumonia*") AND ("broth" AND ("microdilution" OR "macro dilution"))*. Articles published in English between January 2010 and December 2021 were retrieved, regardless of their respective journals. Similarly, further screening was done to include only plant-isolated compounds with MIC values of $\leq$ 100 µg/mL against *E. coli* and/or *K. pneumoniae* as determined by broth dilution methods.

The MIC cut-off points employed in this review were aimed at highlighting only the plant extracts and isolated compounds with a high magnitude of antibacterial activities. Ultimately, selected data extracted from each article was populated in an MS Excel sheet. Further analyses to determine the relationships between reported MIC values and plant families, plant parts, extracting solvents, molecular weights, total polar surface area, ClogP, number of hydrogen bonds acceptors and donors, Kernel density, molecular flexibility and globularity, as well as the number of heavy atoms were carried out using WordCloud, Origin®, ChemDraw®, Molinspiration and Molecular Operating Environment (MOE) software. Evaluation for the presence and level of statistical significance between treatments of different nature was done using one-way Analysis of Variance (ANOVA) with post-hoc Tukey Honestly Significant Difference (HSD) test, allowing for comparison of multiple treatments. Statistical significance was defined as $p < 0.05$.

Common motivations for screening for antibacterial potentials of plants

Various factors were observed to motivate the continued efforts on searching for antibacterial compounds from plants. Among other factors, the existing broad traditional usage of plant-derived materials in the management of different diseases was crucial. Here it was commonly stated that about 80% of the world population is estimated by the WHO to rely wholly or partially on natural remedies as their primary source of health care (Adigüzel et al. 2005; Ayaz et al. 2016; Gbedema et al. 2010; Hassan et al. 2009; Kuete, Kamga et al. 2011; Voukeng et al. 2017). Traditional remedies were reported to be regarded as cheap, readily available, more acceptable and associated with lesser side effects (Hassan et al. 2009; Panghal et al. 2011). These features have contributed to their more extensive favourability in the face of modern medicines which are challenged by their limited availability, high costs, requirements for expertise, being less trusted and being more associated with adverse drug reactions and side effects (Hassan et al. 2009; Madureira et al. 2012; Rashed and Butnariu 2014; Singh et al. 2010).

Further, the rise in antibiotic-resistant infections on top of the existing high burden of infectious diseases in developing countries was noted to prominently stir the ongoing efforts in the search for new accessible and effective treatment options (Camacho-Corona et al. 2015; Fankam et al. 2014; Hossan et al. 2018; Kouitcheu Mabeku et al. 2006; Singh et al. 2010; Tekwu et al. 2012; Voukeng et al. 2017). Based on the broad availability and extensive uses of traditional medicines, their inclusion in the arsenal for fighting AMR was regarded to be essential (Chatterjee et al. 2009).

Nature has contributed to about 60% of the available antimicrobial agents (Madureira et al. 2012), a majority of them being from bacterial and fungal sources (Hoffman 2020; Katz and Baltz 2016). Further, it was estimated that only 6% of plant species have been screened for different biological activities, with an evaluation for phytochemicals conducted in only about 15% of them (Verpoorte 2000). Based on the potential of plants to synthesize compounds with possible ideal features for novel antibiotics (Hossan et al. 2018; Ustun et al. 2016), continued studies in this direction are highly encouraged.

Similarly, the choices of plant species to be studied were noted to be influenced by the existing traditional practices (Noundou et al. 2016; Panghal et al. 2011; Singh et al. 2010; Tankeo et al. 2016; Venkata Ratnam and Venkata Raju 2009), previous scientific reports on antimicrobial or cytotoxic activities (Djeussi et al. 2013; Kuete, Kamga et al. 2011; Voukeng et al. 2012; Wilson et al. 2005), as well as the quest to explore the antibacterial potential of other plant parts (Rashed and Butnariu 2014).

Core objectives in screening for antibacterial activities of crude plant extracts

Based on the prevailing motivations, a range of core objectives in executing the respective studies was

realized. While validation or provision of scientific evidence to the claimed antibacterial properties of traditional remedies was a frequent goal (Gbedema et al. 2010; Rigano et al. 2007; Ruiters et al. 2016; Singh et al. 2008; Siwe Noundou et al. 2014), other typical goals included: general ascertainment of antimicrobial activities (Adigüzel et al. 2005; Arif et al. 2009; Chatterjee et al. 2009; Madureira et al. 2012; Tekwu et al. 2012), evaluating the potency of crude extracts against Multi-Drug Resistant (MDR) bacterial strains (Fankam et al. 2014; Ordonez et al. 2009; Voukeng et al. 2017), and determination of synergistic effects between the crude plant extracts and conventional antibiotics (Chatterjee et al. 2009; Hossan et al. 2018; Noumedem et al. 2013; Seukep et al. 2016).

Additionally, aiming at determining the phytochemical compositions of crude extracts (Rashed and Butnariu 2014), as well as ascertaining the antimicrobial potential of the fractions from crude extracts and isolated compounds (Kuete et al. 2012; Ngameni et al. 2009; Noundou et al. 2016; Tankeo et al. 2016) were prominent.

The portrayed broad scopes of the underlying objectives in studying of the antibacterial properties of crude plant extracts is likely influenced by the differences in core research interests, backgrounds, and skills, in addition to the availability of the needed resources. While it is essential to ensure thorough investigations are conducted on each studied plant extract, a balance between the number of pursued objectives and the quality of the produced data should always be sought.

Traditional practices around plant species studied for antimicrobial properties

Accounting for known traditional uses of the studied plant species was frequently portrayed upon the provision of general descriptions regarding the plants. The studied plant species were commonly described to be used in the traditional management of different types of both infectious and non-infectious diseases (Bitchagno et al. 2015b; Madureira et al. 2012; Mbosso Teinkela et al. 2016; Ruiters et al. 2016; Sahoo et al. 2008), along with usages in wound treatment, as antidotes (Fankam et al. 2014; Noumedem et al. 2013; Voukeng et al. 2017), and as antiseptics (Canales et al. 2016). Moreover, some plants were indicated to be used as parts of diet or food additives (Ordonez et al. 2009; Rao et al. 2010; Siwe Noundou et al. 2014).

The traditional remedies were mostly prepared as decoctions, macerates, infusions, pastes, tonics, diluted latex, sap, or heated bandages (Ayaz et al. 2016; Chatterjee et al. 2009; Panghal et al. 2011; Ruiters et al. 2016; Singh et al. 2007; Siwe Noundou et al. 2014). In cases where prior extraction was needed, water and alcohol were the most implicated extractants (Djeussi et al. 2013; Rigano et al. 2007; Siwe Noundou et al. 2014). Although the information on the route of administration was scarcely provided, oral and topical routes are commonly applicable for many traditional remedies (Adigüzel et al. 2005).

The knowledge of the associated traditional practices prominently informed studies aimed at validating different traditionally claimed biological potentials. Importantly, reports on traditional practices guided the conception and designing of some studies (Gbedema et al. 2010; Rigano et al. 2007; Ruiters et al. 2016; Singh et al. 2008; Siwe Noundou et al. 2014). Studying and documenting the existing ethnomedical knowledge and practices in various societies is therefore of great relevance. This is essential in guiding the choice of plant species, plant parts, extraction techniques as well as species of bacteria to be targeted during the follow-up studies.

Preparation of crude plant extracts

Extraction as a crucial step in studying of biological activities of plant-derived samples was observed to host many variables which can influence the composition of the recovered extract(s). Maceration (Arif et al. 2009; Canales et al. 2016; Kuete et al. 2006; Noundou et al. 2016), Soxhlet (Dhiman et al. 2011; Korukluoglu et al. 2010; Uzun et al. 2004) and percolation (Ordonez et al. 2009; Rigano et al. 2007; Singh et al. 2008) were noted to be the techniques of widespread usage. Further, methanol, ethanol and acetone were markedly the extensively used solvents across different extraction techniques. Additionally, a good number of studies involved the use of multiple extracting solvents in a parallel or sequential manner (Arif et al. 2009; Canales et al. 2016; Madureira et al. 2012; Noundou et al. 2016; Orhan et al. 2009; Sahoo et al. 2008).

Apparently, the choice of an extraction technique is influenced by factors like the availability of resources, skills and the need to reproduce previous protocols. Although stating of extraction temperatures in techniques requiring heating was uncommon, it should be considered necessary. Carrying out extractions using multiple solvents leads to the recovery of compounds across different polarity ranges. However, this approach is more beneficial when sequential rather than parallel extractions are conducted. Following a sequential approach, a more selective extraction based on polarities of the phytochemicals can be achieved which might result in better MIC values in cases where the antibacterial compounds are present.

In other studies, the indication of the exact feeds-to-solvent ratio (Adigüzel et al. 2005; Fankam et al. 2014; Gbedema et al. 2010; Ustun et al. 2016), the overall duration of extraction (Fankam et al. 2014; Noundou et al. 2016; Siwe Noundou et al. 2014) and techniques for removal of the solvent after extraction were reported. Among the drying techniques, rotary evaporation under vacuum (Ayaz et al. 2016; Tankeo et al. 2016), open-air drying (Noundou et al. 2016) freeze-drying/lyophilization (Chatterjee et al. 2009; Panghal et al. 2011; Singh et al. 2008; Siwe Noundou et al. 2014), and nitrogen gas spraying (Gbedema et al. 2010) were commonly applied.

Although rotary evaporation under vacuum was a widely used technique, the equipment is commonly unavailable in resource-limited settings, and the same applies to upper-end techniques like lyophilization. In such cases, drying of crude extracts can solely rely on approaches like open air drying or air blowing. These techniques are prone to result in higher quantities of residual solvents within the 'dried extract', which, depending on the solvent, may influence the observed antibacterial activity in addition to introducing errors in the weighed amounts. Furthermore, while most traditional practices use water as an extractant, its use in many laboratory settings is highly limited by the common lack of powerful drying techniques.

Remarkable aspects of handling dried crude extracts included ensuring proper storage conditions and sterilization of crude extracts before further studies were conducted. Some specified storage conditions for crude extracts included freezing or refrigeration at −80 °C to 4 °C (Adigüzel et al. 2005; Camacho-Corona et al. 2015; Fankam et al. 2014; Madureira et al. 2012; Noumedem et al. 2013). Interestingly, sterilization of crude extracts using UV light (200–400 nm) over a 24 h duration was also described (Chatterjee et al. 2009), in that case, the attainment of sterility of the extract was confirmed by repeated streaking on agar plates.

Efforts to ensure sterility of crude extracts are nevertheless not common. This is perhaps because there are other sterility checkpoints down the line of antimicrobial testing, such as filter sterilization of crude extracts' test solutions or via the inclusion of crude extracts' solutions sterility control(s) in the experiments (Masota et al. 2021).

Antimicrobial susceptibility testing

General aspects and use of AST guidelines

Antimicrobial susceptibility testing (AST) stays at the core of determining the antibacterial activities of crude plant extracts under investigation. Ensuring sterility of the test solution of crude extracts was highly regarded in some studies, whereby it was achieved through the use of sterilization filters with the pore's diameter of 0.22–0.45 µm (Orhan et al. 2009; Ozcelik et al. 2010; Sahoo et al. 2008; Tekwu et al. 2012; Ustun et al. 2016). The use of agar diffusion assays to quickly screen for activities of large quantities of crude extracts before MIC determination by broth dilutional assays was observed (Ayaz et al. 2016; Karsha and Lakshmi 2010; Panghal et al. 2011; Wilson et al. 2005). Besides, discrepancies between the activities determined by diffusion and broth dilution assays were observed (Kouitcheu Mabeku et al. 2006; Sahoo et al. 2008; Ustun et al. 2016; Uzun et al. 2004). In such cases, bacteria found less susceptible using diffusion methods were more susceptible during broth dilution assays, and vice versa.

Among the cited standard AST guidelines were those provided by the National Committee for Clinical Laboratory Standards (NCCLS) (Orhan et al. 2009; Singh et al. 2008; Uzun et al. 2004) or its subsequent organization, the Clinical Laboratory Standards Institute (CLSI) (Ayaz et al. 2016; Canales et al. 2016; Chatterjee et al. 2009; Madureira et al. 2012). Depending on the pursued guideline, the total incubation time at 37° C varied between 18 and 24 h (Ordonez et al. 2009; Orhan et al. 2009; Ozcelik et al. 2010; Rigano et al. 2007; Wilson et al. 2005). While the number of replications per test and repetitions of

the respective experimental sets is crucial, this data was relatively scarce. Though, the inclusion of three replicates and repeating the experiments twice was highlighted in some studies (Ngameni et al. 2009; Panghal et al. 2011; Tekwu et al. 2012; Venkata Ratnam and Venkata Raju 2009).

Furthermore, the observed widespread non-inclusion of experimental controls limits the validity and objective comparison of the reported antibacterial potentials. These methodological disparities are most likely due to the lack of detailed and streamlined guidelines particularly dedicated to the AST of crude extracts from natural sources. Consequently, the scientific community in this field is compelled to use methods which were previously reported in other studies or employing standard guidelines primarily intended for AST of conventional antibiotics (Masota et al. 2021). Regardless of the success attained through this approach, several challenges are eminent as further discussed below.

Crude extracts' test concentration ranges

What range of concentration of crude extracts test solution should be applied during the screening of their antibacterial activities? This remains to be a question open for further discussion. While the maximum tested concentrations of 1000 µg/mL was noted to be common (Ayaz et al. 2016; Ordonez et al. 2009; Rigano et al. 2007; Singh et al. 2008), some studies reported concentrations above 10000 µg/mL (Kouitcheu Mabeku et al. 2006; Ratnam and Raju 2008).

Different scholars have previously attempted to categorize the potency of crude extracts based on the MIC values exhibited. For example, Kuete et al. classified extracts with MICs below 100 µg/mL as significantly active, those between 100 and 625 µg/mL as moderately active, and those above 625 µg/mL as weakly active (Cos et al. 2006; Kuete 2010). Other categorizations by Rios and Rcio regarded extracts with MICs below 100 µg/mL as interesting and those with MICs above 1000 µg/mL as inactive (Rios and Recio 2005). On the other extreme, Farby et al. regarded crude extracts' MIC value below 8000 µg/mL as active (Fabry et al. 1998).

Further, Gertsch strongly discouraged the use of very high concentrations of crude extracts or phytochemicals during evaluation of their biological potentials. While the responses under investigation are typically observed/positive at extremely high concentrations (e.g., 1.5 mg/mL), findings from those studies lack scientific relevance and are generally inacceptable (Gertsch 2009). This is mainly because, at those concentrations, natural products reach their critical concentration, yielding multiple responses due to loss of selectivity (Gertsch 2009).

Based on the observed variations in the used test concentrations and the attempts to categorize the crude extracts potencies, there is an outstanding need to streamline the categorization criteria. This will provide the much-needed guidance and help researchers to objectively decide on the concentration range of the extracts to be tested. On the other hand, it will ease the comparison of the antibacterial activities of crude extracts and optimize the usage of valuable resources for testing of concentrations beyond the commonly agreeable ranges (Madureira et al. 2012). This is partly because follow-up studies are more likely to prioritize plant extracts with reasonably high activities in order to increase the chances of ultimately isolating compounds with higher activity profiles.

Exploring biological activities beyond MIC values

Although the common determination of MIC values serves a big purpose in highlighting the antibacterial potential of crude extracts, exploration of other related potentials was observed. Closely related to MIC was the determination of Minimum Bactericidal Concentration (MBC), especially on extracts with observed inhibitory activity against the particular bacteria (Dhiman et al. 2011; Ngameni et al. 2009; Tekwu et al. 2012; Voukeng et al. 2017). Others included time-kill assays (Chatterjee et al. 2009; Gbedema et al. 2010; Hossan et al. 2018), mode of action studies (Karsha and Lakshmi 2010), as well as the determination of toxicity or cytotoxicity profiles of the crude extracts (Kuete et al. 2006; Ozcelik et al. 2010). Likewise, studies on synergistic effects between the crude extracts and conventional antibiotics (Chatterjee et al. 2009; Hossan et al. 2018; Noumedem et al. 2013; Seukep et al. 2016), as well as the action of the crude extract on bacterial efflux pumps (Kuete et al. 2012; Noumedem et al. 2013; Seukep et al. 2016) were observed. Contrary to the commonest approach focusing on isolating and identifying compounds responsible for observed antibacterial activities, other scholars

have strongly advocated for the advancement of methods geared towards evaluating natural products as complex mixtures. This alternative approach is perceived to generate more understanding on the nature of their interactions, while benefiting from the possible synergistic or additive effects (Vaou et al. 2022).

Despite long-standing research on plant-based antimicrobial synergy, such studies are yet to enter clinical phases. Nevertheless, the existence of synergistic, additive, and antagonistic among the secondary metabolites from plants is of great relevance to the holistic evaluation of biological potentials of natural products. The current lack of consensus on standardization and rationalization of definitions, experimental procedures, and data analysis approaches related to ascertainment of these parameters should therefore be addressed (Vaou et al. 2022).

Establishing the toxicity profile of the tested extracts or isolated phytochemicals was notably uncommon. Testing for toxicity was mainly reported to be conducted using assays based on tetrazolium salts (MTT assay) on a range of human/animal normal and cancer cell lines (Elisha et al. 2017; Frankova et al. 2021; Jaradat et al. 2021; Maneerat et al. 2012; Prema et al. 2019). Additionally, Kathare et al. 2021 conducted acute oral toxicity studies on rats to supplement their findings from brine shrimp lethality test of *B. micrantha* stem bark methanolic extract (Kathare et al. 2021).

A closer look at those studies revealed some of the crude extracts and phytochemicals to possess moderate to high cytotoxities against the tested cell lines (Elisha et al. 2017; Frankova et al. 2021; Jaradat et al. 2021; Maneerat et al. 2012; Prema et al. 2019). Such extracts and compounds were thereafter indicated to be unsuitable for further development as antibacterial agents, although they might be suitable as potential anticancer agents (Elisha et al. 2017; Jaradat et al. 2021; Prema et al. 2019). In addition to guiding the traditional usage of the respective plants, early determination of cytotoxicity profiles is crucial in determining the nature and scope of the subsequent studies on the respective crude extracts or phytochemicals.

Generally, the availability of such data adds a great value with the particular respect to informing the ongoing traditional practices and the usage of the respective herbal preparations or finished herbal products. On the other hand, due to the intrinsic complexity of plant extracts, the observed outcomes on bacterial survival times, mode of action, toxicity and synergistic effects cannot be exclusively linked to particular constituent compounds. Therefore, whether or not any other biological activities should be explored at the crude extract level, depends much on the intended applications and conclusions to be drawn.

Reported antibacterial activities, plant species, parts and extracting solvents

The level of antimicrobial activity MIC $\leq$ 128 µg/mL against *E. coli* and/or *K. pneumoniae* was reported in among crude extracts of 128 plant species originating from a total of 56 families (Table 1). A broad range of bacteria comprising standard reference- and clinical isolates, as well as susceptible and MDR strains were reported to be inhibited by crude extracts from across different indicated plant parts and species (Table 1).

Antibacterial activity across plants' families

To substantiate the observed patterns between most frequently studied plant families and their antibacterial potentials against *E. coli* and *K. pneumoniae*, statistical analyses involving frequencies, means, quantiles (1–3 quartiles), and ANOVA were conducted. Moreover, similar analyses were performed for other parameters including types of plant tissues, nature of the solvents used for extraction and classes of phytochemicals.

The plants studied were noted to belong to a total of 51 plant species, among them, Lamiaceae, Moraceae, Fabaceae, Euphorbiaceae and Rubiaceae formed the five most studied families (Fig. 1, Table 1). Moreover, Fig. 2 indicates the ranking of antibacterial potentials for families with at least 4 plant species studied, in which Berberidaceae, Fabaceae, Lauraceae and Euphorphiaceae were the most active families against both bacteria. Nevertheless, MIC values of $\leq$ 10 µg/mL were reported in plants from the rather less represented families of Apocynaceae, Adiantaceae, Mimosaceae, Moringaceae, Myrtaceae, Piperaceae, Rosaceae and Verbenaceae (Table 1).

The large differences between the lowest and highest MIC values in a given family could be due to the data coming from different laboratories, differences in plant species, parts and extracting solvents. However, all activities were determined via the same

Table 1 Plants species, families, parts and extracting solvents with reported antibacterial activities of ≤ 128 µg/mL against different strains of E. *coli* and/or *K. pneumoniae*

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
1	*Acacia arabica* (Lam.) Wild	Mimosaceae	Leaves	Water	31.4 (O157 EHEC)	30.1 (nd)	Hassan et al. (2009)
2	*Acacia nilotica* (L.) Delile	Leguminosae	Leaves, barks	Ethanol 50% v/v, ethanol 90% v/v	19.5 (ATCC 25922)	9.75 (ATCC 7008030)	Khan et al. (2009)
3	*Acalypha indica* Linn	Euphorbiaceae	Leaves	Methanol	125 (nd)	125 (nd)	Gopalakrishnan et al. (2000)
4	*Adiantum capillus-veneris* L	Adiantaceae	Nd	Methanol	0.48 (MTCC 443)		Singh et al. (2008)
5	*Adiantum venustum* D. Don	Adiantaceae	Nd	Methanol	15.62 (MTCC 443)	7.81 (MTCC 109)	Singh et al. (2008)
6	*Agrimonia pilosa* Ladeb	Rosaceae	Herb	Water	7.81 (ATCC 25922)		McMurray et al. (2020)
7	*Albizia gummifera* (J.F.Gmel) C.A.Sm	Leguminosae	Leaves	Methanol	128 (LMP0101U)		Tekwu et al. (2012)
8	*Alchornea cordifolia* (Schumach. And Thonn.) Muell. Arg	Euphorbiaceae	Leaves	Ethanol, methanol, ethyl acetate (Ec), Chloroform (Kp)	63 (ATCC 25922)	63 (ATCC 13883)	Noundou et al. (2016)
9	*Alchornea cordifolia* (Schumach. and Thonn.) Müll. Arg	Euphorbiaceae	Leaves, stem barks	Methanol & ethanol (Ec), chloroform (Kp)	63 (ATCC 25922)	63 (ATCC 13883)	Noundou et al. (2016)
10	*Alchornea floribunda* Müll. Arg	Euphorbiaceae	Leaves (Ec, Kp), roots (Kp)	Methanol (leaves), chloroform (roots)	70 (ATCC 25922)	63 (ATCC 13883)	Noundou et al. (2016)
11	*Alhagi mannifera* Jaub. & Spach	Fabaceae	Leaves	Petroleum ether	1.25 (ATCC 25922)	0.325 (ATCC 13883)	Jaradat et al. (2021)
12	*Allium sativum* L	Amaryllidaceae	Cloves	Ethanol 95% (v/v)	65 (clin. isol)		Karuppiah and Rajaram, (2012)
13	*Alpinia galanga* L	Zingiberaceae	Rhizomes	Methanol	40 (MTCC 1563)		Rao et al. (2010)
14	*Andrographis echiodes* Nees	Acanthaceae	Whole plant	Chloroform	70 (NCIM 2065)	50 (NCIM 2957)	Umadevi et al. (2003)
15	*Anemone chinensis* Bunge	Ranunculaceae	Root	Water	125 (ATCC 25922)		McMurray et al. (2020)
16	*Annona squamosa* L	Annonaceae	Leaves	Methanol		78 (ATCC 4552)	Campos et al. (2021)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
17	*Artocarpus communis* J.R, &G. Forst	Moraceae	Roots	Methanol	64 (ATCC 8739)	128 (ATCC 11296)	Kuete, Ango et al. (2011)
18	*Asparagus racemosus* Wild	Liliaceae	Tubers	Acetone	125 (clin. isol)	31 (clin. isol)	Panghal et al. (2011)
19	*Asphodelus tenuifoliu* Cav	Liliaceae	Fruits	Water	62.5 (clin. isol)		Panghal et al. (2011)
20	*Balanites aegyptiaca* L	Balanitaceae	Fruits	methanol		31 (clin. isol)	Panghal et al. (2011)
21	*Barringtonia acutangula* (L.) Gaertn	Lecythidaceae	Twigs	Chloroform (Kp), ethanol (Ec)	125 (nd)	125 (nd)	Sahoo et al. (2008)
22	*Beilschmiedia obscura* (Staph). Engl	Lauraceae	Fruits	Methanol	16 (ATCC 8739)	64 (ATCC 11296)	Fankam et al. (2014)
23	*Beilshmiedia acuta* Kostem	Lauraceae	Barks (Ec), leaves (Kp), fruits (Kp)	Methanol	64 (ATCC 10536)	128 (ATCC 11296 & KP63), 32 (KP55),	Tankeo et al. (2015a, b)
24	*Berberis aristata* DC	Berberidaceae	Roots	Aqueous alcohol 50%	0.31 (MTCC 443)	0.62 (MTCC 109)	Singh et al. (2007)
25	*Berberis asiatica* Roxb. Ex DC	Berberidaceae	Stem	Aqueous alcohol 50%	2.5 (MTCC 443)	0.62 (MTCC 109)	Singh et al. (2007)
26	*Berberis chitria* Buch.-Ham. ex Lindl	Berberidaceae	Stem	Aqueous alcohol 50%	2.5 (MTCC 443)	0.62 (MTCC 109)	Singh et al. (2007)
27	*Berberis lycium* Royle	Berberidaceae	Stem	Aqueous alcohol 50%	0.62 (MTCC 443)	0.31 (MTCC 109)	Singh et al. (2007)
28	*Berginia ciliata* (Haw.) Sternb. Revis. Saxifrag. suppl	Saxifragaceae	Roots	Methanol	125 (nd)		Neupane and Lamichhane, (2020)
29	*Bolusanthus speciosus* (H. Bolus) Harms	Fabaceae	Leaves	Acetone	80 (nd)		Elisha et al. (2017)
30	*Bridellia micrantha* (Hochst.) Baill	Euphorbiaceae	Stem barks	Methanol	50 (ATCC 25922)		Kathare et al. (2021)
31	*Caesalpinia bonduc* (L.) Roxb	Fabaceae	Seed coats	Chloroform (Ec), methanol (Ec, Kp)	44 (MTCCB 1662)	88 (MTCCB 109)	Arif et al. (2009)
32	*Calpurnia aurea* (Aiton) Benth spp. aurea	Fabaceae	Leaves	Acetone	40 (nd)	80 (nd)	Elisha et al. (2017)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
33	*Cassia abbreviata* Oliver	Fabaceae	Stem barks	Methanol		125 (ATCC 9997)	Madureira et al. (2012)
34	*Cerbera manghas* L	Apocynaceae	Leaves	Ethanol 80% (v/v)	4 (ATCC 25922)		Frankova et al. (2021)
35	*Chenopodium ambrosioides* L	Amaranthaceae	Aerial parts	DCM		125 (ATCC 9997)	Madureira et al. (2012)
36	*Cichorium intybus* L	Asteraceae	Pods	Ethanol 80%	32.9 (O157 EHEC)	14.3 (nd)	Hassan et al. (2009)
37	*Cinnamomum cassia* (L.) J.Presl	Lauraceae	Barks	*n*-hexane	46.8 (Ec ATCC 25922)	46.8(clin. isol)	Hossan et al. (2018)
38	*Cinnamomum zeylenicum* Linn Cor	Lauraceae	Leaves	Methanol	64 (ATCC 8739)		Voukeng et al. (2012)
39	*Cistus laurifolius* L	Cistaceae	Leaves	Ethanol	32 (ATCC 35218)	32 (RSKK 574)	Ustun et al. (2016)
40	*Clerodendron splendens* G. Don	Verbenaceae	Leaves	Methanol	128 (NCTC 9002)	128 (NCTC 418)	Gbedema et al. (2010)
41	*Clerodendrum viscosum* Vent	Lamiaceae	Leaves	Ethanol		128 (nd)	Oly et al. (2011)
42	*Cremaspora triflora* (Thonn.) K.Schum	Rubiaceae	Leaves	Acetone	80 (nd)	80 (nd)	Elisha et al. (2017)
43	*Crinum purpurascens* Herb	Amaryllidaceae	Leaves	Methanol	128 (ATCC 8739)		Voukeng et al. (2017)
44	*Curcuma malabarica* Vel	Zingiberaceae	Tubers	*n*-hexane, acetone		10 (NCIM 2957)	Wilson et al. (2005)
45	*Curcuma zedoaria* Rosc	Zingiberaceae	Tubers	*n*-hexane, acetone		10 (NCIM 2957)	Wilson et al. (2005)
46	*Cylicodiscus gabunensis* Harms	Mimosae	Stem bark	Ethyl acetate	3.12 (clin.isol)		Kouitcheu Mabeku et al. (2006)
47	*Datura stramonium* L	Solanaceae	Seeds	Petroleum ether	39.1 (ATCC 8739)		Uzun et al. (2004)
48	*Dioscorea bulbifera* L. var sativa	Dioscoreaceae	Bulbils	Methanol	64 (ATCC 8739 & AG 100A), 128 (AG102)	64 (ATCC 11296), 128 (KP55 & KP63)	Kuete et al. (2012)
49	*Dorstenia psilurus* Welwitch	Moraceae	Roots	Methanol	128 (ATCC 10536)		Voukeng et al. (2012)
50	*Dorstenia turbinata* Engl	Moraceae	Twigs	Methanol	19.53 (LMP701)	78.12 (LMP803)	Ngameni et al. (2009)
51	*Echinops giganteus* A. Rich	Asteraceae	Roots	Methanol		32 (K24)	Fankam et al. (2011)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
52	*Elaeodendron croceum* (Thunb) DC	Celastraceae	Leaves	Acetone	80 (nd)		Elisha et al. (2017)
53	*Emblica officinalis* Gaertn	Phyllanthaceae	Fruits	Water	25.5 (O157 EHEC)	16.5 (na)	Hassan et al. (2009)
54	*Embothrium coccineum* J.R. Forst.& G. Forst	Proteaceae	Leaves	Dichloromethane (Ec), ethyl acetate (Kp)	31.125 (clin. isol)	125 (clin. isol)	Canales et al. (2016)
55	*Eruca sativa* (L.) Mill	Brassicaceae	Seeds	Petroleum ether	65 (clin. isol)	68 (clin. isol)	Gulfraz et al. (2011)
56	*Erythrina sigmoidea* Hua	Fabaceae	Barks	Methanol	32 (ATCC 8739), 16 (AG100)	64 (ATCC 11296), 16 (KP63), 128 (KP24), 64 (K2)	Djeussi et al. (2013)
57	*Euphorbia hirta* L	Euphorbiaceae	Leaves	Ethanol	100 (ATCC25922)		Upadhyay et al. (2010)
58	*Euphorbia prostrata* Ait	Euphorbiaceae	Whole plant	Methanol	128 (AG100)		Voukeng et al. (2017)
59	*Faraga tessmanii* Eng	Rutaceae	Roots	Methanol	128 (ATCC10536), 16 (AG 100)	16 (ATCC11296)	Tankeo et al. (2015a, b)
60	*Feijoa sellowiana* (O.Berg) O.Berg	Myrtaceae	Fruits	Water	4 (ATCC 11229)	16 (ATCC 10031)	Vuotto et al. (2000)
61	*Ficus bubu* Warb	Moraceae	Barks	Methanol	39.1 (clin. isol)		Mbosso Teinkela et al. (2016)
62	*Ficus exasperata* Vahl	Moraceae	Leaves	Methanol	128 (LMP0101U)		Tekwu et al. (2012)
63	*Ficus polita* Vahl	Moraceae	Roots	Methanol	64 (ATCC 8739)	128 (ATCC 11296)	Kuete, Kamga et al. (2011)
64	*Garcinia smeathmanii* Oliver	Clusiaceae	Stem barks	Methanol	39.06 (nd)	78.12 (nd)	Kuete, Komguem et al. (2007)
65	*Harungana madagascariensis* Lam.ex Pior	Hypericaceae	Barks	Methanol	< 8 (ATCC 10536), 64 (AG100), 32 (AG 102 & AG100A), 64 (AG100 tet), 128 (MC4100), < 8 (W3110)	16 (ATCC 11296 & KP63),64 (KP55), 128 (KP24)	Tankeo et al. (2016)
66	*Helicanthus elastica* (Desr.) Danser	Loranthaceae	Fresh parts	Ethanol		62.5 (ATCC15380)	Sunil Kumar et al. (2014)
67	*Heteromorpha arborescens* (Spreng.) Chan. & Schltdl	Apiaceae	Leaves	Acetone	80 (nd)		Elisha et al. (2017)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
68	*Hypericum roeperianum* G.W. Schimp.ex A. Rich var roeperianum	Hypericaceae	Leaves	Acetone	80 (nd)		Elisha et al. (2017)
69	*Hyptis albida* Kunth	Lamiaceae	Aerial parts	DCM:methanol (1:1 v/v)		100 (ATCC 700603)	Camacho-Corona et al. (2015)
70	*Iris domestica* (L.) Goldblatt and Mabb	Iridaceae	Rhizome	Water	62.5 (ATCC 25922)		McMurray et al. (2020)
71	*Lycopodium complanatum* L	Lycopodiaceae	Nd	Petroleum ether, chloroform, methanol	32 (ATCC 35218), 64 (clin.isol)	16 (RSKK 574), 32 (clin. isol)	Orhan et al. (2009)
72	*Malva oxyloba* Boiss	Malvaceae	Leaves	Methanol	78 (ATCC 25922)		Shadid et al. (2021)
73	*Markhamia tomentosa* K. Schum	Bignoniaceae	Leaves, barks	Methanol	128 (AG100 & AG100A)	128 (K2)	Voukeng et al. (2017)
74	*Marrubium globosum* Montbr. Et Auch. Ex Benth. spp. Libanoticum	Lamiaceae	Aerial parts	Methanol	32 (ATCC 11229)	16 (ATCC 27736)	Rigano et al. (2007)
75	*Mentha arvensis* L	Lamiaceae	Leaves	*n*-hexane	11.7 (Ec ATCC 25922)		Hossan et al. (2018)
76	*Moringa oleifera* Lam	Moringaceae	Leaves	Methanol	2.5 (ATCC 25922)		Begum et al. (2021)
77	*Morus mesozygia* Stapf ex A. Chev	Moraceae	Leaves	Acetone	80 (nd)	80 (nd)	Elisha et al. (2017)
78	*Murraya koenigii* (L.) Spreng	Rutaceae	Leaves	Benzene (Ec), acetone (Kp)	125 (clin. isol)	62.5 (clin. isol)	Panghal et al. (2011)
79	*Nauclea latifolia* Smith	Rubiaceae	Stem bark (Ec), leaves (Kp)	Methanol	32 (LMP0101U)	64 (LMP 0210U)	Tekwu et al. (2012)
80	*Nauclea pobeguinii* (Pobég. ex Pellegr.) Merr. ex E.M.A	Rubiaceae	Barks (Ec, Kp), leaves (Kp)	Methanol	32 (ATCC 10536), 64 (AG100)	128 (KP55)	Seukep et al. (2016)
81	*Newbouldia laevis* (P. Beauv.) Seem	Bignoniaceae	Root barks (Ec), leaves (Kp)	Methanol	78.12 (LMP0101U), 128 (ATCC10536)	128 (ATCC 11296)	Kuete, Eyong et al. (2007), Tankeo et al. (2015a, b)
82	*Nymphaea lotus* L	Nymphaeaceae	Flowers	Water	32.9 (O157 EHEC)	24.3 (na)	Hassan et al. (2009)
83	*Ocimum basilicum* L	Lamiaceae	Aerial parts	Ethanol	125 (clin. isol)		Adigüzel et al. (2005)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
84	*Ocimum gratissimum* L	Lamiaceae	Leaves	Methanol	62.5 (clin. isol)		Prasannabalaji et al. (2012)
85	*Olea europaea* L	Oleaceae	Leaves	Acetone	60 (UUMF-ST07)	25 (UUMF-KP16)	Korukluoglu et al. (2010)
86	*Parkinsonia aculeate* L	Fabaceae	Aerial parts	*n*-hexane, DCM, ethyl acetate & methanol		125 (ATCC 9997)	Madureira et al. (2012)
87	*Pedalium murex* L	Pedaliaceae	Fruits	Acetone	125 (clin. isol)		Panghal et al. (2011)
88	*Peperomia pellucida* (L.) Kunth	Piperaceae	Aerial parts	Ethanol 80% (v/v)	4 (ATCC 25922)		Frankova et al. (2021)
89	*Phlomis armeniaca* Benth	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
90	*Phlomis bourgaei* Boiss	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
91	*Phlomis leucophracta* P.H.Davis& Hub.-Mor	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
92	*Phlomis lunariifolia* Sm	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
93	*Phlomis lycia* D. Don	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
94	*Phlomis pungens* (var hirta & Pungens)	Lamiaceae	Nd	Petroleum ether, methanol	128 (ATCC 35218)	64 (RSKK574)	Ozcelik et al. (2010)
95	*Picrorhiza kurroa* Royle ex Benth	Plantaginaceae	Roots	Methanol	125 (nd)		Neupane and Lamichhane, (2020)
96	*Piper nigrum* L	Piperaceae	Fruits	Methanol, acetone, DCM	128 (ATCC 8739 & AG100A), 125 (NCIM 2089)	125 (NCIM 2957)	Karsha and Lakshmi, (2010), Noumedem et al. (2013)
97	*Pithecellobium dulce* (Roxb.) Benth	Fabaceae	Stem barks	Ethanol 50% (v/v)		80 (MTCC 109)	Singh et al. (2010)
98	*Pittosporum viridiflorum* Sims	Pittosporaceae	Leaves	Acetone	80 (nd)		Elisha et al. (2017)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
99	*Polygonum hydropiper* L	Polygonaceae	Aerial parts	Methanol 80% v/v	64 (MTCC 739)	53.3 (ATCC 700603)	Ayaz et al. (2016)
100	*Polyscias fulva (Hiern)* Harms	Araliaceae	Leaves, roots (Kp)	Methanol	128 (W 3110)	128 (ATCC 11296 & KP63),	Tankeo et al. (2015a, b)
101	*Psidium guajava* L	Myrtaceae	Leaves	methanol	0.78 (na)		Dhiman et al. (2011)
102	*Psychotria sycophylla* (K. Schum) Petit	Rubiaceae	Aerial parts	Methanol	128 (AG100ATET)	128 (KP55)	Demgne et al. (2021)
103	*Rheum australe* D. Don	Polygonaceae	Roots	Methanol	62.5 (nd)	125 (ATCC 13883)	McMurray et al. (2020)
104	*Rheum emodi* Wall	Polygonaceae	Rhizome	Methanol	62.5 (ATCC 25922)		Rolta et al. (2020)
105	*Ricinus communis* L	Euphorbiaceae	Seeds	Methanol		31 (clin. isol)	Panghal et al. (2011)
106	*Salvadora persica* L	Salvadoraceae	Leaves	*n*-hexane & methanol		125 (ATCC 9997)	Madureira et al. (2012)
107	*Salvia euphratica* Montbret, Aucher & Rech. F. var. Euphratica	Lamiaceae	Aerial parts	Ethanol 96%	125 (ATCC 25923)		Guzel et al. (2019)
108	*Sechium edule* (Jacq.)Sw	Cucurbitaceae	Leaves	Ethanol 80% (v/v)	20 (ATCC 35218 & ATCC 25922), 20–40 (clin. isol)	40 (clin. isol)	Ordonez et al. (2009)
109	*Silybum marianum* (L.) Gaertn	Compositae	Seeds	Water (Ec), ethanol 80% (Kp)	38.2 (O157 EHEC)	20.0 (na)	Hassan et al. (2009)
110	*Smilax acutifolia* Schltdl	Smilacaceae	Roots	DCM:methanol (1:1 v/v)	100 (ATCC 259222)		Camacho-Corona et al. (2015)
111	*Smilax cordifolia* Humb. & Bonpl. ex Willd	Smilacaceae	Roots	DCM:methanol (1:1 v/v)	100 (ATCC 259222)		Camacho-Corona et al. (2015)
112	*Smilax glabra* Roxb	Smilacacaeae	Tuber	Water	125 (ATCC 25922)		McMurray et al. (2020)
113	*Smilax invenusta* Kunth	Smilacaceae	Roots	DCM:methanol (1:1 v/v)	100 (ATCC 259222)		Camacho-Corona et al. (2015)
114	*Smilax schiedeana* Kunth	Smilacaceae	Roots	DCM:methanol (1:1 v/v)	100 (ATCC 259222)		Camacho-Corona et al. (2015)

Table 1 continued

	Plant species and authority(ies)	Plant family	Part with the reported activity	Extracting solvent (s) with the reported activity	MIC (µg/mL) against *E. coli* (Strain number)	MIC (µg/mL) against *K. pneumoniae* (Strain number)	References
115	*Sphaeranthus hirtus* Willd	Compositae	Seeds	Water	39.4 (O157 EHEC)	19.4 (nd)	Hassan et al. (2009)
116	*Syzigium samarangese* (Blume) Merr. & L.M.Perry	Myrtaceae	Fruits	Ethyl acetate (Ec), petroleum ether & methanol (Kp)	125 (MTTC 1687)	125 (MTCC 109)	Ratnam & Raju, (2008)
117	*Tecrium africanum* Thunb	Lamiaceae	Leaves	Methanol: DCM (1:1 v/v)	125 (Ec ATCC8739)		Ruiters et al. (2016)
118	*Tectona grandis* Linn	Verbenaceae	Fruits	Ethanol	64 (ATCC8739)	128 (ATCC 1148)	Bitchagno et al. (2015b)
119	*Terminalia bellirica* (Gaertn.) Roxb	Combretaceae	Fruits	ethanol	23.4 (Ec ATCC 25922)	93.7 (clin. isol)	Hossan et al. (2018)
120	*Trachystemon orientalis* (L.) G. Don	Boraginaceae	Whole plant	Ethanol	39.1 (ATCC 8739)		Uzun et al. (2004)
121	*Trichilia emetia* Vahl	Meliaceae	Leaves	*n*-hexane		125 (ATCC 9997)	Madureira et al. (2012)
122	*Tridesmostemon omphalocarpoides* Engl	Sapotaceae	Stem bark	Methanol	78.12 (LMP010U)		Kuete et al. (2006)
123	*Trigonella foenum-graecum* L	Fabaceae	Leaves	Benzene	31 (clin. isol)	31 (clin. isol)	Panghal et al. (2011)
124	*Vangueria spinosa* Roxb	Rubiaceae	Leaves	Ethanol	32.2 (MTCC 739)	25.5 (MTCC 432)	Chatterjee et al. (2009)
125	*Vitis vinifera* L	Vitaceae	Fruits	Methanol	19.74 (clin. isol)		Guessaibia et al. (2019)
126	*Xylopia aethiopica* (Dunal) A. Rich	Annonaceae	Fruits	Methanol	64 (ATCC 10536)	64 (KP 63)	Fankam et al. (2011)
127	*Zingiber officinale* Roscoe	Zingiberaceae	Rhizomes	Ethanol 95% (v/v)	75 (clin. isol)		Karuppiah and Rajaram, (2012)
128	*Zuccagnia puncata* Cav	Leguminosae	Leaves	Ethanol 96% (v/v)	100 (ATCC 25922)		Zampini et al. (2005)

nd = data not declared; clin.isol = clinical isolate; Ec = *Escherichia coli*; Kp = *Klebsiella pneumoniae*, DCM = dichloromethane

experimental procedure (broth dilution assay). The antimicrobial potentials of Berberidaceae were linked to the presence of the berberine and other isoquinoline alkaloids like chenabine, jhelumine, sindamine, karakoramine, punjabine, and hilgitine (Khan et al. 2016; Srivastava et al. 2015). Moreover, the presence of different lupine and quinolizidine alkaloids, in addition to an array of flavonoids was attributed to the antimicrobial potentials of the family Fabaceae (Ahmad et al. 2016; Krishna et al. 2012; Orni et al. 2018). In that respect, statistically significant differences ($p < 0.05$ and/or $p < 0.01$) were found between the MICs exhibited by the families Berberidaceae or Fabaceae with at least two of the other families across both bacteria (Fig. 2). Similarly, the family Lauraceae is known for high compositions of antimicrobial essential oils among other terpenoids, in addition to alkaloids, flavonoids, lignans, and steroids (Cao et al. 2015; Custódio and Florêncio da Veiga Junior 2014; Damasceno et al. 2019; Wan Salleh and Ahmad 2017). Furthermore, the antimicrobial activities of plants from the family Euphorbiaceae were linked to the presence of terpenoids, flavonoids, saponins, tannins, and alkaloids, among other secondary metabolites (Bijekar and Gayatri 2014; Mwine and Van Damme 2011).

Based on such diverse phytochemical compositions, it is difficult to ascertain if the observed higher antibacterial potentials of those families are functions of a particular class of compounds, a synergistic role of several classes or both. Nevertheless, these findings highlight and provide guidance on the plant families with a higher likelihood for hosting compounds against Enterobacteriaceae and possibly other Gram-negative bacteria. On the other hand, they emphasize on the need for deeper and extensive exploring of antibacterial activities from among the less-frequently studied, yet highly potential families. Similar findings

Fig. 1 Word cloud diagrams representing the type and frequency (based on font size) of the families of plant species with reported MIC values of 128 or lower against either *E. coli* or *K. pneumoniae* or both

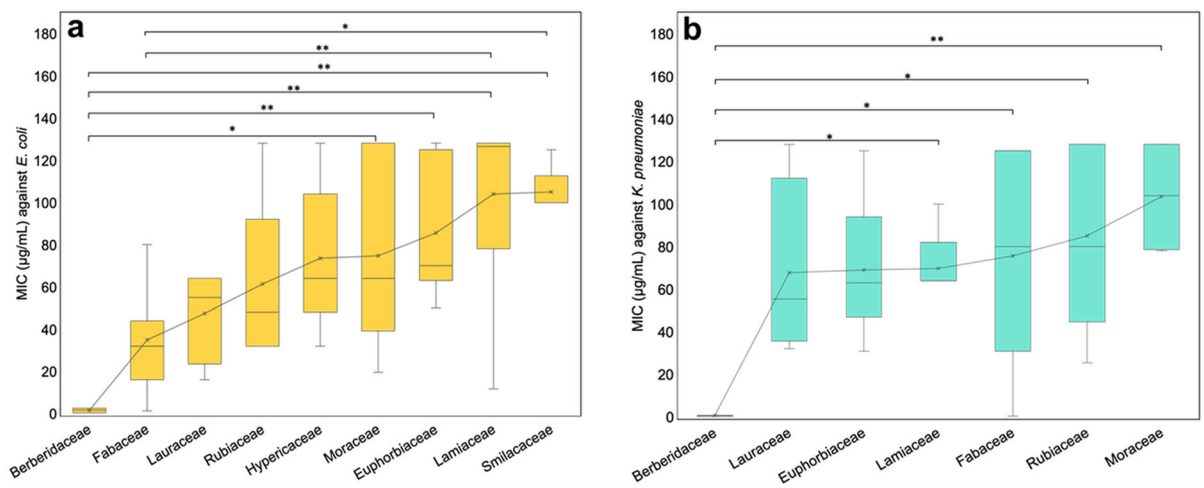


Fig. 2 Box-Whisker plot showing the average distribution of MIC values against *E. coli* **a** and *K. pneumoniae* **b** by plants from across the families with at least 4 studied species (x = mean value, whiskers' span shows the highest and lowest values). Statistical significance, *: $p < 0.05$, ** $p < 0.01$

by Chassagne et al. 2021, showed higher activities across a wide range of Gram-negative bacteria exhibited by plants from the families of Apiaceae, Compretaceae, Fabaceae, Lauraceae, Rutaceae, Rubiaceae, and Zingiberaceae (Chassagne et al. 2020). Moreover, there is a need for further reviews/studies on the comparison of antimicrobial potentials of different plant families/genuses with a focus on more related groups of bacteria.

Antibacterial activities across plant tissues

Leaves, barks, roots, fruits, and aerial parts were noted to be the most used plant tissues among the reviewed studies in the screening for antimicrobial activities of different plants. Among them, the activities from the seeds, barks, rhizomes, and fruits extracts were consistently higher against both bacteria. On the other end, extracts from aerial parts, roots, and leaves were noted to be of lower potencies (Fig. 3). These findings are similar to those reported by Chassagne et al. 2021, whereby extracts from rhizome, fruits, seeds, and stem barks showed higher potentials across a range of Gram-negative bacteria (Chassagne et al. 2020).

The observed differences in antibacterial activities across various plant tissues might be related to the differences in types and quantities of phytochemicals available in each tissue as driven by genetical, seasonal and ecological factors (Drabińska et al. 2021; Lavola et al. 2017). Although no statistical significance was found, these findings could lend higher preferences to extracts from seeds, barks, rhizomes, and fruits in the screening for activities against Gram-negative bacteria, in cases where choices are to be made.

Antibacterial activities across extracting solvents

The current review has indicated methanol, ethanol, acetone, water and petroleum ether and chloroform to be the most frequently used solvents in extraction of plant materials towards screening of their antibacterial potentials. As revealed in Fig. 4, water, chloroform, and ethanol extracts were generally the most potent against *E. coli*, as it was for water, chloroform, and acetone against *K. pneumoniae*. These findings are partly different from previous reports of higher potentials of acetone and methanol extracts among the gram-negative bacteria (Chassagne et al. 2020).

The nature of the extracting solvents is crucial in determining the ultimate polarities of the extracted phytochemicals. The observed higher prevalence and activities of less-polar solvents reflects the higher potentials of more lipophilic phytochemicals

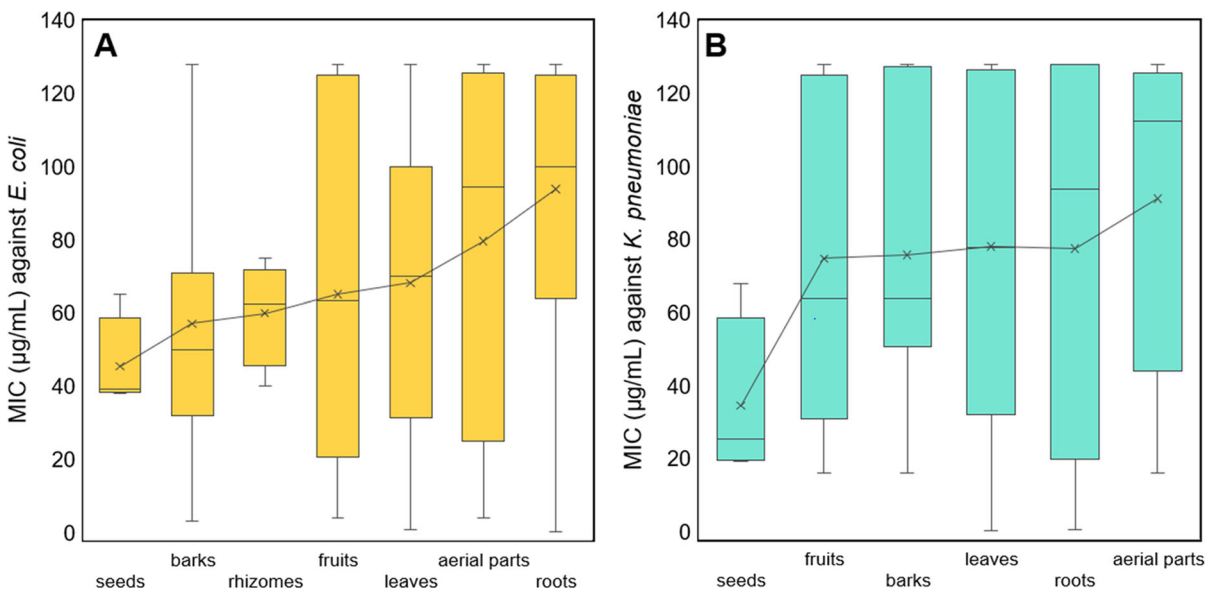


Fig. 3 Box-Whisker plots showing distributions of MIC values against *E. coli* **A** and *K. pneumoniae* **B** by extracts from different plant tissues with at least 4 studied samples (x = mean value, whiskers' span shows the highest and lowest values). Statistical significance: None observed

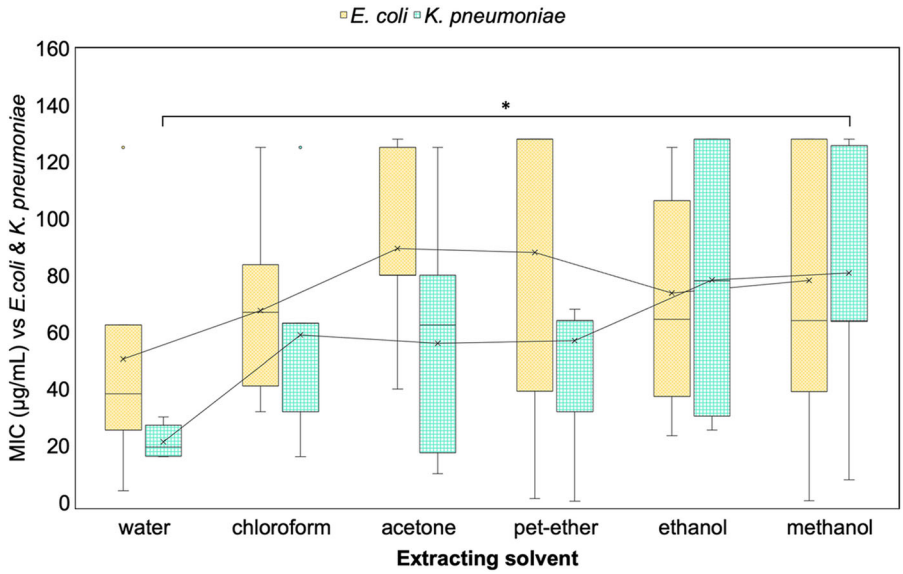


Fig. 4 Box-Whisker plot showing distributions of MIC values against *E. coli* and *K. pneumoniae* by extracts from different solvents with at least 5 studied samples (x = mean value, whiskers' span shows the highest and lowest values). Statistical significance, *: $p < 0.05$

particularly against Gram-negative bacteria (Hatano et al. 2005; Melliou et al. 2005; Merkl et al. 2010). Moreover, this aspect is discussed further in the following sections of this review. Conversely, the observed highest potentials exhibited by water extracts are of interest. This is particularly because of a clear break in the trend of observed activities with an increase in solvents' polarities. Partly, this might be explained by the synergistic effects from many highly polar compounds present in water extracts, which ultimately exhibit lower potentials upon their isolation (Paluch et al. 2021). Nevertheless, the lack of statistical significance in all but the pair between water and methanol extracts against *K. pneumonia* ($p < 0.05$) necessitates further explorations to grant a clearer understanding on this important aspect.

Screening for phytochemicals present in crude extracts

In addition to the provision of accounts on classes of phytochemicals which were previously ascertained in the plants studied (Bitchagno et al. 2015b; Hassan et al. 2009; Ordonez et al. 2009; Rigano et al. 2007), the screening for classes of phytochemicals present in the investigated crude extracts was broadly conducted. Most of such experiments involved semi-quantitative or qualitative approaches using classical methods for the identification of phytochemicals (Bitchagno et al. 2015b; Dhiman et al. 2011), and in some cases, the use of simplified techniques like Thin-Layer Chromatography (TLC) profiling followed by spray reagents was portrayed (Madureira et al. 2012).

The frequently reported phytochemical classes were found to be flavonoids (Dhiman et al. 2011; Kouitcheu Mabeku et al. 2006; Ordonez et al. 2009; Rigano et al. 2007), phenolic compounds (Madureira et al. 2012; Noumedem et al. 2013; Ordonez et al. 2009; Voukeng et al. 2012), alkaloids (Fankam et al. 2014; Kuete et al. 2006; Orhan et al. 2009; Voukeng et al. 2012), steroids (Bitchagno et al. 2015b; Dhiman et al. 2011; Fankam et al. 2014; Panghal et al. 2011) and anthraquinones (Bitchagno et al. 2015b; Kuete et al. 2006; Noumedem et al. 2013; Panghal et al. 2011). Others included terpenoids (Bitchagno et al. 2015b; Madureira et al. 2012; Rashed and Butnariu 2014; Voukeng et al. 2012), carbohydrates (Dhiman et al. 2011; Kouitcheu Mabeku et al. 2006; Rashed and Butnariu 2014), tannins (Dhiman et al. 2011; Fankam et al. 2014; Gbedema et al. 2010), saponins (Fankam et al. 2014; Kuete et al. 2006; Voukeng et al. 2012), and essential oils (Ruiters et al. 2016).

Moreover, the tendency of attributing several observed phytochemical classes to either the observed

antibacterial activities (Karsha and Lakshmi 2010; Rigano et al. 2007; Singh et al. 2010), or possible antibacterial mode(s) of action (Dhiman et al. 2011) of the investigated extract was observed. Nevertheless, the objectivity of such conclusions is limited. This is because primarily, the observed activities are not necessarily the functions of the most abundant phytochemicals within the crude extract, and also, there is a high likelihood of synergistic and addivitive activities of different classes. In the absence of the required resources for the successful isolation and characterization of respective antibacterial compounds, one could more objectively identify the phytochemical class of the active spot(s) on a TLC profile after ascertaining their activities by bioautography techniques (Madureira et al. 2012; Noundou et al. 2016).

Identification, isolation, and characterization of antibacterial compounds

Efforts to establish the identity of compounds responsible for the observed activities were generally portrayed in two main aspects. The first approach involved the use of Gas Chromatography-Mass Spectrometry (GC–MS) through which the masses and relative abundances of a large number of compounds present within the extracts were determined (Canales et al. 2016; Dhiman et al. 2011; Orhan et al. 2009; Rao et al. 2010). Further identification of those compounds with the help of Mass spectral databases was implicated (Kuete, Kamga et al. 2011; Orhan et al. 2009).

This approach has the potential to give hints on the identities of a large number of compounds present within the crude extracts within a relatively short time. Moreover, an analysis of the novelty of the present compounds and any previously reported biological activities can be conducted without the need to pre-isolate the bulk of compounds. Still, the approach is restricted to cases where compounds present in the crude extract were previously isolated and their respective data are retrievable from the reference databases. Further, the observed antibacterial activities are not necessarily the functions of the most abundant compound(s) within the extract (Rao et al. 2010).

The second modality involved a series of methods aimed at isolating and full characterizing compounds exhibiting the observed antibacterial activities. Unlike the previous approach, more focus and prioritization were required to reduce the workload and minimize the utilization of available resources. To enable this, the use of bioassay-guided fractionation and isolation was reported (Kuete et al. 2012; Tankeo et al. 2016). In addition to the common preparation of sub-fractions using silica gel packed open column chromatography (Kuete, Ango et al. 2011; Kuete, Kamga et al. 2011; Tankeo et al. 2016; Zampini et al. 2005), other techniques employing vacuum column chromatography and gel filtration with cross-linked dextran (Sephadex LH-20) were presented (Kuete, Ango et al. 2011; Ngameni et al. 2009).

Furthermore, the widespread utilization of spectrometric and spectroscopic technologies like UV–Vis spectroscopy (Bitchagno et al. 2015b; Rashed and Butnariu 2014), IR spectroscopy (Bitchagno et al. 2015b; Kuete et al. 2012; Noundou et al. 2016), Mass spectrometry (Bitchagno et al. 2015b; Korukluoglu et al. 2010; Rashed and Butnariu 2014; Tankeo et al. 2015a, b)), Nuclear Magnetic Resonance (NMR) Spectroscopy (Bitchagno et al. 2015b; Noundou et al. 2016; Zampini et al. 2005) was observed. Other determined characteristics included melting points (Bitchagno et al. 2015b; Kuete et al. 2012) and optical rotation properties of the isolated compounds (Kuete et al. 2012; Ngameni et al. 2009). Despite its lacking in the reviewed studies, the use of Quadrupole Time of Flight (Q-TOF) mass spectrometry in determination of accurate masses and hence chemical formulas of phytochemicals within plant extracts before their actual isolation is increasingly popular (Raju et al. 2015; Yang et al. 2021).

Generally, carrying out isolation and characterization of the antibacterial compounds from plant extracts following the establishment of their antibacterial properties was noted to be less frequent among the reviewed studies. Among other factors, this may be caused by the overall requirements for more sophisticated expensive equipment expertise usually associated with those experiments. On the other hand, the majority of the authors are likely in favour of reporting such findings in separate subsequent articles. While gaining more publications might motivate this tendency, the resulting gaps complicate the follow-up and application of the subsequent outcomes by the readers.

Prospects from evaluation of crude plant extracts

A number of studies were observed to emphasize the contribution of the reported findings toward supporting the ongoing traditional uses of the investigated plant species (Gbedema et al. 2010; Madureira et al. 2012; Noundou et al. 2016; Ratnam and Raju 2008). Moreover, a number of determined activities were claimed to be reported for the first time (Kouitcheu Mabeku et al. 2006; Ozcelik et al. 2010; Ustun et al. 2016; Uzun et al. 2004), hence underscoring the existence of many yet-to-be-discovered antibacterial potentials hosted among largely unexplored plant biodiversity (Verpoorte 2000).

The shared opinion that screening for antibacterial compounds among plant-derived extracts is of valuable contribution in the search for new antibiotics was realized (Ayaz et al. 2016; Bitchagno et al. 2015b; Tekwu et al. 2012). Moreover, many authors were quick to recommend the need for conducting further studies aimed at isolating the active compounds (Camacho-Corona et al. 2015; Chatterjee et al. 2009; Kouitcheu Mabeku et al. 2006; Orhan et al. 2009; Sahoo et al. 2008; Sunil Kumar et al. 2014; Voukeng et al. 2017) as well as determining the underlying modes of action (Noundou et al. 2016) and toxicity profiles (Chatterjee et al. 2009; Hassan et al. 2009; Noumedem et al. 2013). Recommendations on follow-up studies by other investigators are, however, commonly limited by factors such as the limited availability of plant species of interest along with low rates of success in reproducing findings reported elsewhere (Masota et al. 2021).

Plant isolated compounds effective against E. coli and K. pneumoniae

A total of 122 compounds active against *E. coli* and/or *K. pneumoniae* (MIC $\leq$ 100 µg/mL) isolated from crude plant extracts were retrieved from a literature search between 2010 and 2020 (Table 2). The reported MIC values were determined through broth dilution assays.

The corresponding molecular formula, molecular weight and ClogP values were determined using ChemDraw® software, whereas the number of hydrogen bond donors (nON) and acceptors (nOHNH), as well as the total polar surface areas (tPSA), were calculated on a Molinspiration chemoinformatics software (Table 2). These properties were chosen in the quest of assessing the retrieved compounds in line with Lipinski's rule of 5 (Pollastri 2010).

An account of the structures, names, MIC values, and other selected properties for each compound is provided in Table 2. Whenever possible the simple common names preferably those stated by the authors were indicated. However, in cases where no names were provided, the indicated names were generated on the ChemDraw® software.

Analysis of observed antibacterial potentials versus drug-likeness of isolated compounds

The Principal Component Analysis (PCA) of the data performed here showed that the MICs of the compounds were not correlated to the total polar surface area, molecular weight, as well as the number of hydrogen bond donors and acceptors (angles between their respective vectors $\sim$ 90°) (Fig. 6a). On the other hand, a weak negative correlation (angles close to 180°) was observed between the MICs and the ClogP values of the compounds (Fig. 6a).

Lower MIC values (high antibacterial activity) were therefore fairly linked to higher ClogP (more lipophilic) values of the isolated compounds. On the other hand, compounds belonging to flavonoids and terpenoids showed higher average ClogP values (Fig. 5b), which was consistent to their higher activities against both bacteria as compared to alkaloids (Fig. 6). However, no statistical significance was found on the observed difference at $p = 0.05$.

These observations underline the influence of compounds' lipophilicity on their antibacterial activities against Gram-negative bacteria. Among other prospects, high lipophilicity might yield better interactions between the compounds and components of the outer bacterial cell membranes in Gram-negative bacteria, thus facilitating the exhibition of other antibacterial mechanisms (Podunavac-Kuzmanovic et al. 2008). Other studies have indicated higher antibacterial potentials in compounds of different nature when their lipophilicities were increased through formation of corresponding esters, ethers, prenylation, or substitutions with longer alkylation chains (Hatano et al. 2005; Khameneh et al. 2019; Melliou et al. 2005; Merkl et al. 2010).

Nevertheless, lipophilicity of drugs is a key factor in determining the ultimate target selectivity of drugs

Table 2 Plant isolated compounds (122) active against *E. coli* (Ec) and *K. pneumoniae* (Kp) (MIC $\leq$ 100 µg/mL)

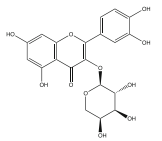
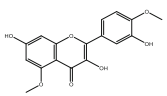
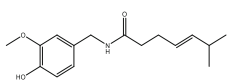
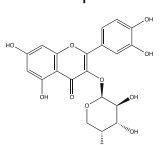
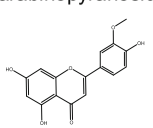
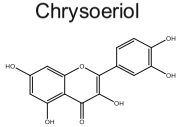
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (µg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
1	 $C_{20}H_{18}O_{11}$ (434.35) Quercetin-3-*O*-*α*-*L*-arabinopyranoside	Flavonoid (Flavonol glycoside)	0.187		− 0.303	1;7	186.37	Metwally et al. (2010)
2	 $C_{17}H_{14}O_7$ (330.29) Quercetin 5,4'-dimethyl ether	Flavonoid (Falvonol)		0.49 (IMI = 0.98)	1.693	7;3	105.45	Elkady et al. (2020)
3	 $C_{16}H_{23}NO_3$ (277.36) Capsaicin	Phenylpropanoid (Capsaicinoid)	5	0.6	2.692	4;2	58.56	Nascimento et al. (2014)
4	 $C_{20}H_{18}O_{11}$ (434.35) Quercetin-3-*O*-*β*-*D*-arabinopyranoside	Flavonoid (Flavonol glycoside)	0.093		− 0.303	11;7	186.37	Metwally et al. (2010)
5	 $C_{16}H_{12}O_6$ (300.26) Chrysoeriol	Flavonoid (Flavone)	0.06	0.25	2.749	6;3	96.22	Nascimento et al. (2014)
6	 $C_{15}H_{10}O_7$ (302.23) Quercetin	Flavonoid (Flavonol)	1.25		1.503	7;5	127.45	Metwally et al. (2010)

Table 2 continued

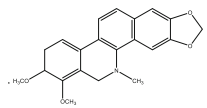
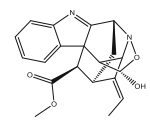
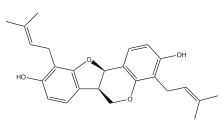
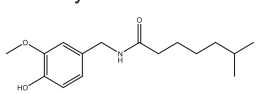
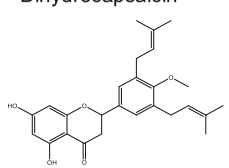
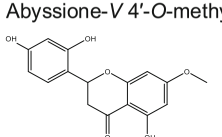
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
7	 $C_{21}H_{21}NO_4$ (351.40) 1,2-Dimethoxy-12-methyl-2,3,12,13-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]phenanthridine	Azaarene (Phenantridine)	16 (GEN = 0.25)		3.767	5;0	40.16	Tantapakul et al. (2012)
8	 $C_{20}H_{20}N2O_4$ (352.39) Nareline	Alkaloid (Indole alkaloid)	50 (CTX = 0.78)	1.56 (CTX = 0.78)	1.771	6;1	71.36	Liu et al. (2015)
9	 $C_{25}H_{28}O_4$ (392.49) Erybraedin A	Flavanoid (Isoflavonoid/ Pterocarpan)	2 (CIP = 0.078)		6.259	4;2	58.92	Sadgrove et al. (2020)
10	 $C_{16}H_{25}NO_3$ (279.38) Dihydrocapsaicin	Phenylpropanoid (Capsaicinoid)	5	2.5	58.56	4;2	3.1762	(Nascimento et al. (2014)
11	 C26H30O5 (422.52) Abyssione-*V* 4′-*O*-methyl ether	Flavonoid (Flavanone)	3.9 (NEO = 1.6)	3.9 (NEO = 1.6)	7.032	5;2	75.99	Chukwujekwu et al. (2011)
12	 $C_{16}H_{14}O_6$ (302.23) Artocarpanone	Flavonoid (Flavanone)	3.9 (AMP = 0.9)	–	2.250	6;3	96.22	Septama and Panichayupakaranant, (2017)

Table 2 continued

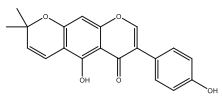
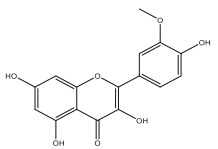
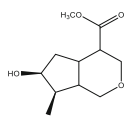
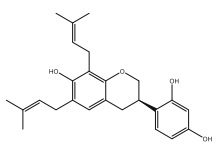
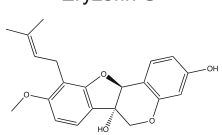
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
13	 $C_{20}H_{16}O_5$ (336.34) Alpinumisoflavon	Flavonoid (Isoflavonoid)	3.9 (NEO = 1.6)	3.9 (NEO = 1.6)	4.469	5;2	75.99	Chukwujekwu et al. (2011)
14	 $C_{16}H_{12}O_7$ (316.27) Isorhamentin	Flavonoid (Flavonol)		3.9 (IMI = 0.98)	1.217	7;4	116.45	Elkady et al. (2020)
15	 $C_{11}H_{18}O_4$ (214.26) Cyclopenta(c) pyran-4-carboxylic acid, octahydro-3,6-dihydroxy-7-methyl ester	Terpenoid (Monoterpenoid/ Iridoid)	4 (GEN = 1.0)	64 (GEN = 4.0)	− 0.145	4;1	55.76	Sarıkahya et al. (2011)
16	 $C_{25}H_{30}O_4$ (394.51) Eryzerin C	Flavonoid (Isoflavonoid)	5 (CIP = 0.078)		6.044	4;2	69.92	Sadgrove et al. (2020)
17	 $C_{21}H_{22}O_5$ (354.40) Cristacarpin	Flavonoid (Isoflavonoid/ Pterocarpan)	6 (CIP = 0.078)		3.896	5;2	68.15	Sadgrove et al. (2020)

Table 2 continued

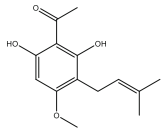
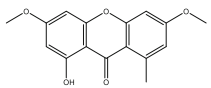
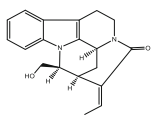
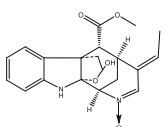
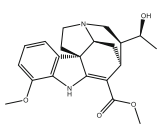
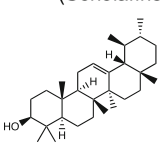
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
18	 $C_{14}H_{18}O_4$ (250.29) Acronyculatin S	Acetophenone	6.25 (CIP = 0.078)		3.388	4;2	66.76	Tchangoue et al. (2020)
19	 $C_{16}H_{14}O_5$ (286.28) Lichenxanthone	Xanthone	6.25 (CIP = 0.078)		4.089	5;1	64.99	Tchangoue et al. (2020)
20	 $C_{19}H_{20}O_2$ (308.381) Normavacurine-21-one	Alkaloid (Monoterpenoid indole alkaloid)	100 (CTX = 0.78)	6.25 (CTX = 0.78)	1.599	4;1	43.78	Liu et al. (2015)
21	 $C_{20}H_{22}N_2O_5$ (370.40) 5-hydroxy-19, 20-*E*-alschomine.	Alkaloid (Monoterpenoid indole alkaloid)	100 (CTX = 0.78)	6.25 (CTX = 0.78)	0.441	7;2	93.59	Liu et al. (2015)
22	 $C_{21}H_{26}N_2O_4$ (370.44) 12-methoxyechitamidine (Scholarine)	Alkaloid	100 (CTX = 0.78)	6.25 (CTX = 0.78)	1.980	6;2	71.03	Liu et al. (2015)
23	 $C_{30}H_{50}O$ (426.38) α- amyrin	Terpenoid (Pentacyclic triterpenoid)	6.25 (CIP = 6.25)		10.66	1;1	20.23	Kaur, (2015)

Table 2 continued

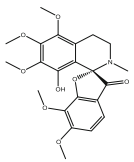
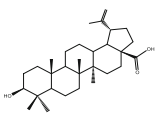
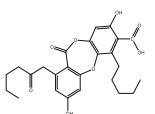
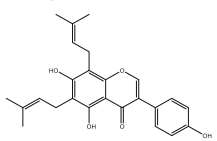
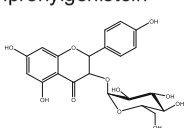
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
24	 $C_{22}H_{25}NO_8$ (431.41) Thalicfoetine	Alkaloid (Spirobenzylisoquinoline alkaloid)	6.25 (CTX = 0.39)		1.900	9;1	95.92	Ding et al. (2019)
25	 $C_{30}H_{48}O_3$ (456.71) Betulinic acid	Terpenoid (Lupane-type terpenoid)	6.25	25	8.477	3;2	57.53	Joshua et al. (2020)
26	 $C_{25}H_{28}O_8$ (456.49) Physodic acid	Depsidone		7.5 (STR = 1.95)	6.397	8;3	130.36	Kosanic et al. (2013)
27	 $C_{25}H_{26}O_5$ (406.47) 6,8-Diprenylgenistein	Flavonoid (Isoflavone)	7.8 (NEO = 1.6)	7.8 (NEO = 1.6)	6.257	5;3	86.99	Chukwujekwu et al. (2011)
28	 $C_{21}H_{22}O_{11}$ (450.39) Astragalin (Kaempferol-3-*O*-*β*-D-glucoside)	Flavonoid (Flavonol glycoside)	–	7.81 (IMI = 0.98)	0.327	11;7	186.37	Elkady et al. (2020)

Table 2 continued

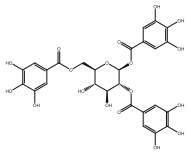
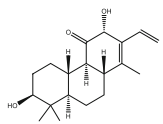
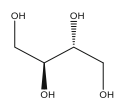
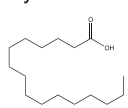
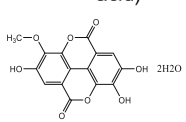
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
29	 $C_{27}H_{24}O_{18}$ (636.47) 1,2,6-tri-O-galloyl-*β*-*D*-glucopyranose	Tannin (Hydrolysable tannin)	12.1–97.5	24.3–97.5	0.111	18;11	310.66	Bag et al. (2013)
30	 $C_{19}H_{28}O_3$ (304.43) Niloticane	Terpenoid (Cassane diterpene)	33 (NEO = 3.3)	16 (NEO = 0.9)	2.739	3;2	57.53	Eldeen et al. (2010)
31	 $C_4H_{10}O_4$ (122.12) meso-Erythritol	Sugar alcohol	12.5 (AMP = 0.8)		− 1.707	4;4	80.92	Mbosso et al. (2010)
32	 $C_{16}H_{32}O_2$ (256.43) Palmitic acid (Hexadecanoic acid)	Long-chain fatty acid	12.5 (CIP = 6.25)		7.212	2;1	37.3	Kaur, (2015)
33	 $C_{15}H_8O_8$ (316.22) 3-*O*-methyl ellagic acid dihydrate (ellagic acid derivative)	Tannin (Hydrolyzable tannin)	12.5		0.589	8;3	122.52	Parveen et al. (2015)

Table 2 continued

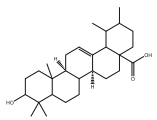
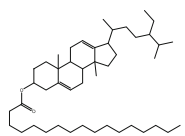
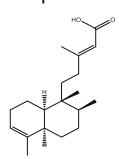
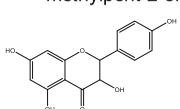
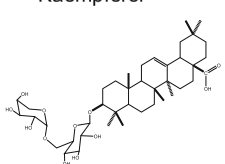
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
34	 $C_{28}H_{55}O_3$ (428.65) Ursolic acid	Terpenoid (Pentacyclic triterpenoid)	[50]	12.5 (CIP = 3.15) [100]	7.589	3;2	57.53	Srinivasan et al. (2017), Wolska et al. (2010), Zhu et al. (2015)
35	 $C_{46}H_{80}O_2$ (665.14) 14-methyl-12, 13-dehydro-sitosterol-heptadeconate	Phytosteroid	12.5 (CIP = 6.25)		18.845	2;0	26.3	Kaur, (2015)
36	 $C_{20}H_{32}O_2$ (304.47) (*E*)-5-[(1*R*,2*S*,4a*R*,8a*S*)-1,2,4a,5-tetramethyl-2,3,4,7,8,8a-hexahydronaphthalen-1-yl]-3-methylpent-2-enoic acid	Terpenoid	15.6 (CIP = 0.156)	93.8 (CIP = 0.078)	5.38	2;1	7.482	Du et al. (2015)
37	 $C_{15}H_{12}O_6$ (286.23) Kaempferol	Flavonoid	16 (GEN = 0.8)		1.367	6;4	107.22	Teffo et al. (2010)
38	 $C_{41}H_{66}O_{12}$ (750.96) adianthifolioside GS1.	Terpenoid (Saponin/ triterpene glycoside)	16 (CHL = 2)	32 (CHL = 32)	6.120	12;7	195.6	Sonfack et al. (2021)

Table 2 continued

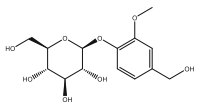
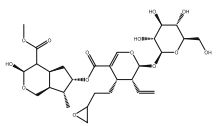
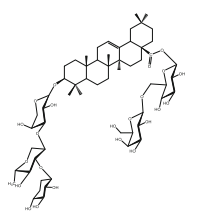
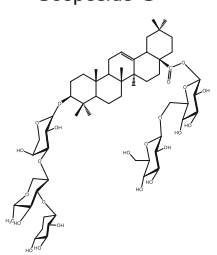
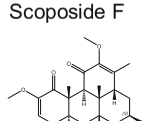
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
39	 $C_{14}H_{20}O_8$ (316.30) Vanilloloside	Phenolic glycoside	16 (GEN = 1.0)	32 (GEN = 4.0)	− 1.320	8;5	128.84	Sarıkahya et al. (2011)
40	 $C_{29}H_{42}O_{14}$ (614.64) Laciniatoside-I	Terpenoid (Monoterpenoid/ Iridoid glucoside	16 (GEN = 1.0)	32 (GEN = 4.0)	− 0.698	14;5	− 0.43	Sarıkahya et al. (2011)
41	 $C_{59}H_{96}O_{23}$ (1173.39) Scoposide G	Terpenoid (Saponin/ triterpene glycosides)	16 (GEN = 1.0)	32 (GEN = 4.0)	4.492	23;12	363.13	Sarıkahya et al. (2011)
42	 $C_{59}H_{96}O_{23}$ (1173.39) Scoposide F	Terpenoid (Saponin/ triterpene glycosides)	16 (GEN = 1.0)	32 (GEN = 4.0)	4.492	23;13	363.13	Sarıkahya et al. (2011)
43	 $C_{22}H_{30}O_6$ (390.47) (16S)-Methoxyjavanicin B	Quassinoid (degredaded triterpene)		19.56	1.755	6;0	71.06	(Prema et al. 2019)

Table 2 continued

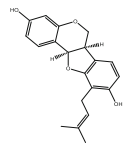
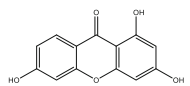
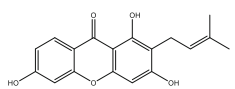
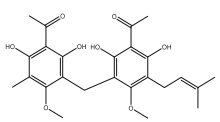
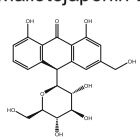
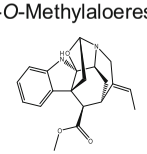
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
44	 $C_{20}H_{20}O_4$ (324.37) Phaseollidin	Flavonoid (Isoflavonoid/ Pterocarpan)	20 (CIP = 0.078)		4.308	4;2	5.92	(Sadgrove et al. 2020)
45	 $C_{13}H_8O_5$ (244.20) 1,3,6-Trihydroxyxanthone	Xanthone	25		2.427	5;3	86.99	Panthong et al. (2013)
46	 $C_{18}H_{16}O_5$ (312.32) 1,3,6-Trihydroxy-2-(3-methyl-2-butenyl)xanthone	Xanthone	25		4.328	5;3	86.99	Panthong et al. (2013)
47	 $C_{25}H_{30}O_8$ (458.50) Mallotojaponin B	Phloroglucinols	25.0 (CIP = 0.078)		5.100	8;4	133.52	Tchangoue et al. (2020)
48	 $C_{21}H_{22}O_9$ (418.39) 7-*O*-Methylaloeresin A	Chromone glycoside	25.1		0.954	9;7	167.91	Asamenew et al. (2011)
49	 $C_{20}H_{22}N_2O_3$ (338.40) Picrinine	Alkaloid (Akuammiline alkaloid)	50 (CTX = 0.78)	25 (CTX = 0.78)	1.614	5;1	50.8	Liu et al. (2015)

Table 2 continued

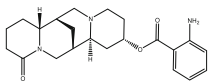
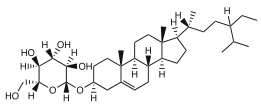
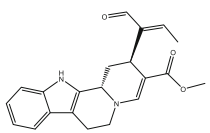
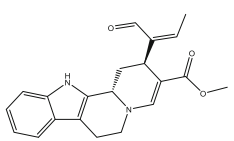
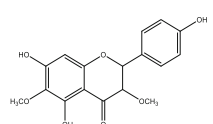
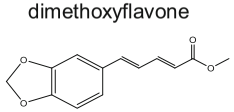
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
50	 $C_{22}H_{29}N_3O_3$ (383.49) Lanatine A	Alkaloid (Quinolizidine alkaloid)	25–50	25–50	2.162	6;2	75.87	Neto et al. (2011)
51	 $C_{35}H_{60}O_6$ (576.85) *β*-sitosterol-3-*O*-*β*-*D*-glucoside	Steroidal glycoside	50	25	9.486	6;4	99.38	Njinga et al. (2016)
52	 $C_{21}H_{22}N_2O_3$ (350.41) Vallesiachotamin	Alkaloid (Monoterpene indole alkaloid)	100 (CTX = 0.78)	25 (CTX = 0.78)	2.978	5;1	58.64	Liu et al. (2015)
53	 $C_{21}H_{22}N_2O_3$ (350.41) Isovallesiachotamine	Alkaloid (Monoterpene indole alkaloid)	100 (CTX = 0.78)	25 (CTX = 0.78)	2.978	5;1	58.64	Liu et al. (2015)
54	 $C_{17}H_{16}O_7$ (332.30) 5, 7, 4'-trihydroxy-3, 6-dimethoxyflavone	Flavonoid (Dimethoxy flavone)	26 (GEN = 0.8)		1.462	7;3	105.45	Teffo et al. (2010)
55	 $C_{13}H_{12}O_4$ (232.24) Methy piperate	Benzodioxole	30		2.884	4;0	44.76	Khaing, (2019)

Table 2 continued

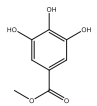
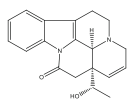
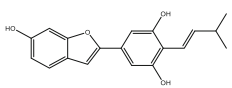
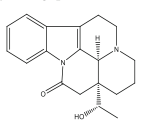
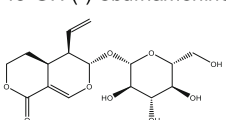
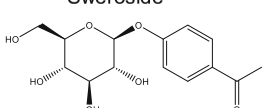
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
56	 $C_8H_8O_5$ (184.14) Methylgallate	Phenolic compound (Galloyl ester)	30 (NEO = 3.06) (78) (CHR = 30)	(78) (CHR = 30)	0.931	5;2	86.99	Madikizela et al. 2013; Oladosu et al. (2019)
57	 $C_{19}H_{20}N_2O_2$ (308.38) Phutdonginin	Alkaloid (Monoterpene indole alkaloid)	32		2.525	4;1	43.78	Cheenpracha et al. (2014)
58	 $C_{19}H_8O_4$ (310.34) 2-[(3,5-dihydroxy)-(Z)-4-(3-methylbut-1-enyl)phenyl]benzofuran-6-ol	Flavonoid (Arylbenzofuran flavonoid)	32 (CHR = 4)		4.98	4;2	69.92	Kuete, Ango et al. (2011)
59	 $C_{19}H_{22}N_2O_2$ (310.39) 19-OH-(-)-eburnamonine	Alkaloid (Indole alkaloid)	32		2.809	4;1	43.78	Cheenpracha et al. (2014)
60	 $C_{16}H_{22}O_9$ (358.34) Sweroside	Terpenoid (Monoterpenoid/ Iridoid glucoside)	32 (GEN = 1.0)	32 (GEN = 1.0)	− 1.598	9;4	134.91	Sarıkahya et al. (2011)
61	 $C_{14}H_{18}O_7$ (298.29) Picein	Phenolic glycoside	32 (GEN = 1.0)	64 (GEN = 4.0)	− 0.281	7;4	116.45	Sarıkahya et al. (2011)

Table 2 continued

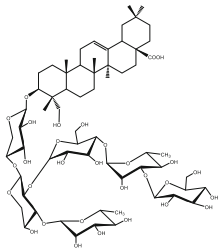
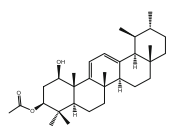
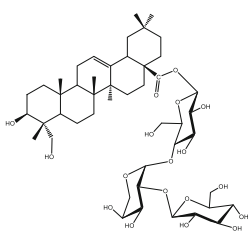
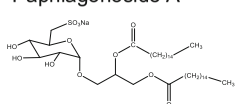
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
62	 $C_{64}H_{104}O_{30}$ (1353.50) Isacoside	Terpenoid (Saponin/ triterpene glycosides)	64 (GEN = 1.0)	32 (GEN = 4.0)	0.558	30;17	471.74	Sarıkahya et al. (2011)
63	 $C_{31}H_{48}O_3$ (468.72) Conrauidienol	Terpenoid (triterpene)	32–64 (CHR = 1.0)	64 (CHR = 2.0)	9.197	3;1	46.53	Kengapa et al. (2011)
64	 $C_{47}H_{76}O_{18}$ (929.10) Paphlagonoside A	Terpenoid (Saponin/ triterpene glycosides)	32	128	2.287	18;11	294.98	Sarıkahya et al. (2011)
65	 $C_{41}H_{77}NaO_{12}S$ (817.09) Sulfonoquinovosyldiacylglyceride (SQDG)	Glycolipid	32–64	256	− 99.99	12;3	175.12	Bharitkar et al. (2014)

Table 2 continued

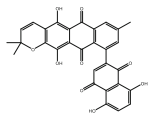
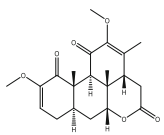
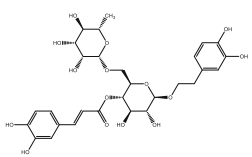
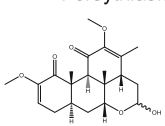
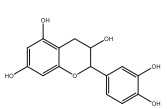
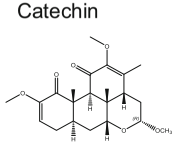
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
66	 $C_{30}H_{20}O_9$ (524.48) Tectograndone	Anthraqunone (Naphtoquinone)	32 (CIP = 5)	> 256 (CIP = 5)	6.632	9;4	158.43	Bitchagno et al. (2015a)
67	 $C_{21}H_{26}O_6$ (374.43) Javanicin F	Quassinoid (Degredaded triterpene)		37.44	0.849	6;0	78.9	Prema et al. (2019)
68	 $C_{29}H_{36}O_{15}$ (624.59) Forsythiaside	Polyphenol (Phenylethanoid glycoside)	38.33 (TET = 29.76)		-0.942	15;9	245.29	Qu et al. (2012)
69	 $C_{21}H_{28}O_6$ (376.44) Javanicin B	Quassinoid (Degredaded triterpene)		37.64	1.151	6;1	82.06	Prema et al. (2019)
70	 $C_{15}H_{14}O_6$ (290.271) Catechin	Flavonoid (Flavanol)	3 (CHR = 30)	39 (CHR = 30)	0.533	6;5	110.38	(Oladosu et al. 2019)
71	 $C_{22}H_{30}O_6$ (390.47) (16*R*)-methoxyjavanicin B	Quassinoid (Degredaded triterpene)		39	1.755	6;0	71.06	Prema et al. (2019)

Table 2 continued

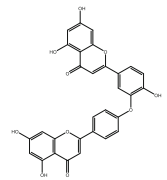
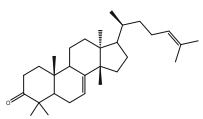
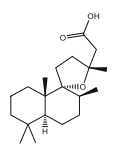
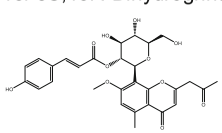
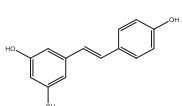
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON; nOHNH	tPSA	Reference
			Ec	Kp				
72	 $C_{30}H_{18}O_{10}$ (538.46) Ochnaflavone	Flavonoid (Biflavone)	41.6 (GEN = 7.0)		5.262	10;5	162.98	Makhafola et al. (2012)
73	 $C_{30}H_{48}O$ (424.71) Lanosta-7,24-dien-3-one	Terpenoid (Triterpenoid)		44.07	10.191	1;0	17.07	Prema et al. (2019)
74	 $C_{20}H_{34}O_3$ (322.48) rel-8*S*,13*R*-Dihydrogrindelic acid	Terpenoid (Diterpene)		46.9 (CIP = 0.078)	6.294	3;1	46.53	Du et al. (2015)
75	 $C_{29}H_{30}O_{11}$ (554.54) Aloin	Anthraquinone glycoside	49.9		0.846	11;4	169.05	Asamenew et al. (2011)
76	 $C_{14}H_{12}O_3$ (228.24) Resveratrol	Polyphenol (phytoalexin)	50 (CHR = 25)		2.833	3;3	60.69	Kusumaningtyas et al. (2020)

Table 2 continued

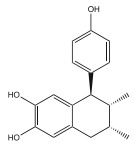
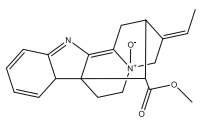
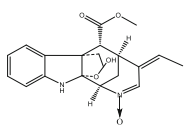
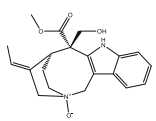
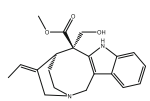
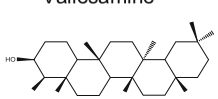
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp		tPSA	Reference				
77	 $C_{18}H_{20}O_3$ (284.35) 3′-demethoxy-6-O-demethylisoguaiacin	Lignin	50 (LEV = 0.78)		4.379	3;3	60.69	Favela-Hernandez et al. (2012)
78	 $C_{20}H_{22}N_2O_3$ (338.40) Strictamine N^4-oxide	Alkaloid (Akuammiline alkaloid)	50 (CTX = 0.78)	50 (CTX = 0.78)	3.189	5;0	338.407	Liu et al. (2015)
79	 $C_{20}H_{22}N_2O_5$ (370.40) 5-hydroxy-19,20-Z-alschomine	Alkaloid (Indole alkaloid)	50 (CTX = 0.78)	50 (CTX = 0.78)	0.441	7;2	93.59	Liu et al. (2015)
80	 $C_{20}H_{24}N_2O_4$ (356.42) Vallesamine N^4-oxide	Alkaloid (Valessaman alkaloid)	50 (CTX = 0.78)	50 (CTX = 0.78)	2.609	6;2	81.62	Liu et al. (2015)
81	 $C_{20}H_{24}N_2O_3$ (340.42) Vallesamine	Alkaloid (Valessaman alkaloid)	50 (CTX = 0.78)	50 (CTX = 0.78)	2.174	5;2	61.8	Liu et al. (2015)
82	 $C_{30}H_{52}O$ (428.74) Epifriedelinol	Terpenoid (Triterpenoid)	50 (CIP = 28.67)	50 (CIP = 28.67)	11.147	1;1	20.23	Kannathasan et al. (2019)

Table 2 continued

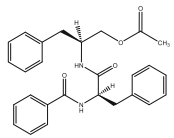
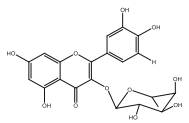
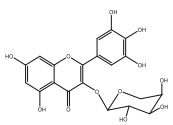
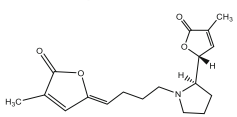
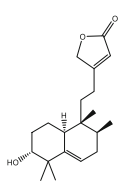
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
83	 $C_{27}H_{28}N_2O_4$ (444.531) Aurantiamide acetate	Phenylalanine (Modified dipeptide)	50 (GEN = 0.025)	50 (GEN = 0.025)	4.18	6;2	84.5	Tamokou et al. (2012)
84	 C21H20O11 (448.38) Myricetin-3-*O*-rhamnoside	Flavonoid (Flavonol glycoside)	60 (STR = 6.13)		0.215	11;7	186.37	Madikizela et al. (2013)
85	 $C_{20}H_{18}O_{12}$ (450.35) Myricetin-3-*O*-arabinopyranoside	Flavonoid (Flavonol glycoside)	60 (STR = 6.13)		-0.969	12;8	206.6	Madikizela et al. (2013)
86	 $C_{18}H_{23}NO_4$ (317.38) Pandamarilactonine-A	Alkaloid (Butenolide)	62.5		1.922	5;0	55.84	Laluces et al. (2015)
87	 $C_{20}H_{30}O_3$ (318.45) 4-(2-((1*R*,2*S*,6*R*,8a*S*)-1,2,5,5,6-pentamethyl-1,2,3,5,6,7,8,8a-octahydronaphthalen-1-yl) ethyl) furan-2(5*H*)-one	Terpenoid (Isolabdane diterpenoid)		62.5 (CIP = 0.156)	3.968	3;1	46.53	Du et al. (2015)

Table 2 continued

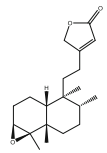
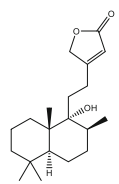
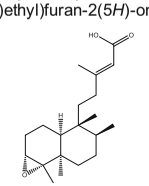
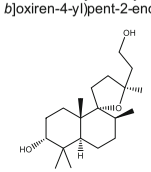
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
88	 $C_{20}H_{30}O_3$ (318.45) 4-(2-((1a*S*,3a*R*,4*S*,5*R*,7a*S*,7b*R*)-4,5,7a,7b-tetramethyldecahydronaphtho[1,2-*b*]oxiren-4-yl)ethyl)furan-2(5*H*)-one	Terpenoid (Clerodane diterpenoid)		62.5(CIP = 0.078)	4.345	3;0	38.83	Du et al. (2015)
89	 $C_{20}H_{32}O_3$ (320.47) 4-(2-((1*R*,2*S*,4a*S*,8a*S*)-1-hydroxy-2,4a,5,5,8a-pentamethyldecahydronaphthalen-1-yl)ethyl)furan-2(5*H*)-one	Terpenoid (Labdane diterpenoid)		62.5 (CIP = 0.078)	4.452	3;1	46.53	Du et al. (2015)
90	 $C_{20}H_{32}O_3$ (320.47) (*E*)-3-methyl-5-((1a*R*,3a*S*,4*R*,5*S*,7a*R*,7b*S*)-4,5,7a,7b-tetramethyldecahydronaphtho[1,2-*b*]oxiren-4-yl)pent-2-enoic acid	Terpenoid (Clerodane diterpenoid)		62.5 (CIP = 0.078)	5.772	3;1	49.83	Du et al. (2015)
91	 $C_{20}H_{36}O_3$ (324.50) (2*R*,2'*S*,4a'*S*,5*S*,6'*R*,8a'*S*)-5-(2-hydroxyethyl)-2',5,5',5',8a'-pentamethyldecahydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-6'-ol	Terpenoid (Labdane diterpenoid)		62.5 (CIP = 0.078)	4.026	3;2	49.69	Du et al. (2015)

Table 2 continued

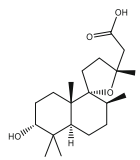
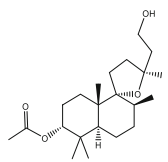
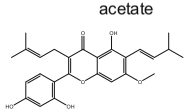
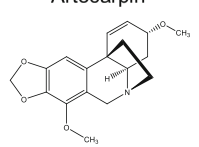
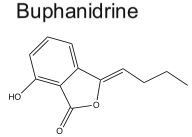
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
92	 $C_{20}H_{34}O_4$ (338.488) 2-((2*R*,2'*S*,4a'*S*,5*R*,6'*R*,8a'*S*)-6'-hydroxy-2',5,5',5',8a'-pentamethyldecahydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-5-yl) acetic acid	Terpenoid (Labdane diterpenoid)		62.5 (CIP = 0.078)	4.207	4;2	66.76	Du et al. (2015)
93	 $C_{22}H_{38}O_4$ (366.54) (2*R*,2'*S*,4a'*S*,5*S*,6'*R*,8a'*S*)-5-(2-hydroxyethyl)-2',5,5',5',8a'-pentamethyldecahydro-2'*H*,3*H*-spiro[furan-2,1'-naphthalen]-6'-yl acetate	Terpenoid (Labdane diterpenoid)		62.5 (CIP = 0.078)	4.972	4;1	55.76	Du et al. (2015)
94	 $C_{26}H_{28}O_6$ (436.50) Artocarpin	Flavonoid (3- prenylated flavone)	62.5 (AMP = 0.9)		6.409	6;3	96.22	Septama and Panichayupakaranant, (2017)
95	 $C_{18}H_{21}NO_4$ (315.36) Buphanidrine	Alkaloid (Morphine alkaloid)	63		1.790	5;0	40.16	Cheesman et al. (2012)
96	 $C_{12}H_{12}O_3$ (204.22) 7-hydroxybutylidene phthalide	Phthalide	64 (CHR = 4)		3.412	3;1	46.53	Miran et al. (2020)

Table 2 continued

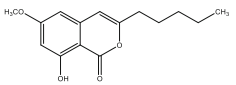
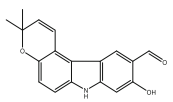
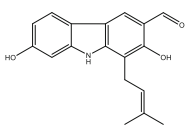
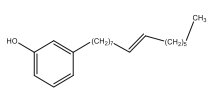
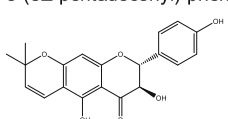
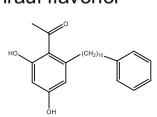
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
97	 $C_{15}H_{18}O_4$ (262.30) 8-hydroxy-6-methoxy-3-n-pentylisocoumarin	Coumarin (Isocoumarin)	64 (CHR = 4)		4.216	4;1	55.76	Taechowisan et al. (2019)
98	 $C_{18}H_{15}NO_3$ (293.32) Clauraila D	Alkaloid (Carbazole alkaloid)	64 (GEN = 0.25)		4.736	4;2	58.56	Maneerat et al. (2012)
99	 $C_{18}H_{17}NO_3$ (295.33) 2,7-dihydroxy-3-formyl-1-(3′-methyl-2′-butenyl) carbazole	Alkaloid (Carbazole alkaloid)	64 (GEN = 0.25)		4.589	4;3	69.56	Maneerat et al. (2012)
100	 $C_{21}H_{34}O$ (298.29) 3-(8Z-pentadecenyl)-phenol	Phenolic compound	64 (CHR = 4)		8.896	1;1	20.23	Taechowisan et al. (2019)
101	 $C_{20}H_{18}O_6$ (354.358) Conraui flavonol	Flavonoid (Conrauiflavonol)	64 (CHR = 0.5)	64 (CHR = 2.0)	3.368	6;3	96.22	Kengapa et al. (2011)
102	 $C_{24}H_{32}O_3$ (368.51) 2,4-dihydroxy-6-(10-phenyldecyl)-acetophenone	Acetophenone	64 (CHR = 4)		8.087	3;2	57.53	Taechowisan et al. (2019)

Table 2 continued

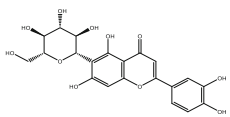
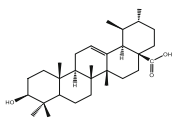
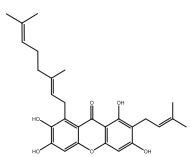
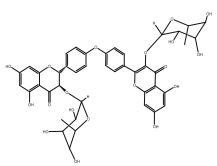
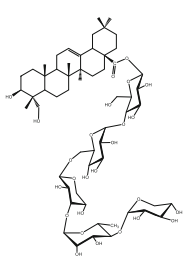
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
103	 $C_{21}H_{20}O_{11}$ (448.38) Isoorientin	Flavonoid (Flavone)	64 (GEN = 1.0)	64 (GEN = 4.0)	0.209	11;8	197.37	Sarıkahya et al. (2011)
104	 $C_{30}H_{48}O_3$ (456.71) Ursolic acid	Terpenoid (Pentacyclic triterpenoid)	64	64	8.627	3;2	57.53	do Nascimento et al. (2014)
105	 $C_{28}H_{32}O_6$ (464.55) Norcowanin	Xanthone (8-prenylated xanthone)	64 (GEN = 0.25)		7.724	6;4	107.22	Siridechakorn et al. (2012)
106	 $C_{42}H_{40}O_{19}$ (848.76) Ericoside	Flavonoid (Biflavonoid glycoside)	64 (CIP = 16)		3.282	18;10	291.82	Bitchagno et al. (2016)
107	 $C_{58}H_{94}O_{26}$ (207.36) Paphlagonoside B	Terpenoid (Triterpenoid glycoside)	64 (GEN = 1.0)	64 (GEN = 4.0)	0.423	26;15	412.82	Sarıkahya et al. (2011)

Table 2 continued

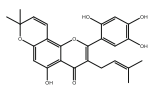
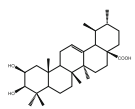
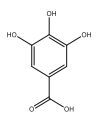
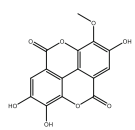
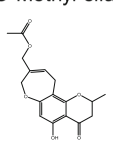
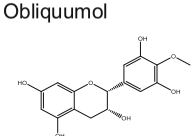
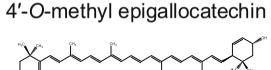
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	nOHNH	
Ec	Kp		tPSA	Reference				
108	 $C_{25}H_{24}O_7$ (436.46) Artonin E	Flavonoid (Prenylated flavonoid)	64 (CHR = 4)	128 (CHR = 4)	5.110	7;4	116.45	Kuete et al. (2011)
109	 $C_{30}H_{48}O_4$ (472.35) 2β-Hydroxyursolic acid	Terpenoid (Pentacyclic triterpenoid)	128 (CIP = 5)	64 (CIP = 5)	7.392	4;3	77.76	Bitchagno et al. (2016)
110	 $C_7H_6O_5$ (170.12) Gallic acid	Phenolic acid (Gallic acid)	78 (CHR = 30)	78 (CHR = 30)	0.425	5;4	97.99	Oladosu et al. (2019)
111	 $C_{15}H_8O_8$ (316.22) 3-*O*-Methyl ellagic acid	Tannin (Hydrolysable tannin)	80 (CIP = 0.015)		0.589	8;3	122.52	Jain et al. (2018)
112	 $C_{17}H_{18}O_6$ (318.32) Obliquumol	Chromone	80 (GEN = 8.0)	–	3.001	6;1	82.06	Ramadwa et al. (2019)
113	 $C_{16}H_{16}O_7$ (320.29) 4′-*O*-methyl epigallocatechin	Flavonoid (Flavanol)	90 (CIP = 0.16)	–	0.117	7;5	119.61	Khumalo et al. (2019)
114	 $C_{39}H_{54}O_2$ (554.85) Lutein	Carotenoid	90 (GEN = 30)		10.709	2;2	40.46	Songca et al. (2012)

Table 2 continued

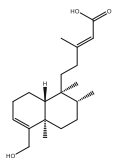
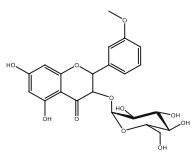
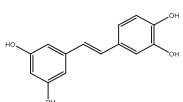
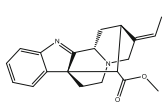
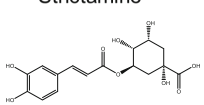
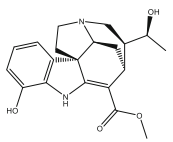
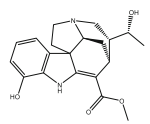
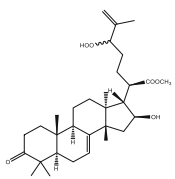
SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;	tPSA	nOHNH
Ec	Kp			Reference				
115	 $C_{20}H_{32}O_3$ (320.47) (*E*)-5-((1*S*,2*R*,4a*R*,8a*S*)-5-(Hydroxymethyl)-1,2-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)-3-methylpent-2-enoic acid	Terpenoid (Clerodane diterpenoid)		93.8 (CIP = 0.078)	5.695	3;2	57.53	Du et al. (2015)
116	 $C_{22}H_{24}O_{11}$ (464.42) Isorhamentin 3-*O*-glucoside	Flavonoid (Flavonoid glycoside)		1.95 (IMI = 0.98)	0.913	11;6	175.37	Elkady et al. (2020)
117	 $C_{14}H_{12}O_4$ (170.12) Piceatannol	Polyphenol (Stillbenoid)	100 (CHR = 25)		2.236	4;4	80.92	Kusumaningtyas et al. (2020)
118	 $C_{20}H_{22}N_2O_2$ (322.40) Strictamine	Alkaloid (Akuammiline alkaloid)	100 (CTX = 0.78)		2.803	4;0	41.9	Liu et al. (2015)
119	 $C_{16}H_{18}O_9$ (354.31) 3-O-caffeoylquinic acid (Chlorogenic acid)	Polyphenol (Quinic acid derivative)	100 (OFL = 20)		− 1.879	9;6	164.75	Xia et al. (2011)

Table 2 continued

SN	Chemical structure, molecular formula and name	Class (Subclass)	MIC (μg/mL)		ClogP	nON;		nOHNH
Ec	Kp		tPSA	Reference				
120	 $C_{20}H_{24}N_2O_4$ (356.42) Scholaricine	Alkaloid	100 (CTX = 0.78)	100	1.210	6;3	82.03	Liu et al. (2015)
121	 $C_{20}H_{24}N_2O_4$ (356.42) 19- Epischolaricine	Alkaloid	100 (CTX = 0.78)	100 (CTX = 0.78)	1.210	6;3	82.03	Liu et al. (2015)
122	 $C_{31}H_{48}O_6$ (516.71) Toosentanin A	Terpenoid (Lanosan-type triterpenoid)		100 (GEN = 3.125)	5.171	6;2	93.06	Zhu et al. (2015)

Compounds are arranged in order of increasing MIC values based on *E. coli* followed by *K. pneumoniae*. Positive controls: AMP = Ampicillin, CIP = Ciprofloxacin, CHR = Chloraphenicol, CTX = Cefotaxime, GEN = Gentamicin, IMI = Imipenem, LEV = Levofloxacin, NEO = Neomycin, OFL = Ofloxacin, STR = Streptomycin, and TET = Tetracycline ClogP = calculated partition coefficient between n-octanol and water; nON = number of hydrogen bonds acceptors (number of oxygen and nitrogen atoms in a molecule); nOHNH = number of hydrogen bonds donors (number of O–H and N–H bonds in a molecule); tPSA = calculated total polar surface area of the molecule

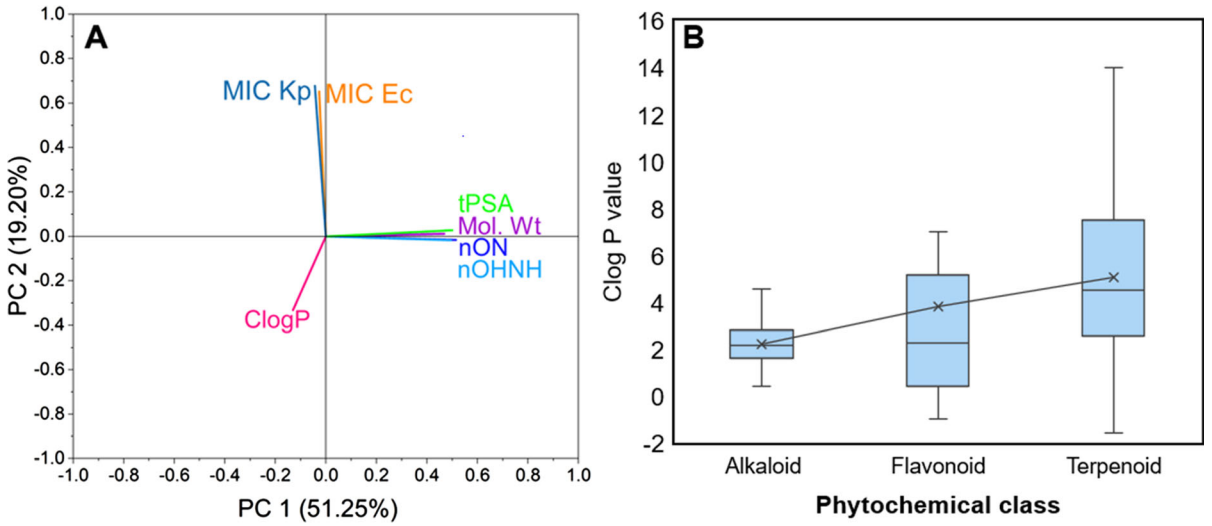


Fig. 5 **A** Principal component analysis for the correlations between the MIC values against *E. coli* and *K. pneumoniae* and the calculated total polar surface area (tPSA), molecular weight (Mol. wt), number of hydrogen donors (nON), number of hydrogen bond acceptors (nOHNH) and Clog P. **B** Distribution of Clog P values across three most frequent phytochemical classes of isolated compounds. Statistical significance: None observed for clogP vs. phytochemical classes ($p = 0.05$)

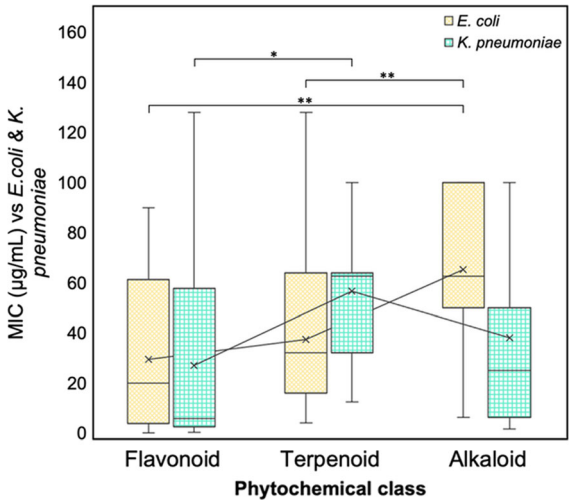


Fig. 6 Distributions of MIC values observed among *E. coli* and *K. pneumoniae* against flavonoids, terpenoids and alkaloids as the three most frequent classes of the isolated compounds. Statistical significance, *: $p < 0.05$, ** $p < 0.01$

(Lewis et al. 2004). The selected classes of antibacterial compounds were indicated to lose their selectivity with increase in lipophilicities. For instance, increasing lipophilicity of the Novel Bacterial Topoisomerase inhibitors (NBTIs) was reported to yield higher potency against Gram-negative bacteria at the expense of considerable inhibition of the human Ether-à-go-go-Related Gene (hERG) (Kolaric et al. 2021). Furthermore, higher lipophilicities among a number of peptide antibiotics were found to result in haemolysis, as a result of developing poor selectivity between bacterial and mammalian cell membranes (Henriksen et al. 2014; Liu et al. 2020).

Antibacterial activities and modes of action across phytochemical classes of isolated compounds

An evaluation of the isolated compounds revealed a majority of them to belong to the terpenoids, flavonoids and alkaloids classes (Table 2, Fig. 6). Among these classes, mean highest activities were observed among flavonoids whose MICs differed significantly from those of alkaloids for *E. coli* ($p < 0.01$) and terpenoids for K. pneumonia ($p < 0.05$) (Fig. 5). Moreover, the activities exhibited by terpenoids against *E. coli* were noted to be significantly higher than those of alkaloids ($p < 0.01$). (Fig. 6). However, MIC values $\leq$ 10 µg/mL were observed among compounds belonging to acetophenones, azaarenes, depsidones and xanthones (Table 2). In all cases where Reference Antibiotics (RA) were used as positive controls, their MICs were noted to be substantially low compared to those reported from the phytochemicals from across all classes (Table 2). This underscores the great need for performing structural modifications aimed at

developing derivatives with increased potencies to match or surpass those of currently used antibiotics.

The antibacterial potentials of flavonoids, terpenoids, alkaloids and other presented classes of phytochemicals are functions of a number of known modes of action, the account of which is provided on Table 3. It is evident that most of the phytochemical classes are proved to exhibit their antibacterial potentials via several modes of action.

Notably, the mechanisms targeting bacterial cell membrane and cell wall, the syntheses of nucleic acids and proteins, electron transport chains and efflux pumps, as well as selected bacterial enzymes were noted to be distributed across many classes. On the other hand, modes of action involving the inhibition of cell division, inhibition of oxygen uptake, disruption of oxidative phosphorylation, deprivation of essential nutrients/substrates and lowering of extracellular pH were only characteristic of selected classes (Table 3). Moreover, the fact that most the phytochemicals act by disruption of the bacterial cell membranes is of interest, given that very few of the antibiotics currently in clinical use are known to act by this mechanism (e.g., colistin and daptomycin) (Elias et al. 2021; Taylor and Palmer 2016).

Molecular weights distribution of isolated compounds in relation to their MIC values

Molecular weights of the isolated compounds were portrayed to be densely distributed within the range of 250–500 g/mol (Fig. 7). Similar to the outcomes of the PCA analysis described above, no particular patterns were observed between the molecular weights and the MIC values against both *E. coli* and *K. pneumoniae*. That is to say, the observed MIC values were rather fairly distributed across the stated range of molecular weights (Fig. 7).

The understanding that the molecular weights of antibiotics are unlikely to be linked to their ultimate antibacterial properties is common. However, different outcomes can be expected in cases where an increase in molecular weight leads to a significant rise in the polarity of the compounds. Moreover, while molecular weight of the test compounds does not highly impact the conduct of in vitro antibacterial susceptibility studies, compounds with higher molecular weights might demand different routes and modes of administration in studies involving higher animals.

Distribution of MIC values with molecular flexibility, globularity, and number of heavy atoms in the isolated compounds

In line with the report from the laboratory of P.J. Hergenrother on the roles of molecular flexibility and globularity on the accumulation of compounds particularly within bacteria, the above library of 122 compounds (Table 2) was further evaluated based on these and other criteria (Richter et al. 2017). Higher mean MICs against *E. coli* and *K. pneumoniae* were observed with an increase in the number of rotatable bonds within the phytochemicals, whereby the MICs against *E. coli* between the phytochemicals with 0–2 and ≥ 5 rotatable bonds were statistically significant ($p < 0.01$) (Fig. 8a). Further, compounds with molecular globularity between 0.05 and 0.08 were observed to exhibit the lowest mean MICs against both bacteria with a notable gradual decrease in activities above and below this range (Fig. 8b). Interestingly, the MICs of the compounds with molecular globularities of 0–0.04 were significantly higher ($p < 0.01$) than those having globularities of 0.05–0.08 across both bacteria (Fig. 8b). An evaluation based on the number of heavy atoms showed a trend of decreasing MIC values with an increase in the number of heavy atoms, with statistically significant differences ($p < 0.05$) noted between phytochemicals with 0–20 and > 35 and between 21 and 25 and > 35 rotatable bonds for *E. coli* and *K. pneumonia* respectively (Fig. 8c). Generally, 84% of the phytochemicals had low globularities of ≤ 0.2, whereas and 70% of them had ≤ 4 rotatable bonds and were therefore densely populated within these two boundaries (Fig. 8d).

The high activities exhibited by the phytochemicals against the two Gram-negative bacteria can hence be linked to their respective flexibility, globularity, and number of heavy atoms present. These observations are in agreement with those from the Hergenrother Lab in terms of a high proportion of the phytochemicals active (MIC $\leq$ 100 μg/mL) against both bacteria showing low globularity (84%) and flexibility (70%), as well as a general increase in mean MICs activity with an increase in globularity moving from 0.05 to 0.62 (Richter et al. 2017).

However, the noted differences with respect to compounds' molecular flexibility and globularity of < 0.04 in relation to their exhibited activities. Among other factors, these discrepancies may be

Table 3 Modes of action of some classes of phytochemicals hosting isolated compounds indicated in Table 2

SN	Phytochemical class	Reported Modes of action	References
1	Acetophenone	Disruption of bacterial cell membrane integrity/ permeabilization	Santander et al. (2015)
2	Alkaloids	Disruption of bacterial cell membrane integrity/ permeabilization	Cushnie and Lamb (2005), Khameneh et al. (2019)
		Inhibition of nucleic acids synthesis (Inhibit dihydrofolate reductase)	
		Inhibition of protein synthesis	
		Inhibition of cell division	
		Disruption of bacterial homeostasis	
		Inhibition of efflux pumps	
3	Anthraquinones	Disruption of bacterial cell membrane integrity/ permeabilization	Alves et al. (2004), Haraguchi et al. (2014), Malmir et al. (2017)
		Inhibition of cell wall synthesis	
		Inhibition of nucleic acids synthesis	
		Inhibition of protein synthesis	
		Interfere respiratory chain on bacterial membranes	
		Inhibition of essential bacterial enzymes	
4	Azaarenes	Inhibition of bacterial respiratory chain	Catallo and Portier (1992)
		Disruption of bacterial cell membrane integrity/ permeabilization	
		Decrease in cellular ATP synthesis	
5	Benzodioxole	Inhibition of protein tyrosine phosphatase	Gordon et al. (2013), Gupta et al. (2016), White et al. (2021)
		Oxidation of redox thiol	
		DNA binding	
		Inhibition of RNAIII promotor activation	
6	Carotenoids	Inhibition of oxygen uptake	Karpinski et al. (2021)
		Modulation of efflux pumps	
		Inhibition of quorum sensing and biofilm formation	
		Oxidative damage of membranes, DNA, proteins, and lipids	
		Disruption of oxidative phosphorylation	
		Anti-virulence activity	
7	Chromones	Inhibition of protein synthesis	Diwakar et al. (2011), Salem et al. (2013), Zhan et al. (2021)
		Inhibition of biofilm formation	
8	Depsidone	Inhibition of protein tyrosine phosphatase 1B (PTP1B)	Seo et al. (2009), Urena-Vacas et al. (2022)
		Inhibition of DNA repair and maintenance (RecA) enzyme	
		Inhibition of bacterial Fatty acid synthesis	

Table 3 continued

SN	Phytochemical class	Reported Modes of action	References
9	Flavonoids	Disruption of bacterial cell membrane integrity/ permeabilization	Cushnie and Lamb (2005), Farhadi et al. (2019), Górniak et al. (2018), Khameneh et al. (2019), Xie et al. (2015)
		Inhibition of cell wall/envelope synthesis	
		Inhibition of bacterial nucleic acid synthesis	
		Inhibition of protein synthesis	
		Inhibition of electron transport chain and ATP synthesis	
		Inhibition of bacterial toxins	
		Reduction of cell attachment	
		Inhibition of biofilm formation	
		Inhibition of porins	
10	Long chain fatty acids	Disruption of bacterial cell membrane integrity/ permeabilization	Desbois and Smith (2010)
		Interference with oxidative phosphorylation	
		Formation of peroxidation or auto-oxidation products	
		Inhibition of nutrients' uptake	
		Enzymes' inhibition	
		Fatty acid biosynthesis inhibition	
		Induction of autolysis/cell lysis	
		Disruption of electron transport chain	
11	Phenolic acids	Lowering of extracellular pH (Hyper-acidification at plasma membrane interphase) causing disruption of cell membrane integrity/permeabilization	Borges et al. (2013), Cueva et al. (2010), Pernin et al. (2019)
12	Phenylpropanoids	Disruption of bacterial cell membrane/permeabilization	Álvarez-Martínez et al. (2021), Nogueira et al. (2021)
		Interference of aerobic metabolism	
		Inhibition of efflux pumps	
13	Phloroglucinols	Disruption of bacterial cell membrane/permeabilization	Celaj et al. (2020), Khan et al. (2021)
		Cell membrane depolarization	
		DNA damage	
		Inhibition of metabolic enzymes	
		Inhibition of biofilm formation	
14	Phthalides	Inhibition of dihydrofolate reductase	Grube et al. (2019), Ibraheem et al. (2022)
		Antiadhesive activity	
15	Phytosteroids	Disruption of bacterial cell membrane	Das et al. (2021), DoĞAn et al. (2017)
		Topoisomerase I inhibition	
		Prevention of transpeptidation by inhibition of cell surface protein, Sortase	
16	Polyphenols	Disruption of bacterial cell membrane/permeabilization	Álvarez-Martínez et al. (2020), Daglia (2012), Jia et al. (2021), Xu et al. (2019)
		Disruption of bacterial cell wall	
		Cell membrane depolarization	
		Inhibition of ion channels	
		Inhibition of biofilm formation	
		Inhibition of cell membrane-based receptors	
		Reduction of intracellular ATP concentration	

Table 3 continued

SN	Phytochemical class	Reported Modes of action	References
17	Tannins	Disruption of bacterial cell membrane/permeabilization Damaging activity of bacterial cell wall Inhibition of extracellular microbial enzymes Inhibition of metabolic enzymes Deprivation of essential substrates	Buzzini et al. (2008), Daglia (2012), Scalbert, (1991)
18	Terpenoids	Disruption of bacterial cell membrane/permeabilization Inhibition of efflux pumps Alteration of oxidative phosphorylation Inhibition of oxygen uptake Inhibition of biofilm formation and quorum sensing Reduction of cell adherence	Khameneh et al. (2019), Mahizan et al. (2019), Moo et al. (2021)
19	Xanthones	Disruption of bacterial cell membrane/permeabilization Reduction of intracellular ATP Inhibition of efflux pumps	Durães et al. (2021), Koh et al. (2016), Sivaranjani et al. (2019)

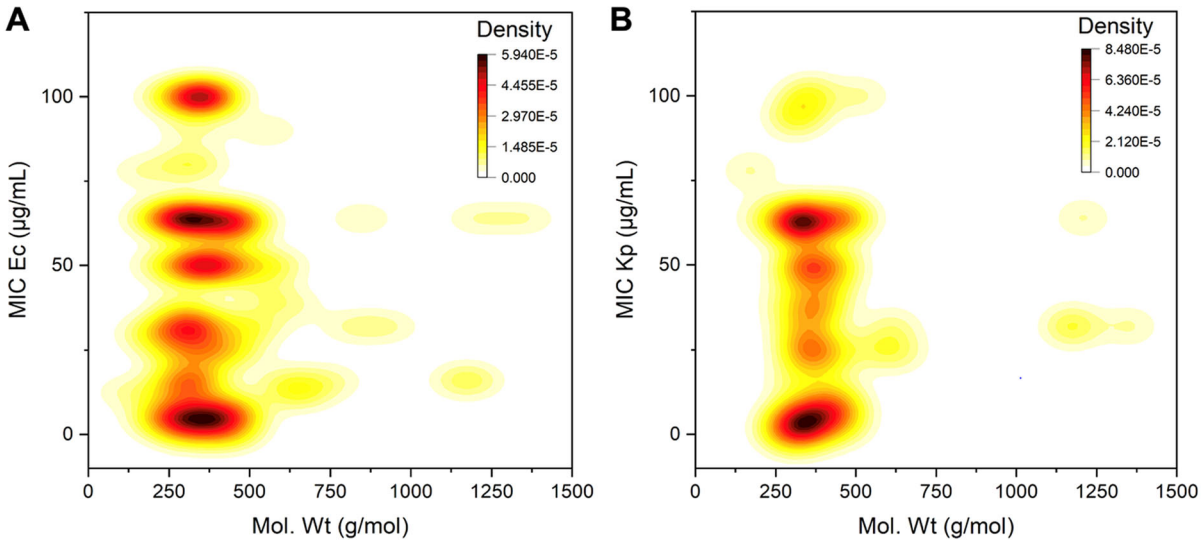


Fig. 7 Kernel density plots showing the density distribution of isolated compounds' molecular weights with their corresponding MIC values against *E. coli* **A** and *K. pneumoniae* **B**

described by the possible lack of direct correlations between the likelihood of phytochemicals to accumulate and their ultimate antibacterial activities. This can be brought about by the general tendency of many phytochemical classes to act by multiple modes of action, which commonly involve the disruption of the integrity of bacterial cell membrane (Table 3). Even so, these observations underscore the essence of considering these parameters in the design of compounds targeting the Gram-negative bacteria.

Conclusion and future perspectives

The current review has highlighted the big, highly valuable, and long-standing efforts in the search for

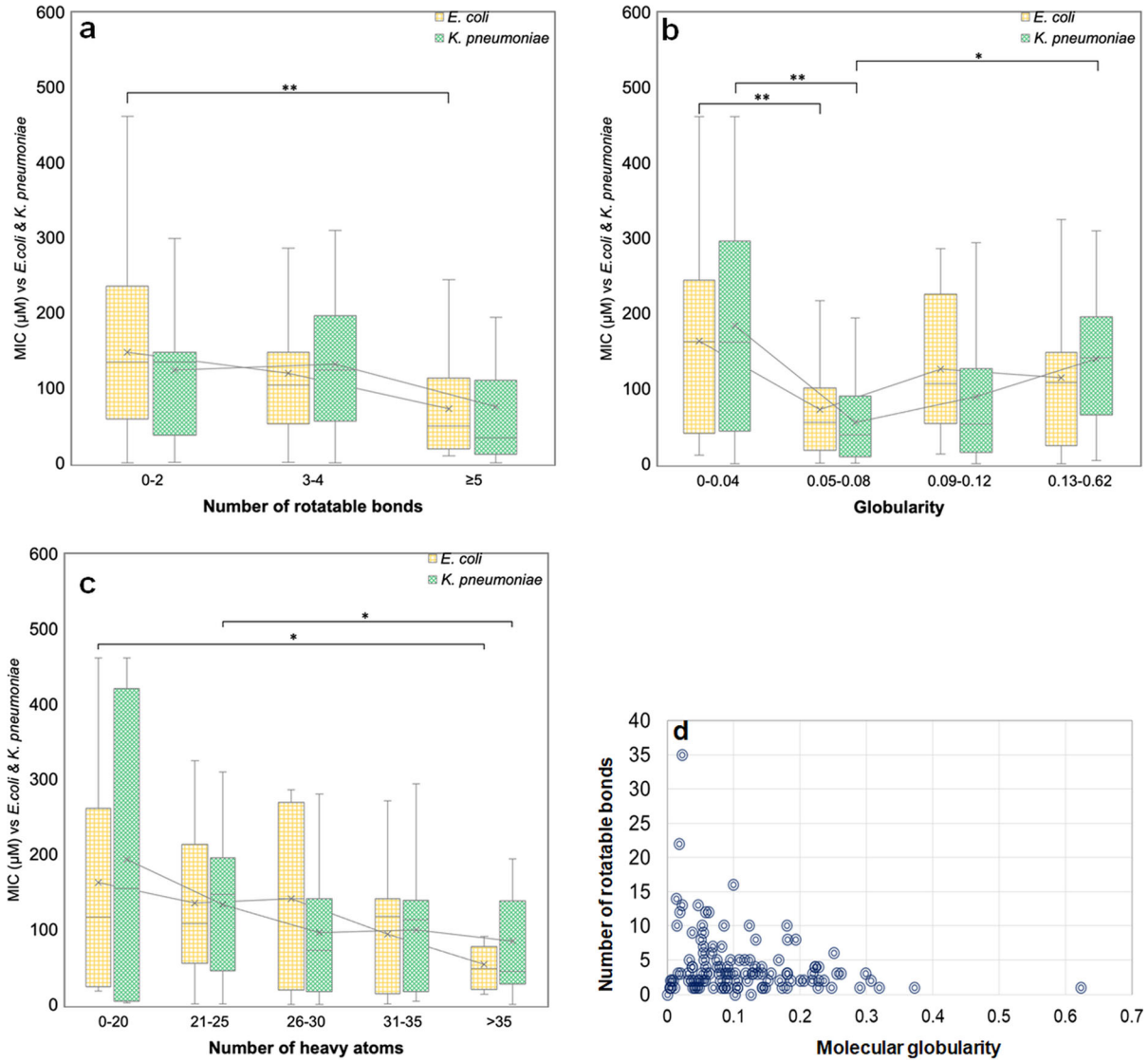


Fig. 8 Distribution of MIC values with molecular flexibility **a**, globularity **b**, number of heavy atoms **c**, as well as between molecular flexibility and globularity **d** among the phytochemicals presented in Table 2. Statistical significance, $*p < 0.05$, $**p < 0.01$

antibacterial compounds against *E. coli* and *K. pneumoniae* from numerous plant species. In that respect, this review has provided a collective up to date appraisal of the recent knowledge on practices, limitations and findings from such studies. Moreover, the study has availed a more focused account offering a detailed evaluation of extracts and phytochemicals against closely related bacteria. This aspect is beneficial by virture of minimizing variabilities and confounders in determining useful patterns via the common approach involving broadly unrelated bacteria. Particularly, the study has revealed diverse approaches in the aspects of preparing crude extracts, conducting antimicrobial susceptibility testing, as well as the isolation and characterization of antibacterial compounds, among others. While many positive lessons from those approaches have been discussed, the need for more streamlining of numerous approaches in this field is eminent.

Plant species and extracts with reported high antimicrobial activities against numerous susceptible and MDR strains of *E. coli* and *K. pneumoniae*

presented in this review can provide a valuable contribution towards further research works on the same or related plant species. Additionally, it is anticipated that the provided overview of approaches undertaken by others is useful towards attaining improved design of experiments and evading the common pitfalls.

Furthermore, this review has provided an account of plant-isolated antibacterial compounds, highlighting various aspects of their chemical natures in relation to the exhibited antibacterial potentials against *E. coli* and *K. pneumoniae*. Notably, higher activities against both bacteria were fairly related to the higher lipophilic character of the isolated compounds, although this character might as well signify their low target selectivity. On the other hand, molecular weight, total polar surface area as well as the number of hydrogen bond donors and acceptors were not correlated to the observed MIC values. Additionally, the evaluated descriptors (molecular flexibility, molecular globularity, and number of heavy atoms) were observed to influence the resulting MIC values in different ways. This biochemometric approach offers an in-depth understanding of the areas and extents at which the presented library of phytochemicals can contribute to further hunting for new antibacterial chemical scaffolds among other aspects of antibiotics design and development.

The global rise of antimicrobial resistance necessitates recruiting all available options in the search for viable solutions. Plants like other natural products are proven to host a valuable potential for the discovery of novel antibiotics. Ongoing efforts on ascertaining potential plant species and isolation of promising antibacterial compounds are therefore highly credible.

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